JMIR Research Protocols

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Corrigenda and Addenda

Preliminary Effectiveness of a Remotely Monitored Blood Alcohol Concentration Device as Treatment Modality: Protocol for a Randomized Controlled Trial

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Abstract

Background: Alcohol use disorder is a chronic disorder with a high likelihood of relapse. The consistent monitoring of blood alcohol concentration through breathalyzers is critical to identifying relapse or misuse. Smartphone apps as a replacement of or in conjunction with breathalyzers have shown limited effectiveness. Yet, there has been little research that has effectively utilized wireless or Wi-Fi–enabled breathalyzers that can accurately, securely, and reliably measure blood alcohol concentration.

Objective: The purpose of this study is to evaluate the impact of a wireless blood alcohol concentration device in collaboration with long-term treatment on dropout rates, psychological distress, treatment motivation, quality of life, and need for higher levels of follow-up care for patients with alcohol use disorder.

Methods: The randomized clinical trial will include two arms, access to the wireless breathalyzer versus no access to the breathalyzer, while both groups have access to treatment. Evaluation will last 3 months with a 6-week follow-up, during which each participant will be interviewed at admission, 1 month in, 2 months in, 3 months in, and follow-up. Individuals will be recruited online through a secure telehealth meeting invitation. Outcomes will focus on the impact of the wireless breathalyzer within the alcohol use disorder population, and the combined effect on psychological distress, treatment motivation, and quality of life. In addition, we intend to investigate the impact of the breathalyzer on dropout rates and participants' need for higher levels of follow-up care and treatment.

Results: The recruitment of this study started in July 2020 and will run until 2022.

Conclusions: This information will be important to develop cost-effective treatments for alcohol dependence. Ongoing monitoring allows treatment providers to take an individualized disease management approach and facilitates timely intervention by the treatment provider.

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Introduction

Prevalence and Relapse

Alcohol use disorder (AUD) is a chronic disorder that presents with a predisposition to relapse and is among the top 5 leading causes of disability-adjusted life years [1]. Worldwide, 5.9% of deaths (7.6% in men, 4.0% in women) are due to alcohol [2], and within the United States, medical costs for AUD are reported to be over $120 billion per year [3]. In addition, AUD has a high occurrence of other comorbid psychiatric conditions (eg, depression and generalized anxiety) [4,5]. Research has shown that individuals with AUD are more likely to have psychiatric conditions, which can lead to increased treatment delays and poor outcomes [6]. This in turn can exacerbate the psychiatric comorbidity [4,7]. Due to these issues, patients can easily become discouraged during treatment, potentially leading to relapses or setbacks [8] along with reductions in treatment motivation [9]. Palmer et al [10] noted that premature client dropout is exceedingly high (74%) in treatment, hindering potential benefits and preventing successful completion. Moreover, relapse rates for AUD are relatively high, ranging between 30% and 70%, 3 months after treatment [11,12]. Due to early dropout and the likelihood of relapse, recovery should be seen as a continuous process instead of a singular incidence [13], and the consistent monitoring of blood alcohol concentration (BAC) is critical to identifying relapse or misuse.

Standard treatment for those with AUD generally provides a highly structured program of care [8,14]. Regardless of the structure of care (group home, step-down approach, individual treatment, or within-home treatment modalities), it is critical to ensure ongoing monitoring by treatment providers to facilitate appropriate patient care and evaluation [15]. In attempting to capture alcohol usage through self-report, many issues can arise, such as lack of recall and deception. To combat these issues, the use of technology via mobile phones, video recording, and behavioral contracts has been utilized [16-18]. It should be noted that Gustafson et al [17] have demonstrated the initial effectiveness of using a smartphone app during recovery in reducing the incidence of hazardous drinking and promoting abstinence. However, a recent systematic review of mobile apps for AUD, showed limited effectiveness when comparing to controlled samples [19]. Devices that can be attached to mobile phones to evaluate BAC have been less than reliable and lack consistency in reporting. There is little research that effectively utilizes wireless or Wi-Fi–enabled breathalyzers that can accurately, securely, and reliably measure BAC [20].

Effectiveness of Breathalyzers

Breathalyzers have been utilized as a reliable method for detecting the presence of alcohol for over 50 years [16,21]. By collecting real time information, the breathalyzer allows for in vivo evaluation, providing the clinician, researcher, and patient further understanding of usage. Wearable monitors have been shown to be reliable in producing alcohol values [22,23]; however, breathalyzers are less intrusive than wearable monitors as they do not need to be worn, the process is automated, and they encourage accountability via physical exertion (eg, by manually blowing into the device). Previous research has

incorporated breathalyzers to ensure that other treatment strategies (eg, contingency management) have been utilized correctly [24]. The authors of the previous study utilized a breathalyzer distributed by Soberlink (Soberlink Healthcare LLC) [24]. Yet, to the best of our knowledge, no randomized clinical trial has been conducted utilizing the breathalyzer in conjunction with the treatment modality, while comparing the absence of the breathalyzer. For that reason, having a device such as Soberlink, which can be utilized as a treatment assessment for the clinician and self-monitoring device for the patient, is critical for treatment centers that take care of individuals with AUD. Building off the research of behavioral psychology [25] and the concept of permanent product, we anticipate that the physical presence of the device will provide accountability, reminder, and reinforcement, which will reduce the likelihood of dropout.

Objectives and Specific Aims

The purpose of this study is to evaluate the usage and impact of the Soberlink BAC device in collaboration with Aware treatment (receiving AUD treatment through Aware Recovery Care) for patients with AUD. The three main objectives are as follows:

1. To determine the initial impact of the Soberlink device in conjunction with the Aware Treatment model to decrease dropout rates for individuals suffering from AUD.

2. To evaluate the combined effect of Soberlink and Aware Treatment on participants' treatment motivation, quality of life, and psychological distress.

3. To evaluate the extent to which the need for higher levels of follow-up care and treatment is reduced for individuals who have had access to the Soberlink device and Aware Treatment.

Methods

Participant Recruitment, Enrollment, and Randomization

Admission staff at Aware Recovery Care will inform all eligible patients about the research opportunity. Admissions staff will direct patients to flyers or provide the contact information of the principal investigator to set up a meeting, if desired. Flyers with the name and telephone number of the principal investigator will be hung around the main facility and breakout rooms where potential participants congregate. The participant inclusion criteria are as follows: (1) they are at least 21 years old; (2) they are currently enrolled with Aware Recovery Care in-home treatment; and (3) they have a primary or secondary *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders*) diagnosis of AUD. Previous research by Brown et al [26] demonstrated that late adolescence (16-20 years) is still considered a developmental stage and has heighted challenges with treatment during this age bracket. The exclusion criteria were as follows: (1) having a current suicide or homicide risk, as defined by the SCID-5 (Structured Clinical Interview for *DSM-5*); (2) meeting the criteria for *DSM-IV* current psychotic disorder or bipolar disorder (previously diagnosed); (3) not having phone access with text message capabilities; (4) being

unable to read or understand English; (5) being unable to complete the study because of anticipated incarceration or move; (6) having life-threatening or unstable medical problems; (7) having current or pending legal action; and (8) Soberlink results being used for child custody or legal circumstance.

Eligibility will be evaluated by the research assistant and reviewed with the project director or principal investigator prior to initiation. All eligible participants are required to be recruited within 72 hours of being admitted to the program. The participants will be interviewed via Zoom using standardized psychological assessments or will complete similar standardized self-report forms. This is a closed, web-based online recruitment in which quasi-anonymous measures are provided to the participants. For all participants, the principal investigator or a research assistant will meet with them to read through the informed consent document. Each participant will be asked several times throughout the consent procedure whether they understand the information presented and implications for participation. In addition, the subjects will be asked to provide a summary of their understanding of the consent. The participants will also be asked what questions they have about

the study procedures, their rights and obligations, and the expectations and obligations of the study staff. When it is clear that the participants understand the material, both the research staff and the participants will electronically sign the consent form.

The study will utilize a parallel randomized controlled trial design including 2 groups (Aware treatment only versus Soberlink plus Aware treatment), in which the Aware treatment only group will act as an active control group (a further detailed explanation of the groups is described below). The block randomization sequence will allow for equal representation between the 2 groups without bias on gender, age, or ethnicity, given that all individuals will be categorized as a single variable [27]. The intervention for both groups will last for 3 months with a 6-week follow-up, during which each participant will be interviewed at admission (T1), 1 month in (T2), 2 months in (T3), 3 months in (T4), and follow-up (T5), as seen in Figure 1 [28]. This study has been approved by the FB human research protection program and is registered at ClinicalTrials.gov (NCT04380116).

Figure 1. CONSORT (The Consolidated Standards of Reporting Trials) study diagram.
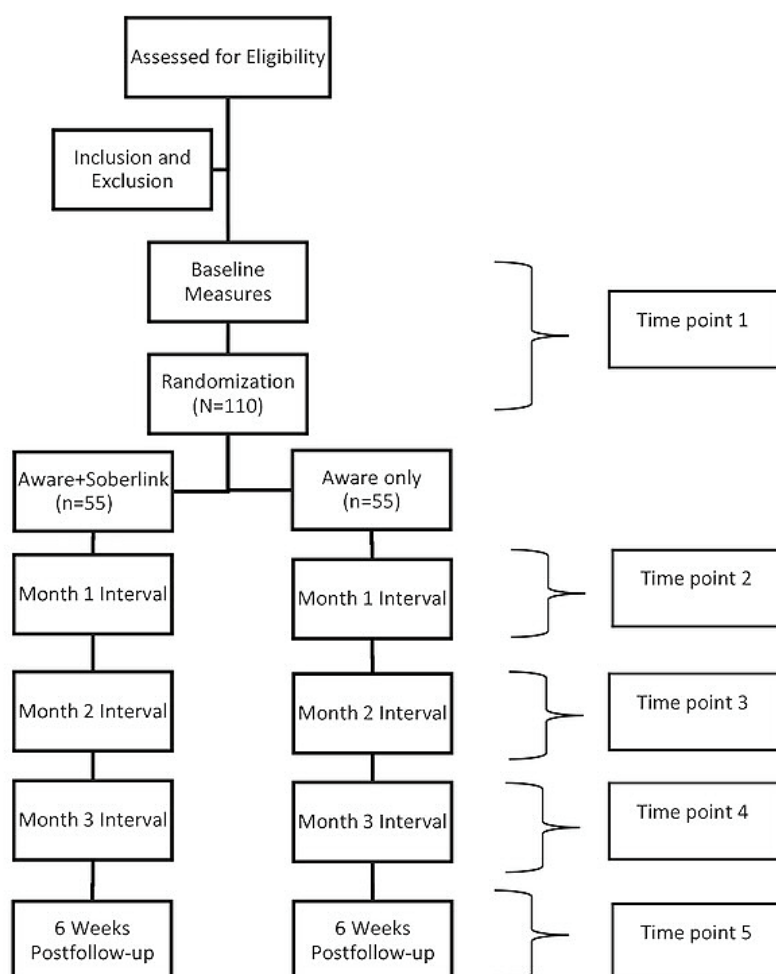
Procedure

We are planning to assess a broad range of subject characteristics, process measures, and treatment outcomes over

the 3-month trial and at the 6-week posttreatment follow-up, in which all assessments are self-reported and completed online. Baseline assessments are designed to ensure that patients meet

eligibility criteria and that important predictor variables such as cognitive impairment are assessed. Baseline measures include evaluation and understanding of the extent of the AUD issue from several different vantage points. Primary outcome measures include reductions in days per week of use and negative BAC screens for alcohol. Monthly assessments will take approximately 30 minutes to complete. Table 1 provides a complete description of the assessments utilized in this study.

Table 1. Description of measures.

Measure and description		Completion time and admission					
		Time to complete	T1[a]	T2[b]	T3[c]	T4[d]	T5[e]
Screening and background measures							
Patient Health Questionnaire (PHQ)	A 9-item self-report scale to evaluate depression, which scores each of the 9 *DSM-5*[f] criteria.	2-3 mins	X	X	X	X	X
Generalized Anxiety Disorder Scale (GAD-7)	A 7-item self-report scale used for screening, diagnosis, and severity assessment of anxiety disorder.	2-3 mins	X	X	X	X	X
Structured Clinical Interview for *DSM-5* (SCID-5)	A semi-structured interview used to determine *DSM-5* diagnoses.	5 mins	X	N/A[g]	N/A	N/A	N/A
Background questionnaire	This questionnaire will assess sociodemographic variables, pain location, number of surgeries, current medications, and access, use, or comfort with smartphones and internet technology.	5 mins	X	N/A	N/A	N/A	N/A
Process measures and treatment outcomes							
Alcohol Use Disorder Identification Test (AUDIT-C)	A 3-item scale used to determine alcohol use disorder or alcohol dependence.	1-3 mins	X	X	X	X	X
Soberlink's engagement	Application usage (eg, login, dropout rates, compliance, and missed tests) at the user and aggregate level.	N/A	X	X	X	X	X
Quality of Life Scale (QOLS)	A 16-item self-report scale used to assess quality of life based on 5 domains of life (material and physical well-being, relationship with other people, social, community and civic activities, personal development and fulfillment, and recreation).	5 mins	X	X	X	X	X
Alcohol Abstinence Self-Efficacy Scale	A 40-item self-report scale with 4 subscales (negative affect, social/positive, physical and other concerns, and cravings and urges) used to determine the ability to avoid drinking in different situations based on temptation and confidence.	5-10 mins	X	X	X	X	X
University of Rhode Island Change Assessment Scale (URICA)	A 32-item self-report scale with 4 subscales (precontemplation, contemplation, action, and maintenance) used to assess stages of change relating to alcohol use.	5-10 mins	X	X	X	X	X
Timeline Follow Back[h]	An instrument used to obtain estimates of the amount of substance used over a period ranging from 30 days to 1 year prior to assessment.	Varies upon interval	X	X	X	X	X

[a]At admission.

[b]After 1 month.

[c]After 2 months.

[d]After 3 months.

[e]At follow-up.

[f]*DSM*: *Diagnostic and Statistical Manual of Mental Disorders*.

[g]N/A: not applicable.

[h]Permission to utilize granted by Mark and Linda Sobell.

Aware Treatment

All individuals will have access to the Aware Recovery Care in-home treatment model, which is a 4-phase step-down model that provides access to continual care through an integrated team of medical, nursing, and home health advisors, as well as counselors coming to the patient's home [29,30]. Aware Recovery Care is an in-home addiction treatment program that provides highly intensive, rigorously monitored, intensive outpatient care, based on a chronic disease model of care. The approach implements principles of evidence-based practices including motivational interviewing, cognitive behavioral

therapy, and dialectical behavioral therapy. Additionally, all families are offered education about AUD, the opportunity to participate in the treatment process, and frequent communication about treatment progress. The patient's individualized treatment team consists of 1 licensed professional (nurse or master's level clinician), 2 certified recovery advisors, and 1 licensed marriage and family therapist. It should be noted that due to COVID-19 restrictions, a majority of sessions are provided remotely through telehealth platforms, instead of in-person.

The patient's care team is overseen by a master's level alcohol and drug counselor, an advanced practicing nurse, and an addiction psychiatrist. The licensed professional is responsible for leading the team, collaborating with external providers, communicating with family members, and providing referrals to external providers as needed. The certified recovery advisors are lived-experience advisors, at least 1 of whom is both age- and gender-matched in order to provide a more intimate therapeutic relationship. Certified recovery advisors are responsible for delivering a staged biopsychosocial curriculum. All care teams include 1 licensed marriage and family therapist for 4 family therapy sessions, as well as 4 family education sessions delivered by 1 specially trained family education facilitator.

The Aware Plus Soberlink Group

This group will include access to the Aware treatment and to the Soberlink device. During enrollment, a research assistant will train the participant and provide an orientation to use the Soberlink device (see "Orientation to Soberlink" below). All participants will complete screening and outcome assessments, along with using the Soberlink device for the first time. The participants' Soberlink device will be set up to test them for alcohol use twice a day. Reminder emails will be sent out the day before and on the day of the 1-month, 2-month, and 3-month surveys. All surveys will be completed online in the participant's home through a secure link sent directly to them. Subsequent phone calls will be made by the research assistant to the participant if they have missed their evaluation. Upon completion of the surveys, the participants in the Aware plus Soberlink group will be paid and reminded of the subsequent follow-ups. The estimated time of the consent process will take 45 to 60 minutes to complete.

Orientation to Soberlink

Patients assigned to the Aware plus Soberlink condition will receive a 30-minute orientation to the Soberlink device, including an initial measurement of their BAC. The Soberlink device consists of a wireless breathalyzer that uses a professional-grade fuel cell sensor to detect alcohol levels at an accuracy of +/-0.005 BAC. The device also has an embedded camera and uses facial recognition software to automatically identify the patient during the test. The participant will have a set testing schedule that consists of 2 tests per day. The participant will have a test window of 2 hours with a late window of 1 hour. When the participant blows into the Soberlink device, it will capture the BAC level while the embedded camera takes a photo of the participant during the test. A visual indicator on the Soberlink device or in the Soberlink app will display "compliant" or "non-compliant" at the time of examination.

The breathalyzer uses wireless technology to send the data in real time. The cloud-based monitoring system includes a scheduler that automatically tracks scheduled tests and sends reminders to the patient for testing. Retesting is automatically scheduled if a positive test is received or if a patient's identity cannot be verified. The device locks out for 15 minutes to ensure alcohol evaporates before the next test. The facial recognition software ensures identity is approved or declined in real time. Artificial intelligence is used to report on testing, and green, yellow, and red visual icons are used in all reporting to identify events.

A testing window will be scheduled with everyone, between 7 AM and 9 AM (morning BAC) and from 8 PM to 10 PM (evening BAC). Individuals in this group can provide the BAC at any time within the testing window. All tests performed outside the window will be recorded but counted as unscheduled tests on the BAC spreadsheet. Previous research has used fixed windows for evaluation. These windows allow for structure in treatment for the individual, reducing the need to always carry the device on one's person [31]. All participants can opt in to receive texts from Soberlink to remind them about their morning and evening BACs.

Aware Group

This group will not receive access or training to a Soberlink device; however, they will be recruited to complete the same set of surveys at the same time intervals (Figure 1). Reminder emails will be sent out the day before, and on the day of the 1-month, 2-month, and 3-month evaluations.

Retention and Adherence

We intend to over-recruit participants by 25% to account for attrition and potential dropouts. In substance use disorder research, it is reported that 73% will drop out of treatment within the first 3 months due to noncompliance of treatment [10]. All participants will be compensated $10 for the baseline and monthly assessments and $25 for follow-up assessment (up to $65 total). Soberlink will purchase gift cards and the principal investigator or research assistant will distribute them to the participants. Patients who are randomized to the Soberlink group will receive the Soberlink device and 4 months of Soberlink service for no charge. To control for attrition and increase compliance with the device, the following protocol will be put into place. If individuals miss 2 consecutive BACs, participant's case managers will be informed by the research assistant or the principal investigator. If an individual misses 4 consecutive BACs without communication, it will result in termination from the study by the principal investigator. Eliminating participants who are not adhering to the research design is a critical element for a successful trial [32,33]. This will reduce the likelihood of those reporting clinical improvement regardless of actual response, while establishing systematic methods to detect and eliminate nonadherence, which is in line with the method utilized by Shiovitz et al [33].

Sample Size

A sample size of 110 would provide >80% power (α=.05) to detect a medium-to-large effect size (d=0.65) and allow to fully evaluate gender differences. Given this, we expect to enroll 145

participants into the study. Both groups should have even distribution (n=55) within each group and estimated equal differences between genders (n=25), allowing up to 5 to be transgender or "not to specify" [34].

Data Analysis

Statistical procedures and models for analyzing data have been selected according to the research hypotheses being investigated and the types of data available. We will use $\alpha < .05$ but will use appropriate corrections for multiple tests. Statistical analyses will be conducted using SPSS (IBM Corp). If missing data occurs from participants who have completed the time intervals, we intend to use missing values analysis prior to running any analysis. The missing values analysis is the most conservative measure, as described by Tabachnick and Fidell [35], to detect any missing values. If more than 5% of the data are missing for a specific assessment, the data will be eliminated from the data set to reduce potential errors and increase of bias.

To understand the first aim, a repeated measures general estimating equation and linear mixed model analysis for the primary outcomes of negative BAC and days or months of self-reported alcohol use will be conducted. This will be used to determine the initial impact of the Soberlink device in conjunction with the in-home addiction treatment model, to evaluate the combined effects, and to assess the need for higher levels of follow-up. Sample size calculations for linear mixed model analysis are dependent on the number of repeated events, the retention rate, and the interclass correlation.

For the second and third aims, chi-square and *t* tests will be used to conduct preliminary analyses of the adequacy of the randomization procedure, the comparability of baseline measures for the 2 groups, and the possible need for covariates in the analyses of treatment outcome data. Repeated-measures ANOVA will be used to evaluate differences in process measures acquisition over time across each grouping. Additionally, the Pearson product-moment correlations will be used to assess the relationship between process measures and active use based on the Soberlink device testing results over the duration of the study.

Results

Recruitment of this study started in July of 2020 and will run until 2022. Enrollment has been slower than anticipated due to the COVID-19 pandemic. This study is expected to conclude on July 1, 2022.

Discussion

This study will assist in evaluating the efficacy of the combined effect of the Soberlink device and Aware Recovery Care model. The study is categorized as "minimal risk," given the limited risks it has (risks are commensurate with everyday risks associated with alcohol abuse treatment as an adequate protection of confidentiality). This information is important in order to develop cost-effective treatments for alcohol dependence, which ultimately would be of great benefit to the society [14]. Considering the anticipated benefits of the study to the subjects and to society, the low risks it poses to the subjects are reasonable. For many patients, AUD is a chronic medical condition characterized by multiple periods of relapse and sobriety. Much like with the management of other chronic diseases, patients with AUD often seek out treatment multiple times to manage the symptoms of their disease [12]. To effectively treat AUD as a chronic disease, it is critical to regularly monitor key indicators of disease control such as BAC. Ongoing monitoring allows treatment providers to take an individualized disease management approach and facilitates timely intervention by the treatment provider. The Soberlink device automatically notifies treatment providers of positive BAC tests in real time. After being notified, treatment providers can respond quickly and determine if changes are necessary to a patient's treatment plan or if the patient should be moved to a higher level of care. In addition to intervening after a positive Soberlink test, multiple missed tests by a patient can also provide valuable information to a treatment provider about a patient's level of engagement and signal the need for outreach.

In this study, the Soberlink device is being used by patients receiving outpatient treatment through Aware Recovery Care. However, the device may be useful to patients with AUD in a variety of settings, across multiple phases of recovery. The device serves as an ongoing source of connection and point of engagement with a treatment provider for patients during treatment and beyond discharge. Using the Soberlink device may provide AUD patients with both personal and social accountability. Patients may also find that the device serves as an external source to support self-control, and those that choose to share results with family members may find that it helps to rebuild trust that may have been lost over time. In addition to reducing alcohol use, using the Soberlink device may positively impact other whole health outcomes such as improved relationships, employment or school engagement, management of health and stress, and reduction of mental health symptoms.

Conflicts of Interest

NW is a research consultant for Soberlink.

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Abbreviations

AUD: alcohol use disorder
BAC: blood alcohol concentration
DSM: *Diagnostic and Statistical Manual of Mental Disorders*
SCID: Structured Clinical Interview for *DSM*

Protocol

The Smarter Safer Homes Solution to Support Older People Living in Their Own Homes Through Enhanced Care Models: Protocol for a Stratified Randomized Controlled Trial

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Abstract

Background: An aging population, accompanied by the prevalence of age-related diseases, presents a significant burden to health systems. This is exacerbated by an increasing shortage of aged care staff due to the existing workforce entering their retirement and fewer young people being attracted to work in aged care. In line with consumer preferences and potential cost-efficiencies, government and aged care providers are increasingly seeking options to move care and support to the community or home as opposed to residential care facilities. However, compared to residential care, home environments may provide limited opportunity for monitoring patients' progression/decline in functioning and therefore limited opportunity to provide timely intervention. To address this, the Smarter Safer Homes (SSH) platform was designed to enable self-monitoring and/or management, and to provide aged care providers with support to deliver their services. The platform uses open Internet of Things communication protocols to easily incorporate commercially available sensors into the system.

Objective: Our research aims to detail the benefits of utilizing the SSH platform as a service in its own right as well as a complementary service to more traditional/historical service offerings in aged care. This work is anticipated to validate the capacity and benefits of the SSH platform to enable older people to self-manage and aged care service providers to support their clients to live functionally and independently in their own homes for as long as possible.

Methods: This study was designed as a single-blinded, stratified, 12-month randomized controlled trial with participants recruited from three aged care providers in Queensland, Australia. The study aimed to recruit 200 people, including 145 people from metropolitan areas and 55 from regional areas. Participants were randomized to the intervention group (having the SSH platform installed in their homes to assist age care service providers in monitoring and providing timely support) and the control group (receiving their usual aged care services from providers). Data on community care, health and social-related quality of life, health service utilization, caregiver burden, and user experience of both groups were collected at the start, middle (6 months), and end of the trial (12 months).

Results: The trial recruited its first participant in April 2019 and data collection of the last participant was completed in November 2020. The trial eventually recruited 195 participants, with 98 participants allocated to the intervention group and 97 participants

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allocated to the control group. The study also received participants' health service data from government data resources in June 2021.

Conclusions: A crisis is looming to support the aging population. Digital solutions such as the SSH platform have the potential to address this crisis and support aged care in the home and community. The outcomes of this study could improve and support the delivery of aged care services and provide better quality of life to older Australians in various geographical locations.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12618000829213; https://tinyurl.com/2n6a75em

International Registered Report Identifier (IRRID): DERR1-10.2196/31970

Introduction

Background and Rationale

Globally, the population is aging. It is expected that by 2050, 1 in 6 people will be over the age of 65 years, representing a significant increase from the current rate of 1 in 11 [1]. Australia's aged population is steadily increasing. A fertility boom from 1946 to 1965, coupled with advances in health care and associated increased life expectancy, resulted in the proportion of the population aged 65 years and over to increase from 11.1% to 14.24% between 2000 and 2020 [2], and it is expected to reach 25% by 2056 [3]. Currently, there are 5 people of working age for every person over 65 years old; however, this number is expected to drop to 2.7 by 2050 [4]. The dwindling of the workforce is further exacerbated in aged care due to the predominance of older workers (48-50 years) [5] reaching retirement and fewer young workers being attracted to working in this area.

With a large percentage of our aging population facing injury, disability or chronic disease, and requiring regular medical care, health expenditure is rising faster than economic growth [6]. Several reports demonstrate the negative impact of an aging population on health care expenditure [7-9]. These reports indicate that the cost of health care increases with age, doubling between 45 and 65 years, and doubling again between 65 and 85 years. The majority of the health care spent on aging is attributed to public hospital funding, with a 5-fold increase on those aged 75 to 84 years and over compared to the median per capita amount [10]. Furthermore, the proportion of those accessing residential aged care facilities increases significantly for those aged 80 years and over.

In line with consumer preferences and potential cost-efficiencies, government and aged care providers are increasingly seeking options to move care and support to the community or home. In Australia, the provision of home-based care has previously been shown to not only significantly cost less (AUD 6.7 billion=US $4.9 billion) compared to residential aged care (AUD 13.6 billion=US $9.9 billion) [11] but also reduced the number of required residential aged care placements. However, this may also put further pressure on families to meet the health, social, safety, and other daily needs of their older members, whereas many families have limited time, physical, or financial capacity to attend to their aging relative's everyday needs and care.

The use of assistive technologies has the potential to support home-based care for older Australians in the community, deliver reduced savings in health expenditure, and increase functional independence [12]. For example, it has been estimated that avoiding as few as 10% of falls would reduce hospital costs by AUD 85 million (US $61.8 million) [13]. Regular medical care, increasing awareness of health and of healthy lifestyles, and monitoring of daily activities from assistive technologies have the potential to further reduce hospital costs through avoidance or early detection of degeneration in health and well-being.

To address issues of limited family support, residential care placement availability, and the impending shortage of the aged care workforce and associated health and aged care costs, we developed a smart home platform called "Smarter Safer Homes" (SSH), which features a lifestyle-based approach in the design and implementation to enable older people to live longer in their own homes, with their choice of how they interact with the technology and engage family and/or aged care support. The SSH platform integrates wireless home sensor and health monitoring devices to allow engagement of informal (eg, family) support and formal aged care services. One of the novel features of the platform is the analytics that capture an individual's profile of activities of daily living (ADL) from which personal-level functional independence or ability can be determined.

The "smart home" concept was introduced in the 1980s when it was used to support independent living and older peoples' health and aging [14]. Along with the emergence of new technology in mobile computing, smart sensors, and the Internet of Things (IoT), the smart home has become topical and relevant with respect to in-home automation and assistance for health and well-being [15-17]. Although various technologies used in smart homes, such as wireless sensor networks [18] and activity recognition algorithms [19], have been evaluated individually, very few randomized controlled trials (RCTs) have been performed to evaluate the entire smart home platform. This includes whether or not implementation of smart home technologies is possible in everyday homes [20], or if the smart home can impact certain clinical diseases such as cognitive decline [21,22] or risks of falls [23].

To evaluate our smart home platform for its use in supporting aged care for residents living at home, an RCT was undertaken. The aim of the study was to evaluate the SSH platform to

support remote care delivery and management of home-based aged care. To our knowledge, our trial is the first RCT to evaluate changes in the health and well-being of older adults living independently using clinically validated instruments. It is also the first to conduct a health care cost-utility analysis to compare the cost-effectiveness of a smart home intervention.

Objectives

The key research question of this trial is whether implementing smart home technology–enabled self-management and care delivery can maintain or improve the impact of care provided by aged care service providers to older people living independently in their own homes.

The aims of the trial were to evaluate the impact of implementing an innovative home care service delivery model via technology on: (1) the impact of care provided by aged care service providers in response to needs arising from physical or sensory impairments for older people living independently in their homes; (2) quality of life for older people living independently in their own homes; (3) factors associated with ADL and instrumental activities of daily living (iADL); (4) depression in older people living independently in their own homes; (5) health service utilization, including presentation to hospital (admitted and emergency department), attendances to general practitioners, and other Medicare-funded community health services; (6) existing model of care, service design, adoption, and aged care service provider experiences; (7) carer burden (informal carers); and (8) costs to the government as a result of deployment of the SSH platform.

Methods

Trial Design

The trial was designed as a single-blind, stratified RTC. Participants were divided into two groups with an allocation ratio of 1:1. Trial participants could not be blinded as the intervention required physical installation of equipment in their homes. Researchers undertaking data analyses are blinded to which participants received the intervention. Access to community health services has previously been identified to vary by geographic location [24]. To ensure balance between the intervention and control groups relative to this potential confounder, stratification based on region (ie, metropolitan or regional area) is used.

Study Setting

Overview

Participants living in community independent dwellings were recruited from two geographic areas, metropolitan and regional, based on the Rural Remote Area and Metropolitan Area classification criteria [25]. Three participating aged care service providers deliver aged care services to one or both geographical areas. Specifically, Anglicare Southern Queensland recruited participants from metropolitan and regional areas in Queensland (QLD), integratedLiving Australia recruited participants from metropolitan and regional areas in QLD, and All About Living is recruited participants from metropolitan areas in QLD.

Anglicare

Anglicare Southern Queensland is a member of the Anglicare Australia Network providing support to aged Australians in partnership with government and other support organizations in response to identified care needs throughout southeast QLD. They offer a range of specialist services within indigenous, homeless, multicultural, and rural and remote communities. The workforce of Anglicare Southern Queensland stretches from Cairns to Coolangatta, and from Birdsville to Brisbane. Recruitment included participants from metropolitan and regional areas in QLD.

integratedLiving Australia

integratedLiving Australia receives funding from the Australian and state governments to provide care services. They provide in-home support services to older people in regional, rural, and remote Australia (including northern and eastern QLD) and have been focusing on ensuring equitable access for health support to these communities. Recruitment included participants from regional areas in QLD.

All About Living

All About Living partners with federal, state, and local government departments, along with several community organizations to deliver a range of high-quality services. All About Living has developed governance, management, and service delivery expertise and excellence that enables consistent service delivery. Recruitment included participants from metropolitan areas in QLD.

Participants

It was anticipated that the trial would include 200 individuals (see the Sample Size subsection below) aged 65 years and older. Table 1 provides a breakdown of the number of individuals planned to be recruited from each service provider in the two areas.

Table 1. Number of participants planned to be recruited.

Area	Anglicare, n	integratedLiving, n	All About Living, n
Metropolitan	100	25	20
Regional	40	15	0

Collaborations With Aged Care Partners

One of the unique features of this RCT is the collaboration between the researchers and the aged care service providers. The relationship was established as a true partnership with a representative of each aged care service provider attending monthly project meetings, the risk and safety committee meeting, and regularly being consulted with as the experts on their own participants. Additionally, while asked to record certain data points, the aged care service providers were asked to develop their own workflows in how they respond to trends produced by the SSH platform and how they check on their participants if flags are raised by the data from the SSH platform. Aged care service providers reported any concerns about data (eg, system glitches) to the project manager and these were reported to the engineering team immediately. The aged care service providers are also involved in all reviews of reports, case studies, and documents associated with the project. A true teamwork collaboration was formed between the researchers and the aged care service providers, which is key to the success of the research as a whole.

Collaborations With Consumers

In addition to the aged care service providers, the project team was fortunate to have the input of a consumer representative (ie, a person with a lived experience in this area of aging). The consumer representative also attended monthly project meetings

and was able to provide guidance on how participant information should be written and delivered, how professionals should approach research participants, and provide the lived experience viewpoint to the research. Unfortunately, the consumer representative ceased attending meetings when the COVID-19 lockdowns commenced in March 2020. The team recognizes the contribution of the consumer representative during the time they were involved and how their influence enhanced the development, design, and implementation of the recruitment phase in particular.

Eligibility Criteria

The inclusion criteria for this trial were people aged 65 years and older; living at home, in the care of a designated aged care service provider; and English-speaking with proficiency in written English. The exclusion criteria were people residing in long-term residential care, not able to give informed consent due to reasons such as severe cognitive impairment, not willing to leave their electricity on overnight, and people residing with others.

Intervention

The intervention involved use of the SSH platform to assist aged care service providers to monitor and provide timely support to their clients. As shown in Figure 1, the SSH platform comprises a client module (data presentation) with a tablet app, family portal, and service provider portal.

Figure 1. Overview of the Smarter Safer Homes platform.

The intervention also provided participants the choice to view their data/progress on the tablet app. This intervention was not a real-time solution, with all data viewed in the platform being from the previous 24-hour period. Participants and aged care service providers were made aware of this multiple times in multiple ways, as there was a risk they would rely on the system as an alert if an adverse incident occurred in the home, such as a fall. All usual care was maintained for all participants, regardless of their allocation to the research groups. Therefore, for those in the intervention group, the SSH installation was an added layer of care intervention.

The interface of the app was co-designed with a network of similar cohorts during the inception of the SSH platform [26]. An example of the SSH app dashboard, as shown in Figure 2A, reflects the daily status of health and well-being, indicated by different sized and colored rays. A full-length green ray indicates the status within the normal range. An amber ray with two-thirds of the length raises concerns about the status, while a red ray with one-third of the length warns that the health and well-being status is abnormal and may require timely intervention from carers. The family portal has the same interface design, but with limited functionality to keep significant others informed about the well-being of their loved one (the participant). Figure 2B shows the interface design of the service provider portal, which provides access to a formal carer (eg, the participant's aged care service provider) to monitor the participant's condition and ADLs. The color schema used in this portal is the same as that used in the SSH app (ie, green dots and grinning faces indicate normal status, amber dots and neutral faces indicate concerned status, while red dots and frowning faces indicate abnormal status). Interventions from aged care service providers, such as phone calls, will be initiated if red dots observed.

The features of the SSH platform include a sensor-based in-home monitoring system (data collection), a cloud computing server (data analyses), and novel analytics to determine functional independence. The novel measure of functional independence features the provision of an objective and personalized measure of ADL components and scoring through nonwearable and nonintrusive sensors in the home environment, and the ability to correlate this measure with self- or care-reported status of health and well-being. The domains (mobility, transfer, hygiene, and meals) of the ADL score are derived through aggregation and artificial intelligence analytics from a range of sensors deployed in the home (eg, motion, accelerometers, power, and the temperature/humidity within a room). Individualized functional independence (Objective ADL [O-ADL]) is measured using the same framework as the ADL assessment performed in clinical settings. This O-ADL is not only an objective clinical assessment using home environmental sensors but is further personalized through learning an individual's activity and profile relative to their health and functional status. This then references their ongoing functional status over time, enabling timely intervention.

Figure 2. Screenshots of (A) the Smarter Safer Homes (SSH) app, and (B) family and service provider portal interfaces.
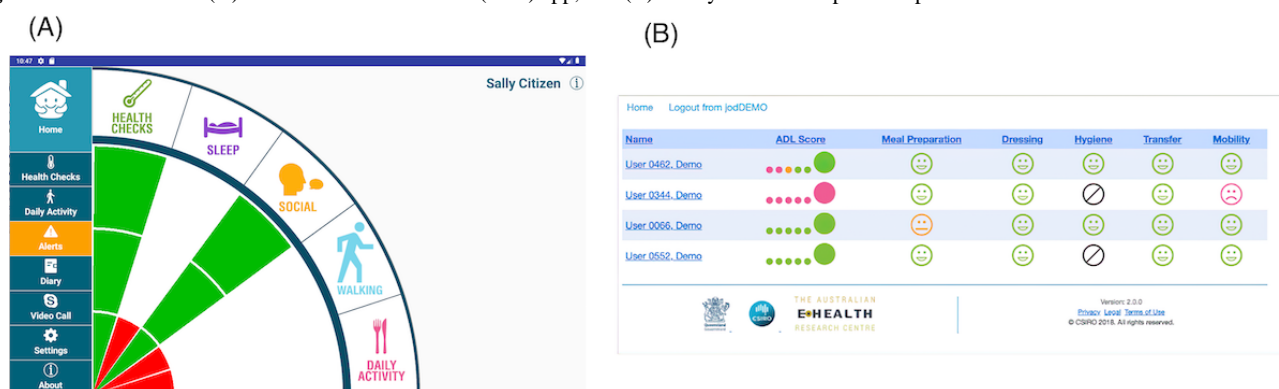
Outcomes

Baseline Characteristics

Baseline characteristics were collected to facilitate the identification of systematic differences between study groups that may increase the risk of bias.

Primary Outcome

The primary outcome was the Australian Community Care Outcome Measurement tool (ACCOM) [27].

Secondary Outcomes

The secondary outcomes included change in health-related quality of Life, as measured by the Five-Dimension EuroQuol (EQ5D 5-L) questionnaire [28]; Katz ADL [29] and instrumental ADL (Lawton iADL [30]); depression (Geriatric Depression Scale [31]); health service utilization, including community prescription medicines (collected based on Pharmaceutical Benefit Scheme [PBS] claims data), community health services (including nonreferred medical attendances such as general practitioner appointments, attendances with medical specialists, pathology, diagnostic imaging, and Allied Health attendances collected from Medical Benefit Scheme [MBS] claims data), hospital attendances (same day and overnight admitted), and emergency department presentations (collected from QLD public hospital data); changes in service design, adoption, and aged care service provider experiences (based on provider staff interviews); care giver burden (Zarit Burden Interview [ZBI]-12 [32]); and costs to deliver the SSH supported care.

Participant Timeline

The trial recruited its first participant in April 2019 and data collection of the last participant was completed in November

2020. The study received participants' health service utilization data in June 2021.

Sample Size

The primary outcome of this trial, the impact of community care for older people, will be evaluated using the ACCOM tool [27], a set of measures of community care suitable for use in the Australian context. The ACCOM mainly uses questions from the Adult Social Care Outcome Toolkit (ASCOT) [33], which is a validated measure of social care related to quality of life. Power was based on a randomized trial design with a clinically important difference of 10% on the primary outcome of ASCOT with a mean 0.80 (SD 0.16) distribution (ie, 0.08, based on previous research [33]). With the threshold of rejecting the null hypothesis of $\alpha \geq .05$, effect size of 0.5 (0.08/0.16), and the same allocation ratio of the two groups in our trial. Figure 3 illustrates the relations between total sample size and statistical power.

To achieve 80% statistical power, we needed a total of 134 participants. Allowing for a 30% attrition rate, the sample size of this trial was computed to be 200 participants. We did not anticipate an attrition rate greater than 30% as all participants were existing clients of the participating aged care service providers and received regular visits throughout the trial period. The intervention and outcome measurement collection processes were designed to minimize participant burden. In addition, the power analysis did not consider the repeated-measures design of the trial. Repeated measures increase the power of the trial to find a significant result and appropriate statistical techniques will be applied to ensure that all data available are used in the analyses.

Figure 3. Total sample size and statistical test power.
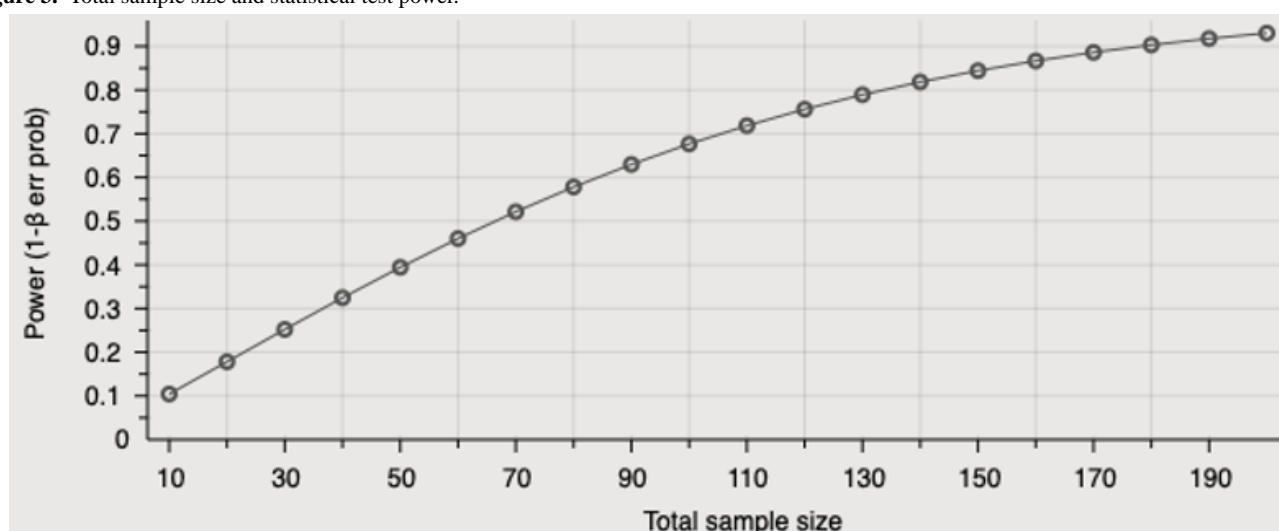
Recruitment

Three project officers were employed to recruit and consent participants for the trial. The project officers made contact with potential participants, after introduction by the aged care service provider. The project officer, via phone call, briefed the individual on the trial, assessed their interest in participating, and checked their eligibility. If the individual agreed to participate, they were asked to nominate their witness, who could be the informal carer (which could include family members or another person that they hold a close relationship with such as a friend or neighbor) to be included in a future face-to-face meeting. During the face-to-face meeting, the project officer confirmed the internet connectivity at home and the cognitive awareness of potential participants. At this point, cognition levels were assessed according to the participant's ability to demonstrate understanding of what the project officer was saying and how the potential participant responded to questions. It was identified during the planning of the trial that research participants would incur a small out-of-pocket fee for the use of their own electricity and internet data. This was calculated to be less than AUD 5 (US $3.6) per month. The budget allowance was established to ensure that all individual participants were repaid for this out-of-pocket expense after their contribution to the research was complete. For example,

a participant received an AUD 60 (US $43.20) gift card for 12 months of participation (5×12 months=60).

Assignment of Intervention

Allocation

Stratified randomization was used with the strata defined by geographical areas (ie, metropolitan and regional). Within each area, simple randomization (ie, randomization based on a single sequence of random assignments [34]) was performed and participants were assigned to either the provider's usual care or their services designed and delivered through the SSH technology platform (smart home group). Randomization of participants was undertaken using a computer program and carried out by an independent researcher using anonymized identifiers. The random allocation sequence was delivered through the REDCap application. Allocation occurred after the baseline survey had been completed.

SSH Kit Installation

Once participants had been consented, a set of surveys was administered by the project officer. The participants allocated to the intervention group received an SSH kit. Installation of the SSH kit (tablet, hub, sensors) was coordinated by the project officer, typically within 2 weeks of consent and randomization.

A user sheet that describes how to interact with the tablet and interpret the information presented on the tablet SSH app was included with the kit. The project officer also demonstrated to the participant how to use the tablet and the SSH app during installation. To obtain valid baseline data after installation, the SSH system gathered 14 days of the participants' normal living routines in their homes. After the baseline data had been gathered, the identified aged care service providers and the nominated family portal users were notified of their user ID, password, and access instructions. During the trial period, the project officer was the point of contact for any problems or questions. Technical issues that were not easily addressable were escalated to the research technical team who worked to find efficient and effective solutions. All reported issues, no matter how minor, were reported to the project manager for inclusion in the monthly project reports. If a participant wished to withdraw from the trial, the project officer arranged for an uninstall to occur as quickly as possible from the home. Upon completion of the project, all homes had their trial equipment removed by the project officer. Participants allocated to the usual care group continued to receive their existing care and social services in line with local aged care service provider protocols for the 12 months of the trial. They did not have any SSH equipment installed in their homes.

Measurements and Data Collection

Overview

Data were collected from participants, informal carers, and aged care service providers from state and national government data sources and home-based sensor systems. These included surveys, raw sensor data, and interview information. The state and national government data sources included hospital linkage data and MBS/PBS data. The measure, context, score meaning, and time points of collection are presented below.

Survey Questionnaires

Baseline

The project officers administered a baseline survey to all consented participants. Questionnaires included in the baseline survey are listed in Table 2. Note that the Abbreviated Mental Test Score (AMTS) was administered by a project officer prior to administering the baseline survey. Follow-up questionnaires at the mid-trial point (around 6 months) and end-trial point (around 12 months) included the same battery of questionnaires except for the demographics and AMTS. The baseline survey was delivered to participants during the consent face-to-face meeting and took approximately 45 minutes to complete.

Table 2. Survey questionnaires.

Domain	Measure	Context	Score meaning/presentation	Time point		
				Start	Mid	End
Demographic information	Individual questions	Gender, age, weight and height (BMI), occupation, marital status, income, computer skills, social media, and NBN[a] connectivity	Individual and coded scores	✓		
Cognitive level	Abbreviated Mental Test Score (AMTS) [35]	To establish baseline cognition (10 questions)	Maximum score 10; a score of less than 7 or 8 suggests cognitive impairment	✓		
Impact of care: participant	ACCOM[b] measure (adapted from ASCOT[c] for the Australian population) [33]	Self-completion (eight attributes): control over daily life, personal cleanliness and comfort, food and drink, personal safety, social participation and involvement, occupation, accommodation cleanliness and comfort, dignity. Additional questions: subjective rating of health, open question	Four levels: Ideal State, No needs, Some needs, High needs; ASCOT scoring [36]	✓	✓	✓
Health-related quality of life	EQ5D[d] [37]	Five generic questions on health status: mobility, self-care, usual activities, pain/discomfort, anxiety/depression; respondents' self-rated health is recorded on a vertical, visual analog scale (VAS: 0-100)	Results presented as an index value (Australian Scoring algorithm); VAS presented as a number from 0 to 100, with 0 indicating the worst and 100 indicating the best imaginable health state	✓	✓	✓
Activities of Daily Living (ADL)	Katz's ADL [29]	Assesses basic ADLs: feeding, continence, transferring, toileting, dressing, bathing	Maximum score of 6 points indicating fully independent, 4 points indicating moderately impaired, and 2 points indicating severely impaired	✓	✓	✓
Instrumental Activities of Daily Living (iADL)	Lawton's iADL [30]	Assesses a person's ability to perform daily tasks, measuring eight domains: using the telephone, shopping, preparing food, housekeeping, doing laundry, using transportation, handling medications, handling finances	Summary score from 0 (low function) to 8 (high function)	✓	✓	✓
Depression	Geriatric Depression Scale (Short Form) [31]	15-item version, used to identify depression in older people	Scores >5 (yes) suggest presence of depression; scores >10 are almost always depression	✓	✓	✓

[a]NBN: National Broadband Network.

[b]ACCOM: Australian Community Care Outcome Measurement.

[c]ASCOT: Adult Social Care Outcome Toolkit.

[d]EQ5D: 5-dimension EuroQuol.

Follow-Up

Participants were contacted by a project officer to complete the same surveys at mid-trial and end-trial. These were preferably conducted over the phone, and particularly during imposed COVID-19 safety measures. For the intervention group, an uninstall of the SSH kit typically took place at the same time as the end-trial survey was administered. Follow-up was systematized through the REDCap system. For participants who withdrew from the trial, all data collected up to the point of withdrawal are included in the analysis of the study, unless formally requested not to be by the participant. This was outlined in the Participant Information and Consent Form (Multimedia Appendix 1) and participants were asked to consent to the inclusion of their data.

Sensor Data

All in-home raw sensor data were transferred to the IoT router and then collected directly to a secured server where all sensor and participant data were gathered. Storage of and access to the project data within the data center were governed by privacy policy and procedures, and limited to the investigators on this project. Data center operations staff had access to the data to perform their normal duties (eg, database backup).

The data gathered through the in-home sensors were categorized into daily living activity domains, as listed in Table 3.

The data were not live-monitored in the trial. Participants were made aware of this prior to the trial commencing to ensure that a false sense of security was not assumed.

Figure 4 shows the spread of sensors installed in the household of the smart home group participants and Figure 5 provides a

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description of the SSH sensors deployed and where they were   installed in the home.

Table 3. The mapping of sensors to daily living activity domains.

Daily living activities	Sensor type	Location
Indoor walking	Motion sensor	All rooms
Sit-stand transition times (out of a bed/chair)	Accelerometer, pressure sensor, sleep sensor	Bedroom, living room
Meal preparation	Motion sensor, electrical power sensor, accelerometers	Dining room, kitchen
Hygiene	Motion sensor, humidity sensor, temperature sensor	Bathroom
Dressing	Motion sensor, accelerometer	Wardrobe

Figure 4. Passive sensors installed in the household to support independent living.

Figure 5. Description of Smart Safer Homes sensors deployed, the data gathered, and where these sensors were installed.

Sensor Type		Data Gathered	Place of installation
	Motion Sensor	Incidents of motion within 5 metres of install	Corner in all rooms
	Light Sensor	The level of lights in a room	Corner in all rooms
	Temperature Sensor	Measuring between -10 ~ 50 °C	Corner in all rooms
	Humidity Sensor	Monitor humidity from 0% to 100%	Corner in all rooms.
	Vibration Sensor	Reporting event-based vibrations	Corner in all rooms
	Power Sensor	Monitor power usages of appliances	Wall outlets
	Sleep Sensor	Heart Rate Variability, Sleep, Movement	Under the bed mattress
	Accelerometer Sensor	Reporting object movements	On the doors of the fridge, pantry and front door
	Chair Sensor	Reporting chair occupancy	Under the chair cushion

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Informal Carer(s)

Data on the burden experienced by the informal carers of the people participating in the trial were collected using the 4-item Zarit Screen (ZBI-12) survey [32] at all three time points (start, mid-trial, and end-trial). The ZBI-12 is a valid and reliable instrument for measuring the burden of carers. A total ZBI-12 score ranges from 0 to 48 based on the summation of 12 items; a score of 0-10 indicates no to a mild burden, 10-20 indicates

a mild to moderate burden, and >20 indicates a high burden. The individual(s) identified as informal carer(s) by the participant were contacted by phone or email and the questionnaire was posted out or delivered through email (depending on preference).

Formal Carers: Aged Care Service Providers

The outcomes collected from the respective aged care service providers at the end of the trial are shown in Table 4.

Table 4. Data collected from aged care providers.

Outcome/objective	Data variable	Data source
Impact of care: case manager	Four-level self-completion questionnaire with eight attributes: control over daily life, personal cleanliness and comfort, food and drink, personal safety, social participation and involvement, occupation, accommodation cleanliness and comfort, dignity. Additional questions: subjective rating of health, open question	ACCOM[a] measure (adapted from ASCOT[b] for the Australian population)
Organizational change management and impact on workplace culture	Administrative/operational changes implemented/required to implement the SSH[c] service	Semistructured interviews during focus groups with the formal carers
User perceptions of the SSH system	Ease of use, quality of training received, easy or hard to take and monitor clients' measurement. Responsiveness of Project Officer to changes in O-ADLs[d], effectiveness in improving ability to deliver care, impact on workload	Semistructured interviews during focus groups with the formal carers

[a]ACCOM: Australian Community Care Outcome Measurement.

[b]ASCOT: Adult Social Care Outcome Toolkit.

[c]SSH: Smarter Safer Homes.

[d]O-ADL: Objective Activities of Daily Living.

Government Data Source

The outcomes collected from the Commonwealth Government Department of Health (Services Australia) and the QLD

Government Department of Health (hospital data custodians) at the end of the trial are shown in Table 5.

Table 5. Data collected at the administrator level.

Outcome/objective	Data variable	Data source
Hospitalization	Admitted hospital separations (same day or overnight) and emergency department presentations	Queensland Hospital admitted patient data collection (Queensland Health Statistical Services Branch), emergency department collection (Healthcare Improvement Unit)
Use of clinical services	Nonreferred (eg, general practitioner) attendances, attendances to specialists, allied health professionals, pathology (hematology, etc), diagnostic imaging (X-ray, etc)	Medicare benefits schedule claims, Services Australia
Pharmaceutical Benefits Scheme (PBS) expenditure	Prescription medications	PBS claims, Services Australia

Data Management

Data were predominantly captured in the ethics-approved and secure REDCap system. All survey responses were collected through REDCap with the exception of interviews that were captured through recordings. Health services utilization data, already captured through business-as-usual processes of the relevant health services, were utilized in the analysis. Every participant was allocated a REDCap identifier. Once allocated, REDCap numbers were the only identifier of research participants. Interviews with aged care service providers were

performed one-on-one with participants and therefore the interviewees were identifiable to the interviewer.

Statistical Methods

Data Collection and Missing Data

Survey results were collected at three time points: at the baseline, middle, and end of the study. The final survey data included in our analyses contain results from participants with a baseline survey and at least one follow-up and middle/end survey. For missing responses in surveys, we will conduct a case-by-case retrospective analysis with project officers and

aged care service providers, and/or use multiple imputation methods to replace missing data.

Survey Data Analyses

At each survey time point, intergroup differences in survey results between the intervention and control groups will be analyzed by χ^2 tests and Wilcoxon rank-sum tests. If significant differences in survey results are observed, a log-binomial regression model will be further used to estimate the relative risk of each group to changes of survey results. Within each group, for all three surveys, the Friedman nonparametric test will be used to understand intragroup differences in survey results. Similarly, if significant differences in survey results are observed, the Wilcoxon signed-rank test with Bonferroni correction will be used to further investigate pairwise differences between surveys.

Cost-Effective Analysis

A within-trial cost-utility analysis will be performed to assess the value for money of the intervention. The time frame will be the end of the trial, consistent with the trial, and the base case perspective will be from the government as the primary funder of health and social services. An incremental cost-effectiveness ratio will be calculated by collating the costs for the intervention and control groups, and using quality-adjusted life years (QALYs) gained as the outcome in the equation. QALYs will be derived using an area under the curve approach based on the health-related quality of life utility index values derived from responses to the EQ-5D-5L. Costs will comprise the costs of the intervention plus health resource use collected through routine databases (hospital, MBS, and PBS) with patient consent and community services support (eg, nursing, home care) collected during the trial period. Appropriate techniques to account for uncertainty in the estimates (eg, nonparametric bootstrapping) will be implemented. Costs will be summed and compared between groups, adjusting for baseline differences.

Monitoring

Data Monitoring

Regular sensor data monitoring was undertaken by engineers in the team. Data checks occurred every 1-2 days. The organizational cybersecurity team was included to support the constant monitoring for cybersecurity threats throughout the data collection period. This monitoring included checking the functional integrity of the REDCap research database.

Any identified issues that required follow up were reported to the project manager for dissemination to the project steering group and/or the risk and safety committee. Due to the governance structures in place across expert engineering teams, and the two project governance committees, a separate data monitoring committee was not identified as a requirement.

Harms

A risk and safety committee was established from the commencement of the project. This committee consisted of an aged care service provider representative from each stakeholder partner, key project staff, and an expert geriatrician to provide any medical oversight required. This committee met bimonthly throughout the project and was available for assessing any unintended effects of the trial intervention or conduct.

Auditing

Two types of audits occurred throughout the trial. An audit of all documentation occurred at regular intervals. This was to ensure all consent forms were completed correctly and any errors could be addressed appropriately and in a timely manner.

Additionally, at the end of the installation phase, an audit was undertaken of sensor placements in the homes. This occurred to ensure consistency of sensor placements across homes.

Ethics and Dissemination

Research Ethics Approval

Ethics approval was obtained from the Commonwealth Scientific and Industrial Research Organisation (CSIRO) Human and Medical Research Ethics Committee (CHMREC) on November 26, 2018 (Proposal # HREC 4/2018).

Protocol Amendments

After the original submission of ethics, which granted approval for the project to commence, there were amendments sought throughout the implementation stage. Amendments typically included additions and/or removal of researchers to the project and extension of approval dates.

Consent

Informed consent was obtained from all research participants, including the older adult participants, carers, and aged care service providers who were interviewed at the end of the trial. During the meeting, the project officer discussed the trial and its requirements with participants and their informal carer(s). Individuals who agreed to participate were asked to sign the ethics-approved Participant Information and Consent Form (see Multimedia Appendix 1). The participants consented that the information gained during this trial may be published and that they will not be identified, and their personal results will not be divulged. To collect MBS and PBS data, all participants were required to sign an additional, separate, Consent Form (according to Consent Trial Guidelines for researchers requesting access to MBS and PBS participant/provider information; see Multimedia Appendix 1). The wording in this form was reviewed by the Health Strategy Branch, Health Services Australia, and subsequently approved by the CHMREC.

Confidentiality

Personal information was collected through surveys approved by the ethics committee. Survey responses were collected via REDCap and did not contain names. Access to demographic information about participants that had potential to identify the participant was restricted. Those conducting the analysis were not provided with this information and only the project officers and engineers (who provided maintenance to the system) had access to individual information. These research professionals are experienced in dealing with sensitive information and they are aware of the implications of accessing this type of information unnecessarily and without reason.

Dissemination Policy

The trial results will be communicated through media release, conference presentations, journal publication, and a final report to all stakeholders involved in the research.

Results

The aim was to recruit 200 participants and a total of 195 participants were finally recruited, with 97 randomized to the intervention group. The study also received participants' clinical service data from government data resources in June 2021. Final data analysis is underway at present and final outcomes will be presented in a future publication.

Discussion

Study Significance

A crisis is looming with the increase in an aging population presenting a large burden on the health system and aged care services unable to support them. Digital technology solutions such as smart homes present real opportunities to address this crisis. Australian aged care reforms have focused on providing aged care support in older peoples' homes. CSIRO has developed a co-designed digital solution, the SSH platform, which features a novel functional independence measure to monitor and support people living in their own home setting. To test this, an RCT was undertaken to evaluate the implementation of this platform in assisting aged care providers to provide timely care and support and improve the lives of older Australians in various geographical settings. The findings of this study will inform the benefits of digital solutions in the support of people aging in the community and defining new age care delivery pathways for more effective aged care in the home.

Expected Findings

This RCT was designed to investigate whether the implementation of the SSH platform for independent-living older adults improves care service delivery, social and health-related quality of life, and reduces the carer burden and the cost to public health services.

Strengths and Limitations

To the extent of our knowledge, this is the first large RCT to comprehensively assess the impact of a smart home–based technology on aged care service delivery, quality of life, and public health service costs. However, during the trial, the participants experienced several weeks of lockdowns in March, May, and August of 2020 due to the COVID-19 pandemic. Whether these unprecedented environmental changes had an impact on the study results is yet unknown.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Participant consent forms.
[DOCX File , 673 KB - resprot_v11i1e31970_app1.docx]

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Abbreviations

ACCOM: Australian Community Care Outcome Measurement
ADL: Activity of Daily Living
AMTS: Abbreviated Mental Test Score
ASCOT: Adult Social Care Outcome Toolkit
CHMREC: CSIRO Human and Medical Research Ethics Committee
CSIRO: Commonwealth Scientific and Industrial Research Organisation
iADL: Instrumental Activities of Daily Living
IoT: Internet of Things
MBS: Medicare Benefits Schedule
O-ADL: Objective Activities of Daily Living
PBS: Pharmaceutical Benefits Scheme
QALY: quality-adjusted life year
QLD: Queensland
RCT: randomized controlled trial
SSH: Smarter Safer Homes
ZBI: Zarit Burden Interview

<u>Protocol</u>

Patient Engagement With a Game-Based Digital Therapeutic for the Treatment of Opioid Use Disorder: Protocol for a Randomized Controlled Open-Label, Decentralized Trial

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Abstract

Background: Prescription digital therapeutics are software-based disease treatments that are regulated by the US Food and Drug Administration; the reSET-O prescription digital therapeutic was authorized in 2018 and delivers behavioral treatment for individuals receiving buprenorphine for opioid use disorder. Although reSET-O improves outcomes for individuals with opioid use disorder, most of the therapeutic content is delivered as narrative text. PEAR-008 is an investigational device based on reSET-O that uses an interactive, game-based platform to deliver similar therapeutic content designed to enhance patient engagement, which may further improve treatment outcomes.

Objective: We aim to investigate how participants interact with the prescription digital therapeutic's new content delivery format. Secondary objectives include evaluating treatment success, symptoms of co-occurring mental health disorders, recovery capital, and skill development.

Methods: Due to the COVID-19 pandemic, this study was redesigned using a decentralized model because it was not possible to conduct medication initiation and study visits in person, as initially intended. A decentralized, randomized controlled trial design will be utilized to compare patient engagement with PEAR-008 and that with reSET-O using both subjective and objective assessments. The study population will consist of approximately 130 individuals with opioid use disorder (based on Diagnostic and Statistical Manual of Mental Disorders 5 criteria) who have recently started buprenorphine treatment for opioid use disorder. Participants will be virtually recruited and randomly assigned to receive either PEAR-008 or reSET-O. All study sessions will be virtual, and the duration of the study is 12 weeks. The primary outcome measure of engagement is operationalized as the number of active sessions per week with either PEAR-008 or reSET-O. (An active session is any session that contains some active participation in the app, such as navigating to a different screen, engaging with a learning module, or responding to a notification.) Subjective dimensions of engagement will be assessed with participant surveys. The hypothesis is that PEAR-008 will have significantly greater participant engagement than reSET-O.

Results: As of February 2021, participant enrollment is ongoing.

Conclusions: This randomized controlled trial will investigate if changing the delivery format and enhancing the content of a prescription digital therapeutic for opioid use disorder will affect how participants use and interact with the prescription digital therapeutic. The study design may serve as a useful model for conducting decentralized studies in this patient population.

Trial Registration: ClinicalTrials.gov NCT04542642; https://clinicaltrials.gov/ct2/show/NCT04542642

International Registered Report Identifier (IRRID): DERR1-10.2196/32759

Introduction

Background and Rationale

The United States is in the midst of an opioid overdose epidemic [1,2]. Underlying opioid use disorder is a key driver of this epidemic, and approximately 1.6 million people in the United States met criteria for opioid use disorder in 2019 [3]. Opioid use disorder is a chronic disease with a range of physical, psychological, and personal consequences, including high mortality. Opioids are particularly hazardous due to the rising prevalence of potent illicit opioids (predominantly fentanyl) with high risk of lethality [4]. During the COVID-19 pandemic, overdose deaths surged to an all-time high of 92,183 in the United States, driven primarily by synthetic opioids [1]. Maximizing the impact of effective therapies that are easily accessible during the pandemic and beyond is critical to helping individuals with opioid use disorder receive optimal and necessary care.

Pharmacologic treatments, such as US Food and Drug Administration (FDA)–approved medications (for example, buprenorphine, naltrexone, and methadone), are the first line of treatment for opioid use disorder, in conjunction with evidence-based behavioral therapies, but the majority of individuals in need of treatment (80% to 90% [2,5,6]) for substance use disorders do not receive care. There are a variety of contributing factors, including refusal to seek treatment, high cost of care, stigma associated with care, homogeneity of treatments offered, and lack of or limited access to treatment [7,8]. For individuals with opioid use disorder who do seek treatment, there is significant variability in quality and utilization of evidence-based therapies across providers [9,10]. Significant training, time, and clinical oversight are required to ensure proper face-to face delivery of behavioral therapy [11]. Digitizing and offering evidence-based therapies on mobile devices can standardize care, ease the burden on clinical staff, and expand access to behavioral treatment.

Prescription digital therapeutics are software-based treatments that have been evaluated for safety and effectiveness in randomized clinical trials and authorized by the FDA. Prescription digital therapeutics have the potential to safely expand access to evidence-based interventions because they are delivered on mobile devices and are prescribed and initiated by treatment providers.

Two prescription digital therapeutics are currently available—reSET and reSET-O—to deliver digitized behavioral therapy for substance use disorder and opioid use disorder, respectively [12,13]. Both prescription digital therapeutics deliver therapy modeled on the community reinforcement approach, which is an evidence-based treatment that promotes behavioral change [14]. Although studies indicate prescription digital therapeutics hold promise in treating substance use disorder and opioid use disorder [15-20], the current content delivery method used by these prescription digital therapeutics is largely didactic, with the majority of content delivered as narrative text. PEAR-008 is an investigational device that delivers therapeutic content similar to reSET-O via an interactive game-like environment designed to maximize patient engagement and satisfaction—factors that are critical in retaining patients in opioid use disorder treatment [21-26]. We hypothesize that the use of a more interactive and engaging platform to deliver similar therapeutic content will enhance patient engagement with a digital therapeutic.

Methods

Overview

We will compare reSET-O to PEAR-008 and evaluate objective differences in participant engagement with each digital therapeutic. Secondary outcomes include subjective differences in engagement, opioid use disorder treatment outcomes (ie, retention in treatment and abstinence from opioids), symptoms of common comorbid mental health conditions, including anxiety and depression, recovery supports (eg, recovery capital and resilience), and participant satisfaction with their assigned digital therapeutic. Exploratory aims include evaluating development of cognitive behavioral therapy skills and buprenorphine adherence.

Study Design

This is a 2-arm, randomized controlled, open-label, outpatient-based study to be conducted virtually by 2 recruitment sites: the New York State Psychiatric Institute's Substance Treatment and Research Services (STARS) program at Columbia University Irving Medical Center and the Addiction Research and Education Foundation (AREF). Study participants will be recruited from outpatient addiction specialty treatment programs and individual providers in the United States.

Study Population and Sample Size

The trial will include 130 adults aged 18 to 60 years with opioid use disorder who are already receiving buprenorphine treatment, with no criteria regarding gender identity, race, or ethnicity.

Inclusion criteria are having the ability to provide informed consent, age 18 to 60 years, having adequate English proficiency, being within the first 120 days of starting buprenorphine, receiving buprenorphine pharmacotherapy under the care of a licensed health care provider and being willing to provide the name of the provider or practice, being capable of using common software apps on a smartphone, and having access to an internet-enabled smartphone that meets minimal operating system requirements for the duration of the study. Exclusion criteria are having a history of reSET-O use, having

participated in user-testing of PEAR-008 or any investigational drug trials within 30 days of trial enrollment, or currently receiving methadone or naltrexone pharmacotherapy.

The sample size and power were based on the primary engagement outcome, determined by frequency of interaction with the intervention, percentage of module completion, and approval ratings. A sample size of 130, α=.05, and power=0.80 will allow for detection of a moderate effect size (d=0.50).

Study Settings and Recruitment Procedures

All study sessions will be conducted virtually by study staff at 2 participating organizations: New York State Psychiatric Institute's STARS and AREF.

Since its establishment in 1997, the STARS clinic of Columbia University has served as the center for clinical trial operations within the Division on Substance Use Disorders. Recruitment will be directed to individuals who live in New York, New Jersey, and Pennsylvania. Participants may be recruited via flyers in office spaces or intake packets (as allowed; flyers will be disseminated electronically to providers and opioid treatment programs) or via word of mouth by providers. In addition, potential participants may be referred to this study after screening procedures conducted in concurrent research studies taking place at STARS (eg, if they are ineligible for concurrent studies, they may be referred to this study for screening).

AREF is a research foundation that conducts and disseminates research related to addiction medicine to advance the science surrounding the treatment of individuals with a substance use disorder. AREF conducts research activities with patients recruited from a multistate network offering guideline-driven outpatient treatment with buprenorphine for individuals with opioid use disorder in a group practice setting. When possible, flyers will be posted in the waiting room at treatment locations (where patients are being seen face-to-face, which is dependent on local regulations related to COVID-19). Flyers will be included in patient packets that are emailed or distributed to new patients. Additional participants may also be recruited via online advertisements (eg, Craigslist).

Participant flyers will provide the URL for the study website as well as a QR code to access the website. On the study website individuals will find information about the study and a form to express interest in participating in the study. Data entered on the website are sent to an encrypted database housed by Formstack, a Health insurance Portability and Profitability Act–compliant platform and to the sites via PGP-encrypted emails.

Randomization and Blinding

Following informed consent, the baseline assessment and confirmation of eligibility, participants will be randomly assigned to 1 of 2 treatment groups: reSET-O or PEAR-008. Randomization lists will be prepared by the study sponsor (Pear Therapeutics) prior to the start of the study. Randomization will be 1:1 and stratified by site and gender with a block size of 10. An electronic list of IDs, access codes, and credentials will be securely provided to the sites. There will be no blinding; this is an open-label study.

Study Interventions

reSET-O

reSET-O is a prescription digital therapeutic for opioid use disorder delivered concurrently with standard buprenorphine treatment [13]. reSET-O delivers therapy in the form of a series of 67 interactive lessons via a patient-facing mobile software app. A typical therapy lesson comprises a behavioral therapy component and skill-building exercises. The therapeutic content is based on the community reinforcement approach, an intensive addiction-specific form of cognitive behavioral therapy that has been validated for opioid use disorder [14]. Therapy lesson content is delivered primarily via written text but may include videos, animations, and graphics. After most therapy lessons, the user undergoes fluency training, which is a method of questioning that has been demonstrated to promote learning and improve both short-term and long-term retention of material [27].

reSET-O also includes contingency management delivered via a virtual rewards wheel. Contingency management rewards are either virtual (thumbs up icon) or tangible rewards (gift card with value range US $5 to $100) that can be earned for completion of therapy lessons. Studies [28] have consistently demonstrated that contingency management interventions, particularly abstinence-based incentives, can support treatment and recovery in individuals with a wide range of substance use disorders. The odds of winning a tangible reward are 50% each time a reward is possible (wheel spin or mystery box), with higher-value rewards occurring less often. The odds of receiving a $100 gift card are 0.2%, whereas the odds of receiving a $5 gift card are 41.8%. The value of the rewards is commensurate with the amount of time users typically spend with the prescription digital therapeutic over the 12 weeks of treatment. Users are also prompted to report substance use, cravings, and triggers every 72 hours. A user can self-initiate reports of substance use, cravings, and triggers at any time. reSET-O contains an optional daily medication reminder that can be set to enhance adherence to buprenorphine for opioid use disorder.

PEAR-008

PEAR-008 is an investigational device with therapeutic content and a contingency management reward system that are similar to those in reSET-O; however, clinical content enhancements have been made, and the therapy has been reformatted as a game with mechanics designed to promote engagement. Content enhancements include use of person-centered language and lowering the reading level to make it more accessible. In PEAR-008, the reSET-O therapy lessons were divided into a tiered structure of shorter chapters with the intent of providing small, achievable goals to help keep users motivated and engaged. Each chapter has an associated quiz based on the fluency training approach.

The PEAR-008 home screen shows a nature scene that transitions from winter to summer as the patient progresses through therapy (Figure 1). The game economy of PEAR-008 is variable, consisting of the ability to earn stars that unlock virtual rewards such as birds and home-screen upgrades, as well as Mystery Boxes. The Mystery Boxes replace the contingency

management rewards wheel in reSET-O and contain either virtual (stars) or tangible rewards (gift card with value ranges from $5 to $100) with the same odds of winning a tangible reward at each level of value as those in reSET-O. Similar to reSET-O users, PEAR-008 users earn the opportunity for contingency management rewards by completing fluency training quizzes (ie, therapy lessons). Engagement is also incentivized: a user can earn rewards by repeating a chapter and by engaging at least once daily with PEAR-008. The user is required to complete a daily check-in the first time they open the app each day. The check-in consists of a series of questions related to substance use, medication use, general recovery status, and recovery-specific questions regarding cravings, triggers, and problems the user is managing.

Figure 1. Screenshots from reSET-O (A) home screen and (B) contingency management rewards wheel screen, and PEAR-008 (C) home screen with winter scene, (D) contingency management rewards mystery box screen, and (E) home screen with summer scene. Content is accessed via the icons on the windowsill, lessons are represented by the stack of books icon, worksheets are represented by paper and pencil, and rewards are represented by the treasure box.
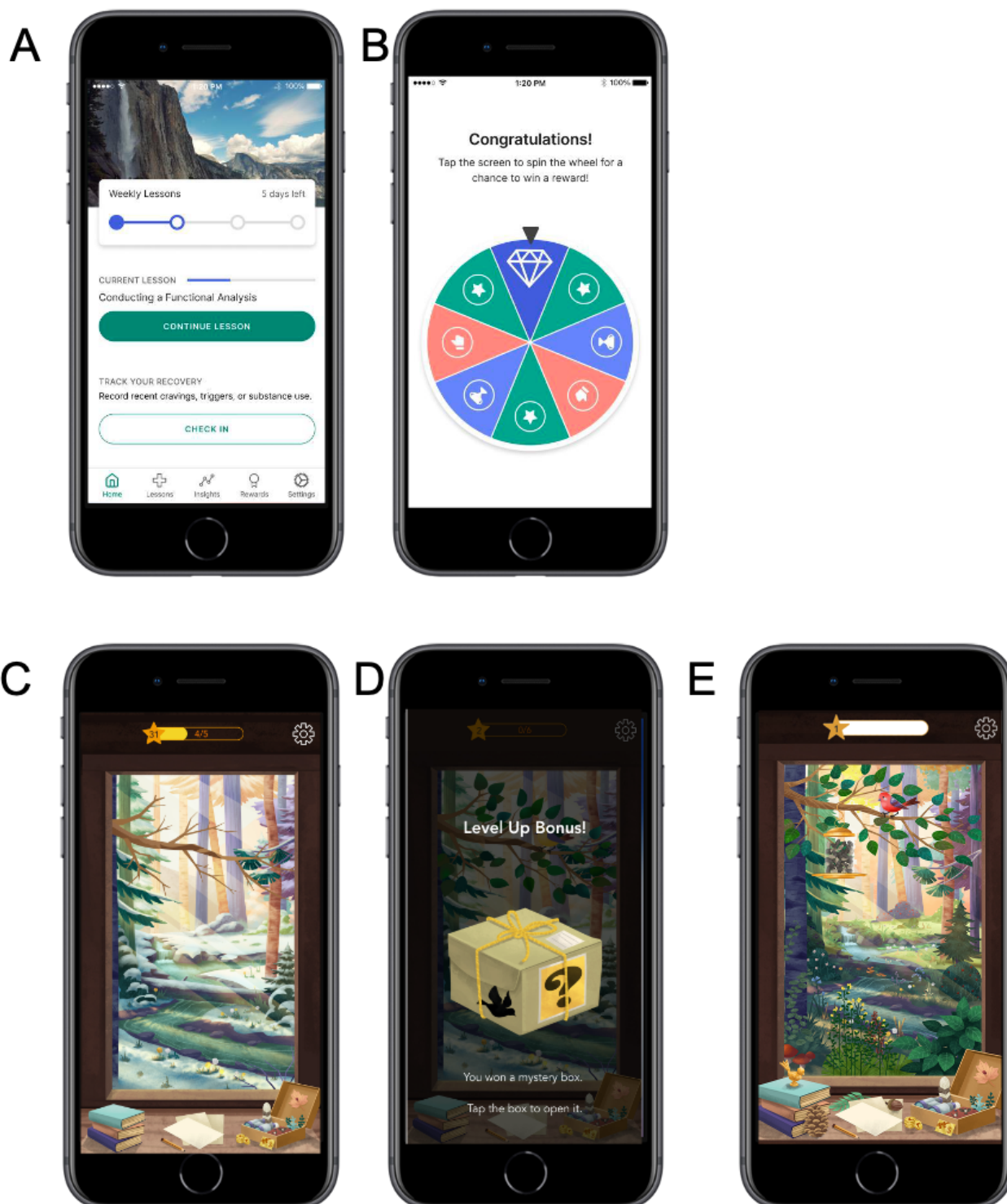
Study Procedures

Overview

All study visits will be conducted remotely. Each prospective participant will complete a short screening assessment, and if basic eligibility is confirmed, complete informed consent procedures and sign an electronic informed consent form prior to completing the baseline assessment. After baseline assessments, participants will be randomly assigned to either reSET-O or PEAR-008 groups. Study staff will assist each participant with installation of their assigned digital therapeutic on their mobile device. Staff will provide training on the app's use. Study participants will be enrolled for 12 weeks, with weekly virtual sessions during weeks 1-8 and a final visit at week 12, to evaluate the impact of reSET-O and PEAR-008 on participant engagement and treatment outcomes. Participants will also complete slightly longer assessments at weeks 4 and 8.

Weekly study assessments completed during the first 8 weeks of treatment include saliva drug screening (participants will receive drug screening equipment on a regular basis by mail; urine drug screen results may be retrieved from the electronic medical record for AREF participants), timeline followback [29], and adverse event reporting. Additional self-report assessments will be delivered at week 4 and week 8.

Participants will attend a virtual end of treatment study session at 12 weeks to complete the following: saliva drug screening, timeline followback, and adverse event reporting assessment. Additional measures will be assessed at the 12-week follow-up visit (Table 1).

Table 1. Study objectives and endpoints.

Objective	Endpoint
Primary	
To evaluate participant engagement with PEAR-008 compared to that with reSET-O. The hypothesis is that PEAR-008 group will have significantly greater participant engagement than the reSET-O group.	Number of active sessions with PEAR-008 or reSET-O per week
Secondary	
To evaluate the impact of PEAR-008 compared to reSET-O on treatment retention	Time to dropout (last contact with a participant)
To evaluate the impact of PEAR-008 compared to reSET-O on abstinence from illicit opioids	Abstinence will be defined as abstinence on patient self-reports (via timeline followback) and the absence of nonbuprenorphine opioids on saliva drug screens. Abstinence (binary outcome: yes or no) will be determined 9 times, weekly during weeks 1-8 and at week 12.
To evaluate participants' digital therapeutic use patterns of PEAR-008 compared to reSET-O	Session duration; number of lessons and chapters completed; number of completed self-report assessments; response to notifications
To evaluate the impact of PEAR-008 compared to reSET-O on change in psychiatric symptom severity between baseline and follow-up	Depression symptoms with Patient Health Questionnaire–8; Anxiety symptoms with Generalized Anxiety Disorder–7
To evaluate the impact of PEAR-008 compared to reSET-O on change in recovery capital and resilience between baseline and follow-up	Brief Assessment of Recovery Capital–10; Connor-Davidson Resilience Scale–10
To evaluate participant motivation and satisfaction over time with PEAR-008 compared to reSET-O	Participant surveys administered at baseline, week 4, week 8, and week 12; participant interview at follow-up
To evaluate a more global measure of engagement by combining data from secondary endpoints 3-6	A multivariate analysis of variance combining data from secondary endpoints 3-6
Exploratory	
To evaluate the association between engagement with PEAR-008 compared to reSET-O and treatment outcomes (abstinence and retention)	Daily and weekly use patterns; saliva (or urine drug screen for AREF[a] participants only) and self-report; time to dropout
To evaluate skills acquisition at week 4 and week 8 of PEAR-008 compared to reSET-O	Cognitive Behavioral Therapy Skills Questionnaire
To evaluate medication adherence of PEAR-008 compared to reSET-O	Saliva drug screen (or urine drug screen, for AREF participants only)

[a]AREF: Addiction Research and Education Foundation.

Assessments

Demographics

Demographic information will be collected at the baseline session. Variables to be collected will include age at time of consent, sex assigned at birth, race and predominant self-reported ethnicity, level of education, marital status, employment status, occupation, and legal status.

Medical and Medication History

Medical history and current medical conditions, with current or prior treatment received, such as mental health disorders, hepatitis C virus, human immunodeficiency virus, and chronic pain syndromes, will be collected at the baseline session. Participant-reported history of substance use will be collected for the following substance categories: opioids, cocaine, stimulants (other than cocaine), alcohol, marijuana, benzodiazepines, other. Data to be collected regarding each substance include age at onset of use, number of years used regularly, amount used, type used (eg, pill vs powder), route of administration, history of overdose, and longest period of abstinence. Participant-reported history of substance use treatment will be collected, including present and prior treatment, type of treatment facility, number of treatment episodes, and current recovery activities. Nicotine use history will also be collected, including type, route, quantity, duration of use, and prior use. Medication history will include the name, dose, frequency, start and stop dates of the medication, and the indication for use. Prior or current medication for substance use disorder and opioid use disorder will also be recorded.

Clinical Assessments

Abstinence From Opioids and Buprenorphine Adherence

Participant self-report of substance use and medication adherence will be collected within the reSET-O and PEAR-008 apps. In PEAR-008, participants are prompted to report use or abstinence each time they open the app as part of the check-in feature. In reSET-O, participants are prompted to report substance use or abstinence every 72 hours and can choose to self-initiate responses anytime.

Timeline followback will be completed at each virtual study session to assess patient-reported substance use since the time of the last assessment. The timeline followback is a validated calendar-based assessment used to obtain self-reports of amount and frequency of substance use retrospectively, using memory aids to enhance recall (eg, patterns of use, key dates).

Participants will self-administer a 12-panel saliva drug test during video sessions with study staff, who can assist in proper administration in addition to providing high-fidelity confirmatory testing. The 12-panel tests detect the presence of the following drugs: amphetamines, cocaine, cannabis, opioids, methamphetamine, barbiturates, benzodiazepines, buprenorphine, oxycodone, methadone, fentanyl, and alcohol. Saliva drug testing will be performed at the baseline session, once weekly during weeks 1-8 of the treatment phase and at the week 12 follow-up session. Participants will receive drug screening equipment regularly by mail.

When available, results of urine drug screening collected as part of routine care at participating treatment centers will also be used for participants recruited by AREF. All urine drug screen data are collected for clinical purposes and not as a study procedure. Urine drug screen results will be exported from the electronic medical record for inclusion in the study database. These data will be used to evaluate buprenorphine adherence and drug use. Results from additional urine drug screen confirmatory analyses for buprenorphine and norbuprenorphine may be available for some participants. When available, these data will be used to evaluate buprenorphine adherence.

Psychiatric Symptoms

Individuals with substance use disorders often experience psychiatric comorbidities, such as depression and anxiety. To evaluate the change in severity of co-occurring depression and anxiety symptoms, Patient Health Questionnaire–8 and Generalized Anxiety Disorder Questionnaire assessments will be delivered at baseline, week 4, week 8, and week 12.

The Patient Health Questionnaire–8 is an 8-item multipurpose instrument for screening and monitoring changes in depression [30]. The Generalized Anxiety Disorder Questionnaire–7 is a 7-item questionnaire for screening and monitoring changes in symptoms related to generalized anxiety disorder [31].

Recovery Status, Resilience, and Cognitive Behavioral Therapy Skills

The Substance Abuse and Mental Health Services Administration developed a working definition of recovery that includes 4 major dimensions: Health, Home, Purpose, and Community [32]. This definition highlights the importance of including measures of recovery across these dimensions in addition to substance use outcomes such as abstinence.

The Brief Assessment of Recovery Capital–10 is a 10-item assessment that will be used to measure participants' level of recovery capital [33]. Recovery capital consists of a variety of resources and strengths that patients can use to support their recovery. The 4 major dimensions of recovery are thought to be strengthened as an individual builds recovery capital and may indicate an individual's likelihood of remaining in remission [34].

The Connor-Davidson Resilience Scale–10 is a 10-item self-rating scale developed to assess resilience [35]. The measure is an abbreviated version of the 25-item version and was established on the basis of a factor analysis in a community sample. The questionnaire asks individuals to indicate how much they agree with a series of statements on a 5-point Likert scale. Resilience is a multidimensional trait characterized by an individual's capacity to maintain normal functioning and resist the development of psychiatric symptoms and disorders in response to stress and adversity. The Connor-Davidson Resilience Scale will be used to evaluate the malleability and stability of trait resilience over courses of treatment with reSET-O and PEAR-008.

The Cognitive Behavioral Therapy Skills Questionnaire is a 16-item assessment that measures the use and acquisition of cognitive behavioral therapy skills during treatment [36] and is

a validated measure of behavioral activation and cognitive restructuring. Development of skills that support behavior change is a key goal of cognitive behavioral therapy. This scale will be used to assess the development of cognitive behavioral therapy skills and whether there is a difference in skill development between individuals treated with reSET-O versus those treated with PEAR-008.

These scales will be administered at baseline, week 4, week 8, and week 12.

COVID-19 Impact

Two exploratory assessments will be used to evaluate the impact of the COVID pandemic on participants. The CAIR Pandemic Impact Questionnaire [37] is a 5-item assessment that measures how the COVID-19 pandemic is impacting participants, using a 5-point Likert scale to evaluate whether the respondent has experienced any growth changes related to COVID-19 in the past 2 weeks. A modified version of the Coronavirus Perinatal Experiences–Impact Survey asks participants how they are coping with stress related to COVID-19 from a list. The respondent is provided with a list of coping strategies and asked to select all strategies they have employed. Both assessments were selected from the PhenX Toolkit [38] and will be administered at baseline, week 4, week 8, and week 12.

Participant Motivation and Satisfaction

Participant motivation and satisfaction will be evaluated via surveys and qualitative interviews. Surveys will be administered at baseline, week 4, week 8, and week 12, with a range of questions designed to evaluate participant motivation (baseline only) and satisfaction with their assigned intervention (eg, ease of use, relevance, satisfaction).

A subset of participants (approximately 10 per treatment arm) will be asked to participate in a 1-on-1 qualitative interview to evaluate their respective experiences with each therapeutic, particularly ease of use and acceptability. Interviews will last approximately 60 minutes, be conducted by study staff, and will be performed remotely via video or phone. Interview transcripts will be coded and analyzed using grounded theory methodology to identify key themes. An inductive, open coding approach will be used to assign emerging categories. Emerging categories will be grouped to arrive at high-level themes during axial coding, and their properties and dimensions will be identified and described in a codebook.

Data Management, Study Oversight, and Monitoring

Oversight of data management, including data collection, storage, export, security, tracking, data analysis, and quality assurance will be the responsibility of the study monitor designated by the study sponsor. Trial data will be managed with an electronic data capture system (Captivate, ClinCapture). Sites have access to this software as does the sponsor data monitor. Data collected by PEAR-008 and reSET-O are stored in the cloud. A data and safety monitoring board will provide additional oversight regarding the safety of study participants.

Adverse Events and Safety Monitoring

The investigator or designee and research site staff will be responsible for the detection, documentation, classification, reporting, and follow-up of events that meet the definition of an adverse event or serious adverse event. Spontaneously reported or observed adverse events will be recorded throughout the study from the time of consent until the end of the last study visit. Adverse events will be elicited using a nonleading question at designated time points. Regardless of seriousness, intensity, or presumed relationship to reSET-O or PEAR-008, all adverse events will be recorded. The site investigator will monitor the occurrence of adverse events during the study.

Adverse events and serious adverse events will be collected and reported using the methods and definitions of the Office for Human Research Protections and National Institutes of Health (NIH) requirements for human participant protection. The investigator or designee is responsible for making an assessment as to the seriousness, intensity, causality, and outcome of an adverse event. The investigator will determine causality as related, possible, unlikely, or unrelated to reSET-O or PEAR-008.

Confidentiality

Procedures to assure confidentiality will be strictly observed. All participant personal information will be kept confidential and will not be released without written permission, except as required by law. All study information will be kept separately from identifying information on consent forms and locator forms.

Data collected by the reSET-O and PEAR-008 system are securely transferred using industry standard encryption to a cloud-based infrastructure that serves and communicates with the patient facing mobile app; the backend services contain all data and analytics for reSET-O, PEAR-008, and clients (participants and clinicians). All data stored by the device are hosted and stored with a cloud-computing service (Amazon Web Services), which follows a variety of internationally recognized security standards, such as National Institute of Standards and Technology SP800-53 [39] and Health Insurance Portability and Accountability Act [40]. All patient information is automatically encrypted when it is entered into the system, which allows for secure data transfer (from patient device to clinician device) and storage.

In accordance with the 21st Century Cures Act [41], all ongoing or new research funded by NIH as of December 13, 2016 that collects or uses identifiable, sensitive information is automatically issued a Certificate of Confidentiality, which protects participants against disclosure of any sensitive information or illicit behavior (eg, drug use).

Statistical Analysis

All statistical methods will be consistent with the International Conference on Harmonization E9 Guidance [42]. Data will be summarized by treatment group. For baseline, safety, and efficacy outputs a total population will combine both groups. Where appropriate, the data will be summarized by session in addition to treatment group. Baseline, demographic, and efficacy output data will be summarized by intended treatment. Safety output will be summarized by the treatment received.

Every effort will be made to obtain required data at each scheduled evaluation. Missing data will not be imputed. Sensitivity analyses incorporating various imputation assumptions may be performed if missing data exceed 5% of the total possible observations.

Descriptive statistics will be used to describe the population of study participants at the beginning of the study (mean, standard deviation, minimum, 25th percentile, median, 75th percentile, and maximum for continuous data; frequencies and percentages for categorical data). Differences in continuous variables will be summarized with Hedges *g* effect size; differences in categorical variables will be summarized with odds ratios.

Endpoints

Primary Endpoint Analysis

Engagement with PEAR-008 and reSET-O will be defined as the number of active sessions per week. A session is defined as a set of in-app events with the same session ID. An active session is any session that contains some active participation in the app such as navigating to a different screen, engaging with a learning module, or responding to a notification. This endpoint was selected to allow a 1:1 comparison of content delivery method (eg, brief chapters vs longer lessons). The number of active sessions per week will be evaluated with a repeated measures mixed model of the form: *Number of Sessions in a Week = Week + Treatment + Week × Treatment + Subject Error + Random Error*. To evaluate the impact of treatment, this repeated measures mixed model will be compared to another of the form: *Number of Sessions in a Week = Week + Subject Error + Random Error* with a likelihood ratio test. The likelihood ratio test will be evaluated using model fit to maximize the log-likelihood.

Secondary Endpoint Analysis

Abstinence will be self-reported by patients via timeline followback and assessed as the absence of opioids (except buprenorphine) on saliva drug screens. Data on abstinence (binary yes and no) will be evaluated with the 9 possible saliva drug screens and urine drug screen and timeline followback data at weeks 1-8 and week 12. Differences between the treatment arms in abstinence will be assessed with a generalized estimating equation analysis using the binomial abstinence outcome as the dependent variable, assessment time, treatment, and the interaction between assessment time and treatment as fixed effects and subject as a random factor. This generalized estimating equation will be compared to a second generalized estimating equation without a treatment term using a likelihood ratio test to evaluate the impact of treatment. A treatment responder analysis will also be conducted, with a treatment responder defined as someone with ≥80% of all saliva drug screens and urine drug screens and timeline followback reports negative for all nonprescribed opioids over the course of the trial.

Treatment retention will be measured as time to dropout (number of days from baseline to last face to face contact) and analyzed using the Kaplan Meier method followed by a log rank test to compare treatment groups.

Patient assessments of recovery capital (Brief Assessment of Recovery Capital–10) resilience (Connor-Davidson Resilience Scale–10) and severity of co-occurring psychiatric symptoms (Patient Health Questionnaire–8 and Generalized Anxiety Disorder Questionnaire–7) will be evaluated with a repeated measures mixed model in a manner consistent with the primary endpoint.

Participants' use patterns with PEAR-008 and reSET-O will include total time engaged, number of lessons and chapters completed, number of lessons and chapters repeated, number of completed self-report assessments, and response to notifications. Descriptive statistics of each treatment arm will be summarized and differences between PEAR-008 and reSET-O will be assessed with a *t* test (or its nonparametric alternative if the distributional assumptions are violated).

Treatment motivation and satisfaction will be evaluated based on individual participants' rating of interest in using (baseline only), ease of use, satisfaction, perceived helpfulness, and likelihood of recommending reSET-O or PEAR-008. Descriptive statistics (mean, median, standard deviation) will be performed on Likert scale and multiple choice items that assess user satisfaction and attitudes about the patient mobile app. Analyses will be conducted on data collected at each assessment point throughout the study, ratings over the course of the study, and for overall user satisfaction as measured at the end of the study.

Exploratory Endpoint Analysis

Data on abstinence (binary—yes and no) will be evaluated at 9 saliva drug screen and timeline followback time points at weeks 1-8 and week 12. The association between abstinence and engagement will be evaluated using a generalized estimating equation model. A given week will be considered negative if a participant has no indication of opioid use on the saliva drug screens or timeline followback. Missing data will be ignored if saliva drug screens or a timeline followback is available for a given time point. In the case where saliva drug screens and timeline followback methods yield data that do not agree, the week will be considered positive.

The relationship between engagement and retention will be assessed using a Cox proportional hazards model with time to dropout as the dependent variable and the number of active sessions as an independent variable. This analysis will be performed separately for each treatment arm.

Patient assessment of skill acquisition (Cognitive Behavioral Therapy Skills Questionnaire) will be evaluated with repeated measures mixed model analysis consistent with the primary endpoint. Results will be presented for the total Cognitive Behavioral Therapy Skills Questionnaire score, the Behavioral Activation Score, and the Cognitive Restructuring score.

Medication adherence will be evaluated using saliva drug screens and, when possible, confirmed by urine drug screen (positive result for buprenorphine and norbuprenorphine). Differences between the treatment arms in medication adherence will be assessed with a generalized estimating equation analysis consistent with the abstinence analysis.

Ethics Approval

This study protocol has been reviewed and approved by the New York State Psychiatric Institute Institutional Review Board. The study is registered on ClinicalTrials.gov (NCT04542642).

Results

Recruitment for this study was active as of February 2021 and will continue until the projected sample size is met.

Discussion

While initially designed as a standard, site-based clinical trial, this study was redesigned as a decentralized study to circumvent challenges in conducting in-person visits that arose as a result of the COVID-19 pandemic. Standard in-person procedures for this patient population that were planned for the study, such as initiation of buprenorphine medication in-clinic or on-site urine drug screening, were no longer feasible. The decentralized study model aligns with a shift in health care delivery observed during the pandemic, as many substance use disorder treatment providers were able to transition to telemedicine for care delivery, including initiation onto buprenorphine and maintenance treatment [43,44]. Digital therapeutics lend themselves to remote therapy delivery models, presenting a unique opportunity to evaluate their use along with existing technology and tools such as videoconferencing, electronic signatures for documenting consent, and video-observed, self-administered saliva drug test kits.

Several challenges arose with the shift in study design. One of the sites, a research clinic, typically manages buprenorphine medication during studies of this patient population. Without in-clinic participant visits, it became necessary for the site to confirm that participants were receiving buprenorphine under the care of a licensed prescriber. This was accomplished by obtaining release of medical information waivers from prospective participants, allowing the site to reach out directly to the individual's treatment provider for confirmation of eligibility. This pivot allowed the research clinic to recruit a broader geographic sample of individuals than is typical for similar studies [45] conducted on-site. Another challenge was ensuring that all assessments could be conducted remotely. While most self-report assessments were easy to transition to virtual delivery, it is challenging to conduct urine drug screening virtually. Saliva drug screening kits were selected as an alternative that allowed participants to self-administer the test during video sessions and under supervision by study staff. Finally, participant recruitment methods shifted toward a strategy focused on digital media and treatment programs using telemedicine.

Several questions about decentralized studies in this patient population will be addressed by this study. For example, it is not yet clear whether it will be easier to recruit and retain individuals with opioid use disorder in a virtual study than in a standard face-to-face study. Providing a more convenient mechanism for conducting study sessions may increase retention, which can be challenging in this patient population. Evaluating the utility of self-administered saliva drug screening may also be beneficial to other investigators who are considering this method of evaluating substance use. Challenges that arise over the course of the study will help elucidate the limitations of this study design. This example of a decentralized clinical trial may provide a useful model for conducting future virtual studies with people with opioid use disorder.

Authors' Contributions

HL, AC, and LC conceived the study concept and design. AW, CB, SM, MD, BI, XX, and YM contributed to the study design. RG is the biostatistician for the study; RG contributed to study endpoint selection and will perform the statistical analyses of study results.

Conflicts of Interest

HL, XX, RG, and YM are current employees and stockholders of Pear Therapeutics, Inc. BI and MD are former employees of Pear Therapeutics, Inc. The authors declare no other conflicts.

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Abbreviations

AREF: Addiction Research and Education Foundation
FDA: US Food and Drug Administration
NIH: National Institutes of Health
STARS: Substance Treatment and Research Services

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Protocol

Gamified Web-Delivered Attentional Bias Modification Training for Adults With Chronic Pain: Protocol for a Randomized, Double-blind, Placebo-Controlled Trial

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Abstract

Background: To date, research has found variable success in using attentional bias modification training (ABMT) procedures in pain samples. Several factors could contribute to these mixed findings, including boredom and low motivation. Indeed, training paradigms are repetitive, which can lead to disengagement and high dropout rates. A potential approach to overcoming some of these barriers is to attempt to increase motivation and engagement through gamification (ie, the use of game elements) of this procedure. To date, research has yet to explore the gamified format of ABMT for chronic pain and its potential for the transfer of benefits.

Objective: The aim of this study is to investigate the effects of a gamified web-delivered ABMT intervention in a sample of adults with chronic pain via a randomized, double-blind, placebo-controlled trial.

Methods: A total of 120 adults with chronic musculoskeletal pain, recruited from clinical (hospital outpatient waiting list) and nonclinical (wider community) settings, will be included in this randomized, double-blind, placebo-controlled, 3-arm trial. Participants will be randomly assigned to complete 6 web-based sessions of dot-probe nongamified sham control ABMT, nongamified standard ABMT, or gamified ABMT across a period of 3 weeks. Active ABMT conditions will aim to train attention away from pain-relevant words. Participant outcomes will be assessed at pretraining, during training, immediately after training, and at the 1-month follow-up. Primary outcomes include pain intensity, pain interference, and behavioral and self-reported engagement. Secondary outcomes include attentional bias for pain, anxiety, depression, interpretation bias for pain, and perceived improvement.

Results: The ethical aspects of this research project have been approved by the human research ethics committees of the Royal Brisbane and Women's Hospital (HREC/2020/QRBW/61743) and Queensland University of Technology (2000000395). Study recruitment commenced in August 2021 and is ongoing. Data collection and analysis are expected to be concluded by October 2022 and January 2023, respectively.

Conclusions: This trial will be the first to evaluate the effects of gamification techniques in a pain ABMT intervention. The findings will provide important information on the potential therapeutic benefits of gamified pain ABMT programs, shed light on the motivational influences of certain game elements in the context of pain, and advance our understanding of chronic pain.

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Introduction

Background

Attention in individuals with chronic pain is often biased toward pain-related information (ie, word or picture stimuli) [1-3]. Such findings have led researchers to investigate whether these attentional biases can be modified with an attentional bias modification training (ABMT) procedure and whether this modification leads to changes in pain intensity and associated pain-related health outcomes [4]. ABMT protocols typically use a modified dot-probe task [5] to train participants to disengage from pain-related information and redirect attention to the competing neutral cues. To date, research has found variable success in using ABMT in pain samples (see the study by Van Ryckeghem et al [6] for an overview). Specifically, in the context of chronic pain, some studies have indicated that ABMT can be effective in improving pain-related outcomes (eg, pain intensity and pain-related disability) [4,7,8], whereas others have failed to replicate these positive effects [9,10].

Several factors could contribute to these mixed findings, including boredom and low motivation. Qualitative studies have indicated that participants experience dot-probe tasks as monotonous, repetitive, and boring [11,12]. Indeed, ABMT procedures require systematic repetition of numerous trials over multiple sessions across several weeks [4,7-10] and typically include a basic layout (ie, stimuli are presented on a plain background), which may make training sessions unappealing. The monotonous nature of such tasks could lead to (temporal) disengagement, low motivation, and high dropout rates, which in turn may compromise intervention efficacy. A potential approach to overcoming some of these barriers is to attempt to increase engagement through the gamification of ABMT. *Gamification* refers to the use of digital game elements (eg, points and avatars) in nonentertainment settings [13]. Qualitative [14] and quantitative [15] reviews on gamified cognitive training tasks have found that adding game elements to repetitive tasks improves motivation and engagement. However, Zhang et al [16], in their systematic review that focused specifically on gamified cognitive bias modification interventions for psychiatric disorders (ie, anxiety, affective, and addictive disorders), found that only 2 of the 4 identified studies reported gamified interventions to be effective [17,18], and only 1 study compared a gamified task directly against a nongamified counterpart [19]. This calls for more rigorously designed and theory-driven research in this field.

To date, research has yet to explore the gamified format of ABMT for chronic pain and its potential for the transfer of benefits. To address this gap in the literature, a gamified web-delivered pain ABMT intervention, based on the standard, modified dot-probe task [5], has been developed and augmented with game elements.

Aims and Hypotheses

The aim of this study is to investigate the effects of a gamified web-delivered ABMT intervention in a sample of adults with chronic musculoskeletal pain via a randomized, double-blind, placebo-controlled trial. To do this, 3 ABMT conditions will be directly compared: nongamified sham control ABMT, nongamified standard ABMT, and gamified ABMT. It is hypothesized that the gamified ABMT condition, relative to both the standard ABMT and control ABMT conditions, will rate more highly on self-reported engagement (ie, task-related engagement, enjoyment, and interest) as well as complete more training sessions and have less dropout. On the basis of the findings from the broader ABMT literature and theoretical considerations [20-22], it is expected that the standard ABMT and gamified ABMT conditions will show a reduction in pain-related attentional biases and interpretation biases after training sessions, with the largest reduction in the gamified ABMT condition. Furthermore, it is expected that both the standard ABMT and gamified ABMT conditions, relative to the control ABMT condition, will show reductions in pain intensity, pain interference, anxiety, and depression scores immediately after training and 1-month later and that these reductions will be greater in the gamified ABMT condition compared with the standard ABMT condition. Finally, it is expected that both the standard ABMT and gamified ABMT conditions, relative to the control ABMT condition, will report global pain-related improvements following training and that these improvements will be larger in the gamified ABMT condition compared with the standard ABMT condition.

Methods

Study Design

This study is a randomized, double-blind, placebo-controlled, 3-arm, parallel-group trial examining the efficacy of a gamified ABMT for chronic pain delivered over the internet. Adults with chronic musculoskeletal pain will be randomly allocated to 1 of the 3 training conditions: control ABMT, standard ABMT, or gamified ABMT. The control ABMT condition comprises a dot-probe paradigm without training direction, whereas the standard ABMT and gamified ABMT conditions will aim to train attention away from pain-relevant words. Outcome assessments for all training conditions will be conducted via the internet at baseline, during training, immediately after

training, and at the 1-month follow-up. Figure 1 shows the trial flow diagram. This study protocol is written in compliance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) [23] guidelines.

Figure 1. Flow diagram of study protocol. ABMT: attentional bias modification training.
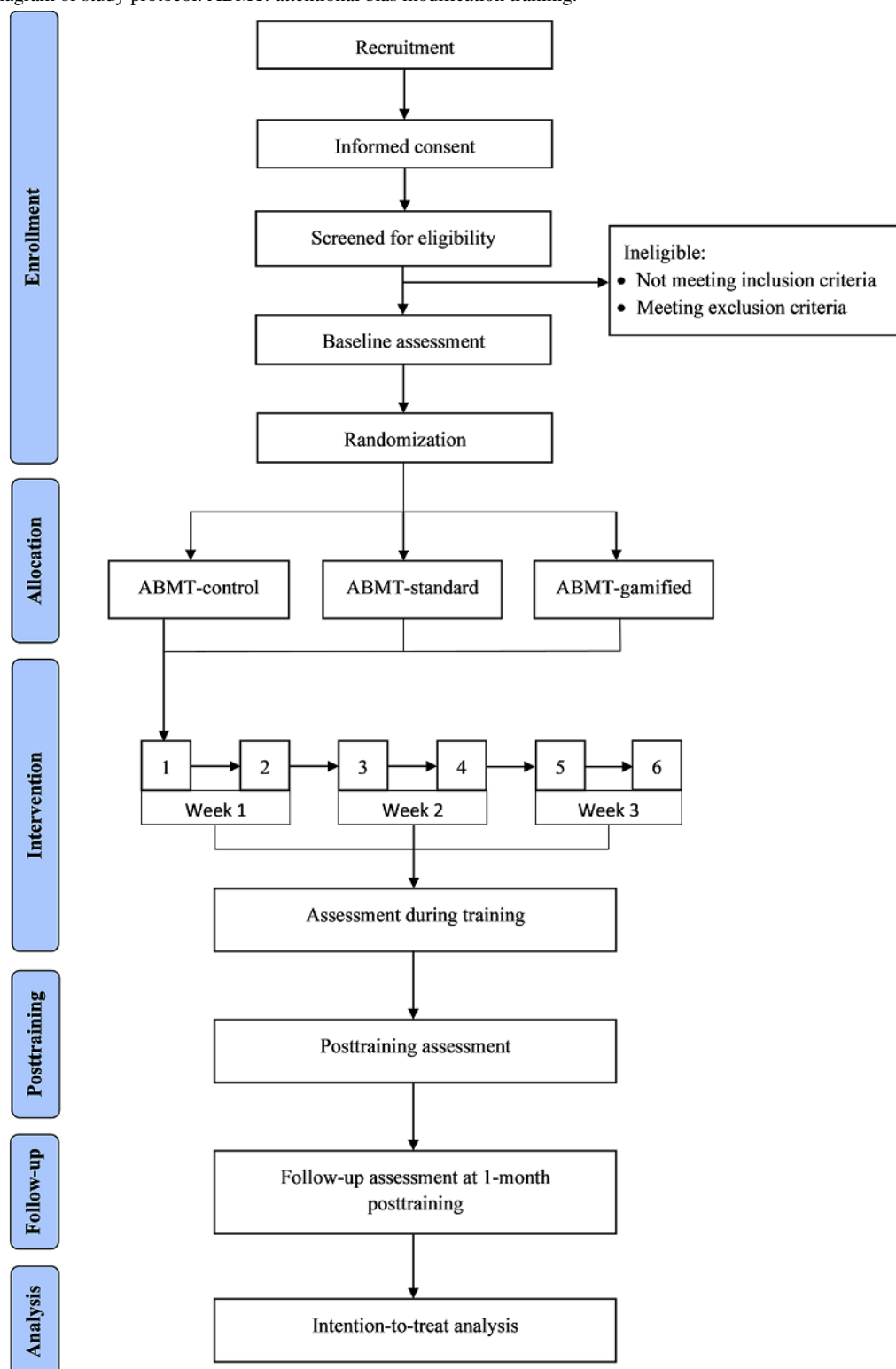
Study Setting

This trial will take place on the web; that is, all outcome assessments and training sessions will be conducted on the web at the participants' place of convenience, using their own computers. The study focuses on adults with self-reported chronic musculoskeletal pain, recruited from both clinical (ie,

outpatient waiting list) and nonclinical (ie, wider community) settings in Australia.

Participants

To participate in this study, individuals must be aged ≥18 years; experience chronic musculoskeletal pain, that is, pain in bones, joints, muscles, or related soft tissues (eg, rheumatoid arthritis

pain, nonspecific back pain, or fibromyalgia pain); meet the criteria for chronic pain, that is, self-reported pain that lasts or recurs for >3 months [24]; and have normal or corrected to normal vision. Participants will be excluded if they are not native English speakers or not fluent in reading and writing English (as participants' reaction time [RT] to English words is used as an index of attentional bias to semantically related pain memory networks), have no access to a desktop or laptop computer connected to reliable internet (as the assessments and training sessions are conducted on the web), or are not able or willing to provide informed consent to participate.

Recruitment and Consent

To optimize the generalizability of the findings, prospective participants will be recruited from a large Australian public hospital outpatient waitlist for pain management (clinical setting) as well as from a wider community (nonclinical setting). Individuals on the hospital outpatient waiting list who have been identified for screening using medical records will be invited to participate through personalized mail correspondence. These individuals may also be approached for recruitment at the introduction to persistent pain management orientation and information sessions held at the hospital every few months. Participants from the wider community will be recruited through university electronic mailing lists, distribution of flyers, social media, and community channels (eg, Facebook advertising, Twitter, LinkedIn, word of mouth, medical practices, and physiotherapy clinics).

All recruitment materials (eg, hospital personalized letters and flyers) will include a survey hyperlink that will direct prospective participants to the necessary study information to decide on participation. This will include information about the research procedures; the voluntary nature of the study, with the freedom to withdraw at any time until the collected data are deidentified (ie, upon completion of the 1-month follow-up survey); the potential risks and benefits of their participation; and whom to contact for questions about the research. All interested participants will be asked to provide informed consent electronically (ie, e-consent) before being taken to the screening questions and then to the first screen of the baseline assessment.

Patient and Public Involvement

Public members with and without chronic pain have been involved in a prior validation study of pain-related and neutral visual word stimuli sets that will be used in this study (Vermeir JF, White MJ, Johnson D, Crombez G, Van Ryckeghem DML, unpublished data, April 2020). For this study, only patients and members of the public who meet the selection criterion of chronic pain experience will be eligible to participate.

Randomization, Allocation Concealment, and Blinding

Participants fulfilling eligibility criteria and willing to participate in this study will be randomly allocated to 1 of the 3 training conditions after the baseline assessment. Randomization will be performed before participants are enrolled by an independent person blinded to all processes within the intervention, using a computerized random number generator. A block randomization technique will be used, allowing 6 participants at a time to be randomized in equal proportions to the 3 training arms. The

allocation numbers will be stored on a password-protected university database maintained by the same independent person and will be revealed after participants are enrolled and baseline assessments are completed.

Each time a participant completes the baseline survey, an automatic email will be sent to the principal researcher (JFV). After receiving this email, the participant will be allocated to the next number on the list and, consequently, be assigned to a training arm. Researchers and participants will be blinded to group allocation throughout the trial (ie, double-blind study design). Furthermore, as assessments and training will occur on the web, in the absence of the investigators, the outcome data will be blinded. However, it is possible that a researcher could become aware of the participants' training conditions to support them adequately in the instance of technical problems. However, it is unlikely that this will entail problems of bias allocation or assessment because of the web-based nature of the study.

Procedure

After informed consent is obtained and participants are eligible, they will complete the web-based baseline assessment (approximately 35 minutes) containing demographic questions as well as questions relating to their general health, current mental health, pain experience, and everyday thoughts and behaviors. At the end of the survey, participants will select their preferred days for training, which will be either (1) Monday and Thursday or (2) Tuesday and Friday. Participants will also be asked to provide an email address so that the research team can send links to the training sessions. Participants will then be randomized into 1 of the 3 groups and be invited by email to start their first training session. This email will include a weblink to the appropriate version of the intervention, as well as instructions on how to download the program.

Training sessions will be performed on the web at the participants' time and place of convenience (using their own computers), twice a week on a separate pair of days (Monday and Thursday or Tuesday and Friday) for 3 consecutive weeks, totaling 6 sessions. This dosage is based on previous pain ABMT literature, which has shown positive training effects for dosages ranging between 4 and 8 sessions [4,7,8]. It is anticipated that the first and final sessions will take approximately 30 minutes, as it includes cognitive assessment measures, whereas sessions 2 to 5 will take approximately 15 minutes to complete. Participants will be asked to complete the sessions during normal waking hours and within 24 hours of receiving a web link. Each session will start with the same instructions, similar to those of previous research [10], and highlight the need to create a quiet and private environment free from distractions for at least 30 minutes. In total, the participants will be sent 6 session links. Necessary reminders will be sent via email and SMS text messages throughout the study.

After each training session, participants will be asked to rate their experience with the task (<2 minutes). Immediately after completion of the final training session, participants will be invited to the postassessment (approximately 15 minutes), with questions relating to their experience of pain, mood, and other relevant psychological experiences associated with their pain.

Finally, 1 month after the end of the training sessions, all participants will receive an email invitation for the follow-up assessment (approximately 10 minutes), with similar questions to that of the postassessment (see *Outcomes and Measures* section for further details).

Study Program

Overview

Participants will be involved in the trial for approximately 2 months, including a 3-week intervention period in which they will be randomized to 1 of the 3 training arms, followed by a 1-month follow-up period. Several strategies will be used to maximize participant retention and follow-up completion. First, we will adopt a web-based completion mode for the surveys and training sessions. Second, participants will receive a personalized email invitation for each training session. These emails will also provide participants the opportunity to ask the research team about any technical difficulties or other obstacles encountered while using the software. Third, we will use a combination of SMS text message and email message reminders according to the participants' preferences. These reminders will be sent to the participants who do not complete the scheduled session within 24 hours of receiving the weblink. When there is no reaction to the training sessions and reminders after 2 weeks (ie, after 4 training sessions and 4 reminders), the participant will be considered as a dropout. Similarly, participants who fail to complete the follow-up assessments will receive up to 2 emails or SMS text message reminders: one after 24 hours and another one after 48 hours. Finally, the gamified ABMT intervention was developed using gamification features to encourage participants to keep using the program. No incentives will be provided to the participants.

Participant care (eg, rehabilitation program, exercise, cognitive behavioral therapy, and pain medications) concomitant with the ABMT (ie, control ABMT, standard ABMT, or gamified ABMT) will be permitted during the trial. It will be monitored through a *pain-treatment* question that will probe participants' pain treatments and frequency since the commencement of the study or previous assessment.

Task Stimuli

Pain words were chosen as stimuli instead of pictures, as meta-analytic results have shown that biases for pain-related information are larger when using (sensory) pain words than when using pictorial stimuli [3]. Furthermore, a study directly comparing ABMT protocols using words versus facial expressions found that attentional biases changed in the predicted direction on the stimuli presented during the training; however, for those trained on words, training effects also generalized to pictorial stimuli [25]. Finally, words have the advantage of being relatively quick to process, easy to implement, and their physical characteristics (eg, word length) can be tightly controlled [26].

A total of 3 sets of word stimuli will be used. The stimulus set for the practice trials (set 1) will comprise 8 neutral word pairs related to the categories of natural (eg, *log*) and manmade (eg, *pot*) resources. The stimulus set for the experimental trials (set 2) will comprise a set of 8 pain-related words and 8 neutral

words. The stimulus set used for the assessment of attentional bias trials (set 3) will comprise 8 different pain-related and neutral word pairs, with the same words presented at pre- and posttraining assessments to investigate the generalization of training effects. Pain words stem from 2 different pain-related categories: sensory (eg, *sharp*) and affective (eg, *agonizing*) pain words. To control for the semantic relatedness of the word set, each pain-related word (eg, *pain*) is matched with a neutral (ie, nonpain) word (eg, *bird*) for length and frequency of use in the English language [27]. Word stimuli in each set will be unique, that is, not replicated in any other set. Each word stimulus will be presented in a black 28-point upper-case Courier New font on a white background. All word stimuli will be taken from a data set of stimulus material, previously created and validated for use in chronic pain samples by the authors of this study (Vermeir JF, White MJ, Johnson D, Crombez G, Van Ryckeghem DML, unpublished data, April 2020). Specifically, in that study, we reviewed the literature on dot-probe studies investigating attentional biases, selected a pool of pain-related and matched neutral words for validation, and then asked participants with and without chronic pain to complete a speeded word categorization paradigm and rate the pain relatedness of a subset of pain words. For this study, we selected sensory and affective pain words that (1) were rated as most relevant to chronic musculoskeletal pain and (2) were categorized the quickest as pain related by adults with chronic pain.

Experimental Tasks

Overview

Tasks will be programmed and presented using Inquisit 6.4 (Inquisit Web Millisecond software package) on participants' internet-connected desktop or laptop computers. Participants will be required to download and install the application using a plug-in. At the end of each training session, a data file containing their RT and accuracy scores will be automatically and securely saved to the researcher's web-based Inquisit account. To account for different screen sizes and ensure consistency in the display of word stimuli across participants, a calibration process will be completed at the start of each session. Participants will be asked to place a credit card (which is universally the same size) on the screen and adjust the length of a horizontal line until it matches the width of the credit card.

All conditions (standard ABMT, control ABMT, and gamified ABMT) will use a modified version of the dot-probe task [5]. Each task starts with a 500-millisecond duration fixation cross to direct attention to the center of the computer screen (Figure 2). Then, a randomly selected stimulus pair comprising 1 pain-related and 1 neutral word will appear for 500 milliseconds, with 1 word located at the top of the screen and the other at the bottom. The word stimuli will be centered horizontally. Once the pairings disappear, a probe (ie, *p* or *q*) replaces the location of one of the words. Participants will be instructed to determine whether a *p* or a *q* appears and respond as quickly and as accurately as possible by pressing the corresponding keys (ie, *p* key pressed with the right index finger and *q* key pressed with the left index finger) on the computer keyboard. The probe will disappear as soon as a response is recorded or after 2500 milliseconds. The intertrial interval will be 500 milliseconds.

To ensure that participants' attention is directed toward the center of the screen, several digit trials will be presented [10,28]. In these trials, a random digit number between 1 and 9 will replace the fixation cross for a duration of 150 milliseconds, and participants will be instructed to type the number on the keyboard. The intertrial interval will be 1000 milliseconds after digit trials so that participants can reposition their fingers on the keys. In the context of this study, incongruent trials will be trials where the probe appears in the opposite location previously occupied by the pain-related stimulus, whereas congruent trials will be those where the probe appears in the location previously occupied by the pain-related stimulus.

Figure 2. Sample congruent trial from one of the nongamified attentional bias modification training tasks where the dot-probe replaces the top, pain-related word. Stimuli are not presented to scale.
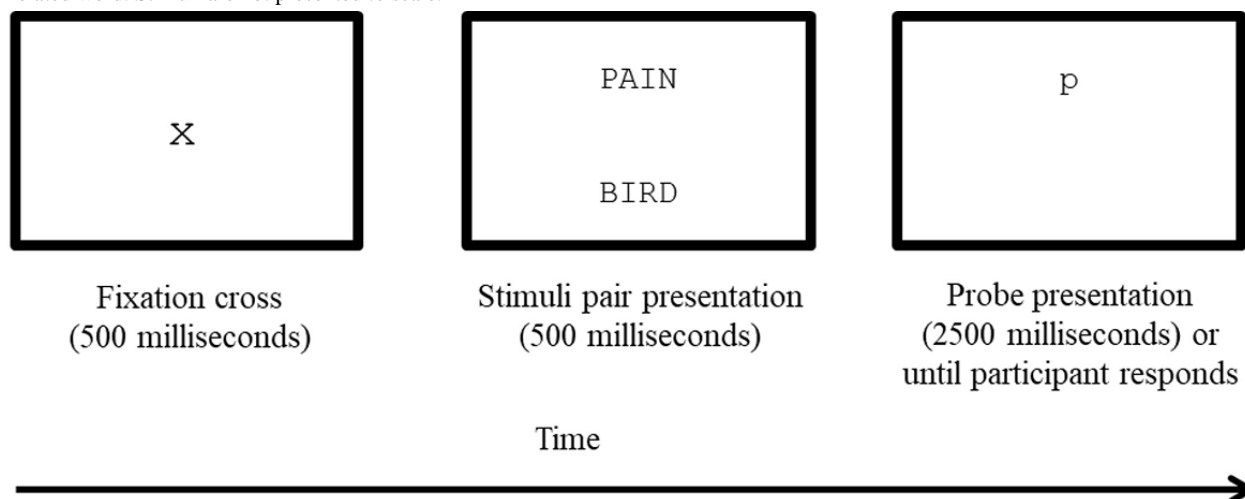
Nongamified Standard ABMT

Each standard ABMT task will start with 1 block of 17 practice trials, comprising 16 neutral stimulus pairs and 1 digit trial. For each correct practice trial, the word *Correct!* will appear on the screen, whereas the word *Incorrect!* will appear for every erroneous response. The training phase will comprise 4 training blocks, each comprising 68 experimental trials (8 [12%] congruent trials; 56 [82%], incongruent trials; and 4 [6%] digit trials), totaling 272 trials and taking approximately 15 minutes to complete. The probe will replace neutral cues in 87.5% (224) of trials and pain cues in 12.5% (32) of trials, thereby training attention away from pain-related cues. This distribution will be used to reduce the obviousness of the probe contingency [29], and participants will not be made aware of it. Word pairs will be randomly presented in each of the 4 possible combinations (probe up and target down, probe down and target up, probe up and target up, and probe down and target down). The selection of a 500-millisecond presentation time for the stimulus pair is guided by previous pain ABMT studies that have shown positive training effects in individuals with chronic pain [4]. Stimuli will be presented in a randomized order across trials and participants, and trials will be intermixed and randomly presented in 4 blocks, with a rest offered between each block of trials.

Nongamified Sham Control ABMT

The control ABMT group will be similar to the standard ABMT group except that the probe will appear with equal frequency in the position of the pain-related and neutral words, totaling 272 trials (128 [47%] congruent trials; 128 [47%] incongruent trials; and 16 [6%] digit trials per session) and taking approximately 15 minutes to complete.

Gamified ABMT

The implementation of gamification has been listed within the group of complex interventions [30]. These interventions refer to activities that comprise multiple interacting components (eg, intensity and setting) that, when applied to the target population, result in a range of possible outcomes [31]. Therefore, the development of the gamified task followed the Medical Research Council framework for complex interventions [31], using theory, review evidence, and expert involvement. The gamified ABMT task was developed in several steps.

In the first step, a multidisciplinary team with research expertise in the fields of eHealth, cognitive psychology, and gamification discussed the core theories, methods, mode of delivery, implementation strategies, and design requirements. Specifically, rather than developing a completely new ABMT intervention, it was decided to design the gamified ABMT task as a so-called *game-shell* [32]; that is, game elements were added as an additional layer to the standard ABMT task without changing the initial structure. This design allows the original evidence-based ABMT paradigm to remain unchanged and has been frequently used in the gamified cognitive literature [17,32,33].

In step 2, the game elements were selected. This was guided by a qualitative and quantitative review, as well as specific theories. First, we undertook a systematic review and meta-analysis assessing the effectiveness of gamification applied to cognitive training tasks to gain a better understanding of the impact of gamification on cognitive training and identify factors that contribute to the optimal design of such programs [15]. The review identified that typically 5 game elements were used and that achievement and progression-oriented game features (eg, rewards and feedback loops) were commonly implemented in cognitive training tasks. Although the review could not show

support for one feature over another (because of a limited number of studies in the subgroups), it provided evidence for the effectiveness of gamification in improving motivation and/or engagement (Hedges g=0.72) and synthesized findings into practical guidelines for implementing gamification for cognitive training.

Second, to increase the likelihood of the effectiveness of the intervention design and respond to the call for more theory-driven research on gamification in the field of health [15,34,35], the implementation of game elements in the ABMT procedure was guided by concepts of self-determination theory [36,37] and self-regulation [38]. According to self-determination theory [36,37], which is a well-established theoretical framework within gamification research [34], competence (ie, feeling effective), relatedness (ie, feeling connected to others), and autonomy (ie, feeling a sense of freedom) are the 3 basic psychological needs that determine intrinsic motivation, sustained engagement, and psychological well-being. Previous research has shown that these needs can be addressed by specific elements such as badges, leaderboards, performance graphs, and social competition [39-41]. Another construct that is fundamental to the success of health-related interventions is self-regulation, defined as a dynamic motivational process of setting, pursuing, and maintaining personal goals [42-44]. Self-regulation techniques such as goal setting and self-monitoring can motivate users to engage and sustain in activities, and there is evidence that these techniques can be facilitated in gamification through a range of features such as rewards, goals, levels, and progress bars [45-47].

On the basis of theoretical considerations and the empirical findings discussed in the previous sections, a combination of 5 game elements was incorporated in the gamified task to keep participants motivated and engaged in the sustained and repeated use of the ABMT procedure. The 5 gamification features are briefly described as follows:

1. Clear gamified goal: At the start of each training session, a clear gamified performance goal will be set for the task to earn as many points as possible and receive badges along the way. Goals that are specific and reasonably challenging are the most effective at increasing motivation and task performance [48] and are likely to increase the satisfaction of the need for competence [40].
2. Feedback loops: During the practice phase, immediate gamified feedback will be provided to help facilitate self-monitoring [46,49] and feelings of competence [40]. For each correct practice trial, the word *Correct!* and a

smiling emoticon will appear on the screen, whereas the word *Incorrect!* and a frowning emoticon will occur in every incorrect practice trial (Figure 3).

3. Task-related progress: During the training phase, a constantly visible progress bar at the top of the screen will indicate the proportion of trials remaining in each block, and a written indicator will reflect the number of blocks completed (Figure 3). These gamification features can facilitate self-tracking and motivate participants toward the attainment of goals [45,46] and fulfill their desire for competence [39].
4. Rewards: Collectible points and badges were implemented to facilitate participant goal setting [45,46] and satisfy their innate psychological needs for competence, autonomy, and relatedness [40]. Specifically, between blocks of trials, participants will receive feedback about their performance in the form of points, calculated for each block of trials (1 point is earned for each correct trial; a maximum of 68 points can be earned per block). We choose to provide feedback after each block of trials rather than after each trial to ensure that the flow of training is uninterrupted. At the end of each training session, the participants will also be rewarded with a badge (Figure 3). There are 6 different badges, each of which has a number of stars on it corresponding to the number of sessions completed.
5. Sound effect (with rewards): To enhance motivation, the task incorporates a pleasant auditory and visual reward in the form of a firework. To ensure that all participants in the gamified ABMT condition are exposed to the same type of game elements, everyone will experience the fireworks after the first block of trials. However, for subsequent blocks of trials, only those who obtain at least 60% (41/68 trials) accuracy will experience the fireworks. This latter criterion involves an element of uncertainty that can further increase motivation.

In step 3, a gamified prototype for the experimental condition was created collaboratively by the authors of this paper, who are experts in the field of gamification and cognitive psychology, and programmed using Inquisit 6.4.

In the last step, all the intervention materials and tasks (nongamified and gamified) were piloted internally by members of the research team to ensure that the program was feasible to deliver over the internet to the target sample. Following discussions, minor refinements were proposed and made to the gamified intervention. For example, the width and height of the progress bar were adjusted to make the visibility of the progression more noticeable.

Figure 3. Sample of game elements used in the gamified task. (A) Smiling (left) and frowning (right) emoticons received during practice trials for correct and incorrect responses, respectively. (B) Badge earned at the end of the first training session. (C) Progress bar representing proportion of trials completed in each block and a written indicator reflecting the number of blocks completed.
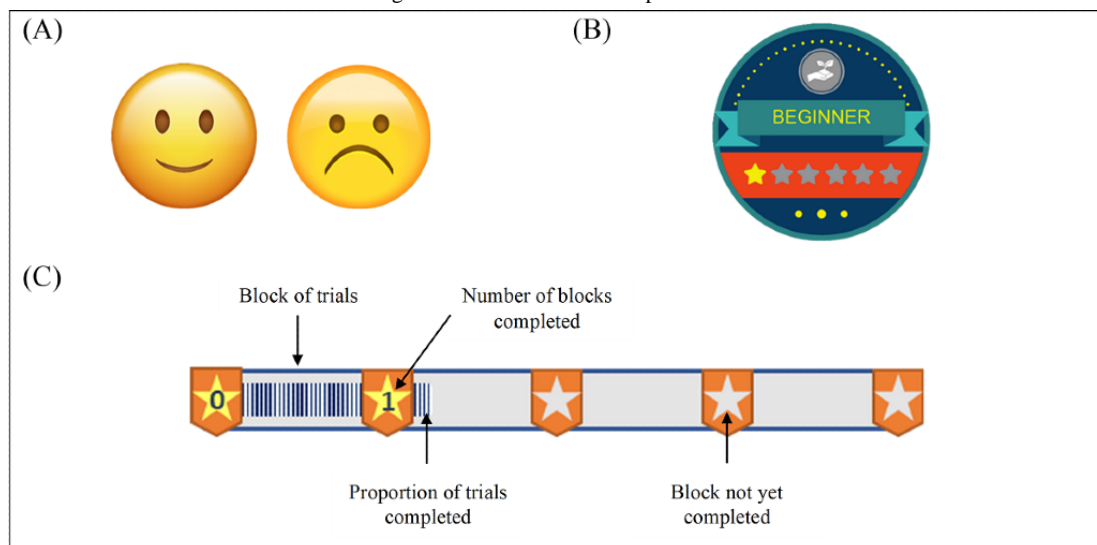
Outcomes and Measures

Overview

Tasks will be presented using Inquisit 6.4 on participants' internet-connected computers, and questionnaires will be administered using the web-based system Qualtrics (Provo),

except for self-reported engagement, which will be administered using Inquisit 6.4. Assessments for all training conditions will be conducted at baseline, during training, immediately after training, and at the 1-month follow-up. A list of all outcomes, measurement instruments, and corresponding time points is presented in Table 1.

Table 1. Study outcome measures by assessment time point.

Outcome and variable	Measure	Assessment time point			
		Baseline	During training	Posttraining	1-month follow-up
Baseline data					
Eligibility screening	Self-report questions	✓			
Demographic information	Self-report questions	✓			
Pain experience information					
	Self-report questions	✓			
	GCPS[a]	✓			
Primary outcomes					
Pain intensity	PROMIS[b] Pain Intensity 3a	✓		✓	✓
Pain interference	PROMIS Pain Interference 8a	✓		✓	✓
Self-report engagement					
	1 self-report question		✓	✓	
	IMI[c] (interest and enjoyment)			✓	
Behavioral engagement					
	Intervention attrition rates		✓	✓	
	Completion rates		✓	✓	
Secondary outcomes					
Attentional bias	Dot-probe task	✓		✓	
Anxiety	PROMIS Anxiety 8a	✓		✓	✓
Depression	PROMIS Depression 8b	✓		✓	✓
Perceived improvement	PGIC[d]			✓	✓
Interpretation bias	Interpretation bias task	✓		✓	
Additional measures					
Attentional control	ACS[e]	✓		✓	
Personality characteristics	BIS and BAS[f] scales	✓			
Pain-related worrying	PCS[g]	✓			
Pain-treatment information	Self-report questions			✓	✓
Validity check	Instructional question	✓		✓	✓
Manipulation check	1 self-report question			✓	

[a]GCPS: Graded Chronic Pain Scale.

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

[c]IMI: Intrinsic Motivation Inventory.

[d]PGIC: Patient Global Impression of Change.

[e]ACS: Attentional Control Scale.

[f]BIS and BAS: Behavioral Inhibition System and Behavioral Activation System Scales.

[g]PCS: Pain Catastrophizing Scale.

Baseline Information

At baseline, participants will report on demographic information pertaining to age, gender, first language, country of birth, country of residence, postcode of current home address, ethnicity, marital status, employment status, education level, and hand preference. Participants will also report on the type of computer (eg, laptop), screen size and keyboard (eg, QWERTY) they are using, their health in general, whether they currently have a mental health condition (eg, depression), and on their pain experience information, including current pain problems, formal diagnosis of the pain condition (ie, by a physician), duration of primary pain condition, body locations where they experience pain, area of the body that hurts the most,

how the primary pain condition began (eg, postsurgical), current treatment for the pain problem (eg, physiotherapy), and frequency of health care use.

To provide additional information characterizing participants' overall pain severity, participants will complete the Graded Chronic Pain Scale (GCPS) [50]. The GCPS is a 7-item self-report instrument designed to assess 2 dimensions of chronic pain severity (pain intensity and pain-related disability) in the general population and in primary health care settings. The scale measures the presence of chronic pain in the past 6 months, and all items, except for the number of days disabled, are scored on an 11-point Likert scale, with responses ranging from 0 to 10. Subscale scores (ie, characteristic pain intensity, disability score, and disability points) for the 2 dimensions are combined to calculate a chronic pain grade that allows individuals with chronic pain to be classified into 1 of 5 hierarchical categories: grades 0 (*no pain problem*) to 4 (*high disability-high intensity*). The GCPS has been found to have acceptable to excellent internal consistency, with a Cronbach α ranging from .74 to .91 [50,51]. Dunn et al [52] found that the test–retest reliability after a 2-week interval was good, with a weighted Cohen κ of 0.81.

Primary Outcome Measures

Pain Intensity

Pain intensity will be assessed using the Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Intensity–Short Form 3a (v1.0; 3 items) [53]. The first 2 items assess pain intensity using a 7-day recall period and are rated on a 5-point Likert scale ranging from 1 (*no pain*) to 5 (*very severe*). The last item asks participants to rate their level of pain *right now* and is rated on a 5-point Likert scale that ranges from 1 (*no pain*) to 5 (*very severe*). Raw score totals are transformed to T-score metrics using the PROMIS conversion tables, such that the average score for the general population is 50 and the SD 10. Higher T-scores represent worse pain. PROMIS Pain Intensity has been shown to be valid for assessing pain in various settings [54].

Pain Interference

The impact of pain on daily life will be assessed using the PROMIS Pain Interference–Short Form 8a (version 1.0; 8 items) [53]. The items have a 7-day time frame and are rated on a 5-point Likert scale ranging from 1 (*not at all*) to 5 (*very much*). Raw score totals are transformed to T-score metrics using the PROMIS conversion tables, such that the average score for the general population is 50 and the SD 10. Higher T-scores represent greater pain interference. PROMIS Pain Interference has been assessed and validated in both general and clinical populations [54,55].

Engagement

Participants' experiences of engagement will be assessed using 2 self-report measures. Task-related engagement will be measured after each training session with a single-item question: *How engaging was this session?* The item is rated on a 10-point Likert scale, ranging from 1 (*not at all*) to 10 (*very much*), with a higher score indicating greater engagement. Task-related interest and enjoyment will be assessed using the Intrinsic

Motivation Inventory—Interest and Enjoyment subscale [56-58]. The subscale comprises 7 items, which are scored on a 7-point Likert scale ranging from 1 (*not at all*) to 7 (*very true*), with higher scores representing higher levels of interest and enjoyment. The reliability and validity of this subscale have been established in previous research [59,60].

Nonuse intervention attrition [61] (ie, the proportion of participants who discontinue using the intervention at each training session) and completion rates (ie, the proportion of sessions, out of 6, that each participant completes during the training period) will be used as objective behavioral measures of engagement.

Secondary Outcome Measures

Measure of Attentional Bias for Pain

Attentional biases will be measured using the standard dot-probe paradigm [62]. This task is similar to the one used during the experimental phase, except that the probe replaces each of the words in each pair with equal frequency. Before the assessment blocks, participants will complete a block of 17 practice trials, comprising 16 neutral stimulus pairs and 1 digit trial. Stimuli will be presented in a randomized order across trials and participants, and trials will be intermixed and randomly presented in 2 blocks, with a rest offered between the blocks. Each block will comprise 68 trials (32 [47%] congruent trials; 32 [47%] incongruent trials; 4 [6%] digit trials), totaling 136 trials. Consistent with previous research [10,28], practice trials, digit trials, incorrect trials, and responses <200 milliseconds or >1000 milliseconds will be excluded from the calculation of mean RTs. An attentional bias index will be calculated using the following formula: mean RT of incongruent trials–mean RT of congruent trials. Positive scores will be indicative of an attentional bias toward pain-related stimuli, whereas negative scores will reflect an attentional bias toward neutral stimuli.

Anxiety and Depression

Negative affect will be assessed with 2 PROMIS measures comprising PROMIS Anxiety 8a (version 1.0; 8 items) and PROMIS Depression 8b (version 1.0; 8 items) [53]. The items have a 7-day period and are rated on a 5-point Likert scale ranging from 1 (*never*) to 5 (*always*). The raw score totals on each scale will be transformed to T-score metrics using the PROMIS conversion tables, such that the average score for the general population is 50 and the SD 10. Higher T-scores represent greater symptoms of anxiety or depression. The 2 PROMIS measures have demonstrated excellent psychometric properties in both population-based [63] and clinical samples [64,65].

Perceived Improvement

Participants' perception of overall pain-related improvement following training will be assessed using the Patient Global Impression of Change (PGIC) scale [66]. This measure comprises a single item rated on a 7-point Likert scale, ranging from 1 (*very much improved*) to 7 (*very much worse*), with *no change* in the middle of the scale (4). For descriptive purposes, participants will be classified into 3 categories according to the PGIC score: disease deterioration (0-3 points), stable disease (4 points), or disease improvement (5-7 points) since the start

of the program [67]. The PGIC has been recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials [68] and is widely used in chronic pain research [67,69].

Measure of Interpretation Bias for Pain

Interpretation bias will be measured using an adapted version of the computerized interpretation bias task [70], which contains 16 vignettes that describe 8 ambiguous situations that may be interpreted as relating to bodily threat or pain and 8 ambiguous social situations. Vignettes were adapted to reflect events that may occur in the workplace, home, or during an adult's everyday life. Participants will be instructed to imagine themselves in the situation, and after reading each ambiguous scenario, they will be offered end words that resolve the situation in a benign or negative manner. Participants will then rate whether each resolution came to their mind on a scale of 1 (*does not pop into my mind*) to 5 (*definitely pops into my mind*) and select the interpretation (word) that most easily popped into their head. Next, participants will be presented with the same scenarios again; however, this time, they will be asked to rate the likelihood that each resolution would actually happen in that situation on a scale of 1 (*not likely*) to 5 (*very likely*). Finally, participants will select the word that they believe is most likely to end the sentence. All items and interpretations will be presented in a fixed random order to ensure all participants view the same order of items and response choices. Studies using this task have found evidence of interpretation bias in relation to pain in individuals with chronic pain [71].

Additional Measures

Measure of Attentional Control

Attentional control will be assessed using the Attentional Control Scale (ACS). The ACS [72] is a 20-item self-report questionnaire used to measure attention focusing and attention shifting. The questionnaire is adapted by including a 7-day time frame for the items. Items are scored on a 4-point Likert scale from 1 (*almost never*) to 4 (*always*), with scores ranging from 20 to 80. Higher scores indicate a better ability to direct and maintain attention. The ACS has been found to have good reliability, with a Cronbach α of .81 [10] and good concurrent validity [72].

Personality Characteristics

Personality traits will be measured using the Behavioral Inhibition System (BIS) and Behavioral Activation System (BAS) scales [73], a 20-item self-report questionnaire that measures trait sensitivity levels of the BIS (punishment; 7 items) and BAS (reward; 13 items). The scales are scored on a 4-point Likert scale ranging from 1 (*strongly disagree*) to 4 (*strongly agree*). Meyer et al [74] found that internal consistency ranged from acceptable to good for the BIS and BAS scales. Test–retest reliability over 2 months was acceptable for both scales [73].

Pain-Related Worrying

Participants' pain-related worrying [75] will be assessed using the Pain Catastrophizing Scale (PCS) [76]. The PCS is a 13-item self-report measure that evaluates 3 subscales: rumination, magnification, and helplessness. Using a 5-point Likert scale,

ranging from 0 (*not at all*) to 4 (*all the time*), participants will be asked to recall past painful experiences and indicate the extent to which 13 thoughts or feelings are associated with these experiences. The 3 subscale scores are summed to provide a total score for pain catastrophizing, which ranges from 0 (*low degree of catastrophizing*) to 52 (*high degree of catastrophizing*). The PCS has been found to have good validity and reliability for individuals with chronic pain [76,77].

Pain-Treatment Information

At the posttraining and 1-month follow-up assessments, there will be a question that probes participants' pain treatments and frequency of health care use since the commencement of the study or previous assessment.

Manipulation Check

At the posttraining assessment, there will be a manipulation check question asking participants which training condition they believe they had received (ABMT or sham training).

Validity Check

As recommended by Oppenheimer et al [78], instructional questions will be included in the pre- and posttraining surveys (eg, please select *5=Always*) to identify careless responding patterns. Participants will be excluded if they answer all instructional questions incorrectly.

Data Management and Monitoring

Owing to the minimal risks associated with study participation, it is not necessary to implement an independent data and safety monitoring board. The research team will be responsible for monitoring and data management and will meet regularly to manage the protocol, monitor recruitment, and deal with any adverse events. The reporting of this study will be conducted according to the CONSORT (Consolidated Standards of Reporting Trials) statement guidelines [79].

All data will be collected via the web using Qualtrics (Provo) for survey responses and Inquisit 6.4 for task data and self-reported engagement responses, and temporarily stored on these servers. Data safety and security measures have been considered, including restricted access to the research team, password protection, firewall, and virus protection. Furthermore, each participant will be assigned a unique participant code (blinded to the group the participant has been assigned to) and will be asked to self-generate an ID code (instead of participants' personal information). Thus, this coded data may be reidentifiable during the research but will be deidentified upon completion of the study. An electronic, password-locked master file will be created that matches the unique participant code to their self-generated code to ensure participants are allocated to the correct experimental group and that the survey and task data match across the different time points. All data will be stored on a secure password-protected university server and accessed only by the research team. Upon completion of the project, electronic research data will be deposited in the university's research data storage system and retained for a minimum of 15 years. The final coding scheme for outcome measures will be available from the authors upon request.

On the basis of previous similar trials, no adverse events are expected [10]. A small amount of fatigue and some mild discomfort during the training task may be experienced. This will be managed by providing participants with enough rest periods between blocks of trials. If the research team becomes aware of any harm or other adverse events, it will be documented and reported appropriately. The research team will also manage any risks and recommend participants to liaise with relevant services, such as psychological assistance, if appropriate. The study will be stopped if evidence emerges that participants can come to harm because of the ABMT intervention.

Sample Size Estimation

To the best of our knowledge, there are no similar published studies on gamified pain ABMT or ABMT for adults with chronic pain that directly compare 3 groups (ie, control ABMT, standard ABMT, and gamified ABMT); therefore, there is no previous effect size on which to base a sample size estimation. As such, a minimum sample size of 30 per training group is planned on the basis that this exceeds the sample size determined by several similar pain ABMT and gamified training studies [7,10,80]. Sharpe et al [7] determined that a sample size of 12 per group was enough to achieve 82% power with a significance level of .05 for their study of ABMT in adults with chronic pain that compared 2 groups (ABMT vs placebo), for which a medium effect size (Cohen d=0.45) on pain interference was found in the intervention group (ABMT: n=22; placebo: n=12). Heathcote et al [10] determined a sample size of 20 per group for their study of ABMT in adolescents with chronic pain that compared 3 groups (ie, ABMT, placebo, and waitlist). Boendermaker et al [80] observed in their study, which involved a sample size of <20 per group, that gamified cognitive bias modification training (for alcohol problems) had a positive impact on motivation to train compared with regular training. Considering attrition rates of previous trials in chronic pain treatment [81] and given the 1-month follow-up measurement, a dropout rate of approximately 30% is expected for the current trial. Therefore, a total target sample size of 120 participants (40 participants per group) will be sought. To help achieve adequate participant enrollment, we developed engaging recruitment materials and selected multiple channels for delivery.

Statistical Methods

Overview

Statistical analyses will be conducted after data collection is completed using the SPSS version 27.0 or later (IBM Corp). Continuous data will be presented as means and SDs, whereas categorical data will be presented as frequencies and percentages. Analyses will follow the intention-to-treat principle and will include all randomized participants who successfully complete at least one training session (ie, minimum threshold exposure to ABMT). To determine whether there are any pretraining differences between the training conditions on demographic variables and baseline characteristics, a series of analyses will be performed. The rates of and reasons for missing data will be reported. To manage missing data, the study will attempt to follow-up on all randomized participants (even if

they withdraw from the trial) and, where appropriate, use multilevel modeling for repeated measure data analyses as it allows the incorporation of all available data. Significance for all statistical tests will be set at P<.05 (2-tailed). Effect sizes will be presented by its most appropriate effect size (and 95% CI), as described by Lakens [82], with a preference for Cohen d where possible [83]. No interim analyses of the trial outcome data are planned.

Symptom Measures

To determine symptom changes (ie, pain intensity, pain interference, anxiety, and depression) in the different training conditions, multilevel modeling analyses will be conducted. For each model, the time point (level 1 units) will be nested within participants (level 2 units). The variable time for each symptom measure will have 3 levels (ie, pretraining, posttraining, and 1-month follow-up), with pretraining as the reference point. The control group (control ABMT) will serve as a reference group for comparisons between the groups over time. A model-building procedure [84] will be used to build the most parsimonious model to test the hypotheses, using the Akaike information criterion (AIC) to identify the most appropriate model. All models will be computed using maximum likelihood estimation.

Engagement Measures

To examine changes in task-related engagement in different training conditions, a multilevel modeling analysis will be conducted. The time point (level 1 units) will be nested within participants (level 2 units). The variable time will have 6 levels (ie, after sessions 1, 2, 3, 4, 5, and 6). A model-building procedure [84] will be used to build the most parsimonious model to test the hypotheses, using the AIC to identify the most appropriate model. The model will be computed using maximum likelihood estimation. To analyze the impact of gamification on interest and enjoyment, a 1-way analysis of variance will be performed. Missing values will be handled using multiple imputations.

Regarding behavioral engagement, Kaplan-Meier survival curves [85] will be calculated to assess the time at which attrition occurred in each training condition and compared statistically using a log-rank test. Participants will be classified as noncompleters if they do not complete all 6 training sessions. Finally, a 1-way analysis of variance will be performed to determine whether there are differences in the mean number of sessions completed between the training conditions.

Cognitive Measures

To determine changes in attentional bias and interpretation bias in the different training groups, multilevel modeling analyses will be conducted. For each model, the time point (level 1 unit) will be nested within participants (level 2 units). The variable time for each cognitive measure will have 2 levels (ie, pre- and posttraining), with pretraining as the reference point. The control group (control ABMT) will serve as a reference group for comparisons between the groups over time. A model-building procedure [84] will be used to build the most parsimonious model to test the hypotheses, using the AIC to identify the most appropriate model. All models will be computed using maximum

likelihood estimation. In addition, Pearson correlations will assess the relationship between changes in attentional bias magnitude from pre- to posttraining and changes in scores on symptom measures (ie, pain intensity, pain interference, anxiety, and depression).

Perceived Improvements

To determine changes in perceived improvement in the different training groups, a multilevel modeling analysis will be conducted. The time point (level 1 units) will be nested within participants (level 2 units). The variable time will have 2 levels (ie, posttraining and 1-month follow-up), with posttraining as the reference point. The control group (control ABMT) will serve as a reference group for comparisons between the groups over time. A model-building procedure [84] will be used to build the most parsimonious model to test the hypothesis, using the AIC to identify the most appropriate model. The model will be computed using maximum likelihood estimation.

Exploratory Analyses and Subgroup Analyses

Additional exploratory and subgroup analyses will be performed to explore the role of engagement metrics (ie, number of training sessions completed) and individual differences (ie, attentional control, pain-related worrying, personality characteristics, and recruitment setting [clinical vs nonclinical]) in the impact of training conditions on the primary outcomes. These analyses will be conducted using appropriate statistics and are subject to the final sample size and power.

Ethics and Dissemination

This trial has been approved by the human research ethics committees of the Royal Brisbane and Women's Hospital and Queensland University of Technology and registered on the Australian New Zealand Clinical Trials Registry, ACTRN12620000803998, version 1.0, approved on August 10, 2020. All participants will provide informed consent electronically before inclusion in the trial. Of note is that participants will not be provided information about the 3 training conditions (ie, control ABMT, standard ABMT, and gamified ABMT). They will be informed that the aim of the study is to test whether a novel psychological program can reduce chronic pain and improve pain-related health outcomes and that they will be randomly assigned to either receive the intervention or complete a similar task (the control group). In doing so, participants will remain blinded to their allocation, as it would be easy to realize whether they are in the *active* gamified group or not (and noting that the control group does not include game-like features). Participants will be debriefed at the conclusion of their study involvement. Participants who received the intervention will no longer have access to the computerized task. Participants in the control ABMT condition will be offered the opportunity to perform the standard ABMT training. No data will be collected, used, or analyzed during that time. At the completion of the final session, the participants will no longer have access to the intervention.

Any modifications to the study protocol will be recorded and communicated with the human research ethics committees and the clinical trial registry. The final data set will be accessible to approved members of the research team. The results of this trial will be reported in the form of a doctoral research thesis (for JFV) and published in a peer-reviewed journal and presented at conferences. No professional writers will be used. A lay summary of the outcomes and results of the study will be made available to the participants.

Results

Ethics approval for this study was granted by the human research ethics committees of the Royal Brisbane and Women's Hospital in April 2020 and Queensland University of Technology in September 2020. Study recruitment commenced in August 2021 and is ongoing. Data collection and analysis are expected to be concluded by October 2022 and January 2023, respectively. The results of this study are expected to be published in mid-2023.

Discussion

Study Contributions

This protocol describes a randomized, double-blind, placebo-controlled trial aimed at evaluating the effects of a gamified web-delivered ABMT intervention on pain intensity, pain-related outcomes, cognitive biases, behavioral and self-reported engagement, and perceived improvement in a sample of adults with chronic musculoskeletal pain. The use of gamification in such programs may have the potential to keep participants engaged and motivated in the sustained and repeated use of the task as well as increase retention.

To our knowledge, this is the first study to evaluate the effects of gamification techniques in a pain ABMT intervention. This study will provide important information on the potential therapeutic benefits of gamified pain ABMT programs and shed light on the motivational influences of certain game elements in the context of pain. If results support its effectiveness, this novel, web-delivered, easy-to-administer cognitive program could open new avenues for alleviation of pain suffering, thereby improving the quality of life for these individuals and their families. This is especially significant considering that chronic pain affects between 19% and 31% of the population worldwide [86-88]. Finally, the expected findings will provide novel contributions to the knowledge base and understanding of chronic pain. This, in turn, may open new directions for therapeutic interventions.

Strengths and Limitations

This study has significant strengths. First, findings from the 3-arm randomized controlled trial design, with the inclusion of a nongamified version of the intervention, will allow us to determine whether the addition of game elements leads to increased motivation, engagement, and intervention efficacy. Further strengths of the study include (1) the rigorous, well-designed, and prespecified study protocol that has been reported as per SPIRIT [23] guidelines and preregistered on a clinical trial registry; (2) the use of an empirically supported set of pain-relevant word stimuli; (3) the inclusion of self-report and behavioral measures of engagement as a primary outcome; (4) the large chronic pain sample drawn from clinical and

nonclinical settings; and (5) the inclusion of a 1-month follow-up assessment.

Despite its strengths, this study also has limitations. First, although restricting our sample to individuals with chronic musculoskeletal pain strengthens the methodology of the study, this may limit the generalizability of the results to other types of chronic pain conditions. However, at this early stage in investigating the impact of game elements on ABMT, we believe that the advantages of researching a homogeneous sample outweigh the benefits of a heterogeneous sample. Second, the current ABMT approach provides limited control over the environment under which ABMT will be completed, which could potentially affect the results. However, again, the use of a web-based delivery mode was an informed choice. There is an increasing need and demand in society for remote delivery

and access to health treatments, which has been highlighted by the current COVID-19 pandemic [89] and isolation environment and is also of particular benefit to those living in regional and remote areas. With the move to web-based administration and the resulting reduction in face-to-face interpersonal interaction, there may arguably be an even greater need for these interventions to include features such as gamification to facilitate engagement and continued motivation to self-administer such tasks. Finally, the use of the dot-probe task will only allow us to provide a static snapshot of the dynamic attentional process that unfolds over time [6]. Currently, web-based measures investigating how attentional dynamics resolve over time are not yet widely accessible; therefore, we opted for the dot-probe assessment paradigm, as it is frequently used in web-based attentional bias research [9].

Acknowledgments

Authors' Contributions

The authors JFV, MJW, DJ, GC, and DMLVR made substantial contributions to the conception and design of the study protocol, which is being conducted as part of JFV's PhD program. JFV drafted the protocol manuscript, and the other authors provided critical feedback and revisions. DMLVR developed the Inquisit tasks for this study. All authors read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ABMT: attentional bias modification training
ACS: Attentional Control Scale
AIC: Akaike information criterion
BAS: Behavioral Activation System
BIS: Behavioral Inhibition System
CONSORT: Consolidated Standards of Reporting Trials
GCPS: Graded Chronic Pain Scale
PCS: Pain Catastrophizing Scale
PGIC: Patient Global Impression of Change
PROMIS: Patient-Reported Outcomes Measurement Information System
RT: reaction time
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

Protocol

A Novel, Scalable Social Media–Based Intervention ("Warna-Warni Waktu") to Reduce Body Dissatisfaction Among Young Indonesian Women: Protocol for a Parallel Randomized Controlled Trial

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Abstract

Background: Despite the prevalence of body dissatisfaction among young Indonesian women and its consequential negative impacts, there are currently no evidence-based, culturally appropriate interventions to tackle this issue. Therefore, there is a need to develop scalable, cost-effective, and accessible interventions to improve body image among this population.

Objective: This paper describes the study protocol of a parallel randomized controlled trial to evaluate the effectiveness of *Warna-Warni Waktu*, a social media–based intervention that aims to reduce state and trait body dissatisfaction and improve mood among young Indonesian women aged 15-19 years.

Methods: The trial will take place online. Approximately 1800 young women from 10 cities in Indonesia, evenly split across the ages of 15-19 years, will be recruited via a local research agency's established research panel. Participants will be randomly allocated to the intervention condition or a waitlist control condition. The intervention consists of six 5-minute videos, with each video supplemented with up to five brief interactive activities. The videos (and associated activities) will be delivered at a rate of one per day across 6 days. All participants will complete three self-report assessments: at baseline (Day 1), 1 day following the intervention (Day 9), and 1 month following the intervention (Day 36). The primary outcome will be change in trait body dissatisfaction. Secondary outcomes include change in internalization of appearance ideals, trait mood, and skin shade satisfaction. Intervention effectiveness on these outcomes will be analyzed using linear mixed models by a statistician blinded to the randomized condition. Intervention participants will also complete state measures of body satisfaction and mood before and after watching each video to assess the immediate impact of each video. This secondary analysis of state measures will be conducted at the within-group level.

Results: Recruitment began in October 2021, with baseline assessments underway shortly thereafter. The results of the study will be submitted for publication in 2022.

Conclusions: This is the first study to evaluate an eHealth intervention aimed at reducing body dissatisfaction among young Indonesian women. If effective, the intervention will be disseminated to over half a million young women in Indonesia via Facebook, Instagram, and YouTube.

Trial Registration: ClinicalTrials.gov NCT05023213; https://clinicaltrials.gov/ct2/show/NCT05023213

International Registered Report Identifier (IRRID): PRR1-10.2196/33596

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Introduction

Body dissatisfaction, defined as the subjective experience of negative thoughts toward one's own body [1], is a growing concern among young people globally [2]. Young women are disproportionately affected compared to young men [3-5]. Although research in Asia is currently limited, cross-cultural research suggests that the prevalence of body dissatisfaction among young people in some Asian countries such as Malaysia, China, and Japan is similar to, if not greater than, that of English-speaking countries [6-8].

Body dissatisfaction is not benign. Extensive research has established that body dissatisfaction is associated with numerous adverse health outcomes. Longitudinal research has found body dissatisfaction to predict eating disorders [9,10], depressive mood and low self-esteem [11], less engagement in exercise [10], and increased risky health behaviors such as drug use and smoking [12]. Research also indicates associations between body dissatisfaction and the desire for cosmetic surgery [13,14], and the avoidance of everyday activities such as participating in school activities or attending classes [15,16]. Although the bulk of this research has been concentrated within English-speaking populations, similar associations are emerging globally, including across Asia [6,17-20].

Indonesia is an upper-middle-income country in Southeast Asia and is the world's fourth most populous country [21]. In the Indonesian context, research shows that more than half of young women experience at least some dissatisfaction with their appearance (unpublished data compiled by the authors KG, NC, LS, and PD, 2021) [22]. Body dissatisfaction among young Indonesian women is linked with disordered eating behaviors [23], including food restriction and avoidance, emotional eating, and excessive exercise (unpublished data by authors KG, NC, LS, and PD, 2021). Further, young Indonesian women report body dissatisfaction specifically with regard to their skin shade [24,25], due in part to the dominant pan-Asian ideal prevalent across Asia, which emphasizes light skin shades [26]. In other populations (eg, India), skin shade dissatisfaction has been associated with the use of potentially harmful skin fairness products [27], lower self-esteem [28], and, unsurprisingly, general body image concerns [28]. As such, ameliorating body dissatisfaction, including skin shade dissatisfaction, among young women in Indonesia is required. Yet, no published evaluations of interventions targeting body dissatisfaction in Indonesia exist.

The creation and dissemination of mental health prevention efforts and interventions across low- and middle-income countries (LMICs), including Indonesia, face cultural-specific obstacles, primarily social stigma connected to mental health concerns, coupled with a lack of mental health professionals and the limited capacity of general health professionals in providing effective mental health treatment [29,30]. Although Indonesia has seen a modest increase in mental health interventions for adolescents in school settings in recent years [31-33], evidence suggests that implementation is not commonplace [34], thus highlighting the need for the dissemination of educational mental health content outside the school system. Digital interventions present a solution to circumvent barriers to dissemination, and have been shown to have similar effectiveness as face-to-face psychotherapeutic interventions [35]. Digital interventions are relatively low in cost, easily accessible, and universally available, thereby meeting three key criteria for overcoming LMIC-specific challenges [36,37]. Further, private, remotely accessible mental health interventions have been shown to increase the likelihood of engagement in help-seeking due to the reduced fear of stigma [38].

eHealth interventions have the potential to reach many young people in Indonesia; according to the Indonesian Internet Providers Association, over 90% of adolescents aged 15-19 years have access to the internet across the country [39]. Moreover, research indicates that young people are already using the internet to seek information [40,41]. Thus, it is perhaps unsurprising that eHealth interventions for mental health have shown preliminary acceptability among young people in Indonesia. For example, eHealth interventions for depression prevention and/or treatment have been well received, with young people showing a willingness to engage with such interventions [42,43].

Social media offer unprecedented capabilities to disseminate mental health interventions cost-effectively and at scale [44], and may be particularly popular with young people. Social media interventions afford unique opportunities to overcome barriers such as cost, geographic distance, and stigma, as they allow for a certain degree of privacy and anonymity. Emerging research suggests that using social media in Indonesia as a vehicle for eHealth interventions shows promise among young people [45,46]. Thus, the combination of the rise in eHealth initiatives for adolescents in LMICs [47] and the notable uptake in social media usage among young people in Indonesia in recent years [48,49] have created a ripe environment for the development of a social media–based intervention to address body dissatisfaction among young Indonesian women. Furthermore, research consistently shows the social media environment in general to be problematic for young people's body image [50,51], due in large part to the objectification and idealization of women's bodies. As such, hosting an intervention to reduce body dissatisfaction on social media may be additionally beneficial in disrupting the harmful effects these sites have been shown to have. Increasingly, the potential for positive content on social media is being explored, which has highlighted the benefits of some types of content on mood and body satisfaction [52,53].

This paper outlines the development and protocol for the evaluation of the first social media–based intervention to target body dissatisfaction among young women in Indonesia, named *Warna-Warni Waktu* (English translation: Colorful Time Travel). The intervention was developed by the academic authors of this paper in collaboration with Girl Effect, an international nonprofit organization that builds media content aiming to arm girls with the skills to make positive choices and changes in their lives during the critical years of adolescence; the Dove Self-Esteem Project, the social mission for Unilever's personal care brand, Dove; Percolate Galactic, an Indonesian-based creative agency that specializes in marketing for youth; and young Indonesian women. The intervention consists of a series of six videos, each approximately 5 minutes long. To disseminate the intervention, the videos will be sequentially delivered to young women in Indonesia through targeted social media marketing on Facebook and Instagram, in addition to being made freely available on YouTube. On Facebook and Instagram, the videos will appear on young Indonesian women's feeds, consistent with other social media advertisements. The series tells the fictitious story of a young woman named Putri who learns strategies to resist appearance pressures across adolescence and young adulthood through the help of animated time travelers, who are on a quest to save the world from appearance-related pressures. The intervention is based upon mounting evidence that psychoeducation, in particular discussing the nature, causes, and consequences of body dissatisfaction, is an effective change technique to reduce body dissatisfaction [54]. Further, the intervention's videos model behaviors to reduce appearance pressure and teach media literacy skills, two further change techniques that have shown efficacy in reducing body dissatisfaction in previous studies [55-57].

The videos target three sociocultural influences of body dissatisfaction, based on the Tripartite Influence Model of body dissatisfaction [58], namely, the media, friends, and family. The Tripartite Influence Model postulates that body dissatisfaction increases via the impact that these sociocultural influences have on two psychological processes: internalization of appearance ideals and social comparisons. These two psychological processes are also addressed directly in the videos by providing media literacy education and examining the consequences of making appearance-based social comparisons. As such, we anticipate that the intervention will reduce body dissatisfaction through diminishing an individual's perceived appearance pressure from the media (including social media), friends, and family members, which in turn will reduce their internalization of appearance ideals and the likelihood of making social comparisons.

The potential impact of the videos is further bolstered through supplementary activities, which again will be disseminated to young Indonesian women via sequential social media marketing. Each video is accompanied by interactive activities, which aim to reinforce the lessons learned in each video. Research consistently shows that elements of active learning (ie, taking control of one's own learning through metacognitive sense-making, self-assessment, and reflection [59]) results in deeper learning [60] and higher engagement levels [61]. Further, eliciting cognitive dissonance has been shown to be a key change technique in reducing body dissatisfaction [54]. As such, active learning activities based upon cognitive dissonance were built into the intervention to be delivered between each video. These include activities such as story completion, self-reflection, writing challenges, and word searches. Details of each activity, along with a breakdown of each video's content, are outlined in Textbox 1.

Textbox 1. Intervention summary.

Video One: Time to Turn Back Time

Key messages:

- People face pressure to look a certain way.

- Pressure comes from the media, as well as from those around us.

- Appearance pressures are associated with body dissatisfaction and can hold us back from living a fulfilling life.

- Strategies can be learned to resist and challenge appearance pressures.

Reinforcer activities:

- Review definitions of key terms in five short videos. Using some of the key terms, explain why the time travelers want Indonesian girls to feel confident about their bodies.

Video Two: That's Fake! (targeting social media)

Key Messages:

- The media often portray just one narrow appearance ideal.

- Images of people in the media are often edited to make the person look more like the appearance ideal.

- The media set an unrealistic appearance standard in order to sell us products.

- We can curate our own media environment to reduce the appearance pressures that we face.

Reinforcer activities:

- Describe your experience of coming across advertisements that promote unrealistic beauty products to help others become more aware.

- Share the transformation video clip seen in this episode on social media, and explain why it is important your friends and followers watch it.

- An edited and unedited image is provided. Identify and list all the edits made to the image.

- Watch the video Putri saw advertising skin-lightening cream, and critically examine its messages about the lifestyle the advert is trying to sell. Share your experience buying (or thinking about buying) a product that you thought would improve your popularity or lifestyle.

- Your Own Words activity: Write about why skin-lightening products are problematic.

Video Three: C'mon, Break the Chain of Comparisons (targeting appearance-based comparisons)

Key messages:

- Appearance-based comparisons are common.

- Engaging in appearance-based comparisons is unhelpful and damaging to body image.

- Focusing on what your body can do, rather than how it looks, is a more helpful way to think about your body.

Reinforcer activities:

- Write a sentence or two on why you appreciate your friends, describing things that have nothing to do with appearance.

- Complete the comic strip: In the context of appearance-based comparisons among friends, explain why appearance-based comparisons are not helpful or necessary.

- Your Own Words activity: Write about all the things you love about your friends that have nothing to do with appearance.

Video Four: Stand up to Appearance-Based Comments (targeting appearance-based teasing)

Key messages:

- Comments from friends and family about our appearance can be hurtful, even if well-meaning.

- Challenging such comments in a nonconfrontational way can prevent future comments from family members, alleviating appearance pressures.

Reinforcer activities:

- Write a short response to a negative appearance-based comment received from a friend or family member.

- Word search: Find 10 hidden example phrases of how to respond to appearance-based comments.

- Complete the comic strip: How to respond to boys teasing girls about their appearance.

- Your Own Words activity: Write about how to stand up to appearance-based comments.

Video Five: Be Your Own Best Friend! (targeting body talk)

Key messages:

- Negative body talk is harmful to our body image.

- Creating a mantra to repeat to oneself instead of getting caught up in negative self-talk is an effective strategy to break the cycle of negative body talk.

Reinforcer activities:

- Create a mantra that can boost your confidence.

- List things that your body allows you to do.

- Your Own Words activity: Write about your mantra, sharing why you created it and what it means to you.

Video Six: The Color of the Future

Key messages:

- By challenging appearance pressures in everyday life, we can reach our full potential.

- The additive impact of resisting and challenging appearance pressures is large, not only for the individual but also for wider society.

Reinforcer activities:

- Watch a short video of Putri sharing the four key lessons she learned throughout her journey. Identify which lesson is most important to you and why.

- Commit to sharing an unedited photo on social media doing something you love.

In addition to detailing the intervention and its development, this paper describes the evaluation protocol for assessing the effectiveness of the intervention among young Indonesian women aged 15 to 19 years through a parallel, two-arm (intervention vs waitlist control) web-based randomized controlled trial (RCT). The decision to utilize a waitlist control condition was informed by recommendations from a National Institutes of Health expert panel [62]. Specifically, it is recommended that the rationale for a comparator group should rest on the primary purpose of the trial. Thus, given that the primary interest of this study was the absolute impact of the intervention rather than the relative impact, and that usual care for body dissatisfaction in Indonesia is no care at all, a waitlist control condition was deemed most appropriate for this purpose. Our hypotheses for this research are: (1) participants randomized to the intervention condition will experience reduced body dissatisfaction, internalization of appearance ideals, and skin shade dissatisfaction, as well as improvements in mood, at postintervention and 1-month follow-up, relative to the waitlist control condition; (2) each video in the *Warna-Warni Waktu* series will elicit immediate state-based improvements in body satisfaction and mood; and (3) greater engagement and adherence in the *Warna-Warni Waktu* intervention will result in greater reductions in body dissatisfaction, internalization of appearance ideals, and skin shade dissatisfaction, as well as greater improvements in mood. This analysis will be exploratory in nature, depending on the participants' engagement and adherence in the intervention during the trial.

Methods

Study Design

The study is a two-arm parallel RCT with an intervention group and a waitlist control group. Randomization will be performed as block randomization with a 1:1 allocation. Participants in the intervention condition will receive the *Warna-Warni Waktu* intervention over a period of 6 days. Participants in the waitlist control condition will receive a link to the *Warna-Warni Waktu* series at the end of the trial. The protocol was designed in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (Multimedia Appendix 1).

For the trial, the videos will not be distributed to recruited participants via social media. Rather, the intervention will be recreated for distribution via Qualtrics software. Six Qualtrics links will be developed, one for each video and its corresponding supplementary activities, and sent to participants daily over a 6-day period. The trial has been designed in this way so that there is an accurate log of intervention adherence at the individual level, an important consideration when evaluating web-based interventions [63]. Careful consideration was given to ensure that the intervention was accurately produced on Qualtrics to appear as closely as possible to how it will look when it is disseminated on social media in the future (see Multimedia Appendix 2).

The Intervention

The intervention *Warna-Warni Waktu* was developed over a 20-month period, from October 2019 to May 2021. Textbox 2 presents the intervention development steps taken, which involved close collaboration among body image academics, a creative agency, social media specialists, a nonprofit organization, as well as an industry funder. The intervention development team consisted of numerous women with lived experience of Indonesian culture; namely, five of the six core team members from the creative agency (Percolate Galactic) were young Indonesian women between the ages of 25 and 30. The wider team also consisted of two female Indonesian

pediatricians (authors KN and BM), who have lived experience of the culture as well as daily contact with young Indonesian women through their work. Finally, the team included an Indonesian Professor of Women's Studies (LS). Further, the process involved three rounds of feedback from young Indonesian women at various stages of development to create an intervention that is both for, and created with, young Indonesian women. The final intervention comprises 6 videos between 4 and 5 minutes each (see Figure 1) and 18 interactive reinforcer activities, ranging from approximately 2 to 10 minutes each in length (see Figure 2 for examples). All content is delivered to young women in Bahasa Indonesia, the official language of Indonesia. The activities encourage the target audience to reflect and apply the learnings from the videos to their own lives (Textbox 1).

Textbox 2. Intervention development stages.

Literature review: October 2019-January 2020

- Common appearance concerns among young Indonesian women include feeling pressure about their weight [64,65], skin shade [25], and skin complexion [66].

- Prominent sources of appearance pressure contributing to negative body image among young Indonesian women were identified as cyberbullying [67,68], appearance comparisons [66], and social media [66].

- eHealth interventions in low- and middle-income countries are increasing in number [47] and are acceptable among young people in Asia [69-72].

Secondary data analysis: December 2019-April 2020

- Secondary data analysis was conducted on data collected from 318 Indonesian girls and young women who participated in The Dove Global Girls Beauty and Confidence Report [73], corroborating the literature review results and further identifying internalization of appearance ideals and self-esteem as important influences of body image concerns (unpublished data of the authors KG, NC, LS, and PD, 2021).

U-Report poll on appearance-related concerns: February 2020

- In collaboration with UNICEF Indonesia, a U-Report poll was conducted among 1441 young women from all 34 Indonesian provinces for an up-to-date assessment of the role body image plays in the lives of young people.

- More than three-quarters of young women wanted to change something about their appearance, and nearly half reported that worrying about their appearance prevented them from doing things they would like to do. Nearly all young women reported that they would like to learn ways to improve how they feel about their appearance [74].

Focus groups: March 2020

- Each of the six focus groups (one face-to-face and five online due to the COVID-19 pandemic) consisted of five or six girls aged 13-18 years from Jakarta province.

- Appearance-based teasing and comments as well as pressure from social media (particularly influencers) were identified as prominent sources of appearance pressure.

- Positive body image traits (such as valuing body functionality and defining beauty broadly, beyond physical appearance) were identified.

Intervention's key messages: April-August 2020

- Four risk factors for the development of body image concerns were identified: (1) social media and influencers, (2) appearance-based comparisons, (3) appearance-based teasing, and (4) body talk.

- It was decided to reinforce the positive body image traits throughout the intervention identified during the aforementioned focus groups.

Mode and format of delivery: April-August 2020

- Storytelling was chosen as the mode of information delivery, as narrative health education is proven to be effective [75] and engaging, even among those with low health literacy [76]. (See Multimedia Appendix 3 for a synopsis of the intervention's narrative).

- Videos were chosen as the intervention format to deliver the core messages owing to their efficiency in delivering content information (see Media Richness Theory [77]) and ability to pique an audience's attention and interest [78].

- Interactive activities to reinforce the key messages learned during the videos were added to elicit cognitive dissonance, an effective change technique seen throughout the body image intervention literature [79,80].

Concept creation: August 2020-January 2021

- Two storyboard concepts were considered: time travel and a detective-based storyline. Time travel was selected given the ability of this concept to convey the additive impact of body image concerns to young people.

- A combination of animated characters and real people was used, as cartoon characters in health intervention studies have been shown to be acceptable to younger and older adolescents [81-83], as is the combined use of cartoon characters and real people [84].

- The plot and story details were drafted and refined over several collaborative discussions among the various project stakeholders.

- Body image change techniques (including those based on psychoeducation and media literacy [54]) were embedded within the video narrative.

- Six time travel–based videos (ie, one for each target risk factor, plus introductory and concluding videos) were drafted using storyboards and basic animation.

U-Report poll on appearance-based teasing: January 2021

- A second U-Report poll with 240 young women was conducted to provide clarity as to how appearance-based teasing presents among young people in Indonesia.

- Poll results provided direction on how to address appearance-based teasing, showing that it is prevalent both online and face-to-face, and that teasing toward young women usually comes from other women, either from friends or family members [85].

Cocreation of videos with the target audience: February 2021

- Findings on rough animated versions of the videos from four online focus groups with young women aged 15-19 years (N=16) showed strong comprehension, acceptability, and enjoyment of the videos.

- The young women provided direction regarding appropriate terminology to aid comprehension within their age group.

Casting, scripts, props, sets, filming: February-March 2021

- Detailed scripts were written, casting auditions held, sets and props sourced, and decisions on futuristic details such as makeup and style were decided.

- Accurate representation of the diverse Indonesian population through the actors and animated characters involved ensuring that various ethnicities, skin shades, hair textures, distinct types of religious dress, body sizes, and regional accents were included.

- The videos were filmed. Numerous alternative versions were shot for scenes considered potentially problematic for comprehension so that options were available to explore with young women, if necessary.

Development of activities: February-April 2021

- Activities were developed to allow users to practice the information learned and/or to reflect on their own cognitions and behaviors in light of the video content.

- The team was guided by Girl Effect and Percolate's prior experience of disseminating similar interactive content for other health campaigns, as well as the body image scholars' expertise in effective change techniques.

- Eliciting cognitive dissonance throughout the activities was prioritized, for example, by asking users to speak out against appearance ideals, challenge body talk, and stand up to those bullying based on appearance.

Acceptability testing of the complete intervention: April 2021

- Six online focus groups of young women aged 15-19 years (N=36) were conducted to assess intervention acceptability and comprehension, revealing strong acceptability, comprehension, and enjoyment of the videos and activities (see the Intervention Acceptability section).

- No issues with comprehension were identified, and thus no alternative scenes were required.

Final intervention edits: May 2021

- Based on focus group feedback, minor edits were made to the instructions for the activities, which focused on making the tone less formal and enhancing comprehension.

Figure 1. The video thumbnails for each of the 6 episodes in *Warna-Warni Waktu*.

Figure 2. Example activities. The activity on the left asks users to identify the differences between an edited and unedited photo (Video 2, Activity 3). The activity on the right asks users to complete the comic strip with a comment about why appearance-based comparisons are unnecessary (Video 3, Activity 2).

Although the majority of the activities are short, four activities are more in-depth, which consist of writing up to 250 words expressively and/or self-compassionately about what they learned in the video, titled "Your Own Words." These activities were deemed important for participants to complete given the emerging evidence that expressive and compassion-based writing are effective at reducing body dissatisfaction across a range of settings [86,87]. As such, all participants in the trial that complete these activities will be entered into a competition to win Rp50,000 (approximately US $3.50) in mobile phone credit. The responses to this activity will be judged by two authors (KN and BM). Judging will be based upon the best response being (1) relevant, (2) of adequate length, (3) original, (4) potentially inspirational to other young women, and (4) sounding sincere/honest. This approach reflects how the intervention will be disseminated on social media, should the trial find it to be effective (ie, girls who engage with the intervention once disseminated will have the opportunity to submit their response to the writing task for the chance to win Rp50,000 in phone credit). This is a tried-and-tested method to improve engagement in activities that Girl Effect has used in previous health campaigns on social media.

Intervention Acceptability

In April 2021, the intervention underwent acceptability testing with 36 young women in six focus groups. All groups watched the entire series; however, to minimize participant burden, three groups completed the activities associated with Videos 1-3 and three groups completed the activities for Videos 4-6, providing acceptability feedback on each. The videos scored high on likeability: scores across the videos ranged from 4.44 to 5 (SD

0-0.98) on a 5-point Likert-type scale ranging from 1 (hated the video) to 5 (loved the video). Only one respondent reported not fully understanding one of the videos (Video Five: Be Your Own Best Friend); all other respondents reported full understanding of each video. This finding was corroborated with qualitative feedback from young women, whereby many successfully restated the key messages from each video.

Similar positive findings were found for each of the activities. Across all activities, likeability scores ranged from 4.42 to 4.89 (SD 0.32-0.90) on a 5-point Likert-type scale ranging from 1 (hated the activity) to 5 (loved the activity). The activities were understood by almost all the young women; 94.44%-100% of respondents reported fully understanding each activity. Again, comprehension was further identified through examination of the young women's qualitative responses to the activities, with the majority of participants responding in a way that exemplified the key messages learned. The authors were particularly keen to understand the likelihood of the target audience to complete the longer Your Own Words tasks. Findings showed that 95% of respondents reported that if they had the time, they would be interested in participating in these tasks.

Based on the acceptability findings, minor edits were made to the reinforcer activity instructions for greater clarity and comprehension. In addition, upon suggestion from the young women, less formal language was adopted to improve engagement. No changes were made to the design or format of the activities.

Study Setting

The web-based trial will be coordinated by a research agency based in Jakarta, Indonesia. The aim is to recruit young women from across 10 of the largest cities in Indonesia: Balikpapan, Bandung, Jakarta, Makassar, Manado, Medan, Palembang, Pontianak, Semarang, and Surabaya.

Eligibility Criteria

Inclusion criteria for participation include identifying as a young woman aged between 15 and 19 years (the target age group for the intervention); having their own mobile phone (to ensure participants receive the WhatsApp notifications regarding the study); and accessing Facebook or Instagram daily (so that the sample consists of those who are most likely to access and engage with the intervention when it is disseminated via social media channels in the future). Exclusion criteria include already following the Girl Effect brand (Springster) on any social media site or having ever accessed the Springster website prior to enrolment (to avoid contamination effects); and, if under 18 years of age, not having written consent from a parent or guardian.

Participant Recruitment and Procedure

The aim is to recruit 1800 young women aged 15-19 years via a local research agency's recruitment panel (ie, a database containing contact details of those who have previously taken part in research conducted by the agency and have agreed to be contacted with regard to future research), with the aim to recruit an equal number of participants from each age (ie, 15, 16, 17, 18, and 19 years of age). The CONSORT (Consolidated Standards of Reporting Trials) flowchart is provided in Figure 3. Women and men over the age of 40 years will be contacted via telephone and screened for whether they have a daughter within the eligible age range. If the respondent has more than one daughter in the age range, only one will be eligible to avoid possible contagion effects. The daughter who is the best fit in terms of reaching the age quota will be selected. If this does not distinguish which daughter is selected, the daughter with the birth date closest to the date of contact will be selected. If the respondent does not have a daughter between 15 and 19 years of age, the recruiter will enquire if they know another family with a daughter of this age. If so, the recruiter will request the telephone number of that family and contact them. Only one phone number will be requested per call.

Figure 3. Participant flowchart.
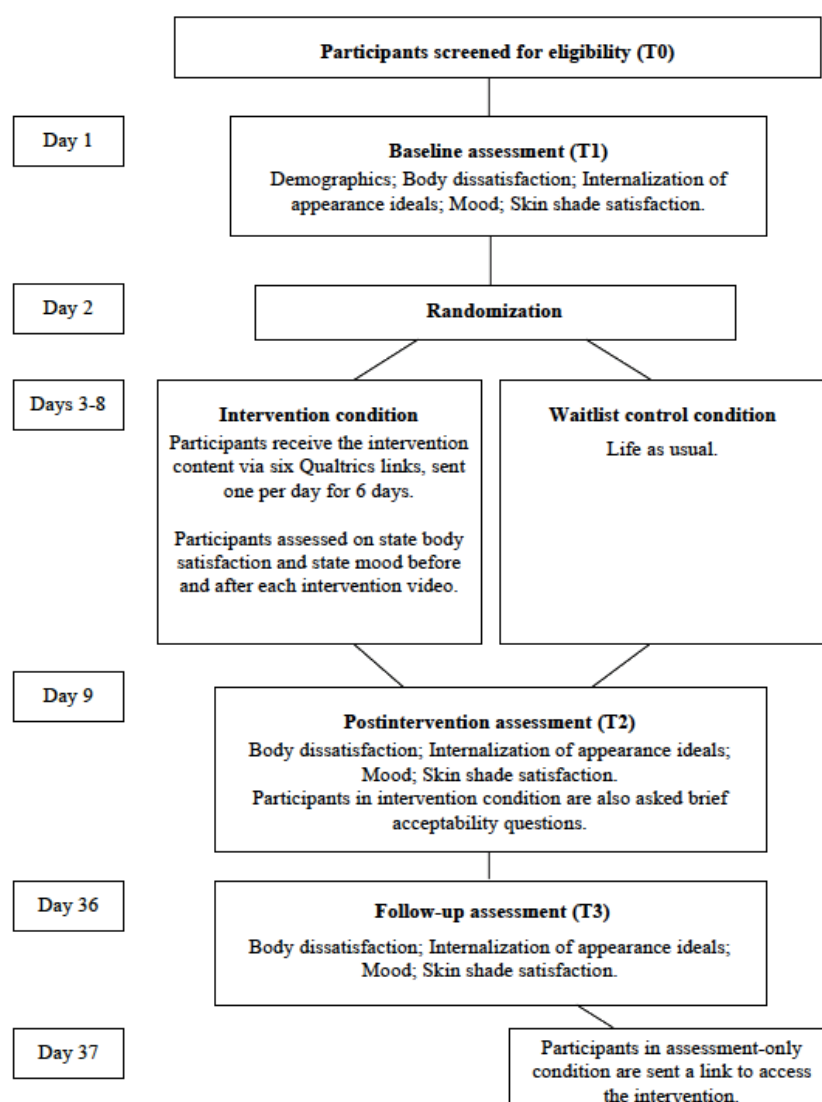
Should an eligible daughter be 15-17 years old, the recruiter will read the parental information sheet to the parent. Parents will then be requested to provide verbal consent for their daughter's participation and verify their identity and daughter's age. Parents will then answer questions relating to their socioeconomic status on behalf of their daughter before the recruiter requests to speak to the daughter. If the daughter is not present, the recruiter will request a call back. The daughter will then be screened for eligibility and informed verbal assent obtained. Following the call, and provided the daughter is eligible and gives verbal assent, the parental information sheet will be sent to the parent via WhatsApp, with informed parental consent obtained once more, this time written, over WhatsApp. WhatsApp was chosen as it is the most used communication app in Indonesia [88].

Should an eligible daughter be aged 18 or 19 years, a similar pattern of communication will occur. Parents will verify their own and their daughter's identity and respond to questions regarding the family's socioeconomic status. Rather than parents providing informed verbal and written consent, this will be completed by the daughters themselves, in the same manner with which it will be completed by parents of those aged 15-17 years. Verification of identities and ages will be achieved through video calls via the presentation of official documentation (eg, National ID card, family registration card, driving license, student ID). Recruitment is anticipated to take 15 days (inclusive of weekends).

All participants will enter the study (ie, complete the baseline assessment survey) on the same day (Day 1). Participants will receive a data package a day prior to this to ensure they have ample mobile phone data to allow them to participate in the study. A link to the baseline assessment hosted on Qualtrics (Provo, UT) will be sent to participants via WhatsApp at 8 AM (UTC +7) on Day 1, along with a unique participant identification number (PIN). Participants will be requested to enter their PIN on the first page of the baseline survey, in order to match participant responses over time. Participants will have 24 hours to complete the baseline assessment; those who have not completed the baseline assessment within the first 8 hours will be sent a reminder message during the early evening of Day 1. Following the 24-hour window, participants who have completed the baseline assessment will be randomized into one of two conditions: the intervention condition or a waitlist control condition. Participants will be alerted on Day 2 to what happens next, depending on which condition they have been randomized. Those randomized to the intervention condition will be informed that they can expect a series of sequential links to be sent to them daily over the following 6 days. Each link will contain one episode of *Warna-Warni Waktu* and its associated activities. The links will again direct participants to Qualtrics, where the intervention has been embedded (see Multimedia Appendix 2). These participants will be requested to engage with the content of those links daily. Those in the control condition will be told that they will be recontacted in 1 week to complete a second assessment.

On the morning of the third day (Day 3), participants in the intervention condition will be sent their PIN and a link to the first video (and associated activity). Again, participants will be

requested to enter their PIN on the first page of the link. Participants will complete state measures of body satisfaction and mood before watching the first video in the *Warna-Warni Waktu* series. State measures of body satisfaction and mood will be asked again immediately after the first video. Next, participants will be presented with the activity for the first video. Before exiting the link, participants will be asked to report on the strength of their internet connectivity while watching the video (see the Measures section below). This process is repeated on Days 4-8 for the remaining five videos (and associated activities). Participants will not be sent reminders to view or engage with the content in these links.

On Day 9 of the study (again, in the morning), participants in both conditions will be sent a link to complete the second assessment. As with the baseline assessment, participants will be given 24 hours to complete this assessment, with reminder messages sent to noncompleters after the first 8 hours. The same process will be executed for the third and final assessment, 1 month later on Day 36. Following the third assessment, all participants will be debriefed on the study aims and provided with additional sources of mental health support, as well as a certificate of participation. Participants who complete all three assessments will be rewarded with Rp125,000 (approximately US $8.75) to encourage participant retention. By this point, the responses to the four 250-word writing activities will have been judged, and those who have won will be contacted and will receive their prize. Those in the waitlist control condition will be provided with a link to the *Warna-Warni Waktu* video series on Day 37. Participants in the waitlist control condition will not be assessed for their engagement with the content. Information sheets and the participant debrief document can be found in Multimedia Appendix 4.

Randomization and Blinding

Participants will be randomized following completion of the baseline survey. Participants will not be blinded due to the nature of the trial design. They will not be told explicitly of their condition but will be made aware on Day 2 (ie, the day after completing the baseline survey) when they will receive the intervention. Randomization and allocation will be performed on an individual level using an automated, web-based randomizer to sequentially allocate participants based on a block design to ensure a balance of participants across conditions. A researcher external to the project will generate the allocation sequence and assign participants to conditions. They will be blinded to participant information and conditions (ie, they will be given a list of participant identification numbers and asked to assign them to Group A or B using the web-based randomizer). Data analysts will be blinded to condition throughout the trial and analysis of the primary and secondary trait-based measures. Blinding of data analysts during state-based analyses is not possible due to the within-group design of this aspect of the trial. Two separate data files will be provided to the statistician to ensure that blinding during analyses of trait measures is retained. Due to the trial design, the research agency and participants will not be blinded to condition.

Measures

Self-report measures selected for use are presented in Table 1. For hypothesis one, the primary outcome measure, the Body Esteem Scale for Adults and Adolescents (BESAA) [89], was selected as it is the only body dissatisfaction measure to have been validated among young people in Indonesia (unpublished data of the authors KG, NC, SH, KN, BM, LS, and PD, along with statistical consultants Chloe Hayes and Silia Vitoratou, 2021) and evidence that this scale is amendable to change following interventions of similar duration and content [90,91]. Two secondary outcome measures assessing internalization of appearance ideals [92] and trait mood [93] (unpublished data of the authors KG, NC, SH, KN, BM, LS, and PD, along with statistical consultants Chloe Hayes and Silia Vitoratou, 2021) were again selected for similar reasoning. Owing to the lack of a validated assessment tool to assess skin shade satisfaction, a purpose-built measure will be used to assess this. For hypothesis two, single-item measures of body satisfaction and mood will be utilized. Full questionnaires are presented in Multimedia Appendix 5.

Intervention adherence will be measured objectively through dwell time spent on the Qualtrics page that contains the video and via participant responses to the activities. Intervention acceptability will be assessed through six self-report items; these were informed by established acceptability frameworks [96].

Table 1. Measures.

Measure	Description	Time assessed
Demographics	Age, country of birth, ethnicity, religion, socioeconomic status, social media usage	T1[a]
Primary outcome: Trait body dissatisfaction	Body Esteem Scale for Adolescents & Adults (BESAA) [89] adapted and validated among adolescents in Indonesia (17 items). Example item: *I like how I look like in photos*. Response options range from strongly disagree to strongly agree. Mean scores range between 1 and 5, with higher scores reflecting higher body esteem.	T1, T2[b], T3[c]
Secondary outcomes		
Internalization of appearance ideals	Internalization-General subscale of the Sociocultural Attitudes Towards Appearance Scale-3 [92] adapted and validated among adolescents in Indonesia (12 items). Example item: *I compare my body to the bodies of people who are on TV*. Response options range from *strongly disagree* to *strongly agree*. Mean scores range between 1 and 5, with higher scores reflecting higher internalization of appearance ideals.	T1, T2, T3
Trait mood	The Positive and Negative Affect Schedule for Children [93] adapted for Indonesia. The validation of this scale among Indonesian adolescents is underway. The factor structure will be determined prior to data analysis and reported in the main effectiveness paper.	T1, T2, T3
Skin shade satisfaction	A purpose-built, single-item, skin shade discrepancy measure will assess skin shade satisfaction. The chart comprises nine skin colors from dark (1) to light (9). Participants are asked to select the shade that most accurately matches their "current skin shade" and the shade that most accurately reflects the skin shade they would prefer (their "ideal skin shade"). The discrepancy between the two will be used as an indicator of skin shade satisfaction, with higher absolute values indicating less skin shade satisfaction. The score ranges from 0 (*satisfied with skin shade*) to 9 (*very dissatisfied with skin shade*). The measure uses colors from The Pantone Skin Tone Guide [94].	T1, T2, T3
State body satisfaction	A single 101-point visual analog scale [95] will assess the immediate impact of each video on participants' state body satisfaction (ie, *How satisfied are you with your appearance, right now, in this moment?*). The total score ranges from 0 (*not at all*) to 101 (*very much*). Higher scores reflect greater satisfaction.	Before and after each video
State mood	A single 101-point visual analog scale [95] will assess the immediate impact of each video on participants' state mood (ie, *How happy are you, right now, in this moment?*). The total score ranges from 0 (*not at all*) to 101 (*very much*). Higher scores reflect greater positive mood.	Before and after each video
Intervention adherence	Digital metrics will assess participants' engagement with the videos and activities, including: (1) percentage of participants who watch each video (determined by the number of participants whose dwell time on the Qualtrics page hosting each video is equal to or longer than the length of the video); (2) percentage of participants who watch all 6 videos (determined by the number of participants whose dwell time on all 6 Qualtrics pages hosting videos is equal to or longer than the length of each video); (3) average number of videos watched; (4) percentage of participants who complete each activity; (5) average number of activities completed; and (6) average length of time spent engaging with the intervention (ie, watching videos and completing activities) over the 6-day period.	Six-day intervention period
Intervention acceptability	Six items will assess participants' acceptability of the intervention. Factors include emotive response to the interventions (eg, enjoyment, likability of characters); relevance (eg, age appropriateness, helpfulness, ease of understanding); ease of use (eg, speed and accuracy of responses); and willingness to recommend (eg, how likely the user would recommend the intervention to a friend). Item scores range between 1 (*strongly disagree*) and 5 (*strongly agree*). Higher scores reflect greater acceptability. Only those randomized to the intervention condition will complete these measures.	T2

[a]T1: baseline assessment.

[b]T2: postintervention assessment.

[c]T3: follow-up assessment.

Sample Size

The predefined primary outcome measure is the BESAA at postintervention assessment (T2) and follow-up assessment (T3). Similar RCTs assessing body dissatisfaction evaluating the same outcome measure reported a range of small to medium standardized effects sizes with Hedges *g* ranging from 0.25 to 0.4 (eg, [89]) with a standardized minimum important clinical difference (MICD) of 0.2 exceeding the minimum detectable difference of the measures. To detect the MICD or larger, our proposed sample size of n=900 per group would provide in excess of 90% power (two-sided α=.05) for between-group

differences at either T2 or T3 with or without a Bonferroni correction for multiple time points. This assumes that dropout does not exceed 20% in any one arm, and is valid for any positive correlation between commensurate measures at baseline (T1) with T2 or T1 and T3. The oversampling includes a COVID-19 contingency plan permitting the sample size to drop to 650 per group should external challenges arise, and further downward revisions in sample size with a tradeoff in power under worst-case scenarios.

Analysis Plan

The intention-to-treat set of participants will form the primary analysis set. An assessment of the impact of missing data on statistical conclusions will be undertaken using sensitivity analyses.

For the first hypothesis, the data will be analyzed on an intention-to-treat basis using a linear mixed model with baseline measures at T1 as a covariate, randomized group as a two-level between-subjects factor, and study phase (T2, T3) as two-level repeated-measures factor. The statistical model will be hierarchically balanced with the three-way interaction between covariate, phase, and randomized group as the generating class. This structure permits an analysis of covariance prior reasoned comparison between randomized arms at T2 and T3, assessing the parallel lines of assumption, homogeneity of variance assumption, and the use of robust estimates, if needed. Changes within the randomized arm between T1 and T2 and between T1 and T3 will be assessed using the paired-samples t-test and effect size quantified with 95% CIs. The reliable change index will be used to determine the percentage of participants reliably improving within each arm.

For the second hypothesis, the nested intervention study comprises state evaluation of body satisfaction and mood immediately before and after each daily video. A component impact analysis will consist of a 2 (pre, post) by 6 (Day 3 to Day 8) fully repeated-measures analysis including linear and quadratic trends for time sequence effects, and a main-effects comparison between components on pre and post change scores. It is not inconceivable that relative effects between days are likely to be small. For an assumed standardized effect of Cohen d=0.1, a sample size of n=800 would be needed for 80% power. These data have further value in evaluating adherence and would permit a dose-response effect to be included in a planned subset analysis.

For the third hypothesis, the relationship between adherence (count of daily completion in each of Day 3 to Day 8) and outcome (primary and secondary) at each of T2 and T3 will be assessed using linear regression controlling for baseline covariates. The cardinal nature of adherence permits Helmert effect coding (difference effect coding) to be used to estimate cumulative dosage effects. The relationship between daily engagement and outcome (primary and secondary) at T2 and T3 will be assessed using linear regression controlling for baseline covariates. These latter models will code each daily engagement as a dummy variable, and will permit a comparison between engagement in each activity. A full statistical analysis plan will be written and approved by the Trial Management Group prior to study closure.

Ethics

This study received ethical approval from the Faculty of Medicine Universitas Indonesia (588/UN2.F1/ETIK/PPM.00.002/2021) and the University of the West of England (HAS.21.04.138). Participation in the study will be completely voluntary. For participants under 18 years of age, parents will be approached first and will be required to give their consent for their daughter's participation. Prior to consent, parents will be provided with a detailed information sheet outlining the requirements of participation, withdrawal procedures, as well as potential risks. When parents provide their consent, participant assent will be obtained, with the details of the study outlined again in a participant information sheet. The same participant information sheet will be given to those participants aged 18 or 19 (without prior parental consent being sought). Participants will be informed that they can withdraw their consent at any point in the research process without needing to give justification. Parental consent and participant assent (or consent if 18 or 19 years old) will be obtained by the research agency.

All information sheets will contain details of two counseling services available to young women in Indonesia if they are experiencing any mental health concerns and require additional support. Further, information sheets will contain the contact details of study author (BM) should they have any concerns relating to the execution of the study. The study is registered with ClinicalTrials.Gov (NCT05023213).

Special ethical consideration was given in light of conducting this research during the COVID-19 pandemic. Although at the time of writing, legal regulations would allow for face-to-face contact between the research agency and participants, it was decided that the research should take place entirely online. Although such a strategy is befitting for the evaluation of a web-based intervention, assurances regarding identity during the recruitment phase required careful consideration. Video calls where parents of potential participants will be required to show official photographic identification will allow for confirmation of participant identities, including age. Owing to the web-based nature of the study, the decision to only include participants who had access to their own mobile phone was made, ensuring that only the recruited participants receive, and respond to, the notifications sent about the study. Anecdotally, the Indonesian-based authors believe that many young women in the target age group own their own mobile phone; therefore, we do not anticipate this impacting the representativeness of the sample obtained. For transparency, participants ineligible due to not owning their own mobile phone will be reported in the main trial.

Data Monitoring and Management

Data from recruited participants will be downloaded directly from Qualtrics; thus, there is no data entry process to consider. Once downloaded, the data will be confirmed correct by checking that the data values are as expected. Participant responses will be matched over time, and any duplication of responses will be examined, and if found, deleted. No personal details will be requested from participants via Qualtrics, and as such, these data files should be anonymous. However, the files

will be screened at the soonest available opportunity to assess for any inadvertent disclosure of personal information in the form of qualitative responses. If identified, this information will be immediately deleted. Downloaded data will be stored on secure university-approved secure cloud storage (ie, OneDrive). When initial screening described above has been completed by two authors (KG and SH), the data file will then be shared with all study authors.

Consent data, containing personal information, will be collected by the research agency. It will be securely stored for 5 years, as stipulated by the ethical committee of Universitas Indonesia. The personal details of consenting parents or participants will not be shared beyond the research agency.

Based on extensive input from young Indonesian women throughout the development of the intervention and the authors' experience of utilizing similar surveys among young women in Indonesia with no harm identified, no serious adverse effects are expected for this trial. As such, a data monitoring committee was not deemed appropriate or necessary. Should a participant contact any member of the research team regarding any concerns as a consequence of taking part in the research, this will be dealt with promptly. Such incidences will be reported at the earliest opportunity to the first author (KG) by the research agency, discussed in an internal audit, and reported with the study findings.

Research Dissemination

For the purposes of disseminating to academic audiences, research findings will be published in peer-reviewed journals and presented at international conferences. Further, the findings will be shared via social media, and websites of the study authors and associated affiliations such as the Centre for Appearance Research, Girl Effect, and Percolate Galactic. The findings may also be shared via communication channels of the funder, the Dove Self-Esteem Project. If the intervention is effective, the intervention content will be disseminated to young women aged 15-19 years via social media marketing campaigns on Facebook, Instagram, and YouTube.

Results

The above protocol will undergo an internal pilot with 150 participants to identify and make any final adjustments to the procedure prior to full execution of the trial. Any deviations from the protocol documented in this paper will be explicitly acknowledged in the publication of the trial findings.

Data collected during the internal pilot from beginning recruitment to the T2 survey will constitute interim analyses. Although T3 data will be collected from pilot participants, this will not form the basis of the interim analyses due to time constraints imposed on the project, along with the minimal additional information this follow-up time point would have on the decision to proceed to the main trial. Progression to the main trial, including decisions regarding any modifications to the protocol, will be based on participant retention, intervention adherence, data quality, and preliminary assessment of harm. Predefined criteria for each of these parameters are outlined in Table 2, using a traffic light system (red: major modifications or termination of the trial required; amber: minor modifications to be considered; green: proceed with protocol as is).

The pilot study was completed in September 2021. Following positive results from the pilot trial, recruitment for the main trial began in October 2021. The results from the trial are anticipated to be published by mid-2022.

Table 2. Progression criteria.

Criteria	Description	Green	Amber	Red
Participant retention (%)	Participant completion of T1[a] and T2[b] surveys	70 or above: continue with main trial	50-69: consult research team to advise on changes to survey administration protocol	Below 50: the main trial will need to reconsider how surveys are administered
Intervention adherence, n (%)	Participants viewing all 6 intervention videos	80 or above: continue with main trial	60-79: consult research team to advise on changes to intervention delivery	Below 60: the main trial will need to reconsider how intervention is delivered
Data quality, n (%)	Accurate completion of survey attention checks	80 or above: continue with main trial	60-79: consult research team on possible changes to survey instructions	Below 60: reconsider survey completion protocol
Assessment of harm	Assessment of change in primary outcome measure in the intervention condition compared to the control condition, between T1 and T2	Relative improvements in intervention condition: continue with main trial	No difference between conditions: continue with main trial	Relative deterioration in intervention condition: consider trial termination

[a]T1: baseline assessment.

[b]T2: postintervention assessment.

Discussion

eHealth interventions offer an unparalleled opportunity to reach young people with mental health education and support at scale. The acceptability and effectiveness of delivering mental health content digitally among young people in LMICs is increasingly being explored, showing positive results [69,97]. Although interventions specifically designed for dissemination via social media are in their infancy, the widespread reach and popularity of social media among young people, including in Indonesia [48,49], offer an ideal platform for such an endeavor. To our knowledge, this is the first study to evaluate an eHealth

intervention aimed to reduce body dissatisfaction among young people in Indonesia. Specifically, *Warna-Warni Waktu* is a video- and activity-based intervention for young women in Indonesia, designed for dissemination via Facebook, Instagram, and YouTube to reduce body dissatisfaction in this demographic.

This protocol outlines an RCT to evaluate the effectiveness of *Warna-Warni Waktu*. The study has a number of strengths, including an adequate sample size to account for attrition (a recurring issue across web-based intervention trials [98]); an objective assessment of adherence (a crucially important consideration in web-based intervention trials [63]); outcome measures validated among young Indonesian women (with the exception of the skin shade satisfaction measure, of which there is no validated measure available and a key future direction for the field); a 4-week follow-up assessment point to detect any continued or delayed effects; and a pilot study.

However, these noteworthy strengths come at a cost. Most notably, the intervention will be accurately created for use on a single-user software platform (Qualtrics) to objectively measure adherence for the trial. Consideration was given to delivering the trial on social media; however, this would have significantly limited individual-level adherence data, even if the research was conducted via a private Facebook group (eg, this would have allowed tracking of still images at the individual level, but not individual-level adherence to watching the videos from start to finish). As such, the approach described in this paper was deemed an appropriate first step in ensuring intervention effectiveness under a somewhat controlled environment where adherence could be tracked. This decision reduces the study's ecological validity in that it will not be displayed to participants on the same platform as it will be when disseminated. When delivered on social media, there may be the additive effect of collaborative and cooperative learning [99], with young women posting responses publicly, as well as potentially liking and commenting on others' responses, in contrast to the didactic fashion to be used in the trial. Note that when disseminated, all public responses will be monitored, with any inappropriate or unhelpful comments removed by moderators. This additional element of having the intervention housed on social media will not be evaluated in the trial described here, but future work could look to explore the impact of this additional element.

If found to be effective, *Warna-Warni Waktu* is a relatively inexpensive, scalable public health intervention to reduce body dissatisfaction among young Indonesian women. It could provide a blueprint for the adoption of this intervention format and modality for other countries and cultural contexts. The intervention's novelty, accessibility, and acceptability among young women are key strengths of the intervention to date; the effectiveness results from this RCT will be invaluable to guide dissemination efforts across social media platforms in Indonesia.

Authors' Contributions

KG: Conceptualization, Methodology, Writing – Original Draft Preparation, Project Administration, Funding Acquisition. NC: Conceptualization, Methodology, Writing – Review & Editing, Funding Acquisition. SH: Resources, Project Administration, Writing – Original Draft Preparation. KN: Resources, Project Administration, Writing – Review & Editing. PW: Methodology, Writing – Review & Editing. LS: Resources, Writing – Review & Editing. BM: Resources, Writing – Review & Editing, Supervision (of KN). Girl Effect: Resources, Writing – Review & Editing. Percolate Galactic: Resources, Writing – Review & Editing. PD: Conceptualization, Writing – Review & Editing, Funding Acquisition. HW: Methodology, Writing – Review & Editing.

Conflicts of Interest

PD and SH are independent consultants to Dove and were on the Dove Self-Esteem Project Global Advisory Board in 2013-2016. The authors declare no other conflicts of interest in relation to this work.

Multimedia Appendix 1
SPIRIT checklist.
[[PDF File (Adobe PDF File), 174 KB](resprot_v11i1e33596_app1.pdf) - [resprot_v11i1e33596_app1.pdf]( )]

Multimedia Appendix 2
Presentation of activities in Qualtrics and Facebook.
[[PDF File (Adobe PDF File), 740 KB](resprot_v11i1e33596_app2.pdf) - [resprot_v11i1e33596_app2.pdf]( )]

Multimedia Appendix 3
Synopsis of the intervention's narrative.
[PDF File (Adobe PDF File), 91 KB - resprot_v11i1e33596_app3.pdf]

Multimedia Appendix 4
Participant information sheets.
[DOCX File , 457 KB - resprot_v11i1e33596_app4.docx]

Multimedia Appendix 5
Questionnaires.
[PDF File (Adobe PDF File), 2675 KB - resprot_v11i1e33596_app5.pdf]

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Abbreviations

BESAA: Body Esteem Scale for Adults and Adolescents
CONSORT: Consolidated Standards of Reporting Trials
LMIC: low- and middle-income country
MICD: minimum important clinical differences
PIN: participant identification number
RCT: randomized controlled trial

SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
T1: baseline assessment
T2: postintervention assessment
T3: follow-up assessment

Protocol

Sensitivity Treatments for Teeth with Molar Incisor Hypomineralization: Protocol for a Randomized Controlled Trial

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Abstract

Background: The sensitivity of teeth with molar incisor hypomineralization (MIH) can affect children's quality of life and is a challenging problem for dentists. Remineralizing agents such as sodium fluoride varnish seem to reduce the sensitivity of teeth with MIH, but long-term clinical trials with large samples are still needed for more evidence about its effectiveness as a desensitizing agent before its clinical recommendation.

Objective: This randomized clinical trial aims to compare three treatment interventions for teeth with MIH and hypersensitivity.

Methods: A total of 60 children aged 6-10 years presenting with at least one first permanent molar with sensitivity and no loss of enamel will be randomly assigned to three groups: the control group (sodium fluoride varnish; Duraphat, Colgate); experimental group I (4% titanium tetrafluoride varnish); and experimental group II (a coating resin containing surface prereacted glass-ionomer filler; PRG Barrier Coat, Shofu). The sodium fluoride varnish and 4% titanium tetrafluoride varnish will be applied once per week for 4 consecutive weeks and the PRG Barrier Coat resin will be applied in the first session and the application will be simulated the following 3 weeks to guarantee the blinding of the study. The primary outcome will be sensitivity level measured at different moments (before each material application, immediately after application or simulation, and 1, 2, 4, and 6 months after the last application/simulation) by one examiner using the Wong-Baker FACES Pain Rating Scale, the Schiff Cold Air Sensitivity Scale, and the FLACC (Face, Legs, Activity, Cry, Consolability) scale. As secondary outcomes, parental satisfaction and child self-reported discomfort after the treatment will be measured with a questionnaire prepared by the researcher. The data will undergo statistical analysis and the significance level will be set at 5%.

Results: The project was funded in 2018, and enrollment was completed in November 2019. The recruitment of participants is currently underway and the first results are expected to be submitted for publication in 2022.

Conclusions: If found effective in reducing the patient's sensitivity long term, these agents can be considered as a treatment choice, and the findings will contribute to the development of a treatment protocol for teeth with sensitivity due to MIH.

Trial Registration: Brazilian Registry of Clinical Trials Universal Trial Number U1111-1237-6720; https://tinyurl.com/mr4x82k9

International Registered Report Identifier (IRRID): DERR1-10.2196/27843

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KEYWORDS

sensitivity; molar incisor hypomineralization; fluoride; dentistry; pediatric dentistry; dental care

Introduction

Molar incisor hypomineralization (MIH) is a developmental defect of the enamel that affects one or more permanent molars, often associated with permanent incisors [1]. The affected teeth have lower mineralization, resulting in weaker enamel, which can undergo posteruptive breakdown [2,3]. The prevalence of hypersensitivity in MIH-affected teeth is around 34%, and some children might complain of spontaneous discomfort or pain triggered by thermal or mechanical stimuli [4].

Acute tooth sensitivity can occur when the dentist applies an air jet or performs clinical procedures. However, sensitivity can persist even after local anesthesia administration, resulting in anxiety and behavioral problems during dental treatment [5]. The cause of MIH sensitivity is not entirely clear [6]. One hypothesis is that repeated stimuli might cause a subclinical pulp inflammatory response due to the porosity of the enamel, which facilitates the penetration of bacteria in the dentinal tubules [6,7].

The management of MIH sensitivity represents a major challenge [1,4,7]. Several treatments are available, including the use of fluoride toothpaste, the use of oral care products containing casein phosphopeptides-amorphous calcium phosphate [8,9], and the application of topical sodium fluoride varnish [10-13] with or without laser therapy [14]. Sodium fluoride varnish retains the fluoride close to the teeth for a longer time, resulting in desensitization [15,16]. However, while the use of these agents is empirical, there are no long-term clinical trials with consistent results that evaluate their effectiveness.

The experimental 4% titanium tetrafluoride (TiF_4) varnish is a promising material for decreasing sensitivity. Several in vitro and in situ studies have shown that TiF_4 varnish has a greater remineralization effect and reduces enamel demineralization when compared to sodium fluoride varnish (5% NaF) [17,18]. Titanium tetrafluoride (TiF4) reacts with hydroxyapatite and induce a higher deposition of calcium fluoride, forming an acid-resistant layer [19,20].

Recently, a new bioactive technology called surface prereacted glass-ionomer (S-PRG) has been tested on many types of dental materials. It is based on a prereacted fluorosilicate particle with polyacrylic acid, allowing the material to have both biological effects from the glass ionomer cement (fluoride release and recharge) [21-23] and the excellent physical, mechanical, and optical properties of nanohybrid composites. The material also has several other ions in its structure, such as aluminum [24], which is related to sensitivity control. Among materials containing S-PRG, a light-cured bioactive coating resin, the PRG Barrier Coat, can provide immediate and long-term relief for up to 6 months [25].

Because new alternatives for the treatment of tooth sensitivity due to MIH are needed, this randomized clinical trial with parallel arms aims to compare three treatment interventions (5% NaF, 4% TiF_4, and a light-curing S-PRG–based bioactive coating resin). If these agents contribute to the reduction of patients' sensitivity, they will be considered a treatment choice. The findings of this study will help inform the development of a treatment protocol for teeth with sensitivity due to MIH.

Methods

Ethical Considerations

This clinical trial was submitted to and approved by the Research Ethics Committee of Bauru School of Dentistry under CAAE number 14958719.5.0000.5417 and was registered in the clinical studies database (Brazilian Registry of Clinical Trials Universal Trial Number U1111-1237-6720). This protocol follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) and CONSORT (Consolidated Standards of Reporting Trials) guidelines for randomized trials of nonpharmacological treatments [26].

Participants will be included after their parents or guardians have signed an informed consent form containing detailed information about the research. The children will receive an assent term, with age-appropriate language, explaining how the research will be conducted and that they will be free to accept or reject participation in the study. Participant confidentiality will be guaranteed, and only researchers will have access to the data. At the end of the study, the researchers are committed to offering treatment with the product that demonstrates the best result, regardless of which experimental group the child was in.

Study Design

This is a double-blind randomized controlled clinical study, conducted with three parallel groups, with a duration of 6 months (Figure 1). The participants and their parents/guardians, as well as the examiners, will not be aware of the group allocation of any patients.

Figure 1. Study Flowchart.
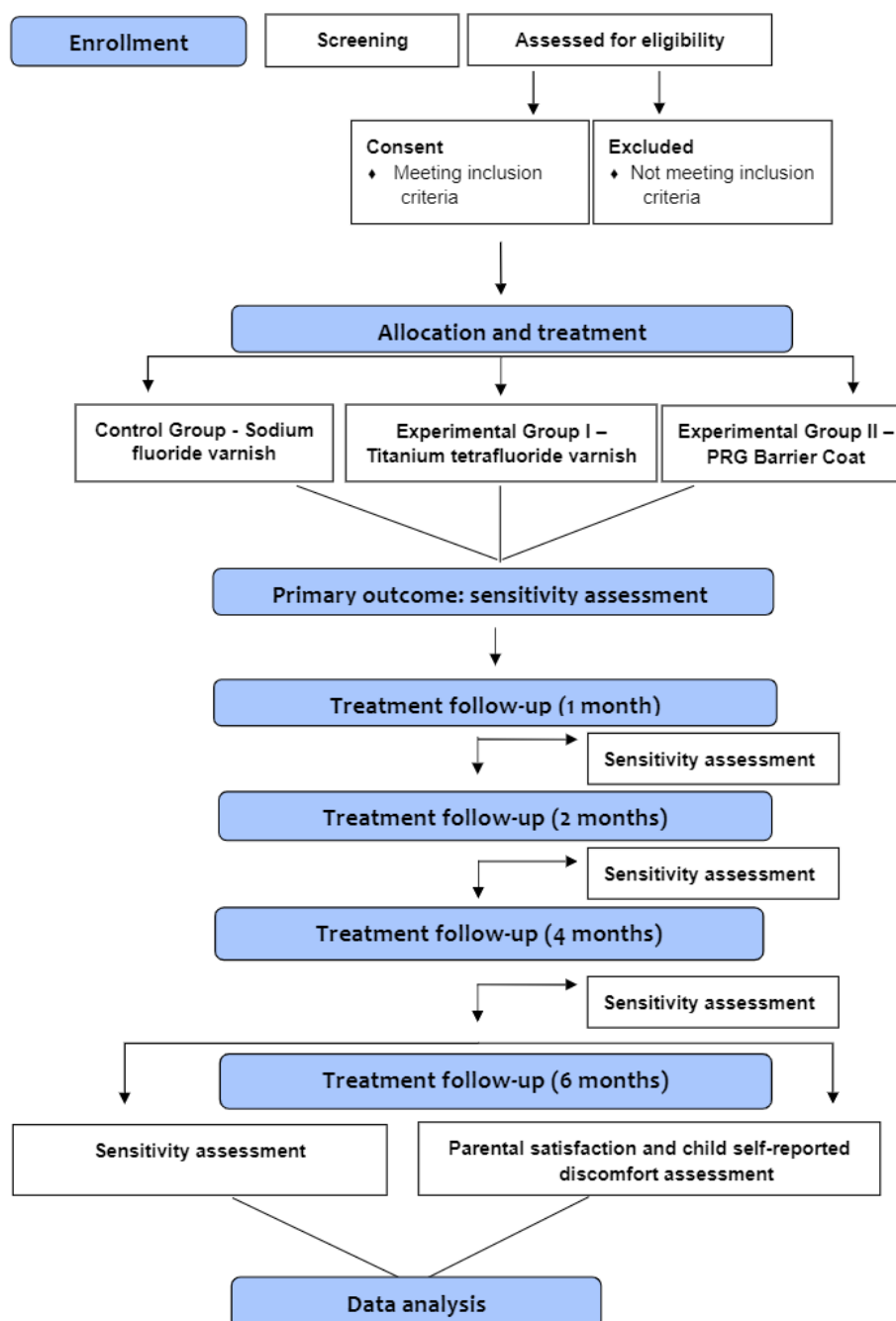
Examiner Calibration

Examiner calibration will be performed using 35 original photographs of teeth with MIH with different degrees of severity and other developmental enamel defects. The photographs will be evaluated based on the MIH index [27]. All photographs will be reevaluated by the two examiners after 15 days to assess inter- and intraexaminer agreement ($\kappa > 0.85$).

Selection of Participants and Sample Size Calculation

The study participants will be selected from the city of Bauru, São Paulo, Brazil, which has a population of 371,690 inhabitants and a Human Development Index of 0.801. Participants aged 6-10 years will be selected from an epidemiological survey in municipal schools. These schools are located in an urban area, in different zones (north, south, east, and west), and will be selected by a draw according to each zone. In the selected schools, all children aged 6-10 years will be evaluated. Children

with potential for inclusion in the research will be referred for a clinical examination at the pediatric dentistry clinic of Bauru School of Dentistry, University of São Paulo, and those that have at least one first permanent molar affected by MIH with hypersensitivity complaint and without loss of structure will be invited to participate. The sensitivity complaint will be confirmed by applying a 1-second air jet at a distance of 1 centimeter from the occlusal surface of the tooth; a score of 2 or 3 on the Schiff Cold Air Sensitivity Scale (SCASS) will be considered as a positive result. Patients with orthodontic appliances, syndromes that involve enamel malformation, or behavioral problems during the clinical examination will be excluded.

The sample size was calculated considering analysis of variance, performed in SigmaPlot (version 12.3; SPSS Inc), and it was considered a minimally detectable difference of 1 on the SCASS scores between groups. A standard deviation of 0.9 was used based on a previous study [28], α error was 5%, β error was 20%, and a dropout rate of 18% was used, which resulted in a total of 60 children (20 per group). The first 60 children who meet the inclusion criteria will be selected to be part of the study, while others who also present with sensitivity but cannot be included will receive the necessary treatment.

Recruitment will take place from October 2019 to December 2021. After allocation and treatment for 4 weeks, the patients will be followed up for 6 months.

Random Allocation

The included patients will be allocated to one of the 3 treatment options by stratified block randomization: (1) the control group (sodium fluoride varnish; Duraphat, Colgate), (2) experimental group I (4% TiF_4), and (3) experimental group II (S-PRG resin coating; PRG Barrier Coat, Shofu). The randomization sequence will be generated using Microsoft Excel 365 (Microsoft Corp) by an examiner who will not be involved in any of the clinical trial phases. To ensure allocation concealment, the randomly generated sequence will be sealed in opaque envelopes that will be opened only after the child is ready to receive treatment. The randomization procedure will be done per block of 3 children with the same SCASS scores to guarantee similar scores among groups at baseline.

The analysis unit will be the child and will be considered one tooth per child. If more than one permanent first molar has the condition, all will undergo the same treatment so that there is no interference from different treatments and other factors such as saliva, and one tooth will be selected by a draw to be included in the data analysis. The order of treatment among affected teeth in a patient will also be defined by a draw.

Treatment Protocol

All children will receive instructions on noncariogenic diet and oral hygiene. Furthermore, the participants will receive an oral hygiene kit with toothbrush and fluoride toothpaste (both Colgate-Palmolive Company). Immediately before treatment, a supervised toothbrushing will be performed with a fluoride-free toothpaste to standardize the treatment phase and to follow the instructions of the S-PRG resin manufacturer. The

study risks for participants are minimal and related to the sensitivity due to MIH.

In the control and experimental I groups, the fluoride varnishes will be applied once per week for 4 consecutive weeks. For the experimental II group, the product will be applied the first week and the application will be simulated the following 3 weeks for patient blinding.

All children in the control and experimental I groups will be treated according to the same protocol:

1. Supervised toothbrushing with fluoride-free toothpaste.
2. Cotton roll isolation of the area.
3. Drying of the tooth using sterile gauze.
4. Varnish application with microbrush according to the manufacturer's instructions.
5. Instruction of the patient not to eat or drink for 30 minutes and not to brush for at least four hours after application.
6. Reapplication once per week for 3 weeks, following the described protocol.
7. Follow-up.

For the experimental II group, the treatment protocol according to the manufacturer is as follows:

1. Supervised toothbrushing with fluoride-free toothpaste.
2. Cotton roll isolation of the area.
3. Drying of the tooth using sterile gauze.
4. Material handling within 2 minutes after mixing.
5. Application of a thin layer with the device provided by the manufacturer, then a 3-second wait.
6. Light curing for 10 seconds.
7. Instruct the patient to avoid colored drinks and food for 3 days.
8. Application simulation the following 3 weeks (repeat steps 1-3).
9. Follow-up.

Sensitivity Assessment

Sensitivity will be assessed before and after treatment (for all groups) using three instruments: the Wong-Baker FACES Pain Rating Scale (WBFPS), SCASS, and FLACC (Face, Legs, Activity, Cry, Consolability) scale, as described below.

First, the researcher will ask whether the child feels any discomfort in his/her teeth. The researcher will also carefully explain that their WBFPS face choice should be related to the toothache and not the child's mood at that moment. The child will then be shown the WBFPS, and the child will be guided to choose the most representative face.

Second, sensitivity will be clinically assessed by applying a 1-second air jet 1 centimeter from the buccal and occlusal surfaces of the tooth. The adjacent teeth will be protected with cotton rolls and the patient's response to the stimulus will be evaluated according to the SCASS. The child's reaction will be recorded according to the codes described in Multimedia Appendix 1.

Third, the examiner will also record the patient's reaction using the FLACC scale (Multimedia Appendix 2). This scale has 5 categories and the responses to each one will be scored from 0

to 2. In each category, the numbers obtained will be summed to obtain the total pain score (0-10). Finally, the child will be asked about discomfort in their teeth again following the use of the air jet and the WBFPS will be applied again.

Primary Outcome: Treatment Effectiveness

A single trained, calibrated, and blinded examiner (not involved in the treatment application) will assess the sensitivity effectiveness of treatment in all groups at different moments: (1) before the application of each material, (2) immediately after application or simulation, (3) one month after the last application/simulation, (4) two months after the last application/simulation, (5) four months after the last application/simulation, and (6) six months after the last application/simulation. For all evaluations, the WBFPS, SCASS, and FLACC scale will be used as previously described.

Secondary Outcomes: Parental Satisfaction and Child Self-reported Discomfort

Parental satisfaction and child self-reported discomfort will be evaluated immediately after the fourth week of application or application simulation. Children and their guardians will be asked to rate their satisfaction with the treatment received as very satisfied, partially satisfied, neither satisfied nor dissatisfied, partially dissatisfied, or very dissatisfied. Furthermore, parents will be asked about the importance attributed to the treatment performed on their children (ie, how important it is to treat the tooth affected by MIH) through 5 questions. Concerning discomfort, the questionnaire will assess the child's acceptability of the treatment, especially the taste of the material, burning sensation, appearance, and duration of the procedure. The questions will be asked by an examiner who did not participate in the treatment stage and is not aware of the type of treatment received by the patient.

Visible Plaque Index and Gingival Index

Considering that hypersensitivity can impact toothbrushing, the child's oral hygiene condition will be evaluated using the visible plaque index (IPV) [29] and gingival index (GI) [30] at different times: (1) before the treatment, (2) before each material application/simulation, and (3) at each follow-up visit (1, 2, 4, and 6 months).

Follow-up Examinations

Patients will be assessed regarding sensitivity 1, 2, 4, and 6 months after the treatment and will receive preventive instructions concerning diet and biofilm control. At the follow-up appointments, if a tooth displays posteruptive breakdown restricted to enamel, the patient will be kept in the study, but if the breakdown affects dentin (or in the case of a cavitated carious lesion), the patient will receive restorative treatment and be excluded from the study. If the patient has relapsed sensitivity, the initial treatment protocol will be maintained according to each group.

Data Analysis

Statistical analysis will be performed with SigmaPlot (version 12.3; SPSS Inc). For the WBFPS, SCASS, and FLACC scale, the three groups and evaluation time will be compared by 2-way repeated measures analysis of variance followed by a Tukey

test, based on the recommendation of Cohen [31], to allow for interaction analysis between study factors and to avoid an inflated α error. A Spearman correlation test will be performed to determine if there is a significant correlation among the WBFPS, SCASS, and FLACC scale. The significance level will be set at 5%. Poisson regression will be used to assess the influence of IPV, GI, and discomfort on the outcome. The satisfaction of parents/guardians and participants will be analyzed descriptively.

Results

The children are currently being recruited. Thus far, 6 patients have been selected and treated, and they are now in the follow-up phase. At the 1-month follow-up, 1 participant was excluded since the tooth under evaluation was restored by a dentist in a private office. The first results are expected to be obtained in 2022.

Discussion

MIH presents with various severity levels and side effects, and a broad spectrum of treatment approaches are available [32]. In some cases, hypersensitivity may be present even when there is no enamel loss and no clinically detectable exposed dentin [1,4], and treatment is not always successful with regard to symptomatology. Currently, there is no consensus on the best treatment for teeth with sensitivity due to MIH. Studies focusing on new therapies to treat this condition should be conducted to guide dentists in the selection of patient-friendly procedures, facilitating restorative treatment.

Although only a few clinical studies have evaluated it, the commercially available 5% NaF varnish is considered the gold standard due to its effectiveness and easy application. However, the TiF$_4$ varnish, which is not yet available, has a similar application protocol; depending on the results of this study, it could be made available in the market and distributed to treat sensitivity in the future. Although more expensive, PRG Barrier Coat has the advantage of requiring a single application, with reapplication considered based on the patient's clinical demand. This clinical trial will evaluate as the primary outcome the efficacy of different materials in decreasing sensitivity in teeth affected by MIH.

In this study, sensitivity will be assessed with 3 instruments. Quantifying sensitivity is not easy, especially in children, since responses to stimuli depend on the individual [4], and this limitation should be considered when interpreting the results. The face scale (WBFPS) has been shown to allow children to respond very subjectively. This scale consists of 6 faces, with the first showing a very happy face and the last showing a very sad face [33]. Children may associate the faces with their emotional state and not with their perception of pain. In this study, the SCASS and FLACC scale will be used concomitantly since both include parameters considered indicative of pain that can be detected and classified by an observer.

A previous study showed that patients benefit from MIH therapy as it reduces hypersensitivity, consequently allowing for proper oral hygiene and biofilm reduction [32]. However, that study

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compared the treatment effects of using fluoride varnish, fissure sealants, fillings, and stainless-steel crowns in teeth with different levels of MIH severity, and most of the teeth that received the varnish treatment had a mild level of MIH, without hypersensitivity. Contrarily, this study will assess only teeth without enamel loss and with hypersensitivity to evaluate the effect of different treatments on pain and consequently on biofilm accumulation and gingival health.

Secondary outcomes include parental satisfaction and child self-reported discomfort. Patient-centered outcomes are important for the selection of the best treatment. As the study will be carried out in children, obtaining the opinions of their family members is important and this will encourage greater involvement, commitment, and cooperation.

Finally, it is important to mention the limitations of the study. MIH is a dynamic condition that can get worse over time due to posteruptive breakdown, which can lead to dentinal exposure. In such a case, the hypersensitivity reported by the patient could be due to dentin exposure rather than the hypomineralized tissue. For that reason, teeth with dentin exposure in the follow-ups will be restored and excluded from the study. Additionally, although the short interval between visits lowers the risk of caries development, teeth that have cavitated caries will be restored and excluded from the study.

Thus, our study will emphasize the importance of treating teeth with MIH to relieve hypersensitivity and consequently improve children's quality of life. If the results are satisfactory, this study will contribute significantly to the establishment of a treatment protocol for the control of sensitivity in teeth with MIH.

Acknowledgments

Conflicts of Interest

None declared.

Multimedia Appendix 1
UntitlSchiff's Cold Air Sensitivity Scale.
[DOCX File , 13 KB - resprot_v11i1e27843_app1.docx]

Multimedia Appendix 2
FLACC (Face, Legs, Activity, Cry, Consolability) scale.
[DOCX File , 14 KB - resprot_v11i1e27843_app2.docx]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
FLACC: Face, Legs, Activity, Cry, Consolability
GI: gingival index
IPV: visible plaque index
MIH: molar incisor hypomineralization
NaF: sodium fluoride
SCASS: Schiff Cold Air Sensitivity Scale
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
S-PRG: surface prereacted glass-ionomer
TiF$_4$: titanium tetrafluoride
WBFPS: Wong-Baker FACES Pain Rating Scale

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Protocol

The Safety, Clinical, and Neurophysiological Effects of Intranasal Ketamine in Patients Who Do Not Respond to Electroconvulsive Therapy: Protocol for a Pilot, Open-Label Clinical Trial

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Abstract

Background: Major depressive disorder is among the most disabling illnesses worldwide, with a lifetime prevalence of 16.2%. Research suggests that 20% to 40% of patients with depression do not respond to pharmacotherapy, developing treatment-resistant depression. Electroconvulsive therapy is the gold standard for treating individuals with treatment-resistant depression, with remission rates of approximately 75% to 90%. However, 10% to 25% of patients do not respond to electroconvulsive therapy, and many are unable to tolerate it due to the side effects. Both groups are considered to be patients who do not respond to electroconvulsive therapy, because both groups continue to exhibit symptoms of severe depression, have a limited number of treatment options available, and are in need of rapid treatment. Ketamine, an N-methyl-D-aspartate receptor antagonist, has been shown to exert rapid antidepressant effects in patients with treatment-resistant depression when administered in subanesthetic doses through 40-minute intravenous infusions. Recently, a ketamine compound, esketamine (Spravato), that is administered through the intranasal route received regulatory approval by the US Food and Drug Administration and Health Canada to treat depression. However, esketamine is challenging to access due to high costs and limited availability. Racemic ketamine (rketamine) is cheap and easy to access; however, the effects in patients who have not responded to electroconvulsive therapy have yet to be understood or tested. This study will use transcranial magnetic stimulation to study mechanisms of human brain cortical physiology at the systemic level to identify neurobiomarkers of response.

Objective: The objective of this open-label pilot clinical trial is to test the feasibility and safety of intranasal ketamine in patients who have not responded to electroconvulsive therapy. The primary outcome is to determine the feasibility of a larger randomized controlled trial to test the efficacy of intranasal ketamine for patients who have not responded to electroconvulsive therapy for clinical indicators in unipolar depression. The secondary outcome is to determine the preliminary effects of an intervention on clinical outcomes, such as depressive symptoms, suicidal ideation, and quality of living. The third outcome is to explore neurophysiological changes as measured by transcranial magnetic stimulation electromyography and electroencephalography to measure changes in cortical excitability as potential predictors of clinical response.

Methods: A sterile solution of racemic ketamine hydrochloride will be administered twice per week for 4 weeks (8 sessions) intranasally to patients with treatment-resistant depression who did not respond to or could not tolerate an acute course of electroconvulsive therapy. We will recruit 25 adults (24-65 years old) over the course of 2 years from an academic psychiatric hospital in Toronto, Canada.

Results: This study has received ethics approval, and funding has been secured. The study is currently active.

Conclusions: This is the first study to test repeated doses of intranasal rketamine in patients who have not responded to electroconvulsive therapy for depression. Results from this study will (1) inform the development of a larger adequately powered

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randomized controlled trial to test the efficacy of intranasal ketamine for depression and (2) determine potential neurophysiological markers of clinical response.

Introduction

Depressive disorders remain common, severe, and debilitating, with a lifetime prevalence estimated at 16.2% [1]. Research suggests that between 20% and 40% of patients with depression do not respond adequately to pharmacotherapies such as selective serotonin and serotonin–norepinephrine reuptake inhibitors, tricyclic antidepressants, or other psychotherapeutic interventions [2], and thus, are diagnosed with treatment-resistant depression [3]. Electroconvulsive therapy continues to be the gold standard therapeutic approach for treatment-resistant depression [3]. The Consortium for Research in Electroconvulsive Therapy [4] reports a 65% remission rate after 10 sessions that is consistent across the spectrum for bipolar and unipolar depression [5], with some previous studies also reporting remission rates as high as 70% to 90% [4,6]. However, despite these high efficacy rates, 10% to 30% of patients do not respond to electroconvulsive therapy, and these patients are left with very few treatment options [7].

Ketamine, a noncompetitive high-affinity *N*-methyl-D-aspartate (NMDA) receptor antagonist, has been shown to exert rapid and robust antidepressant effects in patients with treatment-resistant depression [8]. Studies have demonstrated that a single intravenous infusion of an NMDA antagonist resulted in significant decreases in depressive symptoms [9], making ketamine an attractive treatment option with the ability to simultaneously reduce neuronal activity in the limbic and subcortical regions while increasing activity in the prefrontal cortex [10], an area of core dysfunction reported in those with depression [10]. Numerous studies [11,12] have demonstrated that a subanesthetic dose of ketamine (0.5-0.8 mg/kg) over 40-minute intravenous infusion produces rapid antidepressant effects in patients with treatment-resistant depression. It has also been reported that the route of administration of ketamine can influence the clinical antidepressant effects of treatment owing to its extensive first-pass metabolism; specifically, the highest bioavailability of ketamine is achieved via intravenous infusion, while oral administration yields the lowest bioavailability [13]. Findings suggest that 70% of patients with treatment-resistant depression respond to 1 to 3 administrations of ketamine, and 30% to 60% of patients with treatment-resistant depression experience remission of their depressive symptoms. Research suggests that most responses occur if ketamine is administered in 6 or more sessions over a >2-week period [8,12].

Although intravenous ketamine has demonstrated rapid antidepressant effects, its delivery method remains challenging because it requires specialized expertise and equipment for administration [11]. Intranasal drug delivery, while preserving the rapid onset of therapeutic action, offers a route to the brain that bypasses problems associated with gastrointestinal absorption, first-pass metabolism, and the blood-brain barrier, and thus, minimizes the inconvenience and discomfort of parenteral administration [14]. Studies [15] indicate that intranasal rketamine has an absolute bioavailability of 50%, with a maximum plasma concentration achieved at approximately 20 minutes. This is consistent with other studies [13,15-17] in which the reported bioavailability of intranasal rketamine was demonstrated to be 45% to 50%. Converging evidence indicates that using intranasal ketamine with a dose range of 50-175 mg taken in intervals of 3 to 7 days can positively affect mood symptoms with a limited number of side effects [10]. Recently, esketamine (Spravato) received regulatory approval from the US Food and Drug Administration and Health Canada. However, it remains out of reach for most people with depression due to high costs and limited availability. To our knowledge, the clinical effects of intranasal rketamine have not yet been studied in a group of individuals with treatment-resistant depression who have not responded to electroconvulsive therapy.

Noninvasive brain stimulation neurophysiological tools, such as transcranial magnetic stimulation (TMS), offer an elegant opportunity to study mechanisms of human cortical physiology at the systemic level. The combination of TMS with a central nervous system pharmacological agent, such as ketamine, provides a platform to explore the neurophysiological impact of ketamine and allows neurophysiological biomarkers of treatment response to be identified. Until recently, only a few studies [16-18] have attempted to examine excitatory and inhibitory circuits by using a range of TMS protocols during infusion of incremental doses of ketamine, primarily using very low or single doses of ketamine in healthy volunteers. Currently, the research on predicting therapeutic response in those with mood disorders, measured by changes in cortical excitability, continues to be in very early stages and has not been systematically tested, making this proposal uniquely positioned among other neurophysiological studies [16,17,19] on ketamine and TMS. Our group has previously demonstrated impaired γ-aminobutyric acid inhibition from the motor cortex in patients with depression, a finding that was most pronounced in patients with treatment-resistant depression [18]. Additionally, Croarkin et al [20] demonstrated impaired NMDA receptor-mediated excitation in adolescent depression. The impact of ketamine on an excitatory or inhibitory cortical network will be assessed

using neurophysiological tools such as TMS, specifically via short-interval cortical inhibition paradigms [21],

In this study, we aim to assess the safety and feasibility of intranasal rketamine in patients with unipolar depression who did not respond to the acute course of electroconvulsive therapy to inform a larger randomized controlled trial and examine potential neurophysiological biomarkers of response. TMS-electromyography (EMG) and electroencephalography (EEG) paradigms can be used to investigate the impact of ketamine on cortical activities via intracortical facilitation and short-interval cortical inhibition paradigms [19,22-26]. Based on accumulating evidence supporting the efficacy and tolerability of ketamine, we hypothesize that intranasal rketamine administered twice per week over 4 weeks will (1) result in improvement in depressive; (2) be safe and well tolerated in patients with treatment-resistant depression who could not tolerate or have not responded to electroconvulsive therapy; (3) result in neurophysiological changes. The results of this study will provide an important characterization of the neurophysiological effects of rketamine on cortical neurophysiology [19,22-26], which may serve as a ketamine biomarker and would be a crucial breakthrough in determining potential predictors of clinical response for depression.

Methods

Design

This is an open-label pilot study to assess the feasibility of conducting a randomized controlled trial to test the safety, tolerability, and efficacy of intranasal ketamine in patients with treatment-resistant depression who did not respond or were not able to tolerate a course of acute electroconvulsive therapy.

Ethics Approval

This study has received Centre for Addiction and Mental Health (CAMH) research ethics board (095-2019) and Health Canada approval. For this pilot trial, all relevant adverse events and all serious adverse events will be reported if they meet applicable reporting requirements. All data monitoring, auditing, and harms reporting will be performed according to CAMH research ethics board and regulatory standards.

Recruitment and Feasibility

Recruitment

Over a period 2 years, we intend to recruit 25 adults aged 24 to 65 years old diagnosed with treatment-resistant depression from one site (CAMH).

Participants

Patients will be assessed for eligibility based on inclusion and exclusion criteria.

Inclusion and Exclusion Criteria

Inclusion criteria are patients who (1) have a DSM-5 diagnosis of nonpsychotic major depressive disorder, confirmed by the Mini-International Neuropsychiatric Interview; (2) meet criteria for being nonresponsive to electroconvulsive therapy in the current episode (nonresponse is defined as lack of improvement

in depressive symptoms after 8 acute sessions of electroconvulsive therapy, confirmed with the Hamilton Rating Scale for Depression (HRSD-24 score >14), and nontolerability is determined by a brain stimulation psychiatrist based on side effects, such as postictal confusion, significant cognitive impairment, severe worsening in anxiety preventing a patient from continuous treatment, or failure to secure intravenous access safely); (3) exhibit moderate to severe symptoms of depression (HRSD-24 score >14); (4) are capable of providing consent; (5) are outpatients; (6) are able to speak and understand English; and (7) are aged 24 to 65 years, inclusive.

Exclusion criteria are patients (1) with a history of a substance use disorder within the past month or lifetime history of ketamine substance use disorder, confirmed by the Mini-International Neuropsychiatric Interview; (2) with concomitant major unstable medical illness (eg, poorly controlled blood pressure; enlarged prostate; unresolved urinary related issues); (3)with a confirmed pregnancy or the intention to become pregnant and breastfeeding during the study (self-report), and female participants of reproductive age must be willing to use a medically acceptable method of birth control that includes highly effective (eg, approved hormonal contraceptives, intrauterine device, tubal ligation), double barrier (eg, male condom with a diaphragm, male condom with cervical cap) methods of contraception, or abstinence if that is the usual and preferred lifestyle of the participant; (4) with cardiac decompensation or heart failure; (5) with a DSM-5 diagnosis of any primary psychotic disorder, bipolar disorder, obsessive-compulsive disorder, or current posttraumatic stress disorder, confirmed by the Mini-International Neuropsychiatric Interview; (6) with a diagnosis of severe personality disorder, assessed during the initial consultation with a physician at the study site prior to study entry; (7) with any significant neurological disorder (eg, a space-occupying brain lesion, a history of stroke, a cerebral aneurysm, a seizure disorder, Parkinson disease, Huntington chorea, multiple sclerosis), assessed through medical history review during the initial consultation with a physician at the study site prior to study entry; (8) with a medical condition, taking medication, or with a laboratory abnormality that could cause a major depressive episode or significant cognitive impairment in the opinion of the investigator; (9) requiring a benzodiazepine with a dose equivalent to lorazepam 2 mg/day or higher; (10) on any anticonvulsant (eg, lamotrigine) or opioid medication due to the potential of these medications to limit the efficacy of ketamine; (11) with the inability to communicate in spoken and written English fluently enough to complete the required study assessments due to a language barrier or a noncorrectable clinically significant sensory impairment (ie, cannot hear or see well enough to complete clinical assessments); (12) with any cognitive or physical impairment which may potentially interfere with intranasal ketamine administration or the patient's ability to stay in the same place for a 2-hour monitoring supervision, assessed through medical history review during the initial consultation with a physician at the at the study site prior to study entry; (13) with any intracranial implants (eg, aneurysm clips, shunts, cochlear implants) or any other metal object within or near the head, excluding the mouth, that cannot be safely removed given that we will be using TMS-EMG/EEG; (14)

with the inability to secure escort to accompany them back home after ketamine sessions; or (15) with any known allergy to ketamine or any component or ingredient of the ketamine preparation.

Discontinuation Criteria

Participants will be discontinued from the study if they experience clinically significant worsening depression symptoms (50% increase in HDRS-24 scores from baseline on 2 consecutive ratings); require in-patient hospitalization due to the presence of clinically significant suicidal ideation with imminent intent or attempted suicide; develop clinically significant worsening of mood, psychotic, or physical symptoms (assessed by a study physician); miss more than 2 consecutive treatments during the study; develop any medical illness that may be unstable; experience a seizure; become pregnant; or withdraw consent.

Feasibility

We believe recruiting 25 participants over the course of 2 years is feasible. Participants will be recruited through the Temerty Centre for Brain Intervention at CAMH, which treats approximately 150 to 200 patients with depression with electroconvulsive therapy per year. The principal investigator is a staff psychiatrist at the Mood and Anxiety Division, which provides outpatient services for a large population with mood disorders at local and provincial levels. In addition, this protocol has been piloted with 3 patients who were nonresponsive to electroconvulsive therapy, and the patients were able to comply with a protocol of 2 sessions per week for 8 treatment sessions given very close clinical supervision in a trial (unpublished data, Y. Knyahnytska).

Consent to Participate

Informed consent will be obtained from each individual who agrees to participate in the trial prior to and throughout participation. Patients meeting criteria will be referred to the study coordinator to discuss the study purpose, procedures, potential risks, and rights as research participants. Consent forms describing the study intervention, study procedures, and risks will be given to each participant, and written documentation of informed consent will be required prior to completing the initial screening visit and starting the study intervention. Once consent is obtained, the research personnel will confirm that inclusion and exclusion criteria are met before proceeding with baseline testing. Patients will be informed that they can withdraw from the study at any point. A copy of the information and consent documents will be given to the participants for their records. The informed consent process will be documented, and the form signed before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Data confidentiality and confidentiality of the identities of the individuals participating in this study will be strictly maintained. Data forms that include identifying information will be kept in locked cabinets. Only the unique ID number assigned by the research coordinator will be used to represent participants during data entry, data transfer, data analysis, or other file management procedures. All information linking their identity will be kept separate from the research records. All information entered into a computer will be stored in a password-protected encrypted file format on a secure server. If any participant withdraws from the study, any research information recorded for or resulting from participation prior to the date that the participant formally withdrew consent will continue to be stored and used (in the manner described above) for research purposes (and will be disclosed by the investigators); however, no new data will be collected. Withdrawing from the study will not have any consequences for the participant. Participants' identities will not be revealed in the publication or presentation of any results from this study.

Intervention

Drug Characteristics, Distribution, and Storing

A sterile form of racemic ketamine hydrochloride will be dispensed through the CAMH pharmacy and will be administered intranasally using an atomizer provided by the pharmacy (MAD300, Teleflex). The CAMH research pharmacy will order the investigational product from the supplier (Sandoz Canada Inc) on behalf of the research team with the study investigator's authorization and will be responsible for the receipt and responsible destruction of the investigational product. The investigational product will be stored between 15 ℃ and 30 ℃, protected from light and heat and discarded within 28 days of initial use.

Drug Administration and Scheduling

Intranasal rketamine will be administered twice per week for 4 weeks (8 treatment sessions in total). The dosage schedule will be determined based on participants' weight, clinical response, and tolerability (Multimedia Appendix 1). Given that the absolute bioavailability of intranasal ketamine is 45% to 50 % compared with that of intravenous administration [13,14], intranasal doses will range from 1 mg/kg to 1.6 mg/kg to represent usual intravenous doses of 0.5-0.8 mg/kg and to account for reduced bioavailability of the intranasal form. Participants will be started at the lowest dose during the first treatment session (average 50 mg of intranasal ketamine administered in 2 syringes with 25 mg per syringe).

Dose Adjustment

If the first session is tolerated well, and the patient has no side effects, the session 2 dose will be increased to 1 mg/kg (to represent an intravenous dose of 0.75 mg/kg adjusted to 50% bioavailability). If both sessions are tolerated well, session 3 will start on a full therapeutic dose (1.5-1.6 mg/kg to represent intravenous doses of 0.75-1 mg/kg). Participants will have a weekly visit with the study's medical doctor, and doses will be monitored and adjusted based on tolerability and clinical response; however, they will not exceed 1.6 mg/kg.

Monitoring Schedule

All patients will stay on-site for the administration and 2-hour postintervention monitoring period, per consensus guidelines in ketamine administration [27]. Patients will be provided with a separate quiet space, noise-cancellation headphones, and an

eye mask to minimize environmental disruptions. All patients will be observed 1:1 or 1:2 for the entire duration of the treatment session by trained personnel. The medical doctor is present on-site during the session to address any urgent requests and provide support to the team and patient. Vitals will be taken and recorded consistently during every 30 minutes during the 2-hour monitoring period after administration. A medical team will manage any emergencies that arise, and appropriate medications will be provided to manage treatment-related side effects and any adverse events, if needed (defined by clinical site policies and regulations). Clinical and neurophysiological assessments will be administered according to a schedule for study visits by trained research personnel (Multimedia Appendix 2).

Potential Risks and Mitigation Strategies

Given the potential risks described below, trained medical personnel will be present during the administration and for the entire duration of the 2-hour monitoring period.

Drug-related risks include (1) psychiatric symptoms such as fatigue, dizziness, anxiety, visual and auditory disturbances, panic attacks, increased irritability, or changes in mood and behavior; (2) medical symptoms such as transient increases in blood pressure and heart rate, an increase in need to urinate, headaches, vision changes, chest pain, shortness of breath, confusion, memory impairment, anaphylaxis; and (3) rare risk of dependency. Ketamine is classified as a schedule I controlled substance due to its potential for abuse and addiction and can be abused in a number of ways, including via injection, snorting, or orally [8]. Ketamine can produce vivid dreams and feel that the mind is separated from the body. Regular users of ketamine can become tolerant to the dissociative effects of the drug, meaning more and more is needed to achieve the same effect [8]. To address these risks, in this trial, ketamine will be dispensed by the research pharmacy and administered by a trained medical professional, and the patient will receive close supervision and monitoring. Doses are individually calculated, and treatment sessions are structured to prevent tolerance building. Patients will be strongly discouraged from using ketamine outside of the context of this trial and will be informed that if they have more questions, they can be discussed with their medical provider or study physician.

A potential risk in clinical assessments is that answering multiple questions can, at times, be distressing. These adverse reactions are primarily brief and transient and rarely have any long-term implications.

The ability of TMS to noninvasively stimulate brain areas presents a significant advance beyond techniques that require the invasive method of direct cortical or transcranial electrical stimulation. Magnetic fields pass through the scalp and skull without the impedance encountered by direct electrical stimulation, permitting enhanced control over the site and intensity of stimulation. In numerous studies [23,24], single-pulse TMS has been found to pose no significant health risk to properly screened healthy volunteers. Single-pulse TMS is now in routine clinical diagnostic use in hundreds of neurophysiological laboratories worldwide, and the induced electrical current is well below that which is expected to cause harm to nervous tissue; thus, stimulation at <1 Hz carries virtually no risk of seizure and is therefore classified as a nonsignificant risk device [23,24].

Study Measurements

Given that this trial recruits participants who received at least one electroconvulsive therapy session, and therefore, underwent blood work, electrocardiography, and medical clearance by anesthesia services in accordance with standard clinical procedures, we will use these parameters for this trial. The results will be available for screening and review by the study's medical doctor prior to the start of treatment. Tests completed within the 6 months prior to screening will be used unless new medical symptoms requiring further investigation emerge, in which case, the tests will be repeated. Blood tests will include complete blood count with differential tests (white blood cells, red blood cells, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red cell distribution width, mean platelet volume, platelet, nucleated red blood cell count, neutrophil count, lymphocyte count, monocyte count, eosinophil count, basophil count) and blood chemistry tests for liver function (alanine aminotransferase, aspartate aminotransferase), kidney function (blood urea nitrogen, creatinine), electrolyte levels (sodium, potassium, chloride, phosphate), and thyroid function (thyroid-stimulating hormone). Electrocardiography results will be reviewed by the study's medical doctor. Participant blood pressure will also be monitored before, during, and after treatment.

Clinical assessments will include (1) the Mini-International Neuropsychiatric Interview, to assess current and lifetime depression and other psychiatric disorders and to clarify psychiatric inclusion and exclusion criteria; (2) the 24-item Hamilton Rating Scale for Depression [28], as the primary outcome measure (and a score greater than or equal to 14 will be used to establish eligibility at study entry); (3) the Scale of Suicide Ideation [29], administered at baseline, weekly, at posttreatment, and at follow-up to monitor for any safety concerns and a secondary outcome measure to assess suicidality; and the (4) World Health Organization Disability Assessment Schedule 2.0 [30], used as a standard measure of disability promoted and administered at baseline and posttreatment to assess changes in individual level of functioning.

Demographic information, medical history, concomitant medications, and antidepressant treatment history form information will also be assessed.

Monitoring assessment during treatment sessions will include (1) vital signs collected every 30 minutes during a 2-hour monitoring session (blood pressure, heart rate, and oxygen levels) and (2) behavior changes assessed through observation.

Neurophysiological assessments will include (1) the Transcranial Magnetic Stimulation Adult Safety Screen to assess for potential TMS risk factors; and (2) TMS-EMG/EEG (Multimedia Appendix 2). Our neurophysiological measures have been established and have a high test–retest reliability (ie, intraclass correlation >0.9) [31,32]. Data analysis will be performed using semiautomated methods developed and validated by our group

[31,32]. TMS pulses will be administered to the left dorsolateral prefrontal cortex, using a figure-of-eight coil (7 cm), and 2 Magstim 200 stimulators (Magstim Company Ltd) connected via a Bistim module, and motor evoked potential data will be collected using commercially available software (Signal, Cambridge Electronics). Each TMS session will include the establishment of the individual threshold for stimulation motor cortex, and dorsolateral prefrontal cortex localization will be performed according to previously published methods [31,32]. Resting motor threshold will be determined by applying single pulses of TMS to the motor cortex while the coil is placed at the optimal position to elicit motor evoked potentials from the right abductor pollicis brevis muscle. The resting motor threshold is defined as the minimum stimulus intensity that elicits a motor evoked potential of >50 µV in more than 5 of the 10 trials [33,34]. Electromyography will be recorded from the abductor pollicis brevis with Ag–AgCl electrodes placed over the belly of the muscle. The signal will be amplified (Intronix Technologies Corporation Model 2024F), filtered (bandpass 2 Hz-5 kHz), digitized at 5 kHz (Micro 1401, Cambridge Electronics Design), and stored in a laboratory computer for offline analysis. The participants will be instructed to relax throughout the study. Trials contaminated with voluntary muscle activity will be discarded.

EEG will be used to evaluate TMS-induced cortical evoked activity. EEG recordings will be acquired through a 64-channel EEG system [35]. A 64-channel EEG cap will be used to record the cortical signal, and 4 electrodes will be placed on the outer side of each eye and above and below the left eye for eye movement artifacts. All electrodes will be referenced to an electrode placed on the vertex positioned posterior to the Cz electrode. Direct current EEG signals will be recorded with a 20 kHz sampling rate and with a low-pass filter of 300 Hz, which, in pilot experiments [35], was shown to avoid saturation of amplifiers and minimize the TMS-related artifact. The EEG data will be downsampled to 1 kHz and segmented with respect to the TMS stimulus, such that each epoch includes 1000 ms of prestimulus baseline and 1000 ms of poststimulus activity. Epochs will be baseline corrected with respect to the TMS-free prestimulus interval (1000 ms to 110 ms prior to the TMS). The baseline-corrected poststimulus intervals (approximately 25 ms-1000 ms) that are not contaminated by TMS artifact will be extracted and digitally filtered using a zero-phase shift 1-100 Hz bandpass filter (48 dB per octave). Records will be manually reviewed at this stage, and trials contaminated with muscle activity, movement, and TMS artifacts will be excluded from further analysis. Finally, the average signals at each recording site will be computed from the movement-free epochs (approximately 80 trials per participant) and fed into an automated eye-blink correction algorithm [36]. The eye-blink corrected average EEG waveforms will be imported into MATLAB (The MathWorks Inc), and further analyses will be carried out utilizing the EEGLAB toolbox [37-39]. Further methods in this approach will be conducted according to previously published combined TMS/EEG studies [35].

Statistical Analysis

Statistical and Analytical Plans

Baseline participant characteristics will be reported and described using summary statistics—mean and standard deviation for continuous data and number and proportion for categorical data. The primary analysis to determine if there is a statistically significant effect of intranasal ketamine on depressive symptoms will be the paired 1-tailed t test of the HDRS-24 score at baseline to week 4. We will also report the standardized mean difference as a measure of effect size (small: 0.2; medium: 0.5; large: 0.8 [40]). For tolerability and safety outcomes, we will report the number and proportion of individuals who experience a transient increase in blood pressure, agitation, and behavioral disturbance. To assess suicidality change, we will use the 1-tailed paired t test from baseline to week 4 of the Scale of Suicide Ideation score and calculate the standardized mean difference. For neurophysiology, we will use the 1-tailed independent t test to compare components of TMS-evoked responses at left dorsolateral prefrontal cortex. In addition, we will use the nonparametric cluster-based permutation test to investigate any significant changes in overall EEG channels.

Sample Size

CAMH treats approximately 250 new patients with depression each year with electroconvulsive therapy. Assuming 25% to 30% nonresponse or intolerability and that, of these individuals, 20% will be eligible for treatment, we expect to be able to recruit 25 participants over the course of 24 months.

Results

This study has received ethics approval. We have started recruitment for the trial and anticipate having initial results in spring 2022.

Discussion

To our knowledge, this is the first study to test repeated doses of rketamine delivered intranasally in patients with major depressive disorder who did not respond (either clinically or due to their inability to tolerate) to an acute course of electroconvulsive therapy. The use of neurophysiological tools to assess changes in cortical excitability will provide preliminary data for potential biomarkers of response, which can be further assessed in a larger clinical trial. A lack of control group and small sample size are limitations of the current protocol. However, given that it is a pilot open-label clinical trial, the sample size is sufficient (ie, the goal is not to assess generalizability or statistical significance). The lack of blinding in the control group is a common concern in ketamine trials [27], because a placebo with comparable effects does not exist, and it is impossible to ensure blinding to the full extent. Because the study is being conducted at a single site of a large psychiatric academic facility, the results may not be transferable to a broader population.

Results will be presented during scientific conferences, in clinical rounds, and publications in relevant journals.

Multimedia Appendix 1
Dosage schedule for intranasal rketamine.
[DOCX File , 13 KB - resprot_v11i1e30163_app1.docx]

Multimedia Appendix 2
Study visits.
[DOCX File , 14 KB - resprot_v11i1e30163_app2.docx]

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Abbreviations

CAMH: Centre for Addiction and Mental Health
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition
EMG: electromyography
EEG: electroencephalography
GABA: γ-aminobutyric acid
NMDA: N-methyl-D-aspartate
rketamine: racemic ketamine
TMS: transcranial magnetic stimulation

Protocol

The Role of Carbohydrates in Irritable Bowel Syndrome: Protocol for a Randomized Controlled Trial Comparing Three Different Treatment Options

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Abstract

Background: Although it is widely acknowledged that food intake can worsen symptoms in patients with irritable bowel syndrome (IBS), there is a lack of efficient treatments that can apply to all patients and subtypes of IBS. As IBS can manifest in different ways, it is likely that the most successful treatment option will differ among patients; therefore, this large, randomized controlled trial comparing 3 different treatment options for patients with IBS is highly warranted.

Objective: This study aims to conduct a randomized controlled trial to evaluate the effectiveness of 3 different treatment options for patients with IBS.

Methods: A total of 300 patients with IBS will be randomized (1:1:1) to receive one of the following three treatment options: a diet with low total carbohydrate content; a diet combining low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols and traditional dietary advice in IBS; and optimized medical treatment. The study will comprise a 10-day screening period, 28 days of intervention, and a 6-month follow-up for patients receiving dietary treatment. Questionnaires assessing both gastrointestinal and extraintestinal symptoms will be used as end points, as well as metabolomics, microbiota profiling, and immunological markers. Furthermore, qualitative methods will be used to evaluate the patients' experiences regarding diet treatments.

Results: Recruitment for this study began in January 2017. By May 2021, of the proposed 300 participants, 270 (90%) had been randomized, and 244 (81.3%) participants had finished the 4-week intervention. The study is still in progress, and the results are expected to be published in 2022.

Conclusions: By collecting a wide range of data before, during, and after treatment in a large group of patients with IBS and diverse bowel habits, we will gain new insights into the predictors of response to treatment. That information can, in the future, be used to personalize treatment for the patient, based on the individual's phenotype and IBS symptoms. In addition, the long-term effects of 2 different dietary treatments will be evaluated regarding their impact on gut microbiota and clinical laboratory tests and to ensure that they are safe, effective, and applicable for patients with IBS.

Trial Registration: ClinicalTrials.gov NCT02970591; https://clinicaltrials.gov/ct2/show/NCT02970591

International Registered Report Identifier (IRRID): DERR1-10.2196/31413

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Introduction

Background

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder characterized by abdominal pain and altered bowel habits [1]. Some of the pathophysiological traits of IBS include disturbed gut–brain interactions, GI motility abnormalities, visceral hypersensitivity, or altered gut microenvironments, including unfavorable gut microbial composition [2-4]. However, available treatment options are limited, which leads to unsatisfactory symptom relief in many patients. This leads to a reduced quality of life (QoL) and impaired working ability, with substantial costs for both the individual and society [5].

Most patients with IBS report that their GI symptoms are diet related [5-7]. Different dietary approaches have been proposed to reduce symptoms of IBS [8]. Traditional dietary advice based on the National Institute for Health and Care Excellence (NICE) guidelines focuses on limiting foods that are recognized to provoke symptoms and emphasizes regular meal intake and portion size control [9]. A diet comprising a low amount of fermentable carbohydrates—the low fermentable oligosaccharide, disaccharide, monosaccharide, and polyol (FODMAP) diet—is currently also used as a treatment option for reducing GI symptoms in patients with IBS, most frequently as a second-line treatment option [10]. FODMAPs are found in a wide range of legumes, certain vegetables and fruits, cereals (wheat, rye, and barley), dairy products, and food items containing sweeteners. The intake of FODMAPs is believed to cause symptoms through bacterial fermentation and increased gas production. This, in combination with increased water retention through osmosis, distends the colon and can cause pain and other IBS-related symptoms in susceptible individuals, for example, those with visceral hypersensitivity [11,12]. This dietary regime has been tested in several randomized trials and seems to be effective in 50%-80% of patients with IBS [13]. To our knowledge, no trial has tested the combined effect of traditional dietary advice together with low FODMAP content.

It has been acknowledged that patients who adhere to a low-carbohydrate, high-fat diet for weight loss purposes, or to lower their blood glucose levels, have reported fewer GI symptoms when following this diet [14]. A pilot study investigated the effects of a diet with low-carbohydrate content in patients with IBS, and although the sample size was small, the effect was very promising [15]. However, most patients seeking help for their IBS complaints will most likely see a primary care physician who frequently offers various prescription drugs. To date, no study has compared the effect of a strategy where pharmacological treatment options are used with a diet low in total carbohydrate content, or a low FODMAP diet is used in combination with traditional dietary advice for patients with IBS.

As IBS is a heterogeneous disease with different predominant symptom patterns and underlying pathophysiological traits, personalized treatment options are needed. A better understanding of the predictors of a favorable outcome with different treatment options can facilitate this and reduce the overall symptom burden in this large patient group, which, in turn, could reduce costs for society and the individual. Therefore, a large, randomized trial comparing the effects of these 3 different treatment strategies for patients with IBS, with a thorough examination of the factors predicting treatment outcomes, is warranted.

Research Objectives and Hypotheses

The aim of this study is to compare the effectiveness of three different treatment options for patients with IBS: a low-carbohydrate diet (LCD), a diet combining low FODMAP and traditional dietary advice (LFTD), and optimized medical treatment (OMT). The trial has been registered at ClinicalTrials.gov NCT02970591.

Specific Aims

The specific aims of this study are as follows:

- To compare the response to 3 different treatment options for IBS, defined as a reduction in IBS symptom severity score by ≥50, in a 4-week randomized controlled trial using the validated IBS Severity Scoring System (IBS-SSS) [16]
- To study the effects of these treatment options on QoL, anxiety and depression, fatigue, extraintestinal symptoms, metabolic factors, gut microbiota, and immunological markers
- To study the extent to which participants choose to maintain their allocated diet and whether it will be possible to reintroduce certain amounts of FODMAPs successfully and assess the long-term effects on global IBS symptoms, metabolic factors, and gut microbiota during a 6-month postintervention follow-up
- To identify pretreatment factors, such as sociodemographic factors, IBS symptom severity, predominant IBS symptoms, extraintestinal symptoms, psychological factors, microbiota composition, and metabolic fingerprints that can predict response to the treatments
- To evaluate the participants' subjective experiences related to dietary treatment using qualitative methods

Study Hypotheses

The primary hypothesis is that a diet combining low FODMAP and traditional dietary advice would improve GI symptoms in a larger proportion of patients than LCD or OMT. The secondary hypotheses to be tested are as follows: (1) the reduction in GI symptoms depends on the compliance to the allocated intervention; (2) it is possible to reintroduce FODMAPs in a systematic manner after a 4-week elimination with sustained effect on GI symptoms; (3) the degree to which the patients maintain their allocated diet during the 6-month follow-up depends on how large the symptom reduction was during the intervention period; (4) a treatment aimed at reducing GI symptoms will also favorably affect extraintestinal symptoms, microbiota composition, QoL, work productivity, and psychological factors; and (5) a combination of microbiota composition, metabolic fingerprint, and GI symptom pattern can predict the treatment outcomes.

Methods

Study Setting and Design

The study will be conducted in an outpatient clinic specializing in functional GI disorders at the Sahlgrenska University Hospital, Gothenburg, Sweden, beginning in January 2017. This will be a single-center, single-blinded, randomized controlled trial.

Allocation

Patients will be randomly assigned to receive 1 of the 3 treatments in a ratio of 1:1:1. For the allocation of the patients, an external web-randomization software will be used. One of the study dietitians will log into the webpage and enter the initials of the patient, whereby the patient will get assigned to a treatment. No stratification will be made before randomization.

Eligibility Criteria

Patients eligible for enrollment must fulfill all the inclusion criteria and none of the exclusion criteria shown in Textbox 1.

Textbox 1. Inclusion and exclusion criteria for participation in the Carbohydrates in Irritable Bowel Syndrome (CARIBS) trial.

Inclusion and exclusion criteria for participation in the trial

Inclusion criteria

- Irritable bowel syndrome, according to Rome IV

- Aged ≥18 years

- Irritable bowel syndrome Severity Scoring System score ≥175

- Gothenburg region resident

Exclusion criteria

- Any other serious disease or illness

- Other gastrointestinal diseases, including celiac disease

- Other diseases that may affect gastrointestinal function, including bariatric surgery

- Allergy or food hypersensitivity (other than lactose intolerance)

- Any (major) dietary restrictions

- Pregnant or breastfeeding

- BMI ≤18 kg/m^2 or ≥35 kg/m^2

- Unable to communicate in Swedish

- Previously been treated with any of the intervention arms, including having tested all the pharmacological treatment options of relevance for the symptom profile of the patient

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Recruitment

Patients will be recruited by referral to a dietitian or physician at a specialized GI unit at the Sahlgrenska Hospital, Gothenburg, Sweden, or through advertising. Patients referred to the unit from, for example, primary care, will be sent an invitation letter with a proposal to participate in the study, and upon approval, they will be scheduled for a screening visit at the clinic. Patients will also be recruited through advertisements in local newspapers or social media platforms.

Sample Size

The power calculation is based on the primary outcome, where the expected response rate is set to 40% (LCD), 65% (LFTD), and 40% (OMT) in the treatment arms. With 80% power to detect differences between groups, and α=.05, 83 patients will be needed in each group. To account for a 15% dropout rate, we will assign 100 patients to each treatment arm.

Participant Timeline

The study comprises a 10-day screening period, followed by a 4-week intervention and a 6-month follow-up period. An overview of the enrollment, allocation, and intervention process is shown in Figure 1.

In short, at the first visit, after receiving verbal and written information about the study, all patients will provide their written informed consent. The diagnosis of IBS will be confirmed by a physician, who will perform a physical examination and ensure that the patients fulfill the Rome IV criteria for IBS [1]. Thereafter, a 10-day screening period will begin, where a daily stool diary based on the Bristol stool form (BSF) scale [17] will be completed, and a 4-day food record will be kept. On their return visit, the patients will complete the IBS-SSS to assess the severity of their IBS symptoms during the 10-day screening period. Patients who score ≥175 on the IBS-SSS (ie, moderate to severe IBS symptoms) will be eligible to be randomized into one of the treatment arms. Patients with an IBS-SSS score <175 will be excluded from further participation and will be offered a regular visit to a dietitian or physician at the clinic.

Figure 1. A schematic overview of screening, allocation, intervention, and follow-up. Blood samples include (a) tissue transglutaminase, immunoglobulin A, hemoglobin, white blood cells, platelets, sodium, potassium, creatinine, calcium, c-reactive protein, thyroid-stimulating hormone, free thyroxine, aspartate aminotransferase, alanine aminotransferase, albumin, and (b) plasma glucose, glycated hemoglobin, cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides. BSF: Bristol stool form; CSI: Central Sensitization Inventory; FODMAP: fermentable oligo-, di-, monosaccharides and polyols; GSRS-IBS: gastrointestinal symptom rating scale-IBS; HAD: Hospital Anxiety and Depression Scale; HSP: Highly Sensitive Person scale; IBS: irritable bowel syndrome; IBS-QoL: IBS quality of life; IBS-SSS: IBS severity scoring system; MFI-20: Multidimensional Fatigue Inventory-20; VSI: Visceral Sensitivity Index; WPAI-IBS: work productivity and activity impairment questionnaire.

	Screening		Study period						
	Enrolment	Screening	Allocation	Post allocation				Follow-up	
Timepoint	$-t_{10d}$	$-t_{10} - -t_1$	0	t_{1w}	t_{2w}	t_{3w}	t_{4w}	t_{3month}	t_{6month}
Visit	1		2				3	4	5
Eligibility screen by physician	X								
Informed consent	X								
Demographics questionnaire	X								
Allocation			X						
Interventions:									
Low carbohydrate diet				◆——————————————————◆					
Low FODMAP+traditional IBS diet				◆——————————————————◆					
Optimized medical treatment				◆—————————◆					
Assessments:									
Food record		X						X	X
Questionnaires: IBS-SSS, BSF, GSRS-IBS		X		X	X	X	X	X	X
Questionnaires: HAD, VSI, MFI-20, IBS-QoL, PHQ-15, WPAI-IBS			X				X	X	X
Questionnaires: HSP, CSI			X						
Anthropometry: weight, height	X						X	X	X
Blood samples[a]			X						
Blood samples[b]			X				X	X	X
Microbiota: fecal sample			X				X	X	X
Metabolomics: serum, urine and fecal samples			X				X	X	X
Immunologic markers: serum			X				X		
Treatment satisfaction questionnaire								X	X	X
Qualitative interview (subgroup of n=20)									X

Questionnaires assessing GI symptoms, extraintestinal and psychological symptoms, fatigue, QoL, and work productivity will be completed after allocation and before starting the intervention, at the end of the intervention period, and during follow-up. A 4-day food record will be repeated twice during the follow-up period. During the intervention period, participants will be instructed to complete a daily stool diary (BSF) and note any deviation from their allocated diet intervention. The patients will also complete questionnaires on a weekly basis to assess the severity of their GI symptoms (IBS-SSS and the GI Symptom Rating Scale-IBS [GSRS-IBS]).

Interventions

Overview

Upon fulfilling all the inclusion criteria and none of the exclusion criteria, the patients will be randomized and receive LCD, LFTD, or OMT. The dietary treatment will be administered by a dietitian and the pharmacological treatment by a physician. All patients will be informed that both diets and medical treatments aim to relieve their symptoms and that none of the treatments are believed to cure IBS.

Overview of Dietary Treatments

Participants assigned to a dietary intervention will receive oral and written information about their diet. No detailed information about the compositions or names of the diets will be given. All foods included in the intervention will be delivered to the patient once a week using a conventional grocery supplier with a home delivery service. A booklet with practical considerations, detailed meal plans, recipes, and lists with foods that are allowed and not allowed during the intervention will be provided. The recipes are based on a standardized energy level, regardless of the energy requirement; thus, patients will be instructed to either eat less or add extra foods if needed (according to the lists provided) to maintain weight stability. If patients need to deviate from their detailed meal plan, all deviations from their diet will have to be reported in a daily symptom diary. After 2 weeks of intervention, patients will be contacted by email to check for compliance and record any adverse events.

LCD Intervention

The LCD comprises mainly starch-free vegetables, fish, poultry, beef, dairy products, eggs, nuts, seeds, berries, and fruits that are low in carbohydrates (ie, kiwi, pomegranate, and grapefruit). The diet comprises approximately 10% of total energy (E%) from carbohydrates, 25 E% protein, and 65 E% fat. Detailed information about the nutritional compositions can be seen in Table 1. Patients allocated to this diet will be informed to avoid starchy and sugary foods, such as pasta, rice, potatoes, bread, fruits, and confectionaries. Owing to the reduction in total carbohydrates—and thus the sources of dietary fibers—nuts and seeds are included, providing approximately 25 grams of dietary fiber/day. For participants who normally consume a lactose-free diet, the LCD can be offered without lactose as well.

Table 1. Mean daily energy and nutrient intake in diet A and B.

Energy and nutrients	LCD[a]	LFTD[b]
Energy (kcal), mean (SD)	2353 (158)	2380 (217)
Carbohydrate (g), mean (SD)	48 (10.8)	278 (27.6)
Fat (g), mean (SD)	178 (19.6)	89 (16.4)
Protein (g), mean (SD)	133 (17.1)	99 (16.7)
Dietary fiber (g), mean (SD)	25.4 (5.7)	30.2 (5.4)
Vitamin C (mg), mean (SD)	169 (83.8)	210 (112.1)
Iron (mg), mean (SD)	13.6 (2.8)	12.2 (2.8)
Total FODMAP[c] (g), mean (SD)	16.6 (7.0)	3.4 (0.9)
Lactose (g), mean (SD)	6.3 (3.8)	0.2 (0.2)
Fructose in excess of glucose (g), mean (SD)	2.0 (2.3)	0.7 (0.9)
Fructan (g), mean (SD)	3.3 (1.1)	1.7 (0.3)
Galacto-oligosaccharides (g), mean (SD)	1.1 (2.4)	0.3 (0.1)
Polyols (g), mean (SD)	3.7 (3.0)	0.4 (0.3)
Carbohydrate (E%[d])	10	50
Fat (E%)	67	33
Protein (E%)	23	17
Saturated fat (E%)	25	11
Monounsaturated fat (E%)	25	11
Polyunsaturated fat (E%)	9	9
Total weight of food (g/day), mean (SD)	1368 (148)	1850 (206)
Proportion of animal foods[e], (%)	50	30

[a]LCD: low-carbohydrate diet.

[b]LFTD: low FODMAP and traditional dietary advice.

[c]FODMAP: fermentable oligosaccharide, disaccharide, monosaccharide, and polyol.

[d]Percentage of calories from total energy intake.

[e]Meat, poultry, fish, shellfish, egg, and dairy.

LFTD Intervention

Patients will be advised to eat small meals on a regular basis, with 3 main meals and 3 snacks each day. All meals should be eaten slowly, and the food should be chewed properly; vegetables and fruits will be recommended to be peeled or boiled; food triggers such as coffee, alcohol, fizzy drinks, sweeteners, and fatty and spicy foods will be limited. Intake of dietary fibers will be approximately 30 g/day and mainly comprise soluble fibers from oats, gluten-free bread, chia seeds, vegetables, and fruits. This diet will also be low in FODMAPs and, therefore, will not contain any lactose, onions, legumes, wheat-based products, and high-FODMAP fruits and vegetables. Detailed information about the nutritional compositions can be seen in Table 1.

OMT Intervention

Patients assigned to receive OMT will have their predominant GI symptoms and their history of medications assessed by a physician. After that, a choice of evidence-based medical treatment based on the patient's predominant symptoms will be made, using the list shown in Textbox 2, with a preference for first-line options if they had not been tried before (eg, bulking agent or osmotic laxative for constipation and loperamide for diarrhea). The medications will be tested for 4 weeks, and only 1 medication will be allocated per patient. After 2 weeks, the patient will be contacted by the physician by telephone to check for compliance to treatment and adjust the dosage if necessary. If the medication is terminated because of, for example, side effects by the patient before 4 weeks, no alternative medication will be given during the intervention period.

Textbox 2. Pharmacological treatment options based on predominant symptoms with the used starting dose.

Treatment options based on symptoms with the used starting dose

Constipation

- Bulking agent (Sterculia) 4 g once a day
- Osmotic laxative (Macrogol) 13.125 g once a day
- Linaclotide 290 µg once a day

Diarrhea

- Loperamide 2 mg twice a day
- Cholestyramine 4 g once a day
- Ondansetron 4 mg once a day

Abdominal pain

- Chronic/frequent pain: Amitriptyline 25 mg before bed
- Episodic pain: Hyocyamin 0.2 mg as needed
- Pain with diarrhea: Amitriptyline 25 mg before bed
- Pain with constipation: Linaclotide 290 µg once a day

Follow-up

After their third visit, participants in the OMT arm will end their formal participation in the trial and will be offered a regular visit to a dietitian if wanted. However, they will be contacted by mail after ≥6 months with questions regarding the severity of their GI symptoms and the current treatments being used. They will be financially compensated for the cost of the medication during the intervention. Patients in the dietary intervention arms will be informed that during the next 6 months, they may or may not continue with their allocated diet, and structured follow-up visits with repeated 4-day food records will be scheduled at 3 and 6 months after the end of the intervention.

Systematic Follow-up on Low FODMAP and Traditional Dietary Advice Treatment

Patients in the LFTD arm will be given a structured rechallenge schedule to be able to test whether individual FODMAPs are tolerated. The schedule comprises a comprehensive list of food items within each FODMAP category and selected foods that are suitable for rechallenge tests. The preference of the participant decides which category to test first, and only 1 FODMAP category will be rechallenged at a time. The amount of the selected food will be increased for 3 days to evaluate tolerance and tolerance levels. After a washout period of 4 days, when all FODMAPs will again be limited, the next FODMAP category can then be rechallenged. When individual tolerance to FODMAPs has been evaluated, the patients will be encouraged to reintroduce FODMAPs in their diet in amounts that can be well-tolerated.

Blinding

Patients allocated to the dietary treatment options will be given detailed information about the foods included in the diet but will not be given any specified name of the diet (eg, low FODMAP or low-carbohydrate, high-fat diet). Medical treatment will be open label. Data entry and analyses will be performed by persons blinded to the group assignment.

Research Ethics Approval

The project has received ethical approval from the ethics examination authority of the regional ethics committee in Gothenburg (Dnr 278-16).

Consent

Written informed consent will be obtained from all study participants before they enter the study. All patients will be informed that consent may be withdrawn at any moment if they so wish, without any further notice.

Data Collection Methods

Food Records

Participants will record all foods and drinks consumed during 4 consecutive days before the allocation visit and twice during the follow-up period, which means that random weekdays and weekends will be combined. Verbal and written instructions on how to complete the food record will be given, and patients will be encouraged to maintain their regular diet during the recording days. All records will be kept in a booklet that will be provided, and detailed information about the consumed foods and drinks will be required. Quantities will be estimated using household utensils or standard measures, and food labels and cooking methods will be noted. Trained dietitians will enter all diet records into the nutrient calculation software.

Energy and Nutrient Calculations

Energy and nutrient intakes will be calculated using the software Dietist XP 3.1 (kostdata), which is linked to a Swedish food composition table provided by the National Food Agency, including a FODMAP database add-on [18]. The FODMAP database is aggregated from published sources of analyzed FODMAP content and includes fructose, fructan, lactose,

galacto-oligosaccharide, and polyol content (gram/100 g). As only fructose in excess of glucose counts as a FODMAP, excess fructose will be calculated by subtracting the intake of fructose (gram) from glucose (gram) for each separate meal. If the glucose content is higher than the fructose content, a value of 0 will be denoted for excess fructose. The intakes of nutrients will be first summarized for each meal, and thereafter summarized into intakes per day, and finally presented as the mean intake for all 4 days. Cutoffs for reliable habitual energy intake will be set for energy levels ≤800 kcal/day or ≥4500 kcal/day.

Questionnaires

The *IBS-SSS* [16] evaluates the severity of IBS symptoms (score range 0-500) and will be filled in at day -1, day 7, day 14, day 21, day 28, and 3 and 6 months after completion of the intervention. The *GSRS-IBS* [19] evaluates IBS-specific GI symptoms and will be filled in at day -1, day 7, day 14, day 21, day 28, and 3 and 6 months after completion of the intervention. The *BSF* scale [17] will be used as the basis for a stool diary that is filled in during 10 days of screening, during the 28 days of the intervention, and at 3 and 6 months after the intervention. In this diary, the patient will record their stool and stool consistency.

The Hospital Anxiety and Depression Scale [20] will be used to determine the severity of anxiety and depression and will be filled in at days 0 and 29 and 3 and 6 months after the intervention. The Visceral Sensitivity Index [21] measures GI-specific anxiety, that is, anxiety originating from fear of GI symptoms, which is related to the unpredictable symptom pattern commonly found in IBS. The form will be filled in on days 0 and 29, and 3 and 6 months after completion of the intervention.

The Patient Health Questionnaire (PHQ)–15 [22] measures the severity of somatic symptoms. Excluding the 3 GI symptoms in the questionnaire yields a measure of non-GI somatic symptom severity, that is, the PHQ-12 [23]. The form will be filled in at days 0 and 29 and 3 and 6 months after completion of the intervention. The Multidimensional Fatigue Inventory-20 [24] measures general fatigue, physical fatigue, decreased activity, reduced motivation, and mental fatigue. This form will be filled in on days 0 and 29 and 3 and 6 months after completion of the intervention.

The Work Productivity and Activity Impairment Questionnaire–IBS [25] measures whether IBS symptoms affect the ability to work and perform everyday activities with four different variables: absenteeism, presenteeism, overall work impairment, and activity impairment. The form will be filled in on days 0 and 29 and 3 and 6 months after completion of the intervention.

The IBS-QoL [26] is an IBS-specific QoL questionnaire that measures 10 domains that have been found to be relevant to patients with IBS: emotional health, mental health, health belief, sleep, energy, physical functioning, diet, social role, physical role, and sexual relations. The form will be filled in on days 0 and 29 and 3 and 6 months after completion of the intervention.

The Highly Sensitive Person scale [27] is a questionnaire that assesses the degree of environmental sensitivity and personality traits that categorize individuals into low, medium, and highly sensitive persons. The form will be filled in on day 0. The Central Sensitization Inventory [28] focuses on sensitivity to pain and symptoms associated with central sensitization. It comprises 25 health-related symptoms that are common to central sensitization. The form will be filled in on day 0.

The following questionnaires will be web-based: Hospital Anxiety and Depression Scale, Visceral Sensitivity Index, Multidimensional Fatigue Inventory-20, IBS-QoL, PHQ-15, Work Productivity and Activity Impairment Questionnaire–IBS, the Highly Sensitive Person scale, and the Central Sensitization Inventory. The platform on which these questionnaires will be entered provides automated score calculations and, as it will not be possible to skip questions, there will be no missing data. The IBS-SSS, BSF, and GSRS-IBS during the intervention period will be completed using paper questionnaires.

Biological Samples

Fasting blood samples will be taken and sent to the Department of Clinical Chemistry, Sahlgrenska University Hospital, Gothenburg, Sweden, for analysis of transglutaminase, immunoglobulin A antibodies, total immunoglobulin A levels, hemoglobin, white cell count, platelets, sodium, potassium, creatinine, calcium, C-reactive protein, thyroid-stimulating hormone, free thyroxine, aspartate aminotransferase, alanine aminotransferase, albumin, glucose, hemoglobin A_{1c}, and blood lipids (cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides) at visit 2. At visits 3, 4, and 5, glucose, hemoglobin A_{1c}, and blood lipid levels will be analyzed. At visits 2, 3, 4, and 5, a 4 mL serum sample will be taken and stored at 4 °C for 30 minutes before being centrifuged at 4 °C at 4000 revolutions per minute for 10 minutes, whereby 1 mL serum will be frozen at –80 °C within 2 hours for later analysis of metabolomics as well as for other analyses. Urine samples (3 mL) will be centrifuged at 4 °C at 4000 revolutions per minute for 10 minutes and frozen at –80 °C within 2 hours for later analysis of metabolomics. Serum and fecal and urinary samples will be analyzed with nuclear magnetic resonance and gas chromatography mass spectrometry for metabolomic profiling, and microbial composition and function will be analyzed using whole genome sequencing.

At visits 2 and 3, 3 mL serum and 4 mL heparin plasma will be frozen at –80 °C for later immunological analyses. Biological samples that are not immediately analyzed will be stored at –80 °C in a biobank at our unit.

Results

The study received ethical approval on April 21, 2016, and recruitment began in January 2017. By May 28, 2021, of the proposed 300 participants, 270 (90%) had been randomized, and 244 (81%) had finished the 4-week intervention. Of the proposed 200 participants in the dietary treatment arms who will continue for a 6-month follow-up, 112 (56%) had been on visit 4, and 77 (39%) had been on visit 5.

Outcomes

Primary Outcome

The primary outcome measure will be the proportion of patients who respond favorably to the treatment regarding the severity of IBS symptoms. Responders will be defined as participants with a score reduction in IBS-SSS ≥50 (ie, calculated as the change in IBS-SSS between randomization visit and end of the intervention period, with a total score ranging from 0 to 500), which is considered a clinically relevant symptom reduction [16], and a cutoff that is commonly recommended for use in clinical studies to define responders.

Secondary Outcome

The secondary outcomes are as follows:

- A more conservative cutoff limit in IBS-SSS reduction will be tested, both with a score reduction of ≥100 and ≥50% of the initial IBS-SSS score. Proportions between treatment arms will be compared using chi-square tests.
- The absolute and percent change in IBS-SSS and GSRS-IBS from randomization visit to the end of intervention period will be analyzed using paired-sample *t* tests within groups and analysis of variance (ANOVA) between groups.
- Compliance to treatment in relation to treatment outcome will be analyzed using linear regression, with the measure of compliance as the independent variable and IBS-SSS as the dependent variable.
- Predictors of response to treatment (demographics questionnaire data, microbiota, metabolites, and immunology) will be analyzed using logistic regression, with *responders* and *nonresponders* as the binary outcome variable.
- Determinants of GI symptoms will be assessed using linear regression, with GSRS-IBS and IBS-SSS as dependent variables.
- Maintained adherence to dietary intervention will be assessed using food diaries at 3- and 6-month follow-ups, and differences in nutrient intake will be compared between the 2 diets using unpaired-sample *t* tests. Predictors for long-term adherence to diet will be analyzed using logistic regression, with *adherence* and *nonadherence* as binary outcome variables.
- Changes in extraintestinal symptoms, QoL, work productivity, and psychological factors in relation to treatment will be analyzed using ANOVA for continuous variables and chi-square tests for categorical variables.

Other Outcomes

Other outcomes are as follows:

- Changes in metabolite profiles during intervention and follow-up will be analyzed using orthogonal projections to latent structures discriminant analysis (OPLS-DA) and orthogonal projections to latent structures with effect projection (OPLS-EP).
- Changes in microbiota composition during intervention and follow-up will be analyzed using OPLS-DA and OPLS-EP.
- Changes in immunological markers during the intervention will be analyzed using OPLS-DA and OPLS-EP.

- Patients' subjective experiences related to the dietary intervention will be described by qualitative methods, using inductive content analysis.

Measure of Compliance

During the intervention period, patients receiving dietary treatment should note any deviations from their allocated diet in a daily symptom diary. In addition to the recipes and foods that follow each intervention, there will be specified lists of foods that will be allowed and forbidden during the intervention period. As long as a study participant complies with the foods that are on the *allowed* list and the framework of the dietary regime, the participant will be considered compliant. The compliance will be calculated for each week. Any deviation that does not adhere to the intervention diet will result in a score reduction (at most –1 for each deviation). Compliance with medical treatment will be examined during telephone check-ups and at visit 3 but will not be scored.

Statistical Methods

Normally distributed variables will be presented as mean (SD) and nonnormally distributed variables as median (range). Differences in means between the 3 intervention groups will be analyzed with ANOVA, using Bonferroni corrections for multiple testing. For the main outcome, that is, to compare the proportion of responders in each treatment group, chi-square tests will be applied. For absolute change in IBS-SSS, the percentage change will be calculated and analyzed with paired *t* tests within groups (baseline vs end of intervention) and using ANOVA for comparisons between groups. The proportion of patients with ≥50% decrease in IBS-SSS will be compared using chi-square test between the groups. For comparing the changes at multiple time points (during follow-up), mixed model analyses will be used.

Logistic regression will be applied to evaluate predictors of response for the various treatments (binary outcome responders or nonresponders), and the determinants of GI symptoms (IBS-SSS, as a continuous variable) will be assessed using bivariate and multivariable linear regression analyses. Furthermore, multivariate analyses and bioinformatics will be applied to metabolomics, microbiota, and immunological markers.

Discussion

Principal Findings

The Carbohydrates in Irritable Bowel Syndrome (CARIBS) study is a large, randomized controlled study of high quality, which is of importance when results are interpreted for implementation in the treatment of patients with IBS. As large quantities of data will be collected, exploring both the efficacy of the intervention during a 4-week period, as well as the effectiveness during follow-up, this study will bring new insights into the management of IBS symptoms.

As we do not know the long-term effects of maintaining an LCD or an LFTD, both of which are exclusion diets, we will carefully monitor the 2 groups receiving dietary treatment for 6 months. Studies have demonstrated that a lack of fermentable

carbohydrates in the diet can alter the composition and diversity of the gut microbiota, which could potentially lead to adverse health outcomes in the long run [29]. In addition, studies have shown that restrictive diets can affect the total energy intake, which could lead to unwanted weight loss and a lack of nutrients [30,31]. Therefore, we have added a 6-month follow-up to the study protocol to study the effects on nutrient intake as well as the gut microbiota composition.

We anticipate that this randomized controlled trial will provide a better understanding of the predictors of response to treatment and how best to tailor treatments for patients with IBS with different symptomatology.

Acknowledgments

Conflicts of Interest

None declared.

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Abbreviations

ANOVA: analysis of variance
BSF: Bristol stool form
CARIBS: Carbohydrates in Irritable Bowel Syndrome
FODMAP: fermentable oligosaccharide, disaccharide, monosaccharide, and polyol
GI: gastrointestinal
GSRS-IBS: Gastrointestinal Symptom Rating Scale–IBS
IBS: irritable bowel syndrome
IBS-QoL: irritable bowel syndrome–quality of life
IBS-SSS: IBS Severity Scoring System

LCD: low-carbohydrate diet
LFTD: low FODMAP and traditional dietary advice
NICE: National Institute for Health and Care Excellence
OMT: optimized medical treatment
OPLS-DA: orthogonal projections to latent structures discriminant analysis
OPLS-EP: orthogonal projections to latent structures with effect projection
PHQ: Patient Health Questionnaire
QoL: quality of life

Protocol

Effectiveness of Mindfulness-Based Cognitive Therapy With Follow-Up Sessions for Pharmacotherapy-Refractory Anxiety Disorders: Protocol for a Feasibility Randomized Controlled Trial

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Abstract

Background: Augmented mindfulness-based cognitive therapy (MBCT) with treatment as usual (mainly pharmacotherapy) is reported to be effective after treatment for anxiety disorders. However, whether its effectiveness persists in the long term is unclear.

Objective: This study aims to examine the feasibility, acceptability, and effectiveness of a follow-up program by conducting a feasibility randomized controlled trial (RCT) that compares augmented MBCT with follow-up sessions and that without follow-up sessions in preparation for a definitive RCT.

Methods: The study involves an 8-week MBCT with a 10-month follow-up. Patients aged 20 to 65 years who meet the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for panic disorder, agoraphobia, or social anxiety disorder, which is not remitted with usual treatment for at least 4 weeks, will be included in the study and randomly allocated to receive augmented MBCT with follow-up sessions or augmented MBCT without follow-up sessions. For this feasibility RCT, the primary outcomes are (1) study inclusion rate, (2) dropout rate, (3) attendance rate, and (4) mean and standard deviation of several clinical measures at 8 weeks and 5, 8, and 12 months.

Results: We started recruiting participants in January 2020, and 43 participants have been enrolled up to January 2021. The study is ongoing, and data collection will be completed by May 2022.

Conclusions: This study is novel in terms of its design, which compares augmented MBCT with and without follow-up sessions. The limitations of the trial are as follows: (1) mixed participants in terms of the delivery mode of the intervention, and (2) lack of a pharmacotherapy-alone arm. Owing to its novelty and significance, this study will provide fruitful knowledge for future definitive RCTs.

Trial Registration: UMIN Clinical Trials Registry UMIN000038626; https://tinyurl.com/2p9dtxzh

International Registered Report Identifier (IRRID):   DERR1-10.2196/33776

Introduction

Background

Anxiety disorders are the most prevalent mental disorders worldwide [1]. The global 12-month prevalence rate is estimated to be 7.3% [2,3], although prevalence varies across regions (eg, from 3.3% to 18.1% [4-6]). The early age of onset [7] and high probability of relapse [8] prolong the course of the disease, negatively affecting patients socially and chronically [9]. The cumulative remission rates are as low as 35% for social anxiety disorders, 42% for panic disorders with agoraphobia, and 50% for generalized anxiety disorders over a 10-year period [10]. Such features of the disorder place a considerable burden on society. In 2015, anxiety disorders were the sixth leading contributor to nonfatal health loss globally, generating a global total of 24.6 million years lost due to disability [11]. The impact becomes more obvious when the burden is converted into a monetary measure. The societal costs of anxiety disorders were 42.3 billion USD in the United States (1990) [12], 8.9 billion GBP (11.9 billion USD) in the United Kingdom (2007) [13], and 2.4 trillion JPY (27 billion USD) in Japan (2008) [14].

Major clinical guidelines suggest pharmacotherapy and cognitive behavioral therapy (CBT) as the recommended treatments for anxiety disorders [15-17]. However, because of an overwhelming shortage of CBT therapists, a limited number of patients (4.5% in the United States) are able to access CBT [18]. Consequently, pharmacotherapy is currently the dominant treatment strategy. Although the effectiveness of pharmacotherapy for anxiety disorders has been confirmed, remission rates remain between 25% and 35% [19]. Therefore, developing a subsequent treatment for pharmacotherapy-refractory patients, which is effectual and cost-effective in the long term, is important.

Mindfulness-based cognitive therapy (MBCT) [20], which integrates mindfulness-based stress reduction (MBSR) programs with the essence of CBT [21], is a candidate option. MBCT cultivates mindfulness and nonjudgmental present-moment awareness, which allows people to become aware of their bodily sensations, feelings, and thoughts. MBCT is normally offered in a group format and could be more efficient than individual CBT.

What We Already Know

MBCT has a significant favorable effect on anxiety disorders [22-28]. Even in a setting where the majority of patients manifest pharmacotherapy resistance, MBCT augmented with pharmacotherapy appears to be more effective than pharmacotherapy alone at posttreatment [29]. However, its long-term effectiveness is unclear. For treatment-resistant depression, Eisendrath et al [30] showed that the effects of augmented MBCT on the reduction of Hamilton Depression Rating Scale scores at posttreatment disappeared 1 year later. One possible explanation is that termination of the treatment discourages patients from continuing to practice mindfulness meditation posttreatment.

Rationale for the Study

As Segal et al indicated [31], although the practice time does not directly affect the clinical outcome, it could affect the outcome mediated by the "decentering" skill improved by the meditation practice. Given that the practice time diminishes as the intervention terminates [32], adding follow-up sessions posttreatment would encourage patients to practice meditation continuously, possibly leading to a better outcome through the improvement of the core skill of decentering. Therefore, in anticipation of future definitive randomized controlled trials (RCTs), we decided to conduct a feasibility RCT to compare augmented MBCT (ie, MBCT plus pharmacotherapy) with follow-up sessions and augmented MBCT without follow-up in order to (1) assess the feasibility, safety, and effectiveness of augmented MBCT with follow-up sessions and (2) compare clinical outcomes between the 2 arms.

Aim

This study aims to examine the feasibility, acceptability, and effectiveness of a follow-up program in an augmented MBCT scheme by conducting a feasibility RCT between augmented MBCT with and that without follow-up sessions.

Methods

Participants

The study is being conducted at Keio University Hospital in Tokyo, Japan. We will recruit participants from the Department of Neuropsychiatry. Patients are eligible for the study if they are between the ages of 20 and 65 years; meet the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for panic disorder, agoraphobia, or social anxiety disorder, which is not remitted with usual treatment (pharmacotherapy) for at least 4 weeks; and are capable of providing written consent. The exclusion criteria are substance abuse or dependence, antisocial personality disorder, severe suicidality, self-harm, organic brain damage, severe physical illness, and other appropriate factors deemed by the principal investigator. Patients who are unlikely to attend for 12 months (eg, expected to be moving) will be excluded.

Enrollment

During usual consultation, the psychiatrist will provide brief information on the study with a leaflet and ask the patients about their willingness to participate in the study. If the patients show interest, the study psychiatrist will arrange an appointment for an interview. The study psychiatrist will explain exhaustively the details of the expected benefits and risks of participation in the study, as well as discuss any questions from the candidate participants. The patients will be evaluated for study eligibility by the study psychiatrist or psychologist.

The study psychiatrist or psychologist will assess the diagnosis of the participants using the Japanese version of the Structured Clinical Interview for DSM-IV (SCID) Axis I Disorders [33] under the supervision of MS, who has completed training in the administration of semistructured interviews. Written informed consent will be obtained from eligible participants after the study procedures are explained in detail.

Baseline Assessment

Participants will be asked to fill a battery of questionnaires relevant to demographic and psychosocial data. Psychological scales include the State-Trait Anxiety Inventory (STAI), Panic and Agoraphobia Scale (PAS), Liebowitz Social Anxiety Scale (LSAS), Experiences Questionnaire (EQ), Short-Form 36-Item Health Survey (SF-36), Scale of Positive and Negative Experience (SPANE), Rosenberg Self-Esteem Scale (RSES), Five Facet Mindfulness Questionnaire (FFMQ), Connor Davidson Resilience Scale (CDRISC), Self-Compassion Scale (SCS), 16-item Quick Inventory of Depressive Symptomatology (QIDS), Generalized Anxiety Disorder Assessment-7 (GAD7), Perceived Stress Scale (PSS), World Health Organization Health and Work Performance Questionnaire (WHO-HPQ), Satisfaction With Life Scale (SWLS), Flourishing Scale (FS), Multidimensional Assessment of Interoceptive Awareness (MAIA), EuroQoL-5 Dimensions (EQ-5D), health care service use (including medication), Hamilton Anxiety Scale (HAM-A), and interoception. All assessments, except for the latter 2 (ie, HAM-A and interoception), are intended to be conducted in a self-report format.

Randomization

Eligible participants will be randomly allocated to either the augmented MBCT with follow-up sessions group or MBCT without follow-up sessions group (1:1 ratio). A computer-generated random number stratified by diagnosis (ie, panic disorder/agoraphobia and social anxiety disorder) and baseline score for the STAI will be assigned to each participant. The Project Management Office at Keio Center of Clinical Research, which is an independent institution from the study group, will manage the randomization process. The flow of the recruitment of participants is shown in Figure 1.

Figure 1. Flow of the study. MBCT: mindfulness-based cognitive therapy.
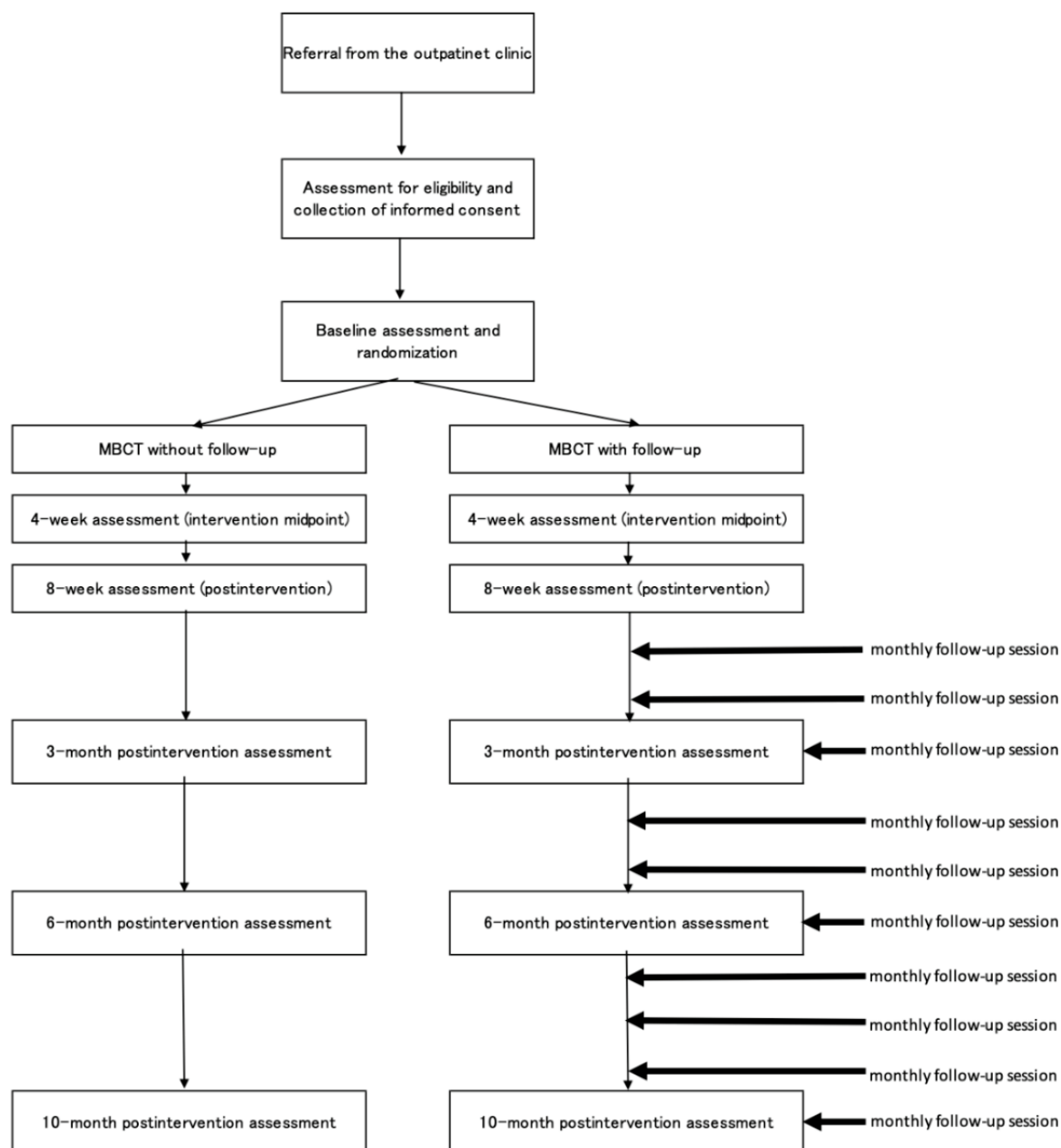
Blinding

The randomization status will not be blinded to both participants and therapists because of the nature of the psychological intervention. The raters blind to the allocation status will perform assessments for interoception and HAM-A. Both participants and therapists will be strongly indicated not to report their treatment allocation at rater-administered assessments. The assessors are independent and not involved in the treatment administration.

Interventions

MBCT With Follow-up Sessions Group

The patients in the intervention group will be offered an 8-week MBCT followed by a 10-month follow-up program. The MBCT

consists of 8 weekly sessions in a group format. Each session lasts for 2 hours. In the program, participants practice mindfulness meditation as well as cognitive exercise. Minimum modifications have been made to the original version of MBCT [20] because the study targets patients with anxiety disorders rather than those with depression. Specifically, we have replaced psychoeducation of depression with that of anxiety. Table 1 describes the themes and contents of each session. The participants will be requested to practice mindfulness meditation for approximately 30 minutes daily and to record the duration of time they meditated and the meditation type.

Table 1. Themes and content of the program.

Session	Theme	Content
1	Automatic pilot	• Psychoeducation: What is mindfulness? • Exercise: Mindfulness eating ("raisin exercise")/body scan • Homework: Mindfulness of a routine activity/body scan
2	Dealing with barriers	• Psychoeducation: Association of mood and thoughts • Exercise: Thoughts and feelings exercise/body scan/mindful breathing meditation • Homework: Body scan/breathing meditation/pleasant events calendar
3	Mindfulness of the breath	• Psychoeducation: Awareness of mind wandering and focusing on the breath • Exercise: Breathing meditation/gentle yoga/mindful walking • Homework: Breathing meditation/gentle yoga/mindful walking/unpleasant events calendar
4	Staying present	• Psychoeducation: Staying present/about anxiety symptoms[a] • Exercise: Meditation of sounds and thoughts/breathing meditation • Homework: Meditation of sounds and thoughts/breathing meditation/3-minute breathing space
5	Allowing/letting be	• Psychoeducation: Exploring difficulty • Exercise: Breathing meditation/meditation of sounds and thoughts/exploring difficulty • Homework: Breathing meditation/meditation of sounds and thoughts/exploring difficulty/3-minute breathing space
6	Thoughts are not facts	• Psychoeducation: Cognitive biases • Exercise: Breathing meditation/meditation of sounds and thoughts/exploring difficulty • Homework: Breathing meditation/meditation of sounds and thoughts/exploring difficulty/3-minute breathing space
7	How can I best take care of myself?	• Psychoeducation: Choosing functional behaviors/behavioral activation/identifying triggers • Exercise: Mindfulness meditation of sounds and thoughts/breathing meditation • Homework: Meditation of sounds and thoughts/breathing meditation/3-minute breathing space plus action plan
8	Using what has been learned to deal with future mood	• Personal reflections of course/plans for future practice and strategies for maintaining momentum/farewell • Exercise: Body scan/breathing meditation

[a]The lecture relevant to depression has been replaced by that about anxiety in session 4.

After the completion of the 8-week MBCT, the participants in the intervention group will be offered to continue the 10-month follow-up program. The program is designed to consist of 2 elements. The first is the 10 monthly follow-up sessions. The participants will be encouraged to attend 1.5-hour–long monthly follow-up sessions, where they will meditate together and share their experiences of mindfulness in daily life. The second element is the use of mindfulness apps in daily life. Participants in the group will be provided with mindfulness apps developed by the research team to be used during the follow-up period. The participants can access the apps either from a smartphone or PC and stream/download the meditation instructions easily. In addition, they are encouraged to send their mindfulness experiences in daily life to the research team every month. The research team will post and share them with other participants on the apps. The research team will also post relevant articles to support participants in continuing the practice. No regular homework will be offered during the follow-up period. Participants will be encouraged to meditate depending on their needs.

The first (MS), second (A Ninomiya), and third (MN) authors led the sessions. The first author is a qualified MBSR teacher at the University of Massachusetts, with 10 years of experience in mindfulness practice. The other 2 authors have been practicing mindfulness for more than 5 years and have experience in offering MBCT 5 times under the supervision of the first author.

MBCT Without Follow-Up Sessions Group

Participants in the control group will also be offered the 8-week MBCT. During the follow-up period, they will be encouraged to continue practicing by themselves. However, no additional intervention is intended to be provided after the 8-week MBCT.

Response During the COVID-19 Pandemic

MBCT and follow-up sessions were initially planned to be offered in person. However, to ensure participant safety during the COVID-19 pandemic, classes will be offered online.

Outcomes

Primary Outcomes

In this feasibility RCT, the primary outcomes are the (1) study inclusion rate, (2) dropout rate, (3) attendance rate, and (4) mean and standard deviation of the below clinical measures at 8 weeks and 5, 8, and 12 months.

Clinical Outcomes

The primary clinical outcome is the mean and standard deviation of the STAI score in both groups at 8 weeks and 5, 8, and 12 months after the start of the intervention. The mean difference and standard deviation of the STAI score between the groups is also assessed.

The secondary clinical outcomes are PAS, LSAS, EQ, SF-36, SPANE, RSES, FFMQ, CDRISC, SCS, QIDS, GAD7, PSS, WHO-HPQ, SWLS, FS, MAIA, EQ-5D, HAM-A, and interoception scores (baseline, 8 weeks, and 12 months only for HAM-A and interoception); health service use; engagement in meditation practice; and satisfaction with and expectation of the classes.

Cost-effectiveness

Cost-effectiveness is assessed by the incremental cost-effectiveness ratio, which represents the incremental cost divided by the incremental effectiveness between the groups. Incremental effectiveness is evaluated using quality-adjusted life years calculated from the results of EQ-5D. The analyses are conducted from a health care system perspective.

Instruments

STAI

The STAI is a commonly used measure of state and trait anxiety. It can be used in clinical settings to diagnose anxiety and distinguish it from depressive syndromes. It has 20 items for assessing trait anxiety and 20 for assessing state anxiety. Possible scores range from 20 to 80. Higher scores indicate higher anxiety [34].

PAS

The PAS is a measure of illness severity in patients with panic disorder (with or without agoraphobia). It has 13 items with a 5-point scale, which covers the following 5 subscales: panic attacks, agoraphobic avoidance, anticipatory anxiety, disability, and functional avoidance (health concerns). Higher scores indicate more severity [35].

LSAS

This instrument is used to assess patients' fear in a range of social interactions and performance situations. The scale consists of 24 items, which are categorized into the following 2 elements: performance anxiety (13 items) and social situations (11 items). Scores are between 0 and 144, with higher scores indicating higher social anxiety [36].

EQ

The EQ is a 20-item self-report measure using a 5-point Likert scale ranging from 1 (*never*) to 5 (*always*). The total score is between 20 and 100. The scale focuses on decentering, defined as the ability to view the self as separate and different from own thoughts, the capacity for not reacting to negative experiences, and the ability to be self-compassionate. The EQ has been found to be reliable, and convergent and discriminant validities are established for both general and clinical samples. The EQ is also internally consistent, with temporal stability over a 1-month period and good convergent validity [37,38].

SF-36

The SF-36 is a 36-item multipurpose health survey to evaluate 8 health domains of functional health and the level of well-being, as well as physical and mental health summary measures and a health utility index. Possible scores for each domain range from 0 to 100, with higher scores indicating a better health status [39].

SPANE

This measure is a 12-item scale to assess positive experiences (6 items) and negative experiences (6 items). Because of the generality of items included in the scale, it can not only assess pleasant and unpleasant emotional feelings that are the focus of most scales, but also reflect other conditions, such as interest, flow, positive engagement, and physical pleasure. The positive (SPANE-P) and negative (SPANE-N) scale scores range between 6 and 30. Higher scores indicate a higher positive or negative affective status. The score obtained on subtracting the negative score from the positive score is called the SPANE-B score, which is between −24 and 24 [40].

RSES

This is a brief self-rated assessment tool to evaluate self-esteem, self-worth, acceptability, and confidence. It is the most recognized and widely used measure for these metrics. It has 10 items with a Likert scale (1 = *strongly disagree*, 4 = *strongly agree*). The total score ranges from 10 to 40, with higher scores indicating better self-esteem [41].

FFMQ

This tool is a self-report questionnaire that assesses mindfulness. It includes 5 factors, which are extracted on the basis of a factor analysis of 5 mindfulness questionnaires developed independently. The 5 facets are observing, describing, acting with awareness, not judging one's inner experience, and not reacting to one's inner experience. The total score ranges from 39 to 195, with higher scores representing a better mindfulness status [42].

CDRISC

The CDRISC is a brief self-rated assessment to measure resilience. The scale contains 25 items, all of which feature a 5-point Likert scale (4 = *true nearly all of the time*, 0 = *not true at all*). The scale is rated based on how the subjects felt over the past month. The total score ranges from 0 to 100, with higher scores reflecting greater resilience [43].

SCS

This scale assesses a person's ability to be kind and understanding toward themself, as opposed to harsh and self-critical in instances of pain or failure. It includes 29 items and produces scores on 5 subscales (self-kindness, self-judgment, common humanity, isolation, mindfulness, and overidentification). The subscale scores represent the mean of each subscale's item scores. Participants are asked to answer how often they had certain thoughts and feelings (1 = *rarely* to 5 = *very often or always*). Therefore, each subscale score is between 1 and 5. Higher scores indicate more self-compassion [44].

QIDS

The QIDS is a self-rated questionnaire to assess depressive symptoms, which is widely used. The responses to 16 separate items on the QIDS are converted into 9 DSM-IV symptom criterion domains. The total score is between 0 and 27. Higher scores indicate higher levels of depressive symptoms [45].

GAD7

GAD7 was developed to ask patients how often they experienced a set of symptoms in the past 2 weeks. Respondents respond using 4 response options on a Likert scale (0 = *not at all* to 3 = *nearly every day*). In addition, an item assessing the duration of anxiety symptoms is included. Therefore, GAD7 scores are between 0 and 21. Scores of 5, 10, and 15 represent mild, moderate, and severe anxiety symptoms, respectively [46].

PSS

The PSS was designed to measure the degree to which situations in one's life are appraised as stressful. The scale has the following 2 versions: the 14-item version (PSS-14) and the 10-item version (PSS-10), with 4 items removed from the 14-item version. We use the PSS-10 in this study. This scale assesses perceived stressful experiences or stress responses in the previous month. Each item is rated on a 5-point Likert scale (4 = *never*, 0 = *very often*) to identify positive experiences or responses. The total score ranges from 0 to 40, with higher scores representing higher stress levels [47].

WHO-HPQ

The WHO-HPQ is a self-report instrument designed to estimate the workplace costs of health problems in terms of self-reported sickness absence and reduced job performance (presenteeism). Presenteeism is measured using the following two questions: "On a scale from 0 to 10, where 0 is the worst job performance anyone could have at your job and 10 is the performance of a top worker, how would you rate the usual performance of most workers in a job similar to yours?" and "Using the same 0-10 scale, how would you rate your overall job performance on the days you worked during the past four weeks?" A low presenteeism score indicates poor performance [48].

SWLS

This scale is a 5-item self-reported questionnaire to evaluate the cognitive aspect of subjective well-being. Scores for each subscale range from 1 (*strongly disagree*) to 7 (*strongly agree*). The total score ranges from 5 to 35, with higher scores indicating higher satisfaction [49].

FS

This scale includes 8 items relevant to significant aspects of human functioning, ranging from positive relationships to feelings of competence, meaning, and purpose in life. Each item is answered on a 7-point scale that ranges from 1 (*strong disagreement*) to 7 (*strong agreement*). Possible scores range between 8 (*strong disagreement* with all items) and 56 (*strong agreement* with all items). Higher scores indicate that respondents viewed themselves positively in important areas of functioning [40].

MAIA

The MAIA is a self-report scale for experimental interoception research and for the assessment of mind-body therapies [50]. It is a 32-item self-report instrument to assess interoceptive awareness on the following 8 subscales: noticing, not distracting, not worrying, attention regulation, emotional awareness, self-regulation, body listening, and trusting. Each subscale has 3 to 7 items, each assessed on a 6-point Likert scale (0 = *never*, 5 = *always*). Scores for each subscale range from 0 to 5. Higher scores indicate better interoceptive awareness [51].

EQ-5D

EQ-5D is a standardized measure for assessing health-related quality of life. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. The score ranges between 0 (death) and 1 (perfect health) [52].

HAM-A

HAM-A is a rating scale used to measure the severity of anxiety symptoms. It includes 14 items that measure both psychiatric and somatic anxiety. Each item is scored from 0 (*not present*) to 4 (*severe*), with a total score between 0 and 56. HAM-A has a structured interview guide (Structured Interview Guide for Hamilton Anxiety Scale: SIGH-A) [53,54].

Interoception

To assess interoception objectively, we use a heartbeat detection task that has been used and validated worldwide. The participants are asked to wear a pulse oximeter on their finger, which is connected to a PC to evaluate their actual pulse. They are also asked to count the heartbeat felt during various measurement periods. Interoceptive accuracy is measured based on the discrepancy between the number of actual and reported heartbeats [55,56]. The validity and reliability of all measures of the original and Japanese versions, except the Japanese version of the PAS, have been confirmed [34-54,57-74]. With respect to the Japanese version of the PAS, although it shows sufficient reliability, the authors recommend using it as a secondary outcome, because the criterion-related validity indicates "relatively strong correlation" (ie, the correlation coefficient ranges between 0.48 and 0.68). We judge it to be sufficient for use as a secondary outcome.

Schedule for Assessments

All participants will be requested to fill the self-report measures at 4 weeks (the intervention midpoint) and 8 weeks (postintervention), and at 3, 6, and 10 months postintervention, as well as complete the baseline assessments. HAM-A and interoception will be assessed at baseline (0 weeks), at the end of the MBCT (8 weeks), and at 10 months postintervention. We will allow for a range of ±2 weeks from the scheduled evaluation date for the evaluation during the intervention period and ±4 weeks from the scheduled evaluation date for the evaluation during the follow-up period. For those who are unable to come to the hospital to complete the self-rated scales, we will contact them and ask them to fill out and return the above evaluation items by mail or telephone. The assessment schedule is presented in Table 2.

Table 2. Schedule of assessments

Timepoint	Screening period	Intervention period 1 wk	2 wk	3 wk	4 wk	5 wk	6 wk	7 wk	8 wk	Follow-up period 1 mo	2 mo	3 mo	4 mo	5 mo	6 mo	7 mo	8 mo	9 mo	10 mo
Screening (SCID[a], etc)	✓																		
Informed consent	✓																		
MBCT with f/u[b]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
MBCT without f/u[c]		✓	✓	✓	✓	✓	✓	✓	✓										
STAI[d]	✓				✓				✓	✓		✓			✓				✓
PAS[e]	✓				✓				✓	✓		✓			✓				✓
LSAS[f]	✓				✓				✓	✓		✓			✓				✓
EQ[g]	✓				✓				✓	✓		✓			✓				✓
SF-36[h]	✓				✓				✓	✓		✓			✓				✓
SPANE[i]	✓				✓				✓	✓		✓			✓				✓
RSES[j]	✓				✓				✓	✓		✓			✓				✓
FFMQ[k]	✓				✓				✓	✓		✓			✓				✓
CDRISC[l]	✓				✓				✓	✓		✓			✓				✓
SCS[m]	✓				✓				✓	✓		✓			✓				✓
QIDS[n]	✓				✓				✓	✓		✓			✓				✓
GAD7[o]	✓				✓				✓	✓		✓			✓				✓
PSS[p]	✓				✓				✓	✓		✓			✓				✓
WHO-HPQ[q]	✓				✓				✓	✓		✓			✓				✓
SWLS[r]	✓				✓				✓	✓		✓			✓				✓
FS[s]	✓				✓				✓	✓		✓			✓				✓
MAIA[t]	✓				✓				✓	✓		✓			✓				✓
EQ-5D[u]	✓				✓				✓	✓		✓			✓				✓
HAM-A[v]	✓								✓										✓
Interoception	✓								✓										✓
Health service use	✓				✓				✓	✓		✓			✓				✓
Homework engagement		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

[a]SCID: Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th edition disorders.

[b]MBCT with f/u: mindfulness-based cognitive therapy with follow-up sessions.

[c]MBCT without f/u: mindfulness-based cognitive therapy without follow-up sessions.

[d]STAI: State-Trait Anxiety Inventory.

[e]PAS: Panic and Agoraphobia Scale.

[f]LSAS: Liebowitz Social Anxiety Scale.

[g]EQ: Experiences Questionnaire.

[h]SF-36: Short-Form 36-Item Health Survey.

[i]SPANE: Scale of Positive and Negative Experience.

[j]RSES: Rosenberg Self-Esteem Scale.

[k]FFMQ: Five Facet Mindfulness Questionnaire.

[l]CDRISC: Connor Davidson Resilience Scale.

[m]SCS: Self-Compassion Scale.

[n]QIDS: 16-item Quick Inventory of Depressive Symptomatology.

[o]GAD7: Generalized Anxiety Disorder Assessment-7.

[p]PSS: Perceived Stress Scale.

[q]WHO-HPQ: World Health Organization Heath and Work Performance Questionnaire.

[r]SWLS: Satisfaction With Life Scale.

[s]FS: Flourishing Scale.

[t]MAIA: Multidimensional Assessment of Interoceptive Awareness.

[u]EQ-5D: EuroQoL-5 Dimensions.

[v]HAM-A: Hamilton Anxiety Scale.

Sample Size

For a feasibility study that involves evaluating the standard deviation of continuous variables, a sample size of 24 to 50 cases is recommended [75,76]. Therefore, in this study, the maximum number of enrolled patients has been set to 50 (25 for each arm).

Statistical Analysis

Statistical analyses and reporting of this trial will be conducted with primary analyses based on the intention-to-treat approach. The full analysis set will include all randomized subjects administered at least one procedure of the investigational treatment. For baseline variables, we will generate summary statistics with proportions and frequencies for categorical variables, and means and standard deviations for continuous data. Statistical data relevant to feasibility will be presented descriptively. For primary and secondary clinical outcome analyses, we will analyze mean changes from baseline with a restricted maximum likelihood-based repeated measures approach. The mixed model for repeated measures analyses will include the fixed and categorical effects of treatment, visit, and the treatment×visit interaction. We will employ Kenward-Roger approximation to estimate the degrees of freedom of the denominator. We will not conduct any adjustment for multiple testing of secondary outcomes because of the exploratory nature of the study. Imputation will not be performed for missing values because mixed models can deal with missing data by maximum likelihood. All comparisons are planned, and all P values are two-sided. A 5% significance level will be set for all statistical analyses. All statistical analyses will be conducted using Stata version 16 (Stata Corp).

Subgroup Analysis

Considering the mixed participants in the study (those being offered face-to-face MBCT and the follow-up sessions online, and those being offered all sessions online), we intend to conduct a subgroup analysis sorted by participants receiving face-to-face MBCT and those receiving online MBCT.

Adverse Events

When participants show serious adverse events, we will immediately contact the Ethics Review Committee at Keio University School of Medicine.

Ethics

All procedures relevant to the study have been approved by the Ethics Review Committee of Keio University School of Medicine (reference number: 20190216). We have also ascertained that all procedures are in accordance with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The study is registered in the UMIN Clinical Trials Registry (UMIN000038626).

Dissemination

We will present the results of the study at academic conferences, and the results are expected to be disseminated as articles in academic journals. The results of the study will comply with the CONSORT (Consolidated Standards of Reporting Trials) statement.

Results

The study began to recruit participants in January 2020, and 43 participants have been enrolled up to January 2021. The intervention is ongoing and scheduled to be completed in February 2022. The participants in the first group (n=20) have been offered the 8-week MBCT intervention delivered in person. Owing to the COVID-19 pandemic, we were forced to switch to an online mode at the end of March 2020. Therefore, the participants in the first group were offered the face-to-face 8-week MBCT first, followed by online monthly follow-up sessions. For the second group (n=23), all interventions will be offered online. Data collection is expected to be concluded by May 2022.

Discussion

The objective of this study is to investigate the long-term effectiveness of augmented MBCT with follow-up for anxiety disorders in comparison with MBCT without follow-up. Considering that the superiority of augmented MBCT posttreatment might not continue in the long term [30], developing a methodology to sustain its effectiveness in the long term is important. To the best of our knowledge, no studies to date have assessed the effectiveness of follow-up sessions after MBCT in comparison with MBCT alone. Therefore, this study is novel in terms of the design that compares augmented MBCT with and without follow-up sessions. Moreover, we expect our feasibility RCT to contribute to the development of well-designed definitive RCTs on the topic.

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The limitations of our study are as follows. First, we expect differences in the participants included in the study in terms of the delivery of the intervention, as an impact of the COVID-19 pandemic (those offered face-to-face MBCT and online follow-up sessions, and those offered all sessions online). To account for the difference in the intervention delivery mode, we plan to conduct subgroup analysis. Second, we are not using a pharmacotherapy-alone arm. Thus, the study will not provide any implications regarding the clinical difference between augmented MBCT and pharmacotherapy alone. Nonetheless, considering that previous studies have already confirmed that augmented MBCT is superior to pharmacotherapy at posttreatment, we consider that our study design is acceptable from an ethical viewpoint. Despite the aforementioned limitations, we believe that this study will provide informative data for future clinical trials in this area.

Authors' Contributions

MS drafted the grant proposal and was responsible for the study implementation, study management, data collection, and supervision. MS, A Nakagawa, A Ninomiya, and DF designed the study. MS drafted the manuscript. A Nakagawa, A Ninomiya, AK, YS, CT, NG, MY, TK, SP, YS, DF, and MM refined the study protocol. All authors critically reviewed the manuscript for content and approved the final version.

Conflicts of Interest

None declared.

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Abbreviations

CBT: cognitive behavioral therapy
CDRISC: Connor Davidson Resilience Scale
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition
EQ: Experiences Questionnaire
EQ-5D: EuroQoL-5 Dimensions
FFMQ: Five Facet Mindfulness Questionnaire
FS: Flourishing Scale
GAD7: Generalized Anxiety Disorder Assessment-7
HAM-A: Hamilton Anxiety Scale
LSAS: Liebowitz Social Anxiety Scale
MAIA: Multidimensional Assessment of Interoceptive Awareness
MBCT: mindfulness-based cognitive therapy
MBSR: mindfulness-based stress reduction
PAS: Panic and Agoraphobia Scale
PSS: Perceived Stress Scale
QIDS: 16-item Quick Inventory of Depressive Symptomatology
RCT: randomized controlled trial
RSES: Rosenberg Self-Esteem Scale
SCID: Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th edition disorders
SCS: Self-Compassion Scale

SF-36: Short-Form 36-Item Health Survey
SPANE: Scale of Positive and Negative Experience
STAI: State-Trait Anxiety Inventory
SWLS: Satisfaction With Life Scale
WHO-HPQ: World Health Organization Heath and Work Performance Questionnaire

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Protocol

Comparing Neuroplasticity Changes Between High and Low Frequency Gait Training in Subacute Stroke: Protocol for a Randomized, Single-Blinded, Controlled Study

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Abstract

Background: Walking recovery post stroke can be slow and incomplete. Determining effective stroke rehabilitation frequency requires the assessment of neuroplasticity changes. Neurobiological signals from electroencephalogram (EEG) can measure neuroplasticity through incremental changes of these signals after rehabilitation. However, changes seen with a different frequency of rehabilitation require further investigation. It is hypothesized that the association between the incremental changes from EEG signals and the improved functional outcome measure scores are greater in higher rehabilitation frequency, implying enhanced neuroplasticity changes.

Objective: The purpose of this study is to identify the changes in the neurobiological signals from EEG, to associate these with functional outcome measures scores, and to compare their associations in different therapy frequency for gait rehabilitation among subacute stroke individuals.

Methods: A randomized, single-blinded, controlled study among patients with subacute stroke will be conducted with two groups: an intervention group (IG) and a control group (CG). Each participant in the IG and CG will receive therapy sessions three times a week (high frequency) and once a week (low frequency), respectively, for a total of 12 consecutive weeks. Each session will last for an hour with strengthening, balance, and gait training. The main variables to be assessed are the 6-Minute Walk Test (6MWT), Motor Assessment Scale (MAS), Berg Balance Scale (BBS), Modified Barthel Index (MBI), and quantitative EEG indices in the form of delta to alpha ratio (DAR) and delta-plus-theta to alpha-plus-beta ratio (DTABR). These will be measured at preintervention (R0) and postintervention (R1). Key analyses are to determine the changes in the 6MWT, MAS, BBS, MBI, DAR, and DTABR at R0 and R1 for the CG and IG. The changes in the DAR and DTABR will be analyzed for association with the changes in the 6MWT, MAS, BBS, and MBI to measure neuroplasticity changes for both the CG and IG.

Results: We have recruited 18 participants so far. We expect to publish our results in early 2023.

Conclusions: These associations are expected to be positive in both groups, with a higher correlation in the IG compared to the CG, reflecting enhanced neuroplasticity changes and objective evaluation on the dose-response relationship.

International Registered Report Identifier (IRRID): DERR1-10.2196/27935

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Introduction

Stroke is one of the most common causes of death and acquired disability worldwide, affecting motor function, speech, swallowing, vision, sensation, and cognition, and poststroke recovery can be slow and incomplete [1,2]. Stroke has been reported by Malaysia's Ministry of Health to be the third leading cause of mortality and morbidity [3]. The rehabilitation process should begin within the first few days after stroke to maximize neurological and functional recovery to achieve the highest possible level of independence. However, rehabilitation therapy for stroke is long term and time-consuming, and can be expensive with the use of advanced equipment or gadgets [4,5]. Hence, determining effective and tailored stroke rehabilitation therapy within limited resources is a matter of priority [6]. Rapid and accurate decision-making is critical to stroke rehabilitation care, for which several factors have proven to affect the stroke outcomes, including therapy frequency, intensity, and task-specific training [7].

Motor learning through stroke rehabilitation is proven to promote cortical reorganization and neuronal synaptogenesis that form the basis of the neuroplasticity concept [8]. Neuroplasticity is the ability for the brain to repair and reorganize after acquiring an injury such as stroke and is primarily affected by three main factors: therapy frequency, intensity, and task-specific training [9-11]. At present, choosing the best rehabilitation therapy for stroke patients is, in part, a trial-and-error process that can take weeks. However, recovery capacity after stroke declines overtime in which maximum recovery is demonstrated within the first 6 months after stroke [12]. It is imperative to choose an effective rehabilitation regime for promoting neuroplasticity within the recovery period. For the majority of clinical settings in lower-income regions, rehabilitation medicine experts assess and decide the best rehabilitation therapy for poststroke patients. Decisions are made based on subjective assessments that may result in contradicting patients', families', and relatives' expectations, and potentially inappropriate advice, treatment, or discharge. Hence, an objective assessment is needed to demonstrate and prove neuroplasticity changes with stroke rehabilitation.

One of the ways such changes can be identified is through a neurophysiological study, which is captured as neurobiological signals. These specific signals can be sensed several ways, but established studies were based on functional magnetic resonance imaging, transcranial magnetic stimulation, and positron emission tomography scan [13-15]. In the majority of lower-income countries, these neuroimaging facilities are only limited to a few tertiary hospitals; thus, it is inconvenient to adopt such practice assessments in a contextual setting. Therefore, other methods of assessments must be sought, and the use of cheaper and conveniently accessible neurobiological signals need to be further investigated for this specific purpose.

Capturing neurobiological signals using electroencephalogram (EEG) that is cheaper and readily available would be more contextually plausible for identifying neuroplasticity changes with stroke rehabilitation. Various studies have been conducted for detecting neuroplasticity effect based on EEG signal analysis in stroke rehabilitation, but these studies are confined in investigating the direct effect of rehabilitation therapy on the neuroplasticity [16-20]. Further investigation on the relationship between neuroplasticity and rehabilitation therapy intensity after stroke were not evaluated in detail. Analyzing parameters of these neurobiological signals after rehabilitation therapy would provide in-depth knowledge on the relationship between neuroplasticity after stroke and therapy intensity.

The activation of neurobiological signals from the affected stroke areas should demonstrate incremental changes with time if rehabilitation therapy is conducted more frequently. It is hypothesized that the neuroplasticity changes occurring with rehabilitation can be objectively measured through the association between analyzed incremental changes derived from the EEG signals and the improved functional outcome measure scores. Based on this hypothesis, the dissimilarity in the associations observed with different rehabilitation frequency may demonstrate a dose-response relationship. The purpose of this study is to identify and determine the changes in the neurobiological signals from the EEG, to correlate these with the improved functional outcome measure scores after rehabilitation as an objective measurement of neuroplasticity, and to compare the associations observed in different therapy frequency for gait rehabilitation among subacute stroke individuals. These objectives are aimed through an interventional, randomized, single-blinded, controlled study.

Methods

Study Type, Blinding, Design, Randomization, Recruitment, and Intervention

The study will be an interventional, randomized, single-blinded, controlled study conducted at an outpatient rehabilitation setting among adult individuals with moderate to severe stroke in the subacute phase. Participants for the study will be recruited at a rehabilitation medicine clinic of a major tertiary hospital in the capital city of Sabah from the period of November 1, 2021, to October 31, 2022. Recruited participants and the in-charge physiotherapist will know the frequency of stroke rehabilitation intervention that each participant would be receiving. However, a separate neurophysiological technologist, EEG signals analyst, and therapist are to be assigned for measuring the outcome measures and analyzing the data without prior knowledge on the type of intervention that each participant will be subjected to.
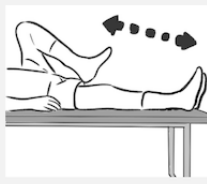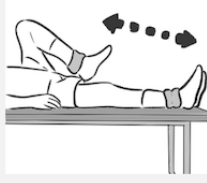
Informed and recruited participants will be randomized into two groups: one group to receive a high frequency gait training (called the intervention group [IG]) and another group to receive

the standard routine, low frequency gait training (called the control group [CG]), in a ratio of 1:1. The expected number of participants for each group is 18 (refer to the Sample Size section). The randomization plan for assigning treatment to each participant will be generated through online randomization software.

Each participant in the IG will have a therapy session three times a week, while a participant in the CG will have a therapy session once a week. Both groups will have to attend the session for a total of 12 consecutive weeks. Each session will last for approximately 40 minutes with a rate of perceived exertion between 3 to 5 minutes as the intensity threshold. The following training will be included: strengthening of hip flexors and knee extensors for approximately 5 minutes (Figure 1); balance training using a functional reach activity for approximately 10 minutes (Figure 2); gait training for approximately 20 minutes and to be conducted with or without walking aids and ankle-foot orthosis, depending on the stability, balance, and confidence level of the participants (Figure 3); and cooling down for approximately 5 minutes.

Figure 1. Strengthening exercise for hip flexor and knee extensor.

Figure 2. Functional reach for balance training.

To perform Functional Reach

- **SETUP:**
  - A yardstick/tape measure is attached to a wall at about shoulder height.
  - The participant is standing, parallel to a wall, close to but not touching, and with their feet open to shoulder height.
  - Participant's intact side should be near the wall.
  - Therapist stand by near the participant to provide support if needed. Supervision/ minimal assist/moderate assist to be given by either:
    - Placing participant's intact side near to the wall or grabbable balance support
    - Placing wall, chair, or plinth at the back in case of backward falling
    - Facilitation of the affected hip and knee by supervising physiotherapist.

- **INSTRUCTIONS:**
  - Position the patient close to the wall so that he or she may reach forward along the length of the yardstick/ tape measure.
  - The shoulders were positioned at 90 degrees of flexion, with elbows and hands extended. The participants held this position for 3 seconds.
  - Therapist takes an initial reading on the yard stick, usually spotting the knuckle of the third metacarpal.
  - A mark approximately 25 cm (10 inches) in front of the initial reading is set as a reaching target.
  - Participant is asked to reach target forward as far as possible and maintained the position for approximately 3 seconds.
  - Any reaching strategy is allowed, but the hand should remain in a fist.
  - The participant returned to the starting position and remained still for 3 seconds before proceeding with the next reach.

Figure 3. Flowchart on selecting mode of gait training.
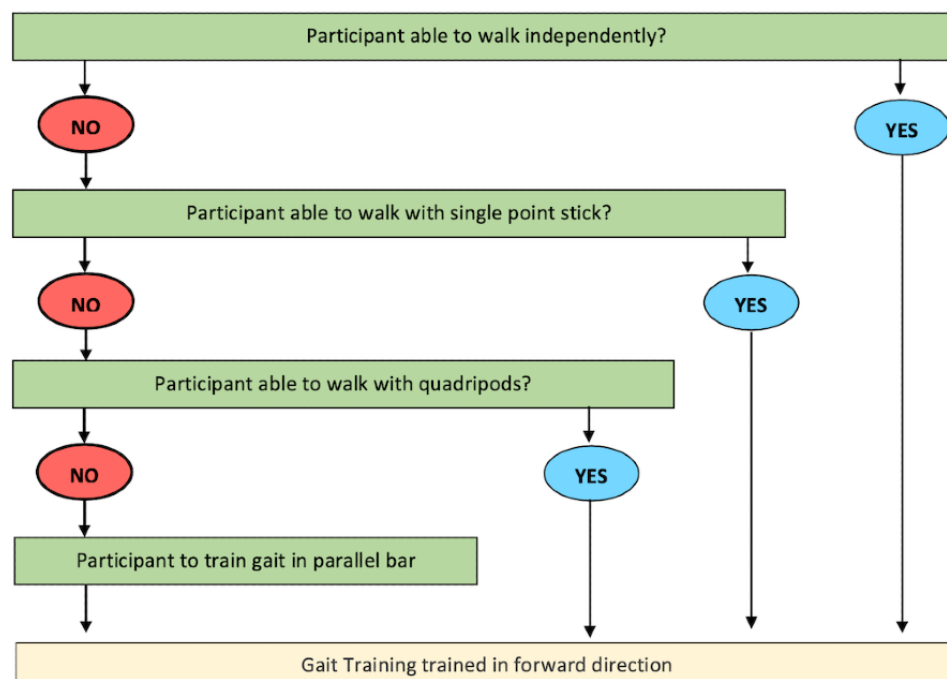
Sampling Plan, Data Collection Procedures, and Sample Size

The heterogeneity of stroke might impose difficulty for generalization of the outcomes, hence the need to impart strict eligibility criteria for the study. Inclusion criteria are adult patients older than 18 years, unilateral stroke, ischemic stroke, moderate to severe stroke severity presentation based on admission NIHSS (National Institute of Health Stroke Scale) score of 16 to 24, and displaying hip flexor and knee extensor muscle strength of MRC grade 3 or above during the subacute phase (at 3-6 months after stroke) before they are randomized for intervention. Exclusion criteria to be considered include recurrent stroke, lactating mothers, pregnant women, brain stem stroke, bilateral limbs (either upper or lower) weakness, reduced cognitive function based on a Mini Mental State Screening score of 18 and less, significant dysphasia, underwent poststroke craniectomy, and presence of severe spasticity or contracture.

One physiotherapist in charge is assigned to monitor participants' therapy, and another will be assigned to ensure blind assessments of the functional outcome measures. The end point of the study for each participant will be achieved when the final assessment is completed at 12 weeks after the intervention has ended or if adverse events are occurring during the study period.

Based on several studies [16-20], the studied population ranges from 10 to 40. A randomized controlled study by Calabrò et al [17] had 20 patients in each arm. At the same time, based on expert consultation from the neurologist at the study site, roughly 3 to 4 new stroke cases that meet the eligibility criteria will be admitted. Considering that the study is focusing on the subacute stroke population, with limited cases to be recruited, the proposed study sample is finalized to 30 participants in each arm.

Variables and Outcome Measures

Two major independent variables for evaluation are patients' demographic and stroke-related clinical information. Patient demographics shall include age, gender, and ethnicity. Stroke-related clinical information will incorporate the admission NIHSS score for classifying stroke severity, duration after stroke, and type of stroke.

The primary outcomes for assessment are brain wave frequencies and functional outcome measures. Brain wave frequencies from EEG signals will be conducted through resting-state EEG recordings at preintervention (R0) and postintervention (R1; within 2-4 weeks before the first and 2-4 weeks after the final therapy session) with the participant in a comfortable supine position. The participant will have to keep the eyes closed while awake and relaxed for 3 minutes during the EEG recording. The signals acquisition will require the use of a cap with 32 scalp monopolar electrodes placed according to the International 10/20 system.

Functional outcome measures based on the 6-Minute Walk Test (6MWT), Motor Assessment Scale (MAS), Berg Balance Scale (BBS), and Modified Barthel Index (MBI) will be assessed at preintervention (R0) and postintervention (R1; before the first and after the final therapy session). The 6MWT assesses endurance level through distance covered as a functional walking test [21]. The MAS is a performance-based scale for assessing everyday motor function in patients with stroke [22]. The BBS measures balance impairment, and its usability in poststroke assessment has been validated [23]. The MBI evaluates functional performances (feeding, bathing, grooming, dressing, bowel control, bladder control, toileting, chair transfer, ambulation, and stair climbing) with a maximum score of 100 [24].

Statistical Analysis and Modeling

Descriptive analysis will be tabulated for demographics, clinical information, and functional measures. Descriptive data will be expressed as means and SDs unless otherwise stated. SPSS version 22 (IBM Corp) will be used for data analysis. One-way analysis of variance (ANOVA) will be used for analysis of normally distributed variables. Kruskal-Wallis ANOVA will be used for nonnormally distributed data. Categorical data will be analyzed using chi-square or Fisher exact test. A value of $P<.05$ is considered statistically significant. The data on the EEG signals will be displayed with graphs whenever appropriate.

The critical analytic comparisons will be as follows:

- Changes of functional outcome measures based on the 6MWT, MAS, BBS, and MBI scores at R0 and R1 in the CG and IG groups
- Changes of brain wave frequencies derived from EEG signals at R0 and R1 in the CG and IG groups
- Admission NIHSS score and admission lower extremity motor score based on NIHSS in the CG and IG groups

Quantitative EEG Indices Analysis

The brain wave frequencies derived from EEG signals are primarily captured for quantitative EEG (qEEG) indices analysis. The four main types of brain wave frequencies are delta (1-4 Hz), theta (4.1-8 Hz), alpha (8.1-12.5 Hz), and beta (12.6-30 Hz). In many established neurophysiological studies, two commonly used qEEG indices are delta to alpha ratio (DAR) and delta-plus-theta to alpha-plus-beta ratio (DTABR). DAR is proven to have the potential for improving the assessment of cerebrovascular pathology and found to be associated with NIHSS score after 30 days of stroke for prognostication [25]. On the other hand, NIHSS scores were not substantially linked with qEEG assessments of theta or beta waves. DTABR is considered as one of the best qEEG indices and demonstrated to be more superior than the ASPECTS measure for predicting poststroke outcome at discharge and up to 12 months after the event [26].

Data analysis for EEG signals will be performed offline in MATLAB (MathWorks) using the EEGLAB toolbox. This process will start by exporting the EEG raw data and saving it in the form of a Mat file for further evaluation. The EEG data is planned to be resampled at 500 Hz, then undergo several filters (bandpass, lowpass, and highpass) before being divided into consecutive nonoverlapping epochs, and will be mean detrended. The bad channels and segments containing gross artifacts that can be identified by visual inspection will be excluded. Next, independence component analysis will be used

to eliminate other artifacts such as loss of electrode connections, ocular artifacts, and muscle artifacts. To extract the spectral power from the EEG data, each resultant component will undergo the time series, the topographic distribution of signal amplitudes, frequency spectra, and frequency loading. The spectral analysis will be done using a specific epoch of discrete fast Fourier transform to obtain and monitor certain frequency resolution.

Association Analysis

The changes observed in the DAR and DTABR will be further analyzed for association with the changes in 6MWT, MAS, BBS, and MBI for both the CG and IG. It is expected that both associations, based on correlation analyses, would be positive in both groups. However, the r value derived from the correlation is expected to be higher in the CG, grounded on the hypothetical assumption that the neuroplasticity changes would be enhanced in higher frequency training.

Ethics Consideration

This study has received the ethics approval from the National Medical Research Register of Malaysia, which is the formal and statutory body that governed all medical-related studies in this country, with ID no NMRR-19-3840-51591 (IIR).

Results

Data analysis will be conducted after interventions are completed for all recruited patients. Of 24 eligible stroke patients attending the study site, we have recruited 18 participants so far and expect to publish our results in early 2023. The remaining 6 patients had logistic issues; hence, they were not able to participate in the study procedure.

Discussion

The findings from this study would objectively demonstrate the enhanced neuroplasticity changes occurring with a higher frequency of rehabilitation training. The significance of these findings explain two major concepts in neuroplasticity post stroke: (1) the enhanced neuroplasticity implies that the stroke recovery with rehabilitation is exponential, likely due to a larger recruitment of synaptogenesis, and (2) a dose-response relationship for poststroke recovery. The dose refers to the frequency of therapy session, and the response reflects the neuroplasticity changes. Demonstrating this effect for the first time would permit a better understanding on the extent of stroke recovery so that the rehabilitation regime delivered is guided based on a more objective manner, rather than a blanket approach for all.

Conflicts of Interest

None declared.

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Abbreviations

ANOVA: analysis of variance
BBS: Berg Balance Scale
CG: control group
DAR: delta to alpha ratio
DTABR: delta-plus-theta to alpha-plus-beta ratio
EEG: electroencephalogram
IG: intervention group
MAS: Motor Assessment Scale
MBI: Modified Barthel Index
NIHSS: National Institute of Health Stroke Scale
qEEG: quantitative electroencephalogram
6MWT: 6-Minute Walk Test

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Protocol

Aerobic Exercise in HIV-Associated Neurocognitive Disorders: Protocol for a Randomized Controlled Trial

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Abstract

Background: Since the introduction of antiretroviral therapy (ART), the incidence of HIV-associated dementia has drastically fallen. Despite using ART, people living with HIV continue to experience less severe but limiting forms of HIV-associated neurocognitive disorder (HAND). People living with HIV who are on ART and experiencing symptoms of HAND may benefit from aerobic exercise.

Objective: This protocol describes a randomized controlled trial designed to determine the effects of a 12-week aerobic exercise program on HAND in Southeastern Nigeria.

Methods: At least 68 patients diagnosed with HAND will be randomly placed into either an aerobic exercise group or control group. Patients in the aerobic exercise group will perform a moderate intensity workout on a stationary bicycle ergometer, 3 times a week for 12 weeks. We will measure the primary outcomes including neurocognitive performance, prevalence of HAND, viral load, and CD4 count. We will evaluate postexercise neurocognitive performance using reliable neuropsychological tests relevant to people living with HIV, in line with the Frascati criteria. We will assess secondary outcomes such as quality of life, activity limitation, and social participation using the World Health Organization Quality of Life (WHOQOL)-Brief, and the Oxford Participation and Activities questionnaire. We will use exploratory statistics to test the data for normality and homogeneity. We will analyze the effect of the exercise program on HAND using relative risk (RR) and absolute risk reduction (number needed to treat). Analysis of covariance will be run to estimate the effect of exercise on quality of life and activity and participation level.

Results: This funded trial was approved by the Institutional Review Board in May 2020. The protocol was approved on June 15, 2020. Enrollment commenced in January 2021 and was completed in May 2021. Over 60% of the participants were recruited at the time of first submission to JMIR Mental Health. Data curation is still ongoing; hence, data analysis is yet to be executed. Study outcomes are expected to be published in March 2022.

Conclusions: This is a protocol for a randomized controlled trial that aims to evaluate the effect of a 12-week aerobic exercise program on HAND in Southeastern Nigeria.

Trial Registration: Pan African Clinical Trials Registry PACTR202009483415745; https://tinyurl.com/2p97zpu9

International Registered Report Identifier (IRRID): PRR1-10.2196/29230

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Introduction

Background

HIV-associated neurocognitive disorder (HAND) is a common neurological complication reported among people living with HIV [1]. Before antiretroviral therapy (ART) was introduced in 1996, HIV-associated dementia was a progressive disorder leading to death within 6 months [2]. Since the introduction of ART, the mean survival rate following HIV-associated dementia has increased, and milder forms of HAND have become more prevalent [1,3-5]. Globally, approximately 50% of people living with HIV are affected by HAND, with rates varying across countries [6-8]. In resource-constrained African settings, the burden of HAND ranges from 14% to 88.3% [1,9,10] in contrast with 19% to 52% in resource-limited countries [11,12]. In sub-Saharan Africa, HAND affects between 18.8% and 88.3% of people living with HIV, with a pooled prevalence of 53% [13]. In Nigeria, the prevalence of HAND fluctuates with ART use and lies between 21.5% and 71.7% [1,14,15]. People living with HIV who have HAND often present with cognitive impairment as well as behavioral and motor abnormalities such as memory loss, impulsiveness, irritability, visuospatial difficulty, dyscalculia, and difficulty with concentration and attention [2,3]. Impaired cognitive ability impacts quality of life (QoL) and treatment adherence [16]. People with HAND may also progress from being asymptomatic to being severely impaired [17,18]. People with HAND generally have limited functional capacity resulting in low productivity, job loss, poverty, poor academic performance, reduced QoL, and poor treatment adherence [19,20].

Global efforts directed at eradicating HAND [20] include early intensification of ART [21] and use of intranasal insulin [22], psychostimulants [23], and adjunctive therapies [21,24]. According to current guidelines, ART should start as soon an individual is diagnosed with HIV with a cluster of differentiation-4 (CD4) count ≤500 cells/mm^3 [25]. Timely ART initiation has led to a marked decline in the incidence of HIV-associated dementia. Although severe forms of HAND have become less common, people living with HIV continue to experience less severe but limiting forms of HAND despite ART use. The increasing incidence of HAND may be due to early HIV entry into the central nervous system, limited permeability of ART through the blood-brain barrier (BBB), reduced ART efficacy, increased drug resistance, virologic failure, adverse effects, and neurotoxicity [26-29].

A recent scoping review revealed limited rehabilitative treatment options for HAND [30]. Rehabilitation may include psychocognitive training [31] and physical exercise [32]. Psychocognitive exercises involving pen-and-paper or computerized cognitive programs are based mainly on restoring cognitive function [28,33]. These interventions often include cognitive training, cognitive stimulation, and cognitive rehabilitation using different tasks [28]. Examples include Captain's log [34], Smart-Brain [35], and InSight [36]. In contrast, physical exercise interventions are compensatory and have been shown to slow down the progression of cognitive disorder in aging HIV-seronegative individuals [31,37-39]. Currently, few exercise interventions and treatment guidelines exist for rehabilitating HAND except for evidence-informed recommendations reported by O'Brien et al [40]. Although physical exercise may slow the decline in cognitive functioning among people living with HIV, research-generated evidence remains inconclusive due to heterogeneity in study designs and use of low-intensity exercises [32,41,42]. A recent systematic review revealed that the effect of structured exercise interventions on cognitive performance of individuals with HAND has not been investigated [43]. In HIV-negative individuals, long-term and intense aerobic exercise improves BBB permeability, enhances synaptic plasticity, improves neurotrophin secretion, and regulates neuroinflammation [15,44,45] and thus may benefit people with HAND. This study therefore aims to determine the effect of a 12-week aerobic exercise program on HAND. This protocol describes procedures that will be implemented to determine the effect of a 12-week aerobic exercise program on HAND. The data will provide supporting evidence about the suitability of aerobic exercise as a complementary therapy for mitigating neurocognitive disorder among people living with HIV. The outcomes will also provide evidence to strengthen the advocacy for including aerobic exercise in the management of people living with HIV experiencing neurocognitive disorder.

Objectives

The specific objectives of this study are to determine the effect of a 12-week aerobic exercise program on the severity of HAND symptoms, determine the effect of a 12-week aerobic exercise program on CD4 count in individuals with HAND, determine the effect of a 12-week aerobic exercise program on plasma viral load in individuals with HAND, determine the effect of a 12-week aerobic exercise program on functional activity and social participation of individuals with HAND, and determine the effect of a 12-week aerobic exercise program on QoL of individuals with HAND.

Trial Design

This is a parallel randomized controlled trial employing a restricted assignment scheme, where participants were allocated in a 1:1 ratio. The intervention is aerobic exercise, and the comparator is a no-treatment control group. All assessors will be blinded regarding participant identification of both the experimental and control groups.

Methods

Study Setting

This study is taking place at the Exercise Immunology Clinic of the Department of Physiotherapy, University of Nigeria Teaching Hospitals (UNTH) Ituku-Ozalla, Nigeria, and the University of Nigeria Enugu Campus (UNEC). A preliminary study revealed that approximately 50% of the prospective

participants that visited the UNTH ART clinic were from Enugu Metropolis. The second site, UNEC, was chosen as a more centralized location for participants who resided in Enugu Metropolis and nearby environs. Participants were purposively selected to participate. To ensure consistency, the intervention team, which is comprised of 2 qualified physiotherapists and 2 trained research assistants, was trained by the principal investigator.

We identified prospective participants during a pilot study. Prospective participants, who lived in the Enugu metropolis and surrounds, were invited by text message to attend the ART clinic. Only participants able to travel to the study site with ease were invited to participate. Participants were randomly assigned to the intervention or control group. First, a sequence of random numbers was generated using Random Restricted Software 2.0. An independent person assigned the random numbers to either the intervention or control group by placing the generated numbers into A4, opaque, sealed envelopes, with only C or E written on an inconspicuous area of the envelope. Envelopes with C are control and E are exercise. The outcome assessors (the principal investigator and clinical psychologist) enrolled participants into the study, without knowing group assignments. Outcome assessors, including the principal investigator, neurologist and clinical psychologist, and data analyst, were also blinded while conducting neurological assessments. Care physicians were asked not to suggest any form of aerobic exercise to the patients throughout the study period. Trained physiotherapists conducted the treatment. Finally, the data were coded (C for control group and B for experimental group) so that the biostatistician will not know which group is experimental or control.

Eligibility Criteria

We included patients if they met the following criteria: diagnosed with HAND and physically inactive (sedentary, <2 hours of exercise per week; ready to exercise upon assessment, not engaged in regular exercise for approximately 3 months before the study). Patients were excluded if they were older than 65 years; had uncontrolled hypertension (blood pressure [BP] 140/90 mm Hg), deafness, severe eye impairment, physical disability, history of traumatic brain injury, psychiatric illness, recent focal neurological deficit, active depression, alcohol or substance abuse, musculoskeletal injury, or acute illness capable of hampering exercise performance; pregnancy; or had angina pectoralis and/or shortness of breath at rest or during exercise. We excluded participants on cognition-enhancing drugs such as eugeroics, attention deficit/hyperactive disorder medications, and nootropic supplements.

Informed Consent

Informed written consent was obtained from each participant before enrollment in the study, provided they had the capacity to give consent.

In this study, the control group receives no treatment. The efficacy of aerobic exercise in HAND rehabilitation has rarely been investigated; therefore, we are comparing aerobic exercise to no exercise, before comparing to other forms of exercise or therapy.

Exercise Testing

Exercise testing is conducted using the Young Men Christian Association (YMCA) bicycle ergometer protocol at baseline and after a 12-week exercise program [46,47]. The YMCA protocol uses 2 to 4 stages of continuous exercise lasting 3 minutes, during which 2 heart rate (HR)-power output data points (steady-state HR) between 110 bpm and 150 bpm are needed. The test is designed to raise the participant's steady-state HR to between 110 bpm and 150 bpm and 70% HR reserve or 85% of the age-predicted maximum HR (HRmax) for at least 2 consecutive stages. Using the Life-Fitness Cycle Ergometer (95Ci, Franklin Park, IL), the first 3-minute workload is set between $150 \text{ kg·m·min}^{-1}$ and $300 \text{ kg·m·min}^{-1}$ (25-50 watts). The speed is set at 50 rpm. HR is measured within the last minute of each stage. If an HR >110 bpm is obtained in the first 3 minutes, then only one additional 3-minute stage is performed by increasing the workload to $450 \text{ kg·m·min}^{-1}$ (75 watts). If the second-stage HR is <110 bpm, the 3-minute third or fourth stage is performed at an additional workload of $150 \text{ kg·m·min}^{-1}$ up to $750 \text{ kg·m·min}^{-1}$ (125 watts), in order to obtain 2 HRs between 110 bpm and 150 bpm. At the end of the test, a 3-minute recovery period (cool down) at zero resistance is administered. HR is measured during the last minute of each stage. The 2 steady-state HRs are plotted against the respective workload on the YMCA graph sheet. The line generated from the plotted points is then extrapolated to the age-predicted HRmax, and a perpendicular line is dropped to the x axis to estimate the work rate (VO_{2max}) that would have been achieved if the individual had worked to maximum capacity [46-48]. At the end of exercise testing, the participants are asked to return to the Physiotherapy department within 2 days to 3 days to commence the intervention.

Exercise Intervention

Participants in the aerobic exercise group exercise on a bicycle ergometer at a low intensity of between 60% and 80% of their HRmax as recommended by the American College of Sports Medicine (ACSM) [49]. Participants train 3 times a week for 12 weeks. Initially, participants train at 60% of HRmax, and this is increased after 4 weeks to 80% HR_{max} for the remainder of the training period. Each training session consists of 20 minutes to 30 minutes of aerobic exercise in the first 4 weeks depending on the patient's tolerance. After the first 4 weeks, training sessions are increased to 30 minutes to 45 minutes and further increased after the eighth week to 60 minutes for the remainder of the intervention. Participants are encouraged to give their best to the moderate-intensity exercise. Participants are prepared for exercise following the ACSM guidelines [46]. All fitness testing is performed by qualified physiotherapists.

Control Group

Participants are educated on the benefits of exercise for people living with HIV but are asked not to engage in any form of structured physical activity for the corresponding 12-week period. The first education session occurs while the exercise participants are being moved to the trial site, which serves to distract the control group participants. The second education session takes place 6 weeks into the intervention, during which

participants are asked if they have engaged in any structured physical activity and if yes, they are asked to quantify the intensity and time. We encourage control group participants to abstain from structured physical activity.

Criteria for Discontinuing or Modifying Allocated Interventions

The aerobic exercise intervention is discontinued or modified if participants experience exercise-related angina pectoralis or shortness of breath during 2 successive sessions, exercise-induced tachycardia during an exercise session, severe illness capable of affecting the participant's exercise capacity, complaints of worsening cognitive ability, or if participants request to discontinue or modify the exercise intensity.

Strategies to Improve Adherence to Interventions

During the pilot study, we noted that one of the major challenges faced by our prospective participants was increased transportation costs and the attendant opportunistic costs of participants who will not be able to work due to the study. Participants are given a sum of N2000 (US $4.86) every 2 weeks to cover transport costs. We call participants on the day before their exercise session to remind them of their appointment. Participants are called by telephone if they fail to show up for training or a periodic appointment to ascertain the reason for their absence and improve compliance.

Relevant Concomitant Care Permitted or Prohibited During the Trial

Participants continue with their ART. Participants are discouraged from continuing any medication not prescribed by a physician. Prospective participants are allowed a washout period of 2 weeks before being eligible to continue.

Study Outcomes

The primary outcomes include neurocognitive performance, prevalence of HAND, viral load, and CD4 count. The secondary outcomes include maximum oxygen uptake (VO_2), QoL, activity limitation, and participation restriction. Potential confounding variables include age, sex, level of education, vaccination, history of virologic failure, level of ART adherence, exercise adherence, ART regimen, ovulation status, history of recent vaccination, and seasonality. These variables will be measured at baseline, after 12 weeks, and 3 months after the intervention. Their change will be measured over time. Aggregation parameters will include proportion, mean, or median depending on how the data are distributed.

Participant Timeline

The proposed timeline for the study and planned elements is shown in Figure 1. All prospective participants were identified in a pilot study. Baseline assessments were conducted from the end of January 2021 to mid-February 2021 and covered neurocognitive performance, BP, HR, respiratory rate, assessment of physical activity readiness, QoL, CD4 count, viral load, and activity limitation and social participation. Before the intervention, all participants undergo an exercise stress test. The aerobic exercise intervention starts a day after exercise testing and lasts for 12 weeks. Following the 12-week aerobic intervention, postexercise assessments are conducted.

Figure 1. Proposed timeline for the randomized controlled trial for measuring the efficacy of exercise for rehabilitating symptoms associated with HIV-associated neurocognitive disorder (HAND) in people living with HIV.

	Enrollment	Allocation	Close-out				
TIME POINT	$-t_1$	0	t_1			t_2	t_3
ENROLLMENT							
Eligibility screening and informed consent	Jan 25, 2021 to Feb 15, 2021						
Allocation into intervention or control group		Jan 25, 2021 to Feb 15, 2021					
INTERVENTIONS							
Exercise testing		Feb 23, 2021 to Feb 25, 2021					
Aerobic exercise			Jan 25, 2021 to Mar 25, 2021	⟵⟶		Apr 25, 2021 to Jun 25, 2021	
Postexercise follow-up							Jun 25, 2021 to Sept 25, 2021

Sample Size

An estimated sample size of 68 (34 in each group) will have 90% power to detect a difference in means of 13.4 (the difference between a Group 1 mean, μ_1, of 56 and a Group 2 mean, μ_2, of 42.6) assuming that the common SD is 16.67 using a 2-group t test with a 5% 2-sided significance level.

Neuropsychological Screening

The principal investigator (who is a physiotherapist working with people living with HIV and neurological conditions), a clinical psychologist, and a neurologist (who is a specialized medical doctor) conduct the neuropsychological screening, which is conducted in 3 stages. First, we conduct a brief neuromedical screening using a pilot assessment guide; then, we administer the neuropsychological instruments and, finally, assess the subjective symptoms of HAND such as difficulty remembering recent events (people, conversations, names, commitments, where things are placed), understanding conversation or reading materials, word finding, planning activities, problem solving, concentrating, thinking clearly or logically, finding his or her way about, calculating, and following direction or instruction.

We administer neuropsychological instruments chosen for their simplicity and ease of administration in any language. Only the Hopkins Verbal Learning Test-Revised (HVLT-R) and Controlled Oral Word Association Test (COWAT) require understanding of some English words. These tests were extracted from the international neurobehavioral test battery used by the HIV Neurobehavioral Research Center [1] and a recent clinical trial on HAND [50,51]. These tests are sensitive to HAND in Nigeria [52,53]. We first screen for probable dementia using the International HIV Dementia Scale (IHDS). Confirmatory neuropsychological tests are administered in the following order: first, we administer the HVLT-R immediate recall (duration 3-5 minutes). After waiting 20 minutes to 25 minutes to administer the second part of the HVLT-R, we administer the Trail Making Test (TMT)-A and -B (5-10 minutes), verbal fluency (3-8 minutes), and the Digit Span Test (5-10 minutes). We then administer the HVLT-R delay recall. We also assess neurocognitive performance in line with the 2007 modified American Academy of Neurology criteria, also known as the Frascati criteria [1,54]. We will convert the raw scale scores using a clinical rating algorithm, to sum the scores to obtain an overall score for each participant. The latter will be used for covariate analysis, if needed.

Tests

Beck Depression Inventory

The Beck Depression Inventory (BDI) [55] measures characteristic attitudes and symptoms of depression using a 21-item self-report rating inventory (Multimedia Appendix 1). The BDI takes approximately 10 minutes to complete and requires a fifth- to sixth-grade reading level to adequately understand the questions. Internal consistency ranges from 0.73 to 0.92, with a mean of 0.86 [56]. The BDI has demonstrated high internal consistency, with alpha coefficients of 0.86 and 0.81 for psychiatric and nonpsychiatric populations, respectively [57]. A score ≥17 indicates borderline clinical depression.

Alcohol Use Disorder Identification Test

The Alcohol Use Disorder Identification Test (AUDIT) [58] is approved by the World Health Organization (WHO) to assess intoxication or withdrawal (Multimedia Appendix 2). The AUDIT is comprised of 10 items, and a score ≥8 indicates alcohol intoxication or withdrawal. Patients with scores >8 were excluded from the study [12]. It takes 2 minutes to 4 minutes to complete.

Drug Abuse Screening Test

The Drug Abuse Screening Test [59] is a valid and reliable instrument consisting of 10 items (Multimedia Appendix 3). Patients who score ≥3 are suspected of drug abuse and were excluded from the study. It takes approximately 5 minutes to administer.

International HIV Dementia Scale

We screen HIV-positive patients for dementia and cognitive impairment using the IHDS [60] (Multimedia Appendix 4). The IHDS tests registration, recall, motor function, and information processing. The IHDS has a sensitivity and specificity of 74% and 46%, respectively, at a cutoff point of 9.5. The test does not require any special instruments except a timer or wristwatch and can be easily administered by other health workers, not necessarily by a physician. The IHDS is also free of cultural bias and can be used in many resource-limited countries.

Controlled Oral Word Association Test

We use the COWAT [61] to assess verbal fluency using FAS letter fluency—number of words generated (Multimedia Appendix 5). Verbal fluency measures cognitive function that facilitates information retrieval from memory, and the verbal fluency test evaluates an individual's ability to retrieve specific information within restricted search parameters [62]. This test requires the individual to name as many words as possible that begin with a given letter (ie, F, A, and S). Each letter is allotted 60 seconds. Individuals cannot use proper names or numbers and cannot use words with different tenses or endings once the root word has been given. They have to do it as quickly as possible, and the number of words produced during 1 minute is scored for both phonemic and semantic verbal fluency [62]. The test takes 3 minutes to 8 minutes to complete. The score equals the mean number of words uttered in the 3 trials corresponding to each initial letter [63]. This test does not require special instrumentation.

Hopkins Verbal Learning Test-Revised

The HVLT-R [64] is used to assess verbal learning and memory or recall (Multimedia Appendix 6). The HVLT-R is simple to administer and is similar to the California Verbal Learning Test [65]. An assessor gives the patient a list of 12 words with an embedded semantic structure (4 categories of 3 words each). The assessor reads the list to the patient, who is then asked to repeat as many words as possible in any order (free recall). This process is repeated 3 times, which represents the 3 learning trials. After a 25-minute break, the patient is again asked to remember as many of the words as possible in any order. The patient's semantic strategy is evaluated by examining the degree to which words are semantically clustered during the 3 learning

trials. In the standard administration, items from the same category are not presented together, and subjects are not informed of the semantic organization. The HVLT-R's 3 learning trials and delay recall trial are scored separately. The 3 learning trial scores (number of correct words) are summed to yield a total score. Overall, this test takes 28 minutes to 30 minutes. This test does not require instrumentation.

Trail Making Test-A and -B

The TMT is a 2-in-1, sensitive, paper-and-pencil measure of information processing speed and executive function [66,67] (Multimedia Appendix 7). The TMT consists of 2 parts (TMT-A and TMT-B). The TMT-A consists of a standardized page on which the numbers 1 to 25 are scattered within circles, and the participants are asked to connect the numbers in order as quickly as possible. Similarly, the TMT-B consists of a standardized page that includes the numbers 1 to 13 and the letters A to L. The participants are instructed to draw lines connecting numbers and letters in order, alternating numbers and letters. Before starting the test, participants are allowed to practice on 6 items to make sure that they understand both tasks. When a participant makes an error during the test, the examiner points it out, explains, and then guides the participant to correctly complete the circles, after which the participants are requested to continue with the task. A maximum time of 300 seconds is allowed before discontinuing the test. Direct scores of TMT will be the time in seconds taken to complete each task (-A and -B). This test takes 5 minutes to 10 minutes.

Digit Span Test

The digit span test (DST) [68] is a pencil-and-paper instrument and evaluates auditory attentional capacity and working memory for orally presented information (Multimedia Appendix 8). In this study, the DST is used to assess attention and working memory. The DST was originally developed for people between 18 years and 97 years old and is appropriate for use in this study. Participants are asked to repeat series of digits that become gradually longer. The maximum digit span that the participants are able to repeat in direct and reverse orders constitutes the forward (DST-f) and backward (DST-b) scores, respectively [51,68]. This test should be completed in 10 minutes to 15 minutes.

The Lawton Instrumental Activities of Daily Living Scale

The Lawton Instrumental Activities of Daily Living Scale is a valid and sensitive measure of instrumental activities of daily living and is comprised of 8 items (Multimedia Appendix 9). Scores <8 may indicate functional impairment [9]. This test takes 3 minutes to 5 minutes to complete.

The WHO Quality of Life-BREF

We use the short form of the World Health Organization Quality of Life (WHOQOL)-BREF, which has been validated in diverse settings, including African countries, and is based on a well-classified definition of QoL (Multimedia Appendix 10). It is comprised of physical, psychological, social, and environment domains. The WHOQOL-BREF is a recommended instrument for people living with HIV infection [69,70]. The WHOQOL-BREF has an internal consistency of α=0.74-0.85 and test-retest reliability of rho=0.64-0.79 [71]. Each of the 4

domains is measured on a 5-point Likert scale: 1 indicates low perception, and 5 indicates high perception [69]. The WHOQOL-BREF measures the perceived QoL and hence contains items asking how patients felt about different facets of life in the week before being assessed.

The Oxford Participation and Activities Questionnaire

The Oxford Participation and Activities Questionnaire (Ox-PAQ) is a 23-item, generic, patient-reported outcome measure (Multimedia Appendix 11). Theoretically, it is grounded in the WHO International Classification of Functioning, Disability and Health [72]. It is primarily used in clinical trials to evaluate interventions targeted at improving or maintaining participation and activity. The measure demonstrates good reliability (Cronbach α=0.81-0.96) and validity and low levels of missing data across all 3 domains [73,74]. It equally demonstrates good convergent validity with the EuroQol-5D questionnaire [75].

Physical Activity Readiness Questionnaire

The Physical Activity Readiness Questionnaire (PAR-Q) was created by the British Columbia Ministry of Health and the Multidisciplinary Board on Exercise [76] (Multimedia Appendix 12). It is a simple self-screening tool that is used to plan an exercise program. The tool helps to determine the readiness for exercise as it reveals the safety or possible risk of exercising for an individual based on their health history, current symptoms, and risk factors. It is often used in clinical trials to ascertain readiness prior to enrollment [77].

Cardiorespiratory Measurements

Participants' resting HR, systolic BP, and diastolic BP are monitored on the right arm [46,78] using an automated digital electronic BP monitor (Omron digital BP monitor, Model M2 Eco; Tokyo, Japan). These measurements are monitored between 7:00 am and 2:00 pm each test day.

Anthropometric Measurements

We assess participants' physical characteristics (% body fat, weight in kg, height in meters, and BMI in kg/m^2) according to a standardized anthropometric protocol [79,80].

Blood Sample Collection

Blood samples are collected using the venipuncture method. We collect venous blood samples both pre- and posttreatment between 8:00 am and 12:00 pm. We collect blood samples using a 5-mL syringe [48]. CD4 count tests are conducted within 12 hours, and samples for viral load are stored in a refrigerator at –80 °C until analysis [81].

Measurement of CD4 Count and Viral Load

Samples are analyzed by the UNTH ART clinic laboratory scientist. To control for the potential effects of rest, time of the day, season, ovulation, and vaccination, pre-exercise blood samples for quantifying CD4 count were drawn when patients arrived at the laboratory, after 60 minutes of rest [82]. To minimize diurnal variation, samples were collected between 8:00 am and 12:30 pm. We aimed to collect pre-exercise blood samples before the heavy rainfall season in June. In Nigeria, rainfall peaks in June [83] and is associated with increased

opportunistic infections that influence CD4 count. After each sample was collected, we examined the tube for integrity before transporting to the testing center. All CD4 counts were measured within 12 hours of sample collection following the recommendation of the WHO [84-86].

Data Management

Data are manually transcribed from paper forms into a Microsoft Excel spreadsheet and exported and secured to MicrOsiris 24.8. Data are verified through independent double data entry, where the principal investigator (data manager) and a data clerk both enter data. Consistency checks are performed during data entry, and warnings are displayed when needed.

Personal information such as contact number and identity number are collected and only used to reach participants when necessary and for possible access to participants' hospital files. Data are handled confidentially and are not shared with a third party. Participants' names do not appear in any data record except in a case of referral.

Statistical Methods

Primary and secondary variables will be tested for normality and heterogeneity using Kolmogorov-Smirnov and Levene tests, respectively. We will compare the control group and exercise group using a 2-way analysis of variance with repeated measurements and Bonferroni correction. Primary outcome measures are cognitive performance, QoL, activity limitation, and participation. We will compute hazard ratios to evaluate the effect of the intervention over time. SPSS version 21 (IBM Corp, Armonk, NY) will be used.

We expect that potential confounding variables, not accounted for by randomization, may influence outcomes between the control and study groups. We will include potential confounding variables in appropriate analysis of covariance. Covariates include neurocognitive performance test scores (clinical rating algorithm), CD4 count (classified as <350 cells/μl or ≥350 cells/μl), viral load (classified as detectable [>400 copies/mL] or undetectable [<400 copies/mL]), age, sex, level of education, BMI, exercise adherence (classified as nonadherent [≤40%] or adherent [>40%]), adherence to ART since the intervention (classified as nonadherent [≤40%] or adherent [>40%]), ART regimen, ovulation, and vaccination status. Also, our findings will be included in an updated meta-analysis of the effects of exercise on cognition in people living with HIV to understand how the study outcome may drive existing associations. The initial meta-analysis was conducted by our team [43].

As per nonadherence to a study protocol, we will employ intention-to-treat analysis. Effort will be made to prevent missing data through cross-checking of the information obtained from participants. In case of missing data, we will explore patterns of missing and, where appropriate, multiple computation will be executed using SPSS version 21.

Plans to Give Access to the Full Protocol, Participant-Level Data, and Statistical Code

This decision is subject to approval by the Physiotherapy Department of the University of Pretoria, South Africa.

Oversight and Monitoring

The trial is conducted by a team of 2 qualified physiotherapists and 2 trained research assistants, while the investigator and research supervisors monitor and oversee data collection and analysis. The intervention administrator provides daily updates regarding the trial to the chief investigator who then provides weekly updates to his supervisors. Challenges encountered during the trial are resolved by the investigators through conference meetings or other feasible alternatives.

Adverse Event Reporting and Harms

Participants are asked to report any adverse event following exercise. Adverse events are formally assessed every 2 weeks using an adverse event form piloted by the US Medical Device and Diagnostic Industry recommendations [87,88] (Multimedia Appendix 13). If an adverse event is reported, the patient is referred to their physician for immediate assessment of underlying cause and possible management. A physiotherapist treats cases of pain, lower back pain, fatigue, and muscle soreness and prescribes rest to the participants when necessary. In cases of spontaneous but mild adverse events, patients are given sufficient time to rest, after which a therapist decides if the participant is fit to continue the scheduled exercise.

Plans for Communicating Important Protocol Amendments to Relevant Parties

Amendments to the trial protocol with respect to eligibility criteria, outcomes, analysis, and frequency and duration of treatment will be communicated first to the researchers' supervisors and then the University of Pretoria, Faculty of Health Sciences Research Ethics Committee, the PAN Africa Trial Registry, and the journal in which the protocol is published.

Dissemination Plans

The outcome of the trial will be communicated to participants and health care professionals through conference presentations and to the general public through publication in a peer-reviewed international journal. No publication restriction applies. The data will be available for sharing upon request, which is subject to approval by the Department of Physiotherapy, University of Pretoria.

Ethics Approval

Ethical approval was obtained from the University of Pretoria research ethics committee (Ethics reference no. 152/2020). Informed consent was obtained before enrollment. Prior to consent seeking, we introduced the study and explained the purpose thereof. Participants reserved the right to make decisions regarding their participation without inducement and such right was upheld throughout the study.

Results

The trial, which secured funding in March 2020, was approved by the Institutional Review Board in May 2020. Data collection commenced in June 2020, with a pilot study to examine the rater reliability and minimum detectable change of the selected neuropsychological tests. Between July 2020 and November

2020, individuals with HAND had been identified. Participant enrollment commenced in January 2021 and was completed in May 2021. An amendment was submitted and secured ethical approval. Over 60% of the participants were recruited at the time of first submission to JMIR Mental Health. Data curation is still ongoing; hence, data analysis is yet to be executed. Study outcomes are expected to be published in March 2022.

Discussion

In line with the ART clinic's COVID-19 prevention guidelines, personal protective equipment including face masks and hand sanitizer are used by research team members and participants, while ensuring social distancing. When considering the acceptability of incentives in clinical trials, evidence suggests that incentives may ensure a good degree of adherence and completion [89-92]. Several systematic reviews [90-92] have argued that incentives cover opportunity costs of participating in behavioral interventions such as exercise. Participants will be compensated for transport money to the hospital only.

Authors' Contributions

MN is the chief investigator; he conceived the study and led the proposal and protocol development. NM contributed to study conception, study design, and development of the proposal. NG and AA contributed to design and development of the proposal. AO provided methodological guidance. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Beck Depression Inventory.
[PDF File (Adobe PDF File), 45 KB - resprot_v11i1e29230_app1.pdf]

Multimedia Appendix 2
Alcohol Use Disorder Identification Test (AUDIT).
[PDF File (Adobe PDF File), 280 KB - resprot_v11i1e29230_app2.pdf]

Multimedia Appendix 3
Drug Abuse Screening Test.
[PDF File (Adobe PDF File), 117 KB - resprot_v11i1e29230_app3.pdf]

Multimedia Appendix 4
International HIV Dementia Scale.
[PDF File (Adobe PDF File), 574 KB - resprot_v11i1e29230_app4.pdf]

Multimedia Appendix 5
Controlled Oral Word Association Test (COWAT) (Verbal Fluency Test).
[DOCX File , 12 KB - resprot_v11i1e29230_app5.docx]

Multimedia Appendix 6
Hopkin Verbal Learning Test-Revised.
[PDF File (Adobe PDF File), 208 KB - resprot_v11i1e29230_app6.pdf]

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Multimedia Appendix 7
Trail Making Test A & B.
[PDF File (Adobe PDF File), 46 KB - resprot_v11i1e29230_app7.pdf]

Multimedia Appendix 8
Digit span test.
[DOCX File , 852 KB - resprot_v11i1e29230_app8.docx]

Multimedia Appendix 9
Lawton Instrumental Activities of Daily Living (IADL) scale.
[PDF File (Adobe PDF File), 221 KB - resprot_v11i1e29230_app9.pdf]

Multimedia Appendix 10
The World Health Organization Quality of Life (WHOQoL) Bref.
[PDF File (Adobe PDF File), 85 KB - resprot_v11i1e29230_app10.pdf]

Multimedia Appendix 11
Oxford Participation and Activities Questionnaire (Ox-PAQ).
[PDF File (Adobe PDF File), 118 KB - resprot_v11i1e29230_app11.pdf]

Multimedia Appendix 12
Physical Activity Readiness Questionnaire.
[PDF File (Adobe PDF File), 112 KB - resprot_v11i1e29230_app12.pdf]

Multimedia Appendix 13
Adverse events form.
[DOCX File , 39 KB - resprot_v11i1e29230_app13.docx]

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Abbreviations

ACSM: American College of Sports Medicine
ART: antiretroviral therapy
AUDIT: Alcohol Use Disorder Identification Test
BBB: blood-brain barrier
BDI: Beck Depression Inventory
BP: blood pressure
CD4: cluster of differentiation-4
COWAT: Controlled Oral Word Association Test
DST: digit span test
HAND: HIV-associated neurocognitive disorder
HR: heart rate
HRmax: age-predicted maximum HR
HVLT-R: Hopkins Verbal Learning Test-Revised
IHDS: International HIV Dementia Scale
NSFAS: National Student Financial Aid Scheme
Ox-PAQ: Oxford Participation and Activities Questionnaire
QoL: quality of life
TMT: Trail Making Test
UNEC: University of Nigeria Enugu Campus

UNTH: University of Nigeria Teaching Hospitals
VO$_2$: maximum oxygen uptake
WHO: World Health Organization
WHOQOL: World Health Organization Quality of Life
YMCA: Young Men Christian Association

Protocol

A Web-Based Alcohol and Other Drug Prevention Program (Strong & Deadly Futures) for Aboriginal and Torres Strait Islander School Students: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: There are no available school-based alcohol and drug prevention programs with evidence of effectiveness among Aboriginal and Torres Strait Islander youth. To address this, we codeveloped the *Strong & Deadly Futures* well-being and alcohol and drug prevention program in partnership with an Indigenous creative design agency and 4 Australian schools.

Objective: This paper presents the protocol to evaluate the effectiveness of *Strong & Deadly Futures* in reducing alcohol and other drug use and improving well-being among Aboriginal and Torres Strait Islander youth.

Methods: The target sample will be 960 year 7 and 8 students from 24 secondary schools in Australia, of which approximately 40% (384/960) will identify as Aboriginal or Torres Strait Islander. The study design is a 2-group, parallel cluster randomized controlled trial with allocation concealment. Recruited schools will be block randomized (ratio 1:1), stratified by geographical remoteness, by an independent statistician. Schools will be randomized to receive *Strong & Deadly Futures*, a web-based alcohol and drug prevention and social and emotional well-being program that delivers curriculum-aligned content over 6 lessons via an illustrated story, or *health education as usual* (control). Control schools will be supported to implement *Strong & Deadly Futures* following trial completion. Surveys will be administered at baseline, 6 weeks, 12 months, and 24 months (primary end point) post baseline. Primary outcomes are alcohol use (adapted from the National Drug Strategy Household Survey), tobacco use (Standard High School Youth Risk Behavior Survey), and psychological distress (Kessler-5 Psychological Distress Scale). Secondary outcomes are alcohol and drug knowledge and intentions, alcohol-related harms, binge drinking, cannabis use, well-being, empowerment, appreciation of cultural diversity, and truancy.

Results: The trial was funded by the National Health and Medical Research Council in January 2019, approved by the Human Research Ethics Committee of the University of Sydney (2020/039, April 2020), the Aboriginal Health and Medical Research Council of New South Wales (1620/19, February 2020), the Western Australian Aboriginal Health Ethics Committee (998, October 2021), and the ethics committees of each participating school, including the New South Wales Department of Education (2020170, June 2020), Catholic Education Western Australia (RP2020/39, November 2020), and the Queensland Department of

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Education (550/27/2390, August 2021). Projected dates of data collection are 2022-2024, and we expect to publish the results in 2025. A total of 24 schools have been recruited as of submission of the manuscript.

Conclusions: This will be the first cluster randomized controlled trial of a culturally inclusive, school-based alcohol and drug prevention program for Aboriginal and Torres Strait Islander youth; therefore, it has significant potential to address alcohol and other drug harms among Aboriginal and Torres Strait Islander youth.

KEYWORDS

Introduction

Background

Despite the ongoing impacts of colonization, disempowerment, and inequity, strong cultural and community connections have persisted as sources of resilience for Aboriginal and Torres Strait Islander young people [1,2]. Nonetheless, intergenerational trauma has contributed to poorer emotional and social well-being, with alcohol and other drug (AOD) use identified as both a risk factor for and a consequence of mental illness among Aboriginal and Torres Strait Islander youth [3]. Over the past decade, encouraging trends have been observed with declines in binge drinking (≥5 standard drinks, each containing 10 g of ethanol) and tobacco use reported among young Aboriginal and Torres Strait Islander adolescents [4]. However, Aboriginal and Torres Strait Islander youth continue to experience disproportionate harm from AOD use and, combined with an average earlier age of use [5,6], are at increased risk of substance use disorders later in life [7-9]. To reduce this inequity, it is critical that alcohol and drug prevention initiatives are designed to be culturally relevant for Aboriginal and Torres Strait Islander adolescents to empower them to reach their full potential.

Schools are an ideal setting to deliver alcohol and drug prevention education [10,11]. School-based programs have demonstrated efficacy in preventing or delaying the uptake of AODs and improving attitudes and knowledge of related harms [12-14]. However, a recent international systematic review identified no well-being and drug prevention programs available for Aboriginal and Torres Strait Islander students that are culturally appropriate and effective [15].

Objectives

To address this gap, *Strong & Deadly Futures* was codeveloped in partnership with an Indigenous Australian creative design agency (Gilimbaa) and with the leadership of Aboriginal and Torres Strait Islander youth (41/77, 53% Indigenous [16]) and staff at 4 Australian secondary schools. The development was informed by stakeholder consultations (17/42, 40% Aboriginal or Torres Strait Islander) and overseen by an advisory group of experts in Aboriginal health, drug prevention, and research (6/16, 38% Aboriginal or Torres Strait Islander). The resulting program, *Strong & Deadly Futures,* is a culturally inclusive curriculum program that aims to reduce harm from AOD use by enhancing coping skills and preventing substance use initiation over the vulnerable adolescent period. The program features web-based delivery to enhance engagement, reach, and implementation fidelity and incorporates core skill development and harm minimization components from the effective *Climate Schools* drug prevention programs [17-25]. It also includes strategies to promote social and emotional well-being, such as coping with stress and effective decision-making. Drawing on feedback from our Aboriginal and Torres Strait Islander stakeholders, *Strong & Deadly Futures* incorporates cultural components to foster pride and appreciation of Aboriginal and Torres Strait Islander culture. Although Aboriginal and Torres Strait Islander culture is central to the program, it was designed to be culturally inclusive so it can be delivered in classrooms with both Aboriginal and non-Indigenous students, reflecting the most common classroom setting experiences of Aboriginal students in Australia. A pilot study showed that *Strong & Deadly Futures* was acceptable and feasible to implement in culturally diverse classrooms, with postprogram improvements observed in students' knowledge of alcohol and drug harms and overall well-being (unpublished data).

This paper presents a trial protocol (Australian New Zealand Clinical Trials Registry: ACTRN12620001038987) to evaluate the effectiveness of *Strong & Deadly Futures* in reducing AOD use and enhancing the emotional and social well-being of Aboriginal and Torres Strait Islander young people. This will be the first randomized controlled trial (RCT) of a school-based, culturally relevant alcohol and drug prevention program for Aboriginal and Torres Strait Islander adolescents. It is hypothesized that *Strong & Deadly Futures* will be more effective than an active control group (*health education as usual*) in delaying students' uptake of alcohol and tobacco and reducing psychological distress over a 24-month period. The secondary aims are to examine the effects of *Strong & Deadly Futures* on students' alcohol and drug knowledge and intentions, cannabis use, binge drinking and alcohol-related harms, well-being and empowerment, appreciation of cultural diversity, and truancy.

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Methods

Overview

Strong & Deadly Futures will continue to be closely developed with Aboriginal and Torres Strait Islander communities. The first phase of the project involves establishing partnerships with local Aboriginal and Torres Strait Islander organizations to conduct community consultations and seek feedback on the program. This feedback will inform adaptations to the program to align it with local priorities and contexts. The second phase involves trialing the adapted program in a school-based RCT. An Aboriginal Reference Group will provide oversight throughout both stages of the project.

Aboriginal and Torres Strait Islander Leadership

Aboriginal Reference Group

An Aboriginal Reference Group will provide oversight and guidance through the consultation, school-based trial, and dissemination phases of the study. The Reference Group will comprise experts involved in the development of the *Strong & Deadly Futures* program and representatives from the local Aboriginal Community Controlled Health Services (ACCHS) or Aboriginal and Torres Strait Islander stakeholder organizations in participating communities. The Aboriginal Reference Group will meet annually throughout the study duration, with the possibility of out-of-session meetings as required.

ACCHS Partnerships

In line with best practices in Aboriginal and Torres Strait Islander health research [26], we will ask the local ACCHS or other relevant Aboriginal or Torres Strait Islander stakeholder organizations to consent to the trial proceeding in their community. The ACCHS will be invited to partner with the research team to conduct consultations in their community, and staff will be invited to participate in consultation sessions. A representative from each ACCHS will be invited to sit in on the Aboriginal Reference Group.

Local Aboriginal or Torres Strait Islander Facilitators

An Aboriginal or Torres Strait Islander facilitator will be employed in each community to conduct local consultations and support research implementation in schools. Facilitators may be recruited from the local ACCHS or the participating trial school. The consultation role will involve recruiting local community members and organizing and facilitating the consultations. School-based project support will include supporting teachers with the cultural aspects of the program, as well as assisting with survey administration and measurement of implementation fidelity through lesson observations. Facilitators will attend a series of training workshops with the research team before community consultations and commencement of the trial and will be provided with a handbook outlining the research process, methods, and program content. Facilitators will receive regular supervision and mentoring from the research team and will be provided with opportunities to participate in conferences and workshops throughout the study.

Phase 1: Community Consultations

Consultations will be conducted in each community to obtain local feedback to inform adaptations to the program to align with the local context.

Participants and Recruitment

Within the local community of schools enrolled in the trial, facilitators will conduct 2 separate consultation sessions with (1) Aboriginal or Torres Strait Islander adults and (2) Aboriginal or Torres Strait Islander young people aged 12-16 years. Participants will be recruited using a variety of channels, including through the local ACCHS, word of mouth, social networking, and by distributing flyers at community events and health or youth services. Written consent from adults, young people, and parents or carers of young people will be obtained before the consultations.

The research team will also conduct 1:1 semistructured interviews with 1-2 teaching staff from the participating trial school to discuss the feasibility and acceptability of the program in the classroom. Written consent will be obtained before the interviews.

Procedure

Consultations with Aboriginal and Torres Strait Islander community members will be conducted using a culturally appropriate research yarning method [27,28]. Research yarning will involve obtaining stories and experiences related to the social and emotional well-being of young people in the community and feedback to inform tailoring of the program to the local context. The yarning circles will be conducted by the local facilitator and audio-recorded if the participants consent. Where possible, a member of the research team will also attend to take notes. If preferred by the community, consultations will be conducted with participants and facilitators of the same gender. Furthermore, 1 or 2 teaching staff from each school will also participate in 1:1 semistructured interviews, conducted on the web by the research team, audio-recorded (with permission), and transcribed.

Consultation Feedback and Program Adaptation

Once the community consultations are complete, the research team will synthesize the feedback and create local adaptations of the program in conjunction with oversight and guidance provided by the Aboriginal Reference Group. Program adaptations may involve changes to illustrations, cultural elements, and language. However, the adaptations will not alter the core prevention, harm minimization, and educational components of *Strong & Deadly Futures*, which are based on a large body of existing evidence regarding effective prevention strategies in mainstream and Indigenous populations. A summary of the consultation feedback and the resulting changes will be disseminated by facilitators to the local community.

Phase 2: School-Based Cluster RCT

Participants and Setting

Participants will be year 7 and 8 students from 24 government, Catholic, and independent schools in New South Wales (NSW), Queensland (QLD), and Western Australia (WA), Australia.

Students in year 8 (aged approximately 12-13 years) will be the primary target group for program implementation. However, schools will also have the flexibility to enroll year 7 students owing to diversity in community needs expressed during our formative consultations [16] and variations in school and class sizes, including combined grades in smaller schools.

Study Design and Randomization

This study will use a 2-group, parallel cluster RCT design. Cluster randomization by schools will be implemented, as randomizing individual students within schools would risk contamination of the control group because of student communication and peer influence effects. Recruited schools will be block randomized (ratio 1:1), stratified by geographical remoteness, to the *Strong & Deadly Futures* group (to implement the program in 2022) or the active control condition (*health education as usual* group). Allocation will be concealed and implemented by an independent statistician using the *blockrand* function in R (R Foundation for Statistical Computing) [29]. Remoteness will be classified using the Remoteness Areas structure within the Australian Statistical Geography Standard [30] and defined as metro or inner regional (major cities and inner regional) and outer regional or remote (outer regional, remote, and very remote). Randomization will occur as soon as a school is recruited and before the community consultations. To ensure that consultations are not influenced by randomization, consultation protocols will prescribe set questions for all sessions. If possible, researchers, facilitators, and participants will remain blind to allocation for the consultations; however, this will depend on consultation timing because of the requirement for schools to have sufficient time to plan class schedules. As schools and teachers play an active role in implementing the program, all schools, facilitators, and researchers will be unblinded before the trial. An overview of the study design is shown in Figure 1.

Figure 1. Anticipated *Strong & Deadly Futures* trial flow based on the CONSORT guidelines.
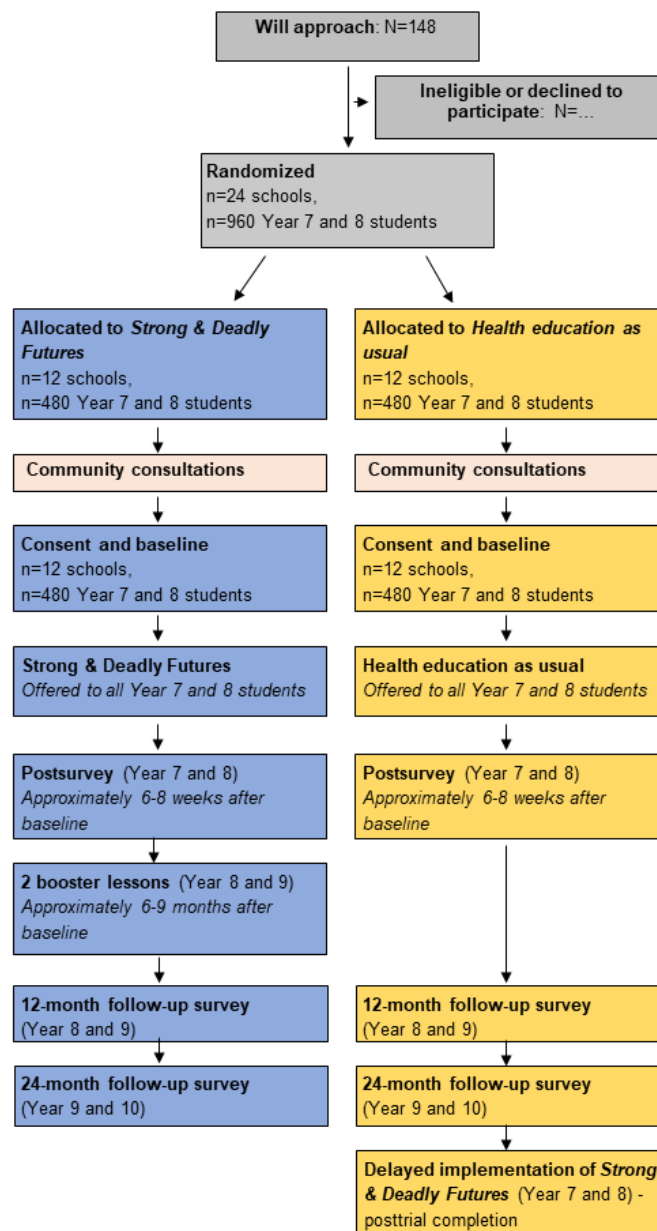
Sample Size Calculations

The sample size has been calculated to account for cluster randomization using the methods developed by Heo and Leon [31] to detect group-by-time interactions in longitudinal cluster RCTs. To adequately power the trial for comparisons among Aboriginal and Torres Strait Islander students, a minimum of 264 Aboriginal or Torres Strait Islander students from 22 schools is required (ie, 12 Aboriginal or Torres Strait Islander students per school). This would achieve 80% power to detect a standardized between-group mean difference of 0.3 (P=.05) in primary alcohol (frequency of drinking a standard drink in the previous 6 months), tobacco (frequency of smoking a cigarette in the previous 6 months), and psychological distress (Kessler-5 Psychological Distress Scale) outcomes at the end of the trial with 4 measurement occasions. No effect size information was available for school-based prevention for Aboriginal and Torres

Strait Islander students; thus, the estimated effect size of 0.3 was based on effects found for continuous alcohol outcomes in previous school-based prevention trials in mainstream populations [10,32]. Accounting conservatively for a higher student attrition rate than that observed in these trials of 30%, we will recruit 24 schools with an average of 16 Aboriginal or Torres Strait Islander students per school, and a total of 40 students per school. This totals 384 Aboriginal or Torres Strait Islander students, and a total sample of 960 students.

Inclusion Criteria

Eligible schools will have at least 12 Aboriginal or Torres Strait Islander students per grade in 2021. Although outcomes will be measured for all students, the primary analyses will be conducted among the Aboriginal subsample in line with the focus of the study. The recruited schools are expected to vary from approximately 10% to 100% of students identifying as

Aboriginal or Torres Strait Islander. All students in year 7 and 8 attending the participating schools in 2022 will be eligible to participate, provided they provide opt-in consent and their parents provide opt-in or opt-out consent (dependent upon ethical requirements; see *Informed Consent*).

Procedure

Recruitment

We will recruit 24 schools across NSW, WA, and QLD during 2021. Researchers will identify and approach eligible schools using data from the MySchool website [33] beginning with those who have previously expressed interest in participating. School principals and health education staff will be emailed an invitation letter detailing the study aims and procedure, followed up by phone calls or emails from the research team.

Informed Consent

Once recruited, principals will be asked to provide written consent for the school to participate in the trial. Schools will distribute information and consent forms to parents electronically or by hard copy and will be required to obtain opt-in (QLD public and WA Catholic schools) or opt-out parental consent (NSW and independent schools), depending on the relevant ethical requirements. Where opt-in parental consent is required, school staff members will be reimbursed to follow a standardized script for obtaining verbal consent over the phone in cases where it is not feasible to obtain written consent from parents. Students will be provided with electronic participant information statements and consent forms before survey commencement. Only students with parental consent and who have assented will complete the survey assessments; however, all students in *Strong & Deadly Futures* schools will participate in the program, as it will be delivered as part of their usual drug education curriculum. Year 7 and year 8 health teachers will also be asked to consent to completing web-based logbooks as a measure of implementation fidelity and to permit facilitators to record their observations from the *Strong & Deadly Futures* lessons.

Strong & Deadly Futures Group

Strong & Deadly Futures is a 6-lesson web-based social and emotional well-being and AOD prevention program that aligns with the Australian year 7 and 8 curriculum and the NSW Stage 4 Syllabus for Health and Physical Education. Each lesson consists of a 10-minute illustrated story, a selection of classroom activities, and teacher and student lesson summaries [16]. Lessons take approximately 45-60 minutes to complete and are optimally delivered once a week for 6 weeks. Program content is based on the established harm minimization [34] and social influence [35,36] approaches to AOD prevention and targets key risk and protective factors identified in our systematic review of effective substance use prevention among Indigenous youth [15]. The individual lesson content and targeted factors are detailed in Multimedia Appendix 1. In brief, the 6 lessons address the following key learning outcomes:

1. Coping with psychological distress, seeking help, and building self-efficacy;

2. AOD education: short- and long-term consequences, harm minimization, helping and coping with other people's AOD use;
3. Corrective information about normative peer alcohol and tobacco use, finding accurate information about AODs;
4. AOD refusal strategies, coping with peer pressure;
5. Positive alternatives to AOD use, role models.

Students and teachers can access *Strong & Deadly Futures* program content by creating accounts on the program website. Student accounts provide access to the illustrated stories and student lesson summaries. Teacher accounts provide access to the stories, teacher summaries, and class activity options (eg, prespecified worksheets, discussion topics, and activities). Teachers are provided with approximately 6 activity options for each lesson, one of which focuses on cultivating awareness of and pride in Aboriginal and Torres Strait Islander culture. Six months after the 6 lessons, 2 booster sessions will be delivered to help students refresh the content. Booster sessions will be delivered 1 week apart and follow the same structure as the original program.

Health Education as Usual Group

Participants in the *health education as usual* group will receive their usual curriculum-based health education classes in 6 weekly 45- to 60-minute lessons over a period of approximately 6 weeks. The Australian and NSW year 7 and 8 Health and Physical Education curriculum mandates that AOD use and social and emotional well-being content be implemented. As such, all *health education as usual* schools will implement curriculum-based drug education during the trial, which will naturally vary in the method of delivery, and serve as an *active control*. Alcohol and drug education in control schools may include tailoring for Aboriginal and Torres Strait Islander students and is expected to vary by school. Details of the content taught will be recorded in logbooks. These schools will be supported to implement the *Strong & Deadly Futures* program with year 7 and 8 students after all trial assessments are complete (from 2024).

Assessments

Students will complete self-report surveys at pre- and postprogram implementation and at 12- and 24-month follow-up to assess program effects. Given the preventive focus of the trial, the primary end point is 24 months post baseline to coincide with the peak onset of AOD use during middle adolescence [37]. All primary and most secondary measures were administered to students in our *Strong & Deadly Futures* pilot trial. Surveys will be accessed via electronic links and captured using REDCap (Research Electronic Data Capture; Vanderbilt University) electronic data capture tools hosted at the University of Sydney [38]. REDCap is a secure research data collection platform that links participant data over time while maintaining rigorous security controls to protect students' privacy. Students will complete surveys in class and be assured by the teacher and facilitator that the data they provide are strictly confidential. If students are absent, teachers or facilitators will arrange an alternate time to complete the survey at school. Follow-up surveys will be sent to students automatically by REDCap using the contact details supplied

during the first survey. Where ethical approvals permit it, students will enter into a draw to receive an Aus $ 30 (US $ 21.67) Prezzee gift voucher (1 or 2 per school, dependent on school size) per assessment occasion to maximize participant retention. The timeline schedule for trial participants is shown in Table 1.

Table 1. Schedule of program implementation and assessments.

	Preprogram survey	*Strong & Deadly Futures*	Postprogram survey	Booster sessions	12-month follow-up survey	24-month follow-up survey
Period	Term 3 or 4, 2022	Term 3 or 4, 2022	Term 3 or 4, 2022	Term 1 or 2, 2023	Term 3 or 4, 2023	Term 3 or 4, 2024
School grade (age group in years)	7 or 8 (11-13)	7 or 8 (11-13)	7 or 8 (11-13)	8 or 9 (12-14)	8 or 9 (12-14)	9 or 10 (13-15)
Strong & Deadly Futures group	✓	✓	✓	✓	✓	✓
Health education as usual group	✓		✓		✓	✓

Demographics

Demographic variables will be recorded at baseline, including gender (*male*, *female*, *nonbinary* or *genderfluid*, *different identity*, *prefer not to say*), age (12-16 years), school year (7-8), and whether students identify as Aboriginal (*Aboriginal*, *Torres Strait Islander*, *Aboriginal and Torres Strait Islander*, *not Aboriginal or Torres Strait Islander*). Socioeconomic status will be assessed using the 4-item Family Affluence Scale [39,40].

Primary Outcomes

Alcohol Use

Alcohol use will be assessed using measures previously used in *Climate Schools* trials [17,21,41], originally adapted from the National Drug Strategy Household Survey [42]. Students will be asked how often they had a standard drink in the previous 6 months (from 1=*Never* to 6=*Daily or almost daily*). This question will be accompanied by a standard drink chart from the Alcohol and Drug Foundation [43] as a guide.

Tobacco Use

Tobacco use will be measured using a single item adapted from the Standard High School Youth Risk Behavior Survey [44] that asks how often students had a cigarette in the previous 6 months.

Psychological Distress

Students will complete the 5-item Kessler Psychological Distress Scale, which has been validated for use with Aboriginal populations [45,46]. Students will be asked to indicate how often in the previous 4 weeks they experienced symptoms of psychological distress, such as feeling nervous, using a 5-point Likert-type scale ranging from *None of the time* to *All of the time*.

Secondary Outcomes

Cannabis Use

Any cannabis use in the previous 6 months will be assessed using measures adapted from the National Drug Strategy Household Survey [42] for use in previous *Climate Schools* trials [17,21,41]. This outcome will not be assessed in all schools because of differing ethics committee requirements.

Binge Drinking

Binge drinking will be assessed using a measure adapted from the School Health and Alcohol Harm Reduction Project [12] for previous *Climate Schools* [17,21,41] trials. Students will be asked how often they consumed ≥5 drinks in the previous 6 months (on a 6-point scale from *Never* to *Daily or almost daily*).

Alcohol-Related Harms

A 9-item version of the Rutgers Alcohol Problems Index [47] abbreviated for use in the *Climate and Preventure* study [48] will be used to measure students' experience of alcohol-related harms. Students will be asked to indicate how often they experienced a range of alcohol-related harms in the previous 6 months as a result of their drinking, using a 5-point Likert-type scale ranging from *Never* to *More than 6 times*. Examples of items include *Got into fights, acted bad, or did mean things* and *Caused shame or embarrassment to someone*.

Knowledge of Harms and Risk Minimization Strategies Related to Alcohol, Tobacco, and Cannabis

Alcohol (11 items) and cannabis (8 items) knowledge will be assessed using items adapted from the School Health and Alcohol Harm Reduction Project [12], as used in previous *Climate Schools* studies [13,21,22,25]. Tobacco knowledge will be assessed using an 8-item scale adapted from questions used in the *Health4Life* study [49], the School Health and Alcohol Harm Reduction Project [12], and the Life Skills Training questionnaire [50]. For all knowledge measures, students will be asked to respond *true*, *false*, or *don't know* to statements such as *You can get addicted to cannabis*.

Intentions to Use Alcohol, Tobacco, and Cannabis

Intentions to use AODs will be assessed using a single item, which asks how likely students are to try alcohol, tobacco or cannabis in the next 12 months, and measured on a 5-point scale from *Very unlikely* to *Very likely*. This measure has been used in previous *Climate Schools* studies [17,21].

Psychological Well-being

The well-being of the students will be measured using the 7-item Personal Well-being Index-School Children scale, which has been validated for use with Aboriginal, Torres Strait Islander, and non-Indigenous young people [51,52]. Students will be asked to indicate their agreement with statements such as *How*

happy are you with your health? using an 11-point scale ranging from 1=*Very sad* to 11=*Very happy*.

Empowerment

Empowerment will be assessed using the 14-item Emotional Empowerment Scale from the Growth and Empowerment Measure, which has been developed and validated for use with Aboriginal and Torres Strait Islander Australians [53]. Students will be asked to indicate their level of agreement with statements according to *the way you usually feel about yourself most of the time* using a 5-point scale ranging from a negative (score of 1) to a positive (score of 5) statement. Example items include scales ranging from *I feel like I don't know anything* to *I am knowledgeable about things that are important to me* and from *I feel slack, like I can't be bothered do things even when I want to* to *I am strong and full of energy to do what is needed*.

Appreciation of Cultural Diversity

To assess the attitudes of the students toward cultural diversity, the adapted 8-item Diversity Attitudes scale from the Civic Attitudes and Skills Questionnaire [54] will be used. Responses will be on a 5-point Likert scale, ranging from *Not at all* to *Very much*. Example items include *I have a strong interest in hanging out with people from different backgrounds* and *Cultural diversity within a group makes a group more interesting and effective*.

Truancy

Days absent from school without explanation will be obtained from schools, where possible and permitted by ethics committee requirements.

Process Outcomes

Appropriateness and Relevance

Students will be asked for feedback on *Strong & Deadly Futures* in the postprogram survey using a 13-item measure adapted from previous *Climate Schools* studies [17]. Students will be asked to rate aspects of the program (overall opinion, lessons, cartoons, activities, relevance, and helpfulness) on a scale of 1-5. Students will also be asked whether they think the skills and information will help them deal more effectively with peer pressure, stress, and drugs and alcohol in the future. Responses will be on a 4-point scale from *Yes, I think they will help a great deal* to *No, I don't think they will help at all*.

Implementation Fidelity

Teachers in both groups will complete web-based logbooks recording lesson procedures and activities as a measure of implementation fidelity. Teachers in Strong *& Deadly Futures* schools will be asked how the stories were viewed (collectively or individually), which activities were completed, whether any issues were encountered, and to record any adaptations they made to the lessons. Local facilitators in *Strong & Deadly Futures* schools will record their observations of student engagement, classroom activities implemented, and any issues the students experienced during class lessons. Teachers in control schools will record summaries of AOD education delivered.

Analysis

Because of the hierarchical nature of the data, outcome analyses will use multilevel mixed effects regression models (modeled using Stata [StataCorp LLC]) and take into account clustering of data at the school level. Multilevel modeling accounts for the expected correlations between repeated measurements from the same individual and between individuals in the same school, which would otherwise violate the assumptions of independence in traditional regression models. The models will take into account individual differences at baseline, estimating participant-specific starting points and change over time from these baseline levels. The randomly allocated groups (*Strong & Deadly Futures* vs *health education as usual*) will be identified by dummy-coding and entered as an independent variable. Hypothesized program effects on alcohol and tobacco uptake, psychological well-being, and secondary outcomes will be assessed by examining the allocated group-by-time interaction effects. Primary analyses will examine program effects specifically among Aboriginal and Torres Strait Islander students, with a secondary analysis conducted on the full sample. All analyses will be conducted according to the intention-to-treat principle, using all available measurements from the participants and according to their allocated group. Missing data will be accommodated based on all available information using maximum likelihood estimation.

Data Safety, Monitoring, and Quality Assurance

The principal investigator (LS) and project manager (KR) will take responsibility for the management and quality control of the study data. Web-based survey data will be collected via REDCap, a secure web-based data management and survey platform that complies with Australian standards in security, ethics, and integrity. Survey data will be stored at the University of Sydney, and all database files will be password-protected with only direct research personnel having access to the databases. Research staff with access to the data will have appropriate training to maintain confidentiality, data integrity, and basic data security measures.

Dissemination

After all trial assessments are completed, the research team will travel to the participating schools and communities to report and gain feedback on the interpretation of the aggregated findings of the study. A summary of the trial results will also be provided to all participating schools and communities at the conclusion of the study. This report will aggregate findings across the trial and not identify results for any individual school or student. Schools and facilitators will be able to distribute the results to participating students, staff members, and parents. Schools will be given the option of opting in to be acknowledged in publications for their participation in the trial. The results will be disseminated broadly through peer-reviewed publications in medical, health, and education journals. The findings will also be disseminated at Aboriginal-specific forums and events, at national and international scientific conferences, and through webinars and seminars.

Results

The trial was funded by the National Health and Medical Research Council in January 2019 and approved by the Human Research Ethics Committee of the University of Sydney (2020/039, April 2020), the Aboriginal Health and Medical Research Council of New South Wales (1620/19, February 2020), the Western Australian Aboriginal Health Ethics Committee (998, October 2021), and the ethics committees of each participating school, including the NSW Department of Education (2020170, June 2020), Catholic Education Western Australia (RP2020/39, November 2020), and QLD Department of Education (550/27/2390, August 2021). The projected dates of data collection are 2022-2024, and we expect to publish the results in 2025. A total of 24 schools have been recruited as of submission of the manuscript.

Discussion

The aim of this paper was to describe the study protocol to evaluate the first web-based well-being and alcohol and drug prevention program for Australian secondary school students that was developed to be culturally appropriate and empowering for Aboriginal and Torres Strait Islander youth. Program effectiveness will be evaluated through a cluster RCT in 24 schools across 3 Australian states. The trial will be powered to detect medium effects (0.3) within the Aboriginal and Torres Strait Islander sample. It is hypothesized that the program will reduce alcohol, tobacco, and cannabis use and improve well-being relative to health education as usual.

Aboriginal and Torres Strait Islander leadership and input have been prioritized since the inception of *Strong & Deadly Futures*, spanning the program planning, development, and now methodology and implementation of the RCT. This continuing priority is reflected through the involvement of Aboriginal investigators (MD and JW) and the strategic oversight and direction provided by the Aboriginal Reference Group. To ensure *Strong & Deadly Futures* addresses the needs of geographically and culturally diverse communities, we will employ a local Aboriginal facilitator to lead consultations with the Aboriginal and Torres Strait Islander community of each participating school. Community members will identify local alcohol, drug, and well-being priorities for young people and provide feedback on the relevance and appropriateness of cultural content, which will be used to adapt the program to the region. Community participation will ensure that the program is aligned with local values and priorities and meets local needs, which is expected to enhance longer-term sustainability.

Participatory research approaches have been recognized for their potential to empower Indigenous communities and improve

health disparities [55], but are often challenging to execute and, more often than not, lack methodological rigor [56]. The participatory approach of this study will combine community participation with rigorous evaluation, with the ultimate aim of developing a flexible, robust program model that is adaptable and generalizable for communities across Australia. This study will also address a critical gap in methodologically rigorous evaluation in Aboriginal and Torres Strait Islander alcohol and drug research [57] and contribute significantly to the field of culturally appropriate, evidence-based prevention. In addition, if effective, *Strong & Deadly Futures* will provide teachers with an evidence-based resource for preventing alcohol and drug use among young people that is accessible, engaging, scalable, and easy to implement.

A limitation of the study protocol is the use of self-report measures to obtain data on alcohol and drug use. However, self-report measures have shown good discriminant [58] and predictive [59] validity for alcohol and drug use, and active measures will be taken to mitigate the risk of over- or underreporting through the use of visual standard drink guides and assurances of anonymity and confidentiality. Another limitation is that blinding to group allocation is not possible because the schools and students are actively involved in the program implementation. However, this is a limitation common to trials of school-based prevention programs. It is also expected that there will be variability in the alcohol and drug education delivered by the control schools. All schools are required to implement alcohol and drug content as part of the curriculum, and this variability will be assessed via logbooks and through implementation fidelity checks. Finally, attrition is a potential source of bias common in longitudinal studies. To ensure sufficient power, the sample size has been calculated using a conservative estimate of attrition, and risks associated with missing data will be mitigated through the use of maximum likelihood estimation in the statistical models. To maximize participant retention, a variety of contact details will be collected to follow up on participants (ie, email addresses, phone numbers, home addresses, and parents' email addresses and phone numbers).

No culturally appropriate school-based alcohol and drug prevention programs have been rigorously evaluated and demonstrated to be effective for Aboriginal and Torres Strait Islander youth. The *Strong & Deadly Futures* program, which was codeveloped in collaboration with an Indigenous creative design agency and with Aboriginal and Torres Strait Islander and non-Indigenous students, has the potential to address this critical need using a strengths-based approach while promoting Aboriginal and Torres Strait Islander culture within culturally and geographically diverse classrooms.

Authors' Contributions

LS was involved in the conceptualization, methodology, writing (original draft, review, and editing), supervision, project administration, and funding acquisition. KR was involved with the methodology, writing (original draft, review, and editing), supervision, and project administration. MS was involved in the conceptualization, methodology, writing (review and editing), project administration, and funding acquisition. MD was involved with the conceptualization, methodology, writing (review and editing), and funding acquisition. KC helped with the conceptualization, methodology, writing (review and editing), and funding acquisition. CC was involved with conceptualization, methodology, writing (review and editing), and funding acquisition. JW was involved in the conceptualization, methodology, writing (review and editing), and funding acquisition. AB helped with writing (review and editing) and project administration. KL was involved with conceptualization, methodology, writing (review and editing), and funding acquisition. MT helped with conceptualization, methodology, writing (review and editing), and funding acquisition. NN was involved with conceptualization, methodology, writing (review and editing), supervision, and funding acquisition.

Conflicts of Interest

NN and MT are 2 of the developers of the Climate Schools programs and directors of Climate Schools Pty Ltd, a social enterprise established in 2015 to distribute the Climate Schools programs and maximize social well-being. The other authors declare no conflict of interest.

Multimedia Appendix 1
Overview of learning outcomes and targeted risk and protective factors for *Strong & Deadly Futures* lessons.
[DOCX File , 32 KB - resprot_v11i1e34530_app1.docx]

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Abbreviations

ACCHS: Aboriginal Community Controlled Health Services
AOD: alcohol and other drug
NSW: New South Wales
QLD: Queensland
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
WA: Western Australia

Protocol

Mobile Phone–Based Intervention Among Adolescents Living With Perinatally Acquired HIV Transitioning from Pediatric to Adult Care: Protocol for the Interactive Transition Support for Adolescents Living With HIV using Social Media (InTSHA) Study

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Abstract

Background: Adolescents living with perinatally acquired HIV often have poor retention in care and viral suppression during the transition from pediatric to adult-based care.

Objective: The aim of this study is to evaluate a mobile phone–based intervention, Interactive Transition Support for Adolescents Living With HIV using Social Media (InTSHA), among adolescents living with perinatally acquired HIV as they transition from pediatric to adult care in South Africa.

Methods: InTSHA uses encrypted, closed group chats delivered via WhatsApp (Meta Platforms Inc) to develop peer support and improve communication between adolescents, their caregivers, and health care providers. The intervention is based on formative work with adolescents, caregivers, and health care providers and builds on several existing adolescent support programs as well as the Social-ecological Model of Adolescent and Young Adult Readiness for Transition (SMART). The final InTSHA intervention involves 10 modules conducted weekly through moderated WhatsApp group chats with adolescents and separately with their caregivers. We will randomly assign 80 South African adolescents living with perinatally acquired HIV who are aware of their HIV status and aged between 15 and 19 years to receive either the intervention (n=40) or standard of care (n=40).

Results: We will measure acceptability of the intervention as the primary outcome and evaluate feasibility and preliminary effectiveness for retention in care and viral suppression after completion of the intervention and at least 6 months after randomization. In addition, we will measure secondary outcomes evaluating the impact of the InTSHA intervention on peer support, self-esteem, depression, stigma, sexual education, connection to health care providers, and transition readiness. Enrollment began on April 15, 2021. As of December 31, 2021 a total of 78 out of expected 80 participants have been enrolled.

Conclusions: If successful, the intervention will be evaluated in a fully powered randomized controlled trial with a larger number of adolescents from urban and rural populations to further evaluate the generalizability of InTSHA.

Trial Registration: ClinicalTrials.gov NCT03624413; https://clinicaltrials.gov/ct2/show/NCT03624413

Introduction

South Africa has the largest antiretroviral therapy (ART) program along with highest burden of adolescents living with HIV (ALHIV) in the world [1]. Survivors of perinatally acquired HIV are now reaching adolescence and beyond, yet the majority of adolescents are poorly prepared for the transition from pediatric to adult care services [2,3]. An estimated 320,000 adolescents with perinatally acquired HIV will transfer from pediatric-based or adolescent-based clinics to adult services in the next 10 years in South Africa [4]. Currently, adolescents living with perinatally acquired HIV transition to adult care at variable ages and developmental stages, without necessary preparation or support throughout the process [5]. Guidelines for transitioning adolescents to adult care are often based on age and are not tailored to the adolescents' developmental levels or needs. The transition from pediatric to adult services is also a challenging time during which clinical outcomes commonly suffer [2,6,7]. In South Africa, adolescents transitioning to adult care have shown lower viral suppression rates than those remaining in pediatric care [2]. Effective interventions are clearly needed to improve clinical outcomes in this highly vulnerable population, particularly in older adolescents transferring clinical care.

Medical care during adolescence is typically complicated by increased risk-taking behavior as well as decreased caregiver involvement, which occur during a time of rapid physical, emotional, and cognitive development [8-11]. When adolescents transition to adult care, they often do not receive the coordinated services that they received under pediatric care [12]. Qualitative studies with adolescents and clinicians from sub-Saharan Africa suggest that peer support, collaboration with health care providers, and communication between adult and pediatric providers might improve the transition to adult services [5,13,14]. The Social-ecological Model of Adolescent and Young Adult Readiness for Transition (SMART) highlights modifiable targets of intervention, such as knowledge, skills/self-efficacy, relationships, and social support, that can be addressed to improve the transition of care [15,16]. It further lays out the roles of 3 key stakeholders (adolescents, caregivers, and health care providers) and their interconnected relationship in influencing a successful transition to adult care. This model thus offers a potential structure with which to design a social support intervention [15-17].

The use of social media and access to mobile phones among adolescents in South Africa is growing rapidly and offers an excellent opportunity to deliver a social support intervention

[18]. Social media is defined as Internet-based applications that allow the creation and exchange of user-generated content; examples include WhatsApp (Meta Platforms Inc) and Facebook (Meta Platforms Inc) [19]. Social media has been shown to support change across several modifiable factors in SMART, such as relationships, social support, and knowledge, in other contexts. A meta-analysis found that social support was the most common reason for patients to use social media for health purposes [18]. Social media has also been used to improve the relationship between caregivers and patients when switching caregivers, a major barrier to transition for ALHIV in South Africa [20,21]. Although results vary in different settings, another meta-analysis showed overall improved adherence to ART and viral suppression among adults living with HIV using social media–based health services technology [22]. Social media may also be able to address additional modifiable factors in SMART, such as self-efficacy and goal development, which could ultimately improve virologic suppression and retention in care during the transition to adult services [23].

In this paper, we describe the research protocol for the pilot clinical trial involving Interactive Transition Support for Adolescents Living With HIV using Social Media (InTSHA).

Methods

InTSHA Intervention

We created a preliminary version of InTSHA as indicated in Table 1, using a participant-centered approach and based on formative interviews with adolescents, caregivers, and health care providers, which will be published separately. In addition, we used SMART [15] to guide intervention development. We also used the in-person adolescent support group discussion material developed by the US Agency for International Development, as part of the Right to Care Flipster tool [24], as a starting point for the development of the 10 skill-building modules. We used Got Transition's Six Core Elements of Health Care Transition [25] to structure the delivery of the clinic's transition policy through WhatsApp messaging. Got Transition also calls for tracking and monitoring of adolescents' progress that we organized through 2-way messaging between adolescents and care providers. To delve into transition readiness and planning itself, we used SMART, focusing on modifiable factors that can be addressed through content delivery, facilitated discussions, web-based meet ups and consultation with the health care team. InTSHA then concludes with WhatsApp discussions between adult and pediatric clinicians through the final 2 elements of Got Transition, transfer of care, and transfer completion.

Table 1. Content and design of the initial Interactive Transition Support for Adolescents Living With HIV using Social Media (InTSHA) intervention.

Got Transition elements	Modifiable SMART[a] factors	Intervention component
Transition policy	N/A[b]	Direct content delivery
Transition tracking/monitoring	N/A	2-way messaging between adolescents and care providers
Transition readiness		
	Knowledge, skills	Content delivery
	Maturity, goals, beliefs, self-efficacy	Facilitated discussions
Transition planning		
	Relationships, social support	Web-based meet ups/discussions
	Clinical support	Health care team consultation
Transfer of care	N/A	Discussions between adult and pediatric clinicians
Transfer completion	N/A	Discussions between adult and pediatric clinicians

[a]SMART: Social-ecological Model of Adolescent and Young Adult Readiness for Transition.

[b]N/A: not applicable.

Participants randomized to the intervention group will receive the InTSHA intervention. The intervention consists of 10 modules which will be delivered weekly by group chat through a closed, encrypted, and password-protected WhatsApp chat group based on preferences determined in formative research. Modules contain topics of interest voiced by formative qualitative interviews and include the following: (1) web-based security, (2) HIV disclosure, (3) drug and substance abuse, (4) sexual and reproductive health, (5) gender roles and sexuality, (6) stigma, (7) HIV knowledge and health care navigation, (8) ART adherence and HIV resistance, (9) healthy relationships, and (10) career planning and future goals. Closed chat groups will consist of mixed genders and up to 10 ALHIV and will be facilitated by a research coordinator. Modules will take place during weekly scheduled sessions with 1 additional brief check-in session per week. Adolescents will have access to the chat group outside of scheduled discussion times to check in with group members, review the content of the sessions, or comment or ask additional questions. Adolescents will also have the opportunity to ask health-related questions to health care providers at the clinic via WhatsApp. Questions are facilitated by the research coordinator to prevent negative messaging and to minimize potential social harm. All discussions are monitored by clinical doctors trained in pediatric HIV for accuracy and clarity. To ensure access to mobile data during scheduled chats, 1 gigabyte of data will be loaded onto each participant's phone prior to scheduled chat discussions.

Caregivers of adolescent participants will participate in separate closed, encrypted, and password-protected WhatsApp chat groups with weekly topics mirroring the adolescent topics to facilitate discussions between adolescents and their caregivers.

Statement of Ethics

The Biomedical Research Ethics Committee of the University of KwaZulu-Natal, KwaZulu-Natal Department of Health, Mass General Brigham (formerly Partners HealthCare) Research Ethics Board, and Emory University Institutional Review Board approved this protocol.

Clinical Trial Research Protocol

We will evaluate the InTSHA intervention in a pilot randomized controlled clinical trial among ALHIV transitioning to adult care. We will measure acceptability, feasibility, and preliminary efficacy of the InTSHA intervention by measuring viral suppression 6 months after transitioning to the adult clinic among the intervention (n=40) and control (n=40) groups.

Participant Selection, Enrollment, and Randomization

Adolescents living with perinatally acquired HIV between the ages of 15 and 19 years from KwaMashu Poly Clinic, KwaMashu, South Africa, and Mahatma Gandhi Memorial Hospital, Durban, South Africa, will be offered enrollment during their routine outpatient appointments if they have been on ART for at least 6 months and are fully aware of their HIV status. Participants will be randomized (1:1) to receive the InTSHA intervention delivered via WhatsApp closed chat groups or standard of care. Randomization will be performed using sealed envelopes containing study assignments. The research team will be blinded to the contents of the envelopes, which will be created using block randomization by a computer-generated random number sequence, then filled and sealed by non–research staff.

Participant Consent

All participants under the age of 18 years will be required to provide written assent to participation in this study. Written informed consent from caregivers will be obtained for adolescents less than 18 years old. Adolescents 18 years or older will provide their own written consent. Assent and/or consent forms will be offered in both English and isiZulu.

Standard of Care

Participants in the standard of care arm will continue usual care at KwaMashu Poly Clinic or Mahatma Gandhi Memorial Hospital. Adolescents typically transition to adult care after the age of 15 years if they are aware of their HIV status and taking a fixed-dose combination ART. In the adult clinic, adolescents are seen together with adults in a general clinic that also attends to patients with other chronic illnesses. Young adults with

perinatally acquired HIV and behaviorally acquired HIV are seen in the same clinic. Patients are seen by a health care provider every 3 months and collect medication monthly at an on-site pharmacy.

Procedures

During visit 1, we will collect baseline demographic data, complete baseline questionnaires, and perform viral load assessments for all participants. The second research visit will take place either 6 months after randomization or after completion of all 10 modules, whichever comes last; although the modules are designed to be completed over 10 consecutive weeks, we anticipate additional time may be needed to accrue an adequate number of participants into the group intervention and alternate scheduling may be needed to accommodate school demands, holidays, and other events. The second research visit will evaluate acceptability and feasibility and perform exit focus group discussions with all participants in the intervention arm. In addition, all subjects will complete follow-up questionnaires and have a viral load assessment.

We will collect demographic data on all adolescents using chart review and will include age, sex, age at diagnosis, history of opportunistic infections, length of time on ART, ART regimen, last viral load, clinic visits, and pharmacy refill information. Data will be collected from a combination of electronic records and paper charts. Additional data on viral status and location of care services will be obtained through an existing patient tracker program.

Ethical Considerations

To address participant concerns voiced during formative work, we have included multiple safeguards. To protect privacy and prevent accidental disclosure of HIV status if others use or share phones, we will ensure that all phones are password-protected. The individual chat discussions will be encrypted and password-protected within WhatsApp. In addition, all participants will choose a pseudonym and actual names will not be visible within the chats. If an adolescent communicates physical or emotional distress, including suicidality, the facilitator and health care providers have established referral networks and collated resources to provide the adolescent. To ensure accuracy of information provided within the chats, the content will be reviewed by the research team and supervising physician.

Results

Primary and Secondary Outcomes

We will determine the primary outcomes of acceptability (acceptability of implementation measure) and feasibility (enrollment, participation, and feasibility of implementation measure) [26]. We will also measure the secondary outcomes of retention in care (pharmacy refill and clinic attendance in the last 6 months) and viral suppression (<400 copies/mL), comparing pretransition with 6 months after randomization. In addition, we will explore other factors based on modifiable variables in SMART including (as indicated in Table 2) the following: adolescent peer support (using the Child and Adolescent Social Support Scale) [27], self-esteem (using the Rosenberg Self-Esteem Scale) [28], depression (using the Patient Health Questionnaire-9 [PHQ-9]) [29], stigma (using the Internalized AIDS-Related Stigma Scale) [30], connection to clinic (using the Working Alliance Inventory) [31], and transition readiness (using the HIV Adolescent Readiness for Transition Scale) [32].

Table 2. Factors associated with SMART[a] and measures to evaluate the impact of the InTSHA[b] intervention on each.

Factors associated with SMART	Measure
Peer support	Child and Adolescent Social Support Scale
Self-esteem	Rosenberg Self-Esteem Scale
Depression	PHQ-9[c]
Stigma	Internalized AIDS-Related Stigma Scale
Connection to clinic	Working Alliance Inventory
Transition readiness	HIV Adolescent Readiness for Transition Scale

[a]SMART: Social-ecological Model of Adolescent and Young Adult Readiness for Transition.

[b]InTSHA: Interactive Transition Support for Adolescents Living With HIV using Social Media.

[c]PHQ-9: Patient Health Questionnaire-9.

Analysis

We will summarize the acceptability and feasibility data in the intervention group using standard summary statistics (eg, counts or percentages, median and interquartile range of continuous measures). We will estimate the difference between the intervention group and the control group for social support, connection to clinic, self-esteem, stigma, retention in care, and virologic suppression 6 months after randomization. The standard deviation for these differences is expected to be on the order of 8%. We will use logistic regression to explore combinations of variables potentially predictive of retention in care and viral suppression. The number of variables analyzed will depend on the number of individuals with each outcome.

Power Analysis for Primary Outcome

This study is powered on the primary outcome of acceptability. With 40 participants in the intervention arm, if the reported acceptability rate is 90%, we will be able to rule out that

acceptability was less than 70% with 90% power (α=0.05, one-sided) using a Fisher exact test.

Timeline

Enrollment began on April 15, 2021. As of December 31, 2021 a total of 78 out of expected 80 participants have been enrolled.

Discussion

Increasing evidence indicates poor clinical retention in care and viral suppression among many adolescents living with perinatally acquired HIV who are transitioning from pediatric to adult care [2,33]. Despite the uptake of social media and mHealth interventions to address gaps in many aspects of the HIV continuum of care in low-income and middle-income income countries (LMIC), there are no interventions addressing the transition to adult care (unpublished study by Goldstein et al). InTSHA is a social media intervention using existing technology that aims to fill this gap. Using a participant-centered design among the 3 key stakeholders—adolescents, caregivers, and health care providers—we created an intervention based on SMART, Got Transition, and the Right to Care Flipster tool by addressing modifiable factors, such as knowledge, skills/self-efficacy, relationships, and social support. To our knowledge, only one other ongoing study is using mHealth to support the transition from pediatric to adult care for adolescents and young adults living with HIV. Specifically, Tanner et al [34] are evaluating a novel smartphone app, iTransition, based on social cognitive theory to support ALHIV in the United States. However, the development, evaluation, and implementation of effective and accessible mHealth interventions are needed to improve health care transition outcomes for adolescents living with perinatally acquired HIV in LMIC, where the majority of youth living with perinatally acquired HIV reside.

Mobile phone ownership and use for health interventions has increased worldwide in recent years [18]. This approach is particularly promising for adolescents who are avid adopters of technology, although few mHealth interventions have shown to be effective at engaging adolescents. Although mHealth technology has the ability to address many barriers to transitional care and improve communication, several practical barriers remain. Socioeconomic pressure from the cost of mobile phones and data plans can be prohibitive for younger adolescents, particularly in LMIC, to engage in mHealth. The practice of sharing phones can reduce associated costs, but privacy and confidentiality may be compromised [35]. In addition, inferior mobile network coverage and limited technological literacy in LMIC can limit the effectiveness of mHealth interventions. Despite these potential barriers, InTSHA is likely to benefit adolescents by providing social support and connections to clinical staff as they transition to adult care. Therefore, studies evaluating the real-world uptake, effectiveness, and cost of mHealth interventions are required if they are going to be utilized and sustained for meaningful impact [36].

InTSHA is a theory-based, participant-centered intervention to support the transition from pediatric care to adult care that will be rigorously evaluated for acceptability, feasibility, and preliminary effectiveness using real-world conditions. If successful, this intervention will be formally tested in a fully powered randomized controlled trial including multiple populations of adolescents for increased generalizability of effect. Such work has great potential to improve the poor outcomes associated with transitioning to adult care for thousands of adolescents living with HIV globally.

Authors' Contributions

BCZ conceptualized and designed the study, performed the literature review, assisted with the analysis, drafted the initial manuscript, reviewed and revised the manuscript, and approved the final manuscript as submitted.

TS coordinated the intervention, performed the data collection, contributed to the drafting of the manuscript, critically reviewed the manuscript, and approved the final manuscript as submitted.

MA assisted with the conceptualization and design of the study, contributed to the data collection, critically reviewed the manuscript, and approved the final manuscript as submitted.

MG, SB, DD, VC, and C Peng assisted in the analysis of formative work, assisted in the creation of the intervention, critically reviewed the manuscript, and approved the final manuscript as written.

C Psaros assisted with the conceptualization and design of the study, assisted in the analysis of formative work, contributed to the data collection, critically reviewed the manuscript, and approved the final manuscript as submitted.

VCM and JEH assisted with the conceptualization and design of the study, contributed to the analysis plan, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Conflicts of Interest

JEH reports consulting for Merck & Co Inc and owns stock in Natera Inc. VCM has received investigator-initiated research grants (awarded to their institution) and consultation fees (both unrelated to the current work) from Eli Lilly and Company, Bayer AG, Gilead Sciences Inc, and ViiV Healthcare Ltd. All other authors have no conflicts of interest relevant to this article to disclose.

Multimedia Appendix 1

Peer-review report by the Center for Scientific Review Special Emphasis Panel - Member Conflict: AIDS and AIDS Related Research (National Institutes of Health, USA).

[PDF File (Adobe PDF File), 151 KB - resprot_v11i1e35455_app1.pdf]

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Abbreviations

ALHIV: adolescents living with HIV
ART: antiretroviral therapy
InTSHA: Interactive Transition Support for Adolescents Living With HIV using Social Media
LMIC: low-income and middle-income income countries
PHQ-9: Patient Health Questionnaire-9
SMART: Social-ecological Model of Adolescent and Young Adult Readiness for Transition

Protocol

Randomized Waitlist-Control Trial of a Web-Based Stress-Management and Resiliency Program for Adolescent and Young Adult Cancer Survivors: Protocol for the Bounce Back Study

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Abstract

Background: The emotional health of adolescent and young adult (AYA) cancer survivors is compromised both during and after cancer treatment. Targeted programs designed to support AYAs' ability to cope with stress in the years following treatment completion are lacking. Mind-body programs may ameliorate the negative psychological and emotional effects of stress and assist AYAs with managing the psychosocial challenges of early survivorship.

Objective: Our randomized waitlist-control trial aims to assess the feasibility, acceptability, and preliminary efficacy of a virtual group program (Bounce Back) to promote stress management and resiliency among posttreatment AYAs.

Methods: Bounce Back is a stress management and resiliency program delivered via videoconference by a trained mental health clinician. Sessions were adapted from an evidence-based mind-body program (Stress Management and Resiliency Training - Relaxation Response Resiliency Program [SMART-3RP]) grounded in relaxation response elicitation, mindfulness, cognitive behavioral therapy, and positive psychology. Seventy-two AYAs (diagnosed with cancer between ages 14 years and 29 years and had completed cancer treatment within the last 5 years) were randomly assigned to the Bounce Back program or waitlist-control group and completed assessments at baseline, 3 months postbaseline, and 6 months postbaseline. The primary aim of the study is to determine the feasibility and acceptability of the Bounce Back program. Descriptive statistics, including means, frequencies, and ranges supplemented by qualitative exit interview feedback will be used to characterize the sample and to summarize feasibility and acceptability. The exploratory aims are to evaluate the preliminary effects of the program on stress coping and psychosocial outcome measures (ie, anxiety, depression) collected across the 3 time points.

Results: This study was funded by the National Cancer Institute in July 2017. Study procedures were approved by the Dana-Farber Harvard Cancer Center Institutional Review Board in October 2018 (Protocol 18-428). The randomized trial was conducted from July 2019 to March 2021. Quantitative data collection is complete, and qualitative exit interview data collection is ongoing. Results are expected to be published in peer-reviewed journals and presented at local, national, or international meetings in the coming years.

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Conclusions: Few evidence-based programs exist that tackle the key transitional issues faced by AYA cancer survivors. Future analyses will help us determine the feasibility and acceptability of the Bounce Back program and its impact on AYA stress coping and psychological well-being.

Trial Registration: ClinicalTrials.gov NCT03768336; https://clinicaltrials.gov/ct2/show/NCT03768336

International Registered Report Identifier (IRRID): DERR1-10.2196/34033

Introduction

Adolescence and young adulthood are life stages marked by peak physical, social, and emotional development. A cancer diagnosis and treatment during this stage can significantly disrupt many key life domains [1]. Adolescent and young adult (AYA) cancer survivors include individuals who are diagnosed with cancer between the ages of 15 years and 39 years. Approximately 89,000 AYAs are diagnosed with cancer annually, and cancer is the leading cause of disease-related deaths among individuals in this age range [2]. According to a recent systematic review, AYAs with cancer have reported difficulties with employment, educational attainment, and financial stability after treatment completion [3]. They also have challenges identifying their social support systems and report problems developing and maintaining peer, family, intimate, and marital relationships [3]. These challenges may impact their psychological well-being as they transition into the early survivorship period.

The emotional health of AYAs can be significantly compromised both during and after cancer treatment. Among AYAs with a history of cancer, stress has been linked to decreased physical activity and increased rates of drinking alcohol, smoking tobacco, and substance use [4,5]. Stress has also been shown to exacerbate the posttreatment symptoms AYAs frequently experience, including pain, fatigue, and insomnia [6]. Their health-related quality of life may be poor, and they experience elevated levels of distress posttreatment [7-10]. Although acute distress symptoms can persist for several years after treatment, peak levels of distress typically coincide with the first few years of treatment completion [10,11]. These consequences combined may increase AYAs' risk for cancer-related morbidity and early mortality, yet targeted programs to support AYAs' ability to cope with stress in the years following treatment completion are lacking [12-17].

Mind-body programs, which teach skills to improve the connection between the mind and body (ie, yoga, tai chi, mindfulness training), may ameliorate the negative psychological and emotional effects of stress and help AYAs manage the psychosocial challenges of early survivorship [18-21]. AYAs have shown interest in using complementary and alternative medicine, which encompasses mind-body approaches, to cope with stress and improve overall well-being [22-24]. However, there are few established programs demonstrating the utility of these approaches for AYAs during the early survivorship period [14,15,25,26].

Here, we describe the protocol for a pilot randomized waitlist-control trial of a scalable virtual group program (Bounce Back) aimed at promoting stress management and coping among posttreatment AYA cancer survivors. With funding from the National Cancer Institute (NCI), we adapted Bounce Back from an existing evidence-based resiliency program, the Stress Management and Relaxation Training - Relaxation Response Resiliency Program (SMART-3RP) [27]. Our program adaptation was informed by a series of qualitative focus groups with AYAs and open pilot testing for program refinement. Based on our qualitative data, we modified the program content to "normalize" the posttreatment challenges (eg, returning to school or work, socializing with peers again) common to the AYA experience. Bounce Back aimed to prevent the emergence of anxiety and depressive symptoms in AYAs by introducing stress coping skills early in the posttreatment experience [28]. To our knowledge, Bounce Back is the first stress management and resiliency program targeting the early posttreatment stressors of AYAs.

The Bounce Back study was a partnership between Massachusetts General Hospital (MGH), the Dana-Farber Cancer Institute (DFCI), and the Consortium for New England Childhood Cancer Survivors (CONNECCS [29]). CONNECCS consists of 14 pediatric cancer clinics located across 6 New England states (Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont). The primary aim of the study is to determine the feasibility and acceptability of the Bounce Back program. The exploratory aims are to evaluate the preliminary effects of the program on stress coping and psychosocial outcome measures (ie, anxiety, depression, intolerance of uncertainty) collected across 3 time points.

Methods

Ethics Approval

Study procedures were approved by the Dana-Farber Harvard Cancer Center IRB in October 2018 (Protocol 18-428).

Study Design

The study was designed as a pilot randomized waitlist-control trial examining the feasibility, acceptability, and preliminary efficacy of Bounce Back delivered during early posttreatment for AYA cancer survivors. Eligible participants were randomly assigned to the Bounce Back program group (PG) or waitlist-control group (CG) and were asked to complete assessments at 3 time points: baseline, 3 months postbaseline, and 6 months postbaseline. Prior to study start, the Dana-Farber

Harvard Cancer Center Institutional Review Board (IRB) reviewed and approved the study protocol and consent forms (Protocol 18-428). Recruitment occurred from May 2019 to September 2020. Figure 1 illustrates the overall design and participant flow of the study.

Figure 1. Participant flow. 3RP: Relaxation Response Resiliency Program; EHR: electronic health record.
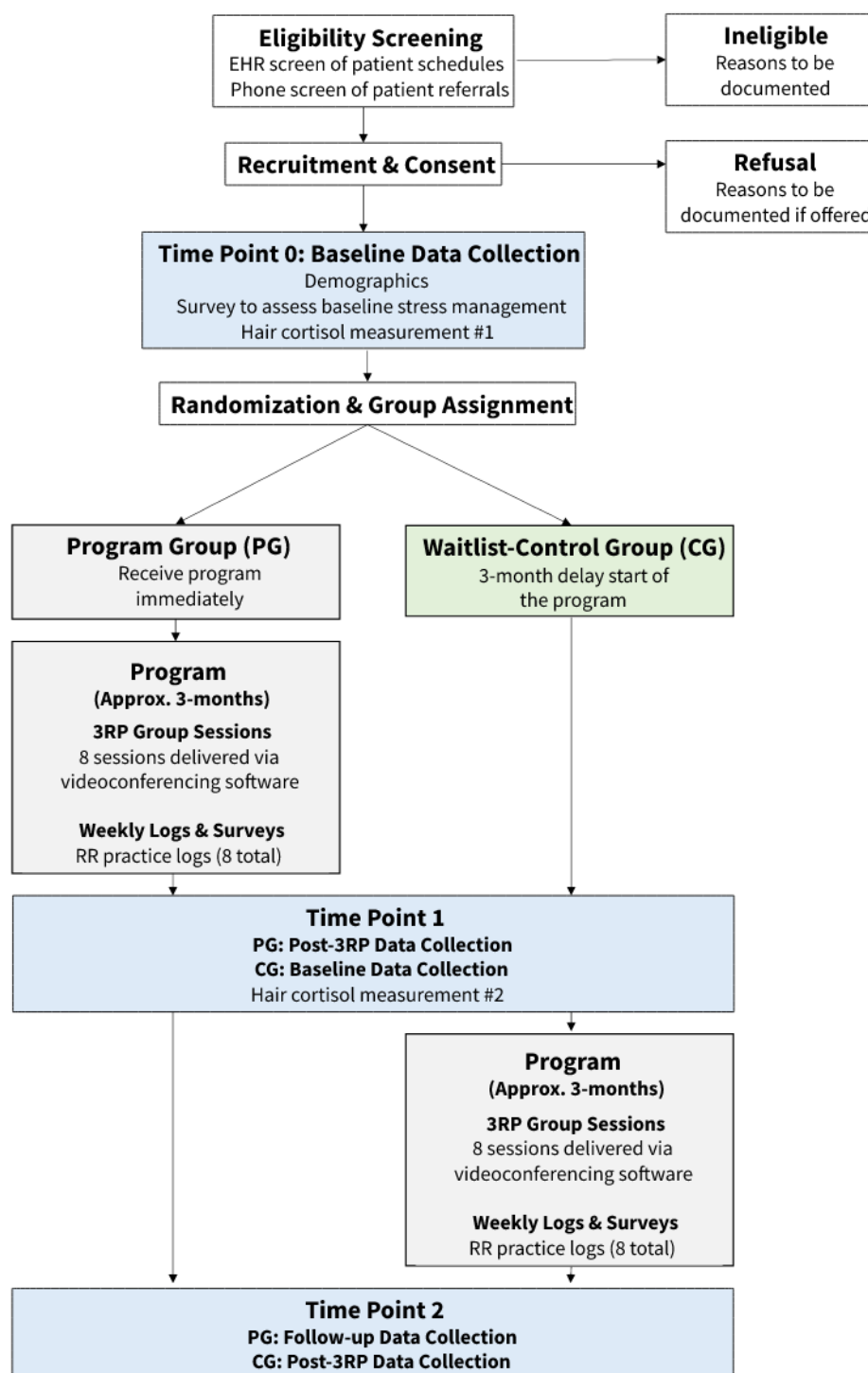
Participants

Eligible participants included survivors of cancer diagnosed during early adolescence and young adulthood (ages 14-29 years) who had completed treatment within the past 5 years and who were between the ages of 16 years and 29 years at study enrollment (Table 1). We defined treatment completion as the date of the last intensive cancer treatment session (eg, chemotherapy, surgery, radiation) with curative intent. AYAs who were within 5 years of completing cancer treatment and did not have evidence of residual disease but who were receiving maintenance or hormonal treatment (eg, rituximab, tamoxifen)

were considered eligible for the study. Given the virtual trial design, AYAs were eligible to participate if they spoke and read English and were able to connect to group sessions via the videoconferencing software. Of note, there were no entry criteria related to the presence of emotional distress.

Table 1. Study eligibility criteria.

Criteria	Rationale
Inclusion criteria	
Diagnosed with any cancer between ages of 14 years and 29 years	To target AYAs[a] diagnosed during a time of significant developmental change; age range also within the focal age range identified by the National Clinical Trials Network–affiliated Children Oncology Group scientific committees that focus on AYA cancer [30]
Completed cancer treatment within the past 5 years	Opportunity to address stressors associated with early posttreatment survivorship; this window for treatment completion consistent with the "early survivorship" period, when concern about recurrence is high [31]
Between 16 years and 29 years of age at time of enrollment	Optimize AYA heterogeneity in terms of life stage; also includes individuals likely to experience insurance changes
Exclusion criteria	
Unable to speak or read English	Limited to English speakers due to breadth and exploratory nature of the study
Is medically or otherwise unable to participate (as determined by a physician or study principal investigator)	For safety, due to virtual nature of the program
Unwilling or unable to participate in study sessions delivered via the Zoom videoconferencing software	Program only offered via videoconference technology

[a]AYAs: adolescents and young adults.

Recruitment

A multimodal approach was used to identify potential AYA participants for this study.

Provider Referral

Clinicians at MGH, DFCI, CONNECCS-affiliated sites, and external health care institutions could present and recommend the study to AYAs during a regular clinic visit. To facilitate provider support and referral, the study principal investigator (PI) presented the trial and solicited provider input at each of the Mass General Brigham and CONNECCS-affiliated sites. Interested patients either contacted the study clinical research coordinator (CRC) directly or provided permission to have the study CRC reach out to them.

Proactive Electronic Health Record Screening

The study CRC screened cancer survivors' electronic health records (EHR) at MGH for demographic and clinical eligibility criteria. Following patient identification, the CRC requested permission from a member of the cancer care team (ie, oncologist, nurse practitioner) to approach the patient for study participation at their next scheduled clinic visit or pursue outreach via phone. DFCI study staff conducted a chart screen and transferred the names and contact information of potentially eligible participants to MGH using a secure study REDCap (Research Electronic Data Capture) database to allow for the CRC to assess eligibility and pursue outreach.

Recruitment Flyers

Recruitment flyers were distributed through social media; by providers at external, interested health care institutions and clinics, including the CONNECCS network; and at cancer and survivor-related conferences and organizations (eg, Stupid Cancer; Cancer Con).

Research Portals

The Bounce Back study appeared as a public page on the Mass General Brigham Rally Research Recruitment Portal, a tool that allows patients to express interest in ongoing research studies.

Social Media Recruitment

Social media advertisements were used to disseminate information about the Bounce Back study and to direct AYAs to contact the study team for more information. Both recruitment flyers and text posts were posted on a variety of social media outlets and forums including Reddit, Facebook, Instagram, and Twitter.

Outreach and Follow-up Procedures

Patients who directly reached out to express interest in the study through recruitment flyers, research portals, or social media were contacted by the CRC within 1 to 2 business days of their initial outreach. Patients who were referred by providers or identified by proactive EHR screening were contacted by the CRC within 1 week after receiving permission from their health care provider(s). Phone calls, voicemails, and recruitment emails were also utilized as initial outreach methods.

For the initial phone outreach, the CRC followed an IRB-approved phone script to introduce the study and gauge interest in participating. Interested AYAs proceeded to complete the eligibility screening process.

During initial email outreach, the CRC sent an IRB-approved templated email to potential participants containing a brief overview of the study and a PDF of the study recruitment flyer.

AYAs were prompted at the end of the email to reply if they were interested in enrolling or learning more information. They were also given the options to decline participation and decline to receive further communication. The CRC then assessed eligibility and completed the electronic informed consent process via phone or a Zoom call.

Often, referring providers shared contact information for an AYA with the study team, which turned out to be parental contact information instead of the AYA survivors' personal contact information. On these occasions, outreach proceeded with contacting the parent. For parents of AYAs under the age of 18 years, the CRC encouraged co-participation of the AYA at the initial call. For parents of AYAs over the age of 18 years, the CRC asked the parent to provide the AYA's phone number or email address so they could pursue direct outreach.

Up to 3 repeated contact attempts were made using the aforementioned outreach methods.

Screening

To confirm eligibility prior to enrollment, the CRC administered a series of screening questions to all interested AYAs over the telephone or Zoom videoconferencing. During eligibility screening, all individuals were asked to verify (1) their date of birth, (2) their date of cancer diagnosis, and (3) details regarding their cancer treatment history (eg, date of treatment completion) and trajectory (eg, no further treatment planned apart from surveillance, no evidence of disease but use of rituximab).

Consent

Once the CRC confirmed an AYA's eligibility, they obtained informed consent using an electronic research consent form hosted on MGH REDCap. Participants were informed of the program components in greater detail, the required and optional assessments, potential risks and benefits of study participation, and the breakdown of the study compensation (up to US $120). They were also informed of the approximate start dates of the next 2 scheduled Bounce Back groups; groups were run consecutively so they would be later randomized to join one of the 2 next groups. Consented participants were emailed a PDF copy of the consent form for their records.

For participants under 18 years old, the CRC explained the study procedures to both the individual and their parent or legal guardian concurrently, and assent was obtained by the minor participant and their parent.

Enrollment

After informed consent, participants were assigned a study ID number, which was linked to their baseline assessment survey. To standardize the date of survey completion between groups, the baseline survey was sent approximately 2 weeks before the start of a new group to all participants who had consented. Participants were considered "enrolled" in the study following completion of the baseline survey (T0) and after randomization.

Randomization

Participants were randomized to the Bounce Back PG or CG following completion of the baseline survey (T0). Study staff developed a computer-generated randomization schema and stored condition assignments in concealed envelopes. Envelopes containing the randomization assignment were opened by the CRC while on the phone with participants.

Participation Timeline

Participants randomized to the PG initiated the Bounce Back program in the next scheduled group. After program completion, they completed a posttreatment questionnaire (T1) to examine pre-post treatment changes in exploratory measures and a 3-month follow-up (T2) questionnaire to examine potential maintenance of program benefits (by evaluating change in scores from T1 to T2).

Participants randomized to the CG enrolled in the study and completed the baseline survey (T0) at the same time as the PG. They then completed the baseline a second time (T1) after the PG completed the Bounce Back program to allow for pre-post treatment group comparisons (T0 vs T1). After program completion, the CG completed a posttreatment assessment to examine pre-post treatment changes in exploratory measures (T1-T2).

Participant Communication Methods

Previous literature has shown that recruiting AYAs for research studies can be difficult [32-34]. Informed by our previous work, we maintained contact with participants through communication methods with which they were comfortable and familiar, including phone, secure videoconferencing (eg, Zoom), email, and SMS texting [28].

Preprogram

To facilitate proficiency, familiarity, and comfort with the Zoom videoconferencing software, participants were required to meet with the CRC for a 10-15–minute Zoom test call approximately 1 week prior to the start of the program. During these test calls, the CRC provided an overview of the Bounce Back program (ie, surveys and hair samples) and addressed any remaining questions or concerns. Participants were also offered the opportunity to have a brief individual meeting with the group facilitator prior to the first group session. These optional, 15-minute meetings were designed to establish rapport, review group expectations, and address any remaining concerns about participating in an online virtual group. The CRC documented the number of participants who completed test calls and optional pre-program group facilitator meetings along with reasons for refusal.

Treatment Overview

The SMART-3RP program [27] was adapted to create the Bounce Back program, which was designed for virtual clinician-directed delivery over videoconference to groups of AYAs. Program adaptations were informed by reviews of the literature identifying gaps in posttreatment care for AYAs, meetings with AYA experts and clinicians, and focus groups and interviews with AYAs [28]. In Bounce Back, topics relevant to AYAs were interwoven throughout the program and used as a guide for applying techniques to relatable challenges. For instance, social and educational topics identified in qualitative interviews [28], such as how to tell friends about their cancer experience, having empathy for "small things," relating to others

postcancer treatment, preparing for high school or college, and managing parents' anxieties, were interwoven throughout the program and used to guide survivors in applying learned skills (eg, identifying types of social support needed and developing strategies to facilitate social outreach and connection).

Participants were emailed a PDF copy of the next chapter of the Bounce Back treatment manual the day before each weekly session to follow along with the program content. Please see Table 2 for a session-by-session overview of the Bounce Back program.

Table 2. Bounce Back program session-by-session content.

Program session	Educational content	Exercises and skills
Session 1: Stress Management and Resiliency Training	• Group member introductions • The science of mind-body medicine • Components of Bounce Back (practicing relaxation response [RR] techniques, stress awareness, adaptive strategies) • Breath awareness	• Body awareness • Photography as RR • RR practice: simple breath awareness
Session 2: The RR	• A closer look at the RR • Appreciations • Components of the stress response • Sleepiness vs fatigue • The MINI: an RR tool to use in the moment	• RR practice: autogenic training • Stress warning signals • Fatigue warning signals • RR practice: MINIs
Session 3: Stress Awareness	• Mindful awareness • Awareness of emotions and physical sensations • Social support • Changes in the self before and after cancer • Mindful eating exercise	• RR practice: mindful awareness • Mindful eating • Identifying emotions and positive physical sensations • The social support diagram • I am "Me"
Session 4: Mending Mind and Body	• Awareness of movement • Negative automatic thoughts • Pleasant activities • Values	• RR practice: yoga • Coping log • Reflecting on what's important • MINI: walking meditation
Session 5: Creating an Adaptive Perspective	• Guided imagery • Coping strategies: acceptance versus problem solving • Promoting physical activity	• RR Practice: Insight Imagery • Creating Adaptive Perspectives
Session 6: Promoting Positivity	• Contemplation • Optimism versus pessimism • Healthy eating after cancer	• RR practice: contemplation • Comparing optimism and pessimism • Relaxation signals
Session 7: Healing States of Mind	• Empathy and compassion • Self-empathy • Creative expression	• RR practice: compassion meditation • Root fear • Poetry
Session 8: Humor and Staying Resilient	• Humor and coping • Laughter • Humor strategies • Staying resilient: plan for long-term resiliency	• RR practice: idealized self • Energy battery 2 • Finding humor in your life • Laughter • Empathy: relating to others

Throughout the program, participants were encouraged to practice RR strategies at home for at least 10 minutes to 20 minutes each day. To facilitate practice, participants received mailed copies of weekly relaxation response (RR) practice logs before the start of the program as well as weekly electronic practice logs following each session. The physical and electronic practice logs were identical. Both included questions about weekly RR elicitation and appreciations, as well as stress, distress, and coping Likert scales. AYAs were encouraged to document the frequency and duration of their RR practice each

week on either the paper copy or electronic copy of the practice log, as per their preference.

Treatment Administration

The Bounce Back program consisted of 8 weekly, 90-minute sessions delivered virtually by a clinician via Zoom videoconferencing software. Groups consisted of approximately 8 participants (mean 8, range 4-10), with group size varying slightly based on pace of recruitment. To optimize the pace of enrollment and trial completion, groups were comprised of

immediate start and CG participants (who had already completed their waiting period).

Training and Supervision

Prior to running the Bounce Back groups, the group facilitator and CRC were trained on the experiences of AYAs. CRC training included a general overview of common diagnoses, treatment trajectories, late effects, challenges, and stressors associated with the early posttreatment period. Additional instructional sessions included how to engage AYAs, manage distressed or frustrated AYAs, communicate with AYAs and parents of different cultural backgrounds, and communicate with providers about eligible AYAs.

The Bounce Back group facilitator was a doctoral-level clinical psychologist trained to deliver the SMART-3RP. This foundational training was supplemented by additional trial-specific training to review manual adaptations specific to Bounce Back, learn study protocols, and review physical and emotional challenges related to cancer treatment. Additional didactics included interpersonal skills to deliver a virtual group program and manage group dynamics over videoconferencing. The group facilitators were instructed to strictly adhere to the treatment protocol, which included reviewing previous material at the start of each session, covering all prescribed educational material, and leading in-session exercises.

Prior to the group start date, the study PI reviewed any potential participant concerns with the group facilitator to ensure proper implementation and tailoring of the program protocol. During the program, the study team (PI, group facilitator, and CRC) met weekly for clinical supervision and to review any changes or variations in program content delivery (ie, due to time constraints) and fidelity, as well as to troubleshoot barriers to participant engagement, attendance, and group cohesion.

Fidelity

We developed a REDCap fidelity database to track Bounce Back program content and program engagement. The database included fields to track (1) session duration, (2) program content and exercises covered, (3) between-session practice goals assigned, (4) notable tech issues, (5) group cohesion, (6) participant attendance, and (7) participant engagement. Group cohesion was assessed through an investigator-developed measure asking the facilitator to rate the presence of the Group Therapeutic Factors (eg, altruism, interpersonal learning) defined by Yalom and Leszcz [35] on a 3-point Likert scale (not at all present, somewhat present, highly present). Immediately after each session concluded, the group facilitator tracked these items on the fidelity database, which was reviewed by the study PI to ensure protocol fidelity.

Outcome Measures and Assessment Periods

Participants completed electronic study surveys via REDCap at 3 time points. Each self-report survey took approximately 15 minutes to 20 minutes to complete. The baseline (T0) survey was completed approximately 2 weeks before a new group was scheduled to begin. The time point 1 (T1) survey was completed up to approximately 12 weeks (±2 weeks) after T0, and time point 2 (T2) was completed up to approximately 24 weeks (±2 weeks) after T0. The CRC followed up weekly with participants who had outstanding surveys using multiple modalities. If the CRC could not reach a participant with incomplete surveys, the group facilitator also called and left a voicemail for participants to encourage survey completion. Outcome measures collected at screening and in study questionnaires are detailed in Table 3.

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Table 3. Outcome measures.

Data	At screening	At baseline	At program	At postprogram	At 3-month follow-up
Date of birth	x	—[a]	—	—	—
Gender	x	—	—	—	—
Languages spoken	x	—	—	—	—
Cancer diagnosis	x	—	—	—	—
Date of diagnosis	x	—	—	—	—
Treatment type(s)	x	—	—	—	—
Date of treatment completion	x	—	—	—	—
Demographic factors	—	x	—	—	—
Psychosocial measures					
Visual Analog Scales (VAS): Stress and Distress	—	x	—	x	x
Intolerance of Uncertainty Scale (IUS-12)	—	x	—	x	x
Measure of Current Status – Part A (MOCS-A)	—	x	—	x	x
Patient-Reported Outcomes Measurement Information System (PROMIS) Measures (PROMIS anxiety - short form 4a; PROMIS depression - short form 4a; PROMIS anger - short form 5a; PROMIS fatigue - short form 7b; PROMIS sleep disturbance - short form 8a; PROMIS social isolation - short form 4a)	—	x	—	x	x
Coping Self-Efficacy Scale (CSES)	—	x	—	x	x
Relaxation response (RR) practice	—	x	—	x	x
Health behavior questions	—	x	—	x	x
Penn State Worry Questionnaire (PSW-Q)	—	x	—	x	x
Interpersonal Reactivity Index (IRI)	—	x	—	x	x
Current Experiences Scale (CES)	—	x	—	x	x
Hair cortisol measurement	—	x	—	x	—
Program acceptability questionnaire	—	—	—	x (PG[b] only)	x (CG[c] only)
COVID-19 supplementary questions	—	x	—	x	x
Optional weekly RR practice logs	—	—	x	—	—
Optional exit interview	—	—	—	—	x (after completion of all study measures)

[a]Not measured at this time point.

[b]PG: program group.

[c]CG: waitlist control group.

Primary Outcome Measures

The primary aim of the study is to determine the feasibility and acceptability of the Bounce Back program.

Feasibility

Feasibility metrics were modeled after resiliency studies led with survivors and other medical populations [36,37]. We evaluated program feasibility by examining several process variables, including rates of study eligibility (percent of individuals who were eligible), recruitment (number of eligible individuals who expressed interest in our study), enrollment (percent of eligible pool who consented and enrolled), and retention (percent of enrollees who completed the follow-up). Our primary measure of feasibility was determined by the proportion of patients who completed the program, defined as participating in 6 out of 8 sessions. We documented reasons for ineligibility and refusal as well as sociodemographic characteristics, medical history, and cancer characteristics of refusers.

Acceptability

Program acceptability was assessed at the postprogram data collection period (T1 for PG, T2 for CG) with 5 questions on an acceptability questionnaire rated on a 4-point Likert scale (1=not at all to 4=very much). Items prompted participants to rate the extent to which they found the Bounce Back program to be (1) enjoyable, (2) helpful, (3) applicable or relevant (ie, is it appropriate and applicable), (4) convenient (ie, in regard to delivery modality), and (5) likelihood of future use (eg, "Will

you continue to use RR strategies in the future?"). Treatment satisfaction was assessed by items on the acceptability questionnaire, which asks participants to rate their level of satisfaction with the following items using a 4-point Likert scale (1=not at all satisfied to 4=very satisfied): (1) treatment structure, (2) treatment timing (ie, early survivorship period) and (3) treatment content. We qualitatively explored overall satisfaction by asking 3 open-ended questions regarding treatment likes, dislikes, and recommendations. Additional acceptability data are collected in the optional qualitative exit interview.

Secondary (Exploratory) Outcome Measures

Stress Coping: Measure of Current Status

The Measure of Current Status Part A (MOCS-A) is a 13-item measure that assesses participants' self-reported ability to deal with daily stresses. Composite scores range from 0 to 52, with higher scores demonstrating greater self-perceived confidence in handling daily stressors. The MOCS-A has 4 subscales that can be analyzed: relaxation, awareness of tension, assertiveness, and coping confidence [38].

Resilience: Current Experiences Scale

Resilience was measured using 18 items from the Current Experience Scale (CES). The questionnaire reflects current self-perceived functioning in the domains of appreciation for life, adaptive perspectives, personal strength, spiritual connectedness, relating to others, and health behaviors. For each item, responses range from 0 (not at all) to 5 (a great deal). Composite scores range from 0 to 90, with higher scores indicating resiliency; greater scores on each of the 6 subscales indicate greater resiliency [39].

Stress, Distress: Visual Analogue Scale—Stress, Distress

The visual analogue scale (VAS)-Stress is a 1-item scale asking individuals to rate their current level of stress. The VAS-Distress is a 1-item scale asking individuals to rate their current level of distress on a scale of 0 to 10. Higher scores on each scale indicate greater levels of the construct being measured [40].

Patient-Reported Outcomes Measurement Information System Measures

Patient-Reported Outcomes Measurement Information (PROMIS) measures evaluate and monitor physical, mental, and social health in adults and children. The following subscales were utilized: PROMIS ED Anxiety – short form 4a, PROMIS ED depression – short form 4a, PROMIS ED anger – short form 5a, PROMIS fatigue - short form 7b, PROMIS sleep disturbance - short form 8a, PROMIS Social Isolation - short form 4a. PROMIS measures were scored by the HealthMeasures Scoring Service using response pattern scoring. PROMIS raw scores are converted into T-scores for each participant and compared to US population averages.

Worry: Penn State Worry Questionnaire

The Penn State Worry Questionnaire (PSWQ) is a 16-item measure used to assess worry. It is rated on a 5-point scale ranging from 1 (not at all typical of me) to 5 (very typical of me); select items are reverse scored. Total scores range from 16 to 80, with higher scores indicating greater worry [41].

Uncertainty Tolerance: Intolerance of Uncertainty Scale

The Intolerance of Uncertainty Scale (IUS-12) is a short version of the original 27-item Intolerance of Uncertainty Scale [42] that measures responses to uncertainty, ambiguous situations, and the future. The 12 items are rated on a 5-point Likert scale ranging from 1 (not at all characteristic of me) to 5 (entirely characteristic of me). The IUS-12 is scored on a scale from 12 to 60, with greater scores indicating greater intolerance of uncertainty. IUS prospective and inhibitory subscale scores will also be examined [43].

Perspective Taking: The Interpersonal Reactivity Index Perspective-Taking Subscale

The Interpersonal Reactivity Index (IRI) perspective-taking subscale is a 7-item measure that assesses the tendency of an individual to take on the perspective of another in daily life. Items are rated on a scale of 0 (does not describe me well) to 4 (describes me very well). We used 6 of the 7 items in the subscale. Total scores range from 0 to 24, with higher scores indicating greater perspective-taking ability [44].

Coping Self-Efficacy: Coping Self-Efficacy Scale

The Coping Self-Efficacy Scale (CSES) is a 26-item measure of self-perceived efficacy for coping with challenges and threats. Respondents are asked to rate their confidence performing adaptive coping behaviors (ie, talking positively to oneself) on a scale of 0 (Cannot do at all) to 10 (Certain can do). Scores range from 0 to 260, with higher scores indicating greater coping self-efficacy [45].

Relaxation Response Practice: RR Practice Measure

A single-item, investigator-developed measure was administered to assess frequency of self-guided RR exercise practice. Participants were asked to describe the frequency of their RR exercise (eg, mindfulness, guided imagery, deep breathing) practice on the following scale: Daily, A few times per week, Once or twice a month, or Never.

Health Behaviors: Health Behavior Questionnaire

The Health Behavior Questionnaire is an investigator-developed questionnaire designed to assess habits related to substance use, exercise, and nutrition.

Impact of COVID-19: COVID-19 Measure

This measure was added mid-study to account for any COVID-19–related stressors that occurred during study participation that may have influenced prior survey responses. Participants were asked to report on their COVID-19–related concerns, COVID-19–related lifestyle changes (ie, diet, sleep), changes in stress level, changes in cancer-related concerns, and more broadly how the virus was impacting their life.

Hair Cortisol Measurement

Participants were asked to provide hair samples to measure potential changes in cortisol (ie, a stress hormone). We found that hair cortisol sampling was feasible in a similar behavioral trial conducted with posttreatment lymphoma survivors [46].

Participants were instructed to provide 1 hair sample preprogram (T0 for PG, T1 for CG) and 1 sample at the end of the program (T1 for PG, T2 for CG). The CRC sent detailed hair sampling instructions and stamped, pre-addressed envelopes to facilitate returns. Participants were instructed to cut a small sample of hair (approximately 150 strands, about the diameter of a pencil eraser) from the back of their head, as close to the scalp as possible. They were asked to tie the strands near the scalp end, place the sample in aluminum foil, and mail back to the research team. The hair sampling instructions also included 6 questions about hair care, exercise, and glucocorticoid use, as these can affect hair cortisol measurements. Hair samples were not collected from participants who had taken glucocorticoid medications (eg, prednisone) within the past 3 months, as these medications can suppress endogenous cortisol levels or cause cortisol measurements to be inaccurate. We tracked the reasons why any hair samples were not collected to inform the feasibility and acceptability of hair cortisol collection and analysis for this population. We also collected feedback and perceptions of hair sampling measures at study completion. Prior to processing, samples remained wrapped in aluminum foil, labeled with a study ID, and stored at room temperature in a padded envelope. Hair samples were processed by Dr. Jerrold Meyer's laboratory at the University of Massachusetts, Amherst using an ELISA assay kit.

Qualitative Exit Interviews

Qualitative data collection for this trial is ongoing. A randomly selected subset of 20 participants will be invited to participate in one-on-one exit interviews after study completion. To ensure inclusivity and take into account the effects of the COVID-19 pandemic on the program delivery, the sample will be stratified based on the following characteristics: (1) gender, (2) race (ie, non-Hispanic White; survivors of color), and (3) time of study participation (ie, before, during, or after onset of COVID-19 pandemic). Exit interviews may be completed via Zoom videoconferencing to explore additional barriers or facilitators to study participation, treatment adherence, program engagement, and study completion. Participants will be asked more detailed information about perceptions of the treatment and preferences for further adaptation after having participated in the program. A series of questions will be asked about using social media outreach for future research recruitment. We will also ask participants to report on how COVID-19 may have impacted their stress levels or ability to participate in the program. These interviews will be audio-recorded and qualitatively analyzed for themes that will help to determine whether treatment modifications are needed in future work. It is estimated that the interviews will take approximately 45 minutes to complete. Participants will be informed that the qualitative exit interviews are an optional portion of the study but if completed, will result in additional compensation (US $30).

Safety

Data Safety Monitoring Plan

The PI monitored the safety of this trial and complied with reporting requirements. All adverse events were reported to the IRB within 24 hours. Study recruitment, enrollment, and retention were reviewed by the PI and CRC weekly. The PI's mentor, co-mentors, consultants, and scientific advisors functioned as a Data Safety and Monitoring Board. This group convened on a semi-annual basis to monitor study participant safety and to review study progress and other study-related events (including, but not limited to, enrollment, recruitment, retention, and adverse events). During these meetings, any study-related concerns were reviewed, and as needed, an action plan was established. The outcome of these meetings and proposed action plans were summarized and distributed to all mentors, consultants, and scientific advisors. The PI and her team also met quarterly with collaborators within the CONNECCS network to review study progress, request referrals, and discuss other study-related activities and events. Study updates were summarized and distributed to all CONNECCS collaborators following the quarterly meetings.

Privacy and Confidentiality

We instructed participants to maintain the confidentiality of the group by not discussing anything that occurred in the group with anyone outside of the group. Group privacy and confidentiality were discussed at the first session and in the subsequent session to reinforce practice. Careful attention was taken during the informed consent process to explain the limits of confidentiality. Participants were advised to wear headphones and sit in a quiet place to protect their own and other group members' privacy. All data and personal information created by this research study were stored in password-protected computer files accessible only to study staff and stored on a secure drive only accessible by members of the research team.

Statistical Analysis

The primary study endpoints are the feasibility and acceptability of the Bounce Back program for AYA cancer survivors who are within 5 years posttreatment completion. Data analysis is ongoing, and the data analysis plan is reported in the following sections.

Sample Size and Power Calculations

Consistent with best practices in treatment development, the aim of this pilot is to establish the feasibility and acceptability of a stress management and resiliency program for early posttreatment AYAs [37,47]. We consider 75% session completion rate (approximately 6 of 8 sessions) as a threshold for program completion. As such, we consider 60% of participants reaching the threshold to establish program feasibility. With a sample size of 60 participants, we would have 80% power to demonstrate a difference of 15% from our preset criterion with a one-sided significance level of .05. Therefore, we believe our sample size of 72, accounting for 10%-15% attrition based on prior trials [46], will be sufficient to answer our questions about feasibility and acceptability.

Primary Analysis Plan

Descriptive statistics, including means, frequencies, and ranges, will be used to describe the sample and to summarize feasibility, acceptability, and program satisfaction. Feasibility outcomes will be assessed by determining the proportion of individuals who were recruited, screened, and enrolled in the study. Response frequencies will summarize reasons for ineligibility

and refusal. We will also determine the proportion of enrolled participants who complete the program. Participants who complete at least 75% of the treatment sessions (6 of 8 sessions) will be identified as treatment completers. We will examine the proportion of individuals who attend each session. For acceptability, response frequencies will summarize quantitative feedback on the acceptability questionnaire. Together with qualitative feedback from the exit interviews, this information will be used to inform the feasibility and acceptability of the program.

Exploratory Analysis Plan: Psychosocial Measures

Preliminary outcome data may be used to inform future assessment instruments and methods. We may also conduct exploratory hypothesis testing to examine preliminary changes in our proposed program targets (changes in psychosocial outcomes, including mindfulness, depressed mood, anxiety, and stress). A priori statistical tests of program-related changes will be planned for a future efficacy trial of this program. First, we will examine the frequency distributions of all variables. Potential variables of interest (eg, gender, history of RR practice) will be included as covariates if they are significantly correlated with each outcome of interest at $P<.25$. We will also compare the baseline characteristics of completers versus study noncompleters. The primary analysis will be a completer analysis limited to those with complete data, and we will conduct a sensitivity analysis using multiple imputation for missing data. For our exploratory psychosocial outcomes, we will examine between-group differences in change scores from enrollment (T0) to T1 (posttreatment for PG, 3 months postenrollment/baseline #2 for CG). To further explore preliminary efficacy, we will evaluate within-group changes from pre- to postprogram (using T0 to T1 data for the PG and T1 to T2 data for the CG) for each condition separately and then for both groups combined. Finally, within the PG only, we will explore potential maintenance of program benefits with a repeated measures analysis of variance (ANOVA), including the 3 survey time points. Exit interviews will be audio-recorded and transcribed; NVIVO software will be utilized in the thematic analysis, which will be led by members of the study staff under the mentorship of the study PI. Coders will meet on a weekly basis to discuss the coding framework, categories, and coding plan. To ensure coding reliability, coding discrepancies will be resolved through discussion and comparison of raw data. Coding will continue until a high level of reliability (kappa ≥0.80) is established.

Exploratory Analysis Plan: Hair Samples

We will examine the feasibility, acceptability, and preliminary effects of collecting hair samples to examine changes in stress reactivity. Feasibility metrics for the hair sampling include hair return rates. For measures of acceptability, response frequencies will summarize quantitative feedback from the acceptability questionnaire about the acceptability of hair collection procedures. Hair cortisol samples will be analyzed in a laboratory, and group differences in hair cortisol concentration at T1 will be examined using independent samples *t* tests. Pearson correlation or Spearman rank correlation will examine the association of hair cortisol concentration with each of our psychological outcomes, controlling for potential confounders

Missing Data

We will assess whether the mechanism of missing data is missing at random. We will explore differences between study completers and noncompleters on participant demographic and other relevant variables to inform the next phase of this trial. We will perform sensitivity analysis using (1) a completer analysis limited to those who have complete data and (2) multiple imputations for missing data [48].

Results

This project was part of a 5-year grant funded by the NCI in July 2017. The randomized controlled trial portion of the Bounce Back study occurred from July 2019 to March 2021. Of the 72 participants who enrolled in the study, 70 remained eligible (2 had a recurrence before groups began), and 64 initiated treatment. We ran 9 consecutive 8-week Bounce Back groups from July 2019 through December 2020. Quantitative data collection is complete, and qualitative exit interview data collection is ongoing but expected to be completed by June 2022. Data analysis is ongoing, and results are expected to be published in peer-reviewed journals and presented at local, national, or international meetings in the coming year(s).

Discussion

This paper details the study protocol and methodology for a pilot randomized waitlist-control trial to examine the effects of a virtual program (Bounce Back) aimed at promoting stress management, resiliency, and coping among posttreatment AYAs.

Survivors of cancer diagnosed during adolescence and young adulthood are a largely understudied and underserved population. A cancer diagnosis during this life stage can cause significant disruption in several key life domains. Rates of stress and distress are high among this population, who often have poor health-related quality of life in the years after treatment [7-10]. Despite the prevalence of these challenges, few AYAs receive mental health services after treatment completion [2,49]. Without sufficient psychosocial supportive care, the rates of distress, morbidity, and mortality in this population will remain high. There are currently few evidence-based programs for AYAs in the years following treatment that tackle the key transitional issues they face [14,16,17,25,26]. As such, programs that promote stress management, coping, and connection among this population are warranted.

Other psychosocial programs targeting AYAs have been individually delivered, did not include mind-body skill acquisition, or focused on teaching a single skill (ie, mindfulness, positive psychology) for stress reduction [12-17,25,26]. Few have targeted a wide range of AYAs, particularly during the early posttreatment period. The use of both quantitative (surveys) and qualitative methods (exit interviews) will help us gain a richer understanding of AYAs' experience in the program and its impact on their stress coping and psychological well-being. The wait-list control trial design allowed us provide support to all research participants who

sought help while maintaining a nonprogram comparison group to enhance scientific rigor.

Historically, low research participation and a wide geographic distribution have made it difficult to identify AYAs and provide targeted treatment [32,33]. The virtual modality of the Bounce Back program promoted accessibility of our research study to participants who may not have been able to receive mental health care due to travel, financial, or health-related barriers. By using social media as a research recruitment tool and opening recruitment outside of our direct hospital system, we aimed to reach a more diverse and representative sample. With few restrictions in our inclusion and exclusion criteria, we ensured that the program was accessible to as many AYAs as possible. Notably, the Bounce Back trial and procedures spanned the timeframe of the COVID-19 pandemic. We did not cease operations of the trial during this time, acknowledging the need to support AYAs during a period of unprecedented uncertainty and health-related anxiety affecting individuals around the globe. To tease out the impact of the pandemic on our study outcome measures, we included a COVID-19 measure to our survey battery and exit interview for the subset of participants who were in the trial after the pandemic onset.

The Bounce Back program was adapted from an existing evidence-based mind-body program, the SMART-3RP [27]. The SMART-3RP has been proven to decrease stress and improve psychological and physical health symptoms among several different patient populations [46,50-53]. Offering a tailored mind-body program centered on the RR to AYAs may help mitigate the negative psychological and physiological effects of stress in the early posttreatment period. Additionally, few studies have examined hair cortisol as a biomarker of stress in the AYA population.

This study protocol does have some limitations. One limitation of this study is the potential for attrition. We expected that the rate of attrition would be similar to other randomized controlled trials of cognitive behavioral programs for children and adolescents with chronic illness [54].

Due to the waitlist-control trial design, participants had to wait up to 3 months before starting the treatment program. Some CG participants became unreachable during this waiting period prior to program participation. Additionally, with the AYA population, academic course schedules, work obligations, and extracurricular activities could conflict with the scheduled group program. Given that AYA schedules were often fluctuating, we enrolled individuals who stated their interest in participating regardless of their availability. This flexibility may have elevated our rate of attrition, resulting in some AYAs becoming unavailable for program scheduling after enrolling. Another limitation was exclusion of individuals who did not have access to appropriate technology, working internet, or an electronic device with a webcam to attend the virtual group sessions. However, in today's digitally interconnected society, we did not anticipate that this requirement would preclude many AYAs from participating. Despite these limitations, our study participation rate remained quite high and was higher than those commonly noted in other behavioral trials [12,14]. Finally, we excluded non-English-speaking participants as the study measures and program were targeted towards an English-speaking audience. We hope to open future studies of the Bounce Back program to non-English speakers.

Our study results will add to the existing literature surrounding the feasibility and acceptability of delivering virtual programs to AYAs in the early posttreatment period. We will learn if the Bounce Back program can improve stress coping, distress, and psychological well-being in this understudied population. Our findings will help us gain a richer understanding of the psychosocial functioning of early AYAs as well as their perceptions surrounding mind-body and psychosocial supportive group programs. If the Bounce Back program is found to be efficacious, it will inform the design of future psychosocial programs for this population. If any psychosocial outcomes do not improve, it will allow us to determine what constructs to target in future programs for AYAs.

Acknowledgments

Authors' Contributions

All of the co-authors approve of the manuscript and played a significant role in the study design, implementation, or protocol preparation. Specific contributions include the following: GKP was the principal investigator and provided clinical expertise, developed the protocol, performed data monitoring and analysis, and provided study oversight. HM acted as the clinical research coordinator (CRC), performed data monitoring, and conducted trial recruitment and study operations. BG was the program facilitator and provided clinical expertise. ERP provided implementation and dissemination expertise, integrated the program, contributed mind-body medicine expertise, performed data monitoring, and developed the protocol. CR contributed adolescent and young adult (AYA) oncology and distress screening expertise, performed data monitoring, and developed the protocol. JAG provided intervention design and psychosocial oncology expertise and developed the protocol. YC analyzed the data and developed the protocol. NF, MDT, MH, AH, GNU, and AA contributed clinical and AYA oncology expertise and assisted with site recruitment. KM contributed neuroendocrine expertise and performed data monitoring. JP performed data monitoring and contributed ethics and oncology expertise. EAW acted as a CRC, performed data monitoring, and conducted trial recruitment and operations. LK

contributed AYA oncology expertise, developed the protocol, and was a site investigator. JD contributed mind-body medicine and biobehavioral measurement expertise and conducted data monitoring.

Conflicts of Interest

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Abbreviations

ANOVA: analysis of variance
AYAs: adolescents and young adults
CES: Current Experiences Scale
CG: waitlist control group
CONNECCS: Consortium for New England Childhood Cancer Survivors
CRC: clinical research coordinator
CSES: Coping Self-Efficacy Scale
DFCI: Dana-Farber Cancer Institute
EHR: electronic health records
IRB: Institutional Review Board
IRI: The Interpersonal Reactivity Index
IUS-12: Intolerance of Uncertainty Scale
MGH: Massachusetts General Hospital
MOCS-A: Measure of Current Status Part A
NCI: National Cancer Institute
PG: program group
PI: principal investigator
PROMIS: Patient-Reported Outcomes Measurement Information System
PSW: Penn State Worry Questionnaire
REDCap: Research Electronic Data Capture
RR: relaxation response
SMART-3RP: Stress Management and Relaxation Training - Relaxation Response Resiliency Program
VAS: visual analogue scale

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Protocol

Effects of Aerobic Exercise and High-Intensity Interval Training on the Mental Health of Adolescents Living in Poverty: Protocol for a Randomized Controlled Trial

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Abstract

Background: The increasing rate of mental health issues among adolescents has recently been a considerable concern in Hong Kong. In particular, adolescents with low socioeconomic status (SES) are likely to experience poor mental health, including low self-esteem and high levels of anxiety, anger, and depression. Previous research has found that physical activities have a positive impact on improving mental health outcomes among adolescents. However, approximately 96% of adolescents in Hong Kong do not engage in regular exercise, which potentially increases the risk of poor mental health.

Objective: In this study, we aim to examine whether changes in the 3 indicators (reduced ill-being, enhanced well-being, and cognitive functions) of mental health among adolescents with low SES are evident before and after exercise. In addition, this study compares the effectiveness of aerobic exercise and high-intensity interval training on these indicators among adolescents with low SES.

Methods: A total of 78 participants from low-income families aged between 12 and 15 years from 3 to 4 secondary schools will be recruited for this study. They will be randomly assigned to either an aerobic exercise group (26/78, 33%), a high-intensity interval training group (26/78, 33%), or a control group (26/78, 33%). Participants in the first 2 groups will take part in a 10-week training program period. Participants in the control group will participate in other physical activities during the same intervention period. The training sessions will be conducted 3 times per week on nonconsecutive days. A range of neuropsychological tests and psychometric scales will be used to measure the executive functions and indicators of psychological well-being and ill-being, including enjoyment, self-efficacy, mood, depression, anxiety, and stress at pretest, posttest, and follow-up assessments.

Results: The project was funded in 2021 by the Research Matching Grant Scheme, through the University Grants Committee of the Hong Kong Special Administrative Region Government. Ethical approval has been obtained from the author's institution. Participant recruitment will begin in January 2022 and continue through to April 2022. Data collection and follow-up are expected to be completed by the end of 2022. The results are expected to be submitted for publication in 2023.

Conclusions: The findings will help inform policy makers and practitioners in promoting the importance of physical exercise to enhance mental health.

Trial Registration: ClinicalTrials.gov NCT050293888; https://clinicaltrials.gov/ct2/show/record/NCT05029388

International Registered Report Identifier (IRRID): PRR1-10.2196/34915

KEYWORDS

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Introduction

Mental Health in Adolescents in Hong Kong

Poor mental health among adolescents has serious implications for adult morbidity and mortality. Mental health involves the absence of mental illnesses and life satisfaction [1]. In Hong Kong, the mental health of adolescents has been a subject of considerable concern in recent years. A recent survey of 11,493 local citizens revealed that approximately 74% of adolescents aged <25 years exhibit moderate to high levels of depressive symptoms (eg, depression, anxiety, and stress), 41% of the adolescents exhibit moderate to high levels of posttraumatic stress symptoms, and 36% of the adolescents have both diagnoses [2]. However, previous research has demonstrated that poor mental health is unevenly distributed across different socioeconomic groups, with high clusters in families with a low socioeconomic status (SES) [3].

Families in this category are deprived in multiple ways and are affected by numerous stressors related to finances, social relations, employment opportunities, and physical illness compared with families from other socioeconomic groups [4]. For instance, adolescents with low SES often have worse access to education and social participation than their peers with an average or high SES [5]. In addition, the results from a meta-analysis study of 34 countries from 2002 to 2010 indicated that adolescents with low SES are affected by physical symptoms and have poor mental health, including low self-esteem and high levels of anxiety, anger, and depression [6]. In a sample of Chinese adolescents in Hong Kong, adolescents who grew up in families with a Comprehensive Social Security Assistance (CSSA) scheme had significantly higher levels of suicidal intention than those in families without CSSA [7].

Interventions for Mental Health

Numerous mental health interventions are popular, but the scope of their effects is unclear. Costigan et al [8] stated that effective mental health interventions should address the following 3 indicators: (1) cognitive function, (2) well-being, and (3) ill-being. Conventional strategies such as cognitive behavioral therapy (CBT) [9] and dialectical behavior therapy (DBT) [10] are mainly based on therapeutic models. CBT focuses on challenging and changing dysfunctional thoughts, and DBT encourages clients to accept and validate their feelings [9]. Although the results in terms of reducing clinical symptoms are promising, their effectiveness in enhancing overall well-being is debatable. Moreover, one has to commit themselves to the process to benefit from CBT or DBT; these strategies may not be suitable for individuals with low capacity to change themselves (their thoughts, feelings, and behaviors). Moreover, school-based prevention programs [11] and web-based self-help interventions [12] are commonly used as preventive measures in school settings. School-based programs are implemented in schools to minimize high-risk behaviors [11]. Web-based self-help interventions allow individuals to work in their own time and use web-based resources to assist with their problems [12]. Similar to conventional strategies, the effectiveness of these intervention programs relies heavily on an individual's

motivation and capacity. Individuals with low SES often perceive themselves as incompetent, and this stigma contributes to their low motivation to change [13]. Furthermore, several studies have criticized that prevention programs fail to target the enhancement of mental health among *at-risk* students and to train school personnel, such as teachers and social workers, to identify these students [14]. Therefore, physical exercise is presently considered as an effective intervention because of its safe, nonpharmacological, and cost-effective nature [15] that can provide a range of health benefits, including improvements in body composition and physical capacity, among individuals [16]. Recent evidence has confirmed that physical exercise has a positive effect on mental health outcomes for youth through physiological and psychological pathways [17].

Previous Research on Physical Exercise

Physiological Evidence

Studies that are focused on physiological evidence have commonly demonstrated a direct positive effect of physical exercise on individuals' neurological processes, thereby indicating that cardio activities are directly and immediately beneficial to mental health. Two main research streams that cite physiological evidence, namely, those that focus on monoamines and those that focus on endorphins, are present. The first research stream reveals that physical activity upregulates the synaptic transmission of monoamines, including the 3 major neurotransmitters, namely, norepinephrine, dopamine, and serotonin [18]. A similar effect has been found for antidepressant drugs [19], although exercise has been proven to be as effective as antidepressants for alleviating depressive symptoms among patients with major depression [20]. The hypothesis regarding endorphins is also popular for explaining the impact of aerobic exercise on mental health. Several researchers have believed that endorphins may lead to energy conservation during exercise and consequently exhibit psychological effects, such as improved mood states and reduced anxiety [21]. Direct evidence stating that physical activity can elevate plasma endorphin levels also exists [22].

Psychological Evidence: 3 Mental Health Indicators

Although physiological evidence has established a direct association between physical activity and mental health, researchers are also keen to identify how physical activities may benefit mental health. Several researchers have conducted studies based on the three indicators of mental health that were proposed by Costigan et al [8]: (1) cognitive function, (2) well-being (eg, enjoyment), and (3) ill-being (eg, depression and negative affect).

With regard to cognitive function, growing evidence indicates that participating in exercise positively affects the executive functions [23]. Executive function is an umbrella term that covers a wide array of cognitive processes that govern goal-directed actions and adaptive responses to novel, complex, or ambiguous situations [24]. Numerous studies have found that intense physical exercise improves working memory [25], inhibitory control [25], and cognitive flexibility in typical [26] and low-income adolescents [27].

Physical exercise has been associated with improved well-being, including life satisfaction and self-esteem [8]. Exercise is a challenging activity, but the process of engaging in exercise could provide individuals with a meaningful experience of mastery that may lead to improved mood states and self-confidence [28]. Affect regulation theory suggests that exercise could regulate affect by reducing negative mood states and enhancing positive mood states that are conducive to mental well-being [29-31]. Furthermore, as described in the relevant literature, exercise can divert an individual from unfavorable stimuli (eg, worries, stress, and depressive thoughts), leading to improved mood [32,33].

Physical exercise has also been associated with reduced ill-being. A meta-analysis of 73 studies confirmed that increased levels of physical activity significantly reduced depression, anxiety, psychological distress, and emotional disturbance among children [34]. Archer and Garcia [35] found that regular physical exercise ameliorated the symptoms of anxiety and depression. Behavioral activation theory posits that depressive symptoms may be alleviated when individuals replace passive activities with exercise and other entertaining activities [36].

Exercise Regimen

Although a lack of consensus regarding the most effective training regimen for physical exercise is evident in clinical review studies from 2000 to 2014, Ranjbar et al [37] have recommended the following components of an effective exercise program to benefit adolescents with poor mental health. On the basis of the frequency, intensity, time, and type principle, an exercise program should include the following characteristics: (1) structured aerobic exercise, which requires the heart to pump oxygenated blood for delivering oxygen to working muscles and stimulates an increase in the heart rate (HR) and breathing rate [38]; (2) group exercise, particularly for adolescents; (3) low (40%-55% maximal oxygen consumption) to moderate (65%-75% maximal oxygen consumption) intensity exercise; (4) 45- to 60-minute exercise sessions; (5) exercise frequency of at least three to four sessions per week, which is equal to ≥150 minutes of exercise per week; and (6) an exercise duration equal to ≥10 weeks.

Overall, extensive research has confirmed that physical exercise can significantly improve physical and mental health, whereas aerobic exercise has been the main focus of most previous studies. Recent studies have attempted to determine whether low-volume high-intensity interval training (HIIT) could be a time-efficient exercise strategy for improving health and fitness among the general population.

High-Intensity Interval Training

HIIT is a time-efficient type of aerobic training that involves a short duration of full-effort exercise, followed by a rest period. HIIT is mainly appealing because it can be completed in a relatively short period and results in physiological adaptations that are equivalent to long sessions of traditional aerobic training and improvements in physical and mental health. This strategy may be feasible and effective for increasing physical health outcomes among young people [39,40]. Compared with low-intensity, high-volume (duration) endurance aerobic training

(ie, cycling), HIIT can result in better oxygen uptake, greater muscle deoxygenation, and better exercise performance [41]. A previous study also revealed that patients participating in high-intensity interval running reported higher perceived enjoyment than those participating in moderate-intensity continuous running [42]. A pilot study of a 10-week HIIT program resulted in improved metabolic outcomes among patients with schizophrenia, thereby supporting the benefits of HIIT for physical fitness and mental health. Furthermore, studies have also shown that HIIT reduces distress and anxiety [43].

Despite the promising evidence that supports the adoption of HIIT among adults with various conditions, limited research that targets adolescents, particularly those with low SES, is available [39,40]. High-intensity activities performed in short, repeated bouts with periods of recovery in-between could be an achievable and enjoyable alternative to high-volume continuous exercise for adolescents, including *low-active* adolescents [40,44].

Research Gaps and Study Objectives

The conditions and ability of poor individuals to manage and potentially escape poverty are the core of policy agendas and ethical and economic concerns among societies. Behavioral research has recently been applied to policy-relevant challenges and has explored the significant potential of simple interventions to influence cognition and behavior [45]. Poor individuals, particularly young poor individuals in Hong Kong, have received little attention as part of this endeavor despite their characteristics that satisfy the qualifications of clear candidates for interventions that could improve disadvantaged situations.

Although several longitudinal studies have confirmed that growing up in a disadvantaged family is a significant risk factor for poor mental health, numerous research gaps should be addressed by further investigation. For instance, most studies on mental health and socioeconomically disadvantaged adolescents have been restricted to understanding and confirming the link between mental health and SES. Research that aims to examine whether mental health can be enhanced through physical exercise is scarce. However, such research would be extremely useful for expanding early interventions. To date, a steady decline in the number of physically active students in Hong Kong is evident. Furthermore, the situation among adolescents in Hong Kong is worse, given that 96% of them are insufficiently active [46]. Hence, there is a considerable need for this kind of research to arouse public awareness of the link between physical activity and mental health. Although previous studies have reported improvements in the mental health of adolescents after exercise sessions, a lack of follow-up data is available on assessing the sustainability of exercise intervention with moderate intensity over a long duration. In addition, relatively few studies have directly compared the effects of aerobic exercise and HIIT on the mental health of adolescents with low SES. Given that HIIT training has become popular and effective in improving health and well-being, HIIT exercise should be used as the comparison group to examine the effectiveness of traditional aerobic exercise.

Following the health benefits of regular exercise and the limited research on exercise-based interventions (aerobic exercise vs

HIIT) in low-SES adolescents, this study primarily aims to investigate the effectiveness of aerobic exercise and HIIT on the 3 indicators of mental health among low-SES adolescents. This study particularly intends to answer the following two research questions: (1) Is there any change in the 3 indicators of mental health (ie, cognitive function, well-being, and ill-being) before and after exercise? and (2) Which exercise regimen (aerobic exercise or HIIT) is more effective in reducing ill-being and enhancing well-being and cognitive function among adolescents with low SES?

Methods

Overview

Participants will be randomly assigned to an aerobic exercise group, an HIIT group, or a control group. Participants in the first 2 groups will partake in a 10-week training program, conducted 3 times per week on nonconsecutive days. Participants in the control group will participate in other physical activities during the same intervention period.

Study Design

A randomized controlled trial will be used to examine the effects in individuals who are assigned to either a 10-week aerobic exercise training group, a 10-week HIIT training group, or a control group. A total of 78 secondary school adolescents will be recruited for this study. Subsequently, the adolescents will be randomly clustered in a controlled intervention trial. The effectiveness of the intervention will be assessed through a pretest, posttest, and a follow-up design that will be evaluated based on the degree of improvement in performance across the 3 time points. If any important protocol modifications are made, all relevant parties will be informed. These include the trial registry, human research ethics committee, research team members, all participating students and their parents, the journal that publishes the study protocol, and the funding body.

Participants

G*Power [47] was used to estimate the sample size based on analysis of variance (ANOVA) with Cohen f [48] medium effect size set as 0.25 and Cronbach α, as .05. A total of 45 participants are required to achieve sufficient statistical power. Assuming a 20% attrition rate [49] and clustering effect (assumed as 0.01) [50], the principal investigator (PI) will gather a total of 78 participants aged between 12 and 15 years from 3 to 4 secondary schools in Hong Kong. Each group will comprise 33% (26/78) of participants.

We will conduct the study across 3 to 4 secondary schools that will be randomly selected. Students will be invited to participate in the study given that they (1) are aged between 12 and 15 years and (2) belong to a family with a household income below half of the median household income reported in Hong Kong, which is adjusted by household size. These selection criteria are based on a study by Costigan et al [8], which examined the effect of HIIT on cognitive and mental health among adolescents. Participants (1) with hypertension or diabetes mellitus without control; (2) with a history of brain injury and other neurological diseases, epilepsy, or myocardial infarction; (3) with recent musculoskeletal disease; (4) who use medication that affects HR (eg, β-blockers, asthma medications, stimulants, digoxin, and antiarrhythmic agents); or (5) with cardiovascular disease will be excluded from this study. All participants in the exercise groups must complete a Chinese version of the Physical Activity Readiness Questionnaire for a safe preliminary screening before the exercise class [51].

Procedures

After obtaining ethical approval from the institution, the author will contact the principals of the selected secondary schools to seek their permission to recruit participants from the pool of students. A research assistant will obtain informed consent forms and the Physical Activity Readiness Questionnaires from the participating students and their parents. Before the intervention, the students will be asked to complete the baseline assessment for the exercise programs. They will be asked to perform the assessment again after completing the exercise programs. A cluster design will be used for all the participants in the same school to delegate them to the same combination of 2 intervention groups and a control group. The participants will be randomly assigned to 1 of the 3 groups. The trial is designed to simultaneously evaluate the impact of the 2 interventions. Randomization will be performed using computer-generated random numbers by a trained research assistant blinded to the identities of the participants. The research assistant conducting the randomization will not be involved in any data collection. The entire process of data collection and intervention will be conducted by other trained research assistants who are blinded to the participants' group assignments. A follow-up assessment will be conducted 3 months after the exercise program to examine the long-term effects of such an intervention. All assessments will last for 45 minutes. All participants will be given an exercise diary or logbook to keep track of their exercise habits (ie, record the type of exercise or activity, hours, and intensity of exercise or activity every day) throughout this study (Figure 1).

Figure 1. Flow diagram: study design and data collection procedures. HIIT: high-intensity interval training; HR: heart rate.
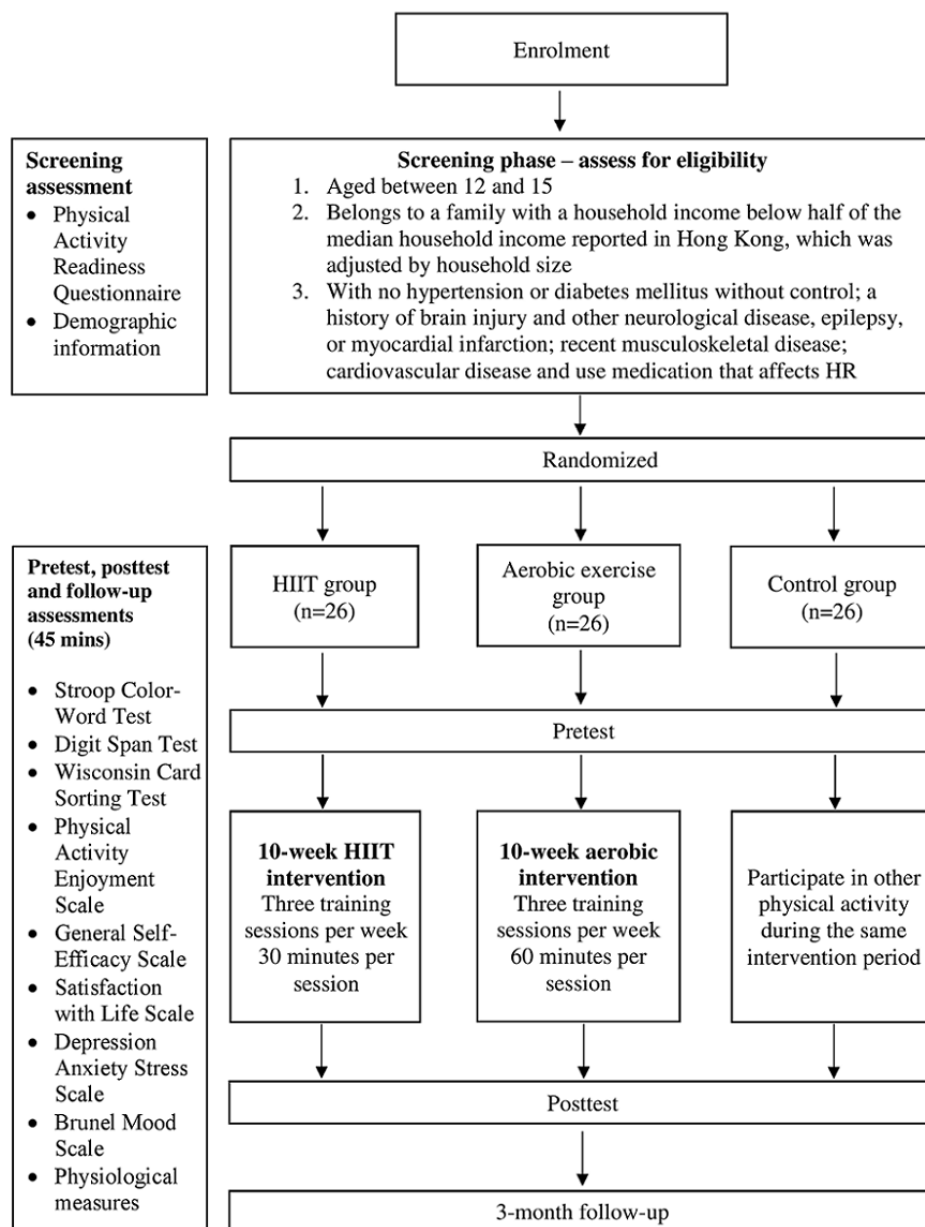
Aerobic Exercise Group

Following the exercise recommendation in the literature review and the study by Ranjbar et al [37], this study will conduct the aerobic exercise classes over a period of 10 weeks. The participants will complete 3 training sessions per week. In addition, each aerobic training program will last for 1 hour. The session will include a 10-minute warm-up period, followed by a 45-minute aerobic workout, wherein the participants can choose to use either a treadmill, a cycle ergometer, or a rowing ergometer. After the workout, a 5-minute period of stretching will be provided for cooling down. The intensity during the workout will be set at 40%-55% of the individual's maximum HR [37].

HIIT Group

The HIIT protocol has been adopted from the studies by Giannaki et al [52] and Wu et al [43] and has been slightly

modified. The intervention will be conducted over a period of 10 weeks, and the participants will complete 3 training sessions per week. Each HIIT training program will last for 30 minutes. The session will include a 10-minute warm-up period, followed by a 15-minute HIIT workout, and a 5-minute period of stretching to cool down. The exercise will include repeated, high-intensity intermittent bursts of vigorous activity at maximal effort. The HIIT will mainly include bodyweight exercises (eg, push-ups, squats, and lunges) that disregard equipment use. The intensity during the workout will be set to 85%-95% of the individual's maximum HR (Textbox 1). The exercise was designed by a registered physiotherapist with more than 10 years of clinical experience. A half-day training workshop will be provided to the personal trainer to ensure that they know the exercise and can demonstrate them to the participants.

Textbox 1. Design of the high-intensity interval training (HIIT) program.

Study design for HIIT

- Start: 10-minute warm-up.

- HIIT program: Every circuit takes 3 minutes 45 seconds.

- Work: 15 seconds.

- Rest: 10 seconds.

- Work: 15 seconds.

- Rest: 20 seconds.

- Work: 15 seconds.

- Rest: 30 seconds.

- Work: 15 seconds.

- Rest: 40 seconds.

- Work: 15 seconds.

- Rest: 50 seconds.

- Repeat 4 circuits.

- End: 5 minutes of stretching.

The *work* period indicates the short-duration, full-effort exercise to boost the heart rate (HR) to 58%-95% or to the maximum HR.

The *rest* period indicates the active recovery with light stepping or *jumping jack* exercise at the effort to achieve 40%-50% of the maximum HR [53].

The HIIT and aerobic exercise groups will be led by a certified personal trainer with at least three years of experience in guiding adolescents in group exercise. In terms of the duration of intervention for the HIIT and aerobic exercise groups, research has shown that approximately 30 minutes is the ideal session length for an HIIT work out with an HR >90% for 3 days per week over a period of 10 weeks. For aerobic exercise, research has revealed that participants who exercise 3 times per week for 45-minute sessions over 10 weeks exhibited improved mental health. By contrast, exercising for >90 minutes per session could lead to poor mental health, which includes physical and mental exhaustion [54]. To prevent symptoms of overreaching (eg, fatigue, mood disturbance, and disrupted sleep), the aforementioned intensity and duration of the exercise will be applied in this study. Aerobic exercise and HIIT training will be conducted in the fitness room of a local sports center hosted by the Leisure and Cultural Services Department in Hong Kong [55].

HR Monitoring

To monitor the intensity of the training during the program, the participants are required to wear HR monitor watches (Polar Electro Oy). The recorded HR data will be uploaded to a computer and will be checked regularly by investigators to determine whether the participants could reach the target HR during the exercise. Furthermore, the length of time (number of minutes and average session duration) when the participant reaches the HR targets will be recorded. The participants will also be encouraged to achieve the target HR during the session. The maximum HR will be calculated according to the age-based formula (220-age). To ensure their safety and manage unexpected situations, a subjective measurement of physical exertion (using Borg scale 6-20) will also be monitored during every training session by an assistant trainer [56].

Promoting Participants' Adherence to Exercise

Given that adolescent girls and boys alike may have difficulty in starting and adhering to a regular exercise program, several approaches will be conducted to promote their adherence to such programs. First, to develop an enjoyable session, fun warm-up and cool-down activities or games will be included, and participants will work with their preferred partner. To create a supportive environment, a reward and peer support system will be incorporated (eg, for pairs who provide verbal encouragement and support their peers and for their hard work during the HIIT sessions). In addition, a certificate will be awarded to recognize the participants who exert outstanding effort and dedication during the workout. Thus, positive feedback and motivation are encouraged among the partners. To promote autonomy, participants will be allowed to choose the music, select particular exercises to be completed during the workout, and choose a workout when the exercise has been mastered [39]. Participants' responses to the intervention and reasons for early withdrawal during the intervention will also be documented in the intervention logs and the content analyzed.

Outcome Measures

The SES data will be obtained from 2 independent sources, namely, self-reported parent questionnaires (including parents' income and education level) and the school-reported government subvention record. Parental education will be assessed based on a 4-point scale, ranging from 1 (*primary school*) to 4 (*master's degree or above*). The family's monthly income will also be measured using a 23-option item with options in Hong Kong Dollar from 1 (*none*) to 23 (HK$ 32,000-$ 33,999; US $4000-$4400).

The low-SES category will be constructed based on the calculation of the income-to-needs ratio, which will be

calculated by dividing the total family income by the poverty threshold for the appropriate family size following the Hong Kong government's calculation. Families living below the poverty line with an income-to-needs ratio between 0 and 1 [57] will be classified as having low SES. The question of whether they have received financial income from several sources, including wages, family members or friends, a CSSA, an old age allowance and other government assistance, pensions, rental income, investment income, and other income will also be asked as supplementary information.

Measures of the 3 Indicators of Mental Health

Cognitive Function

A range of neuropsychological tests from the Millisecond software [58] will be administered to the participants. A computerized battery of neuropsychological tests to measure the 3 core executive functions would include the Stroop Color-Word Test (inhibition), the Digit Span Test (working memory), and the Wisconsin Card Sorting Test (cognitive flexibility). These neuropsychological tests have been proven to be valid and reliable measures of adolescents' cognitive functions in previous research [59]. The author has been using these 3 executive functioning tests to measure adolescents' cognitive functions [60].

Well-Being

Enjoyment

A short Chinese version of the Physical Activity Enjoyment Scale (S-PACES) [61] will be used to measure their enjoyment before and after exercise. The S-PACES includes 7 negatively worded items (eg, "It is not at all interesting") anchored on a 5-point Likert scale that ranges from 1 (*disagree a lot*) to 5 (*agree a lot*). The internal consistency of the S-PACES is high (Cronbach α=.96) [61].

Self-efficacy

A Chinese adaptation of the General Self-Efficacy Scale [62] will be administered to measure the adolescents' self-efficacy. The General Self-Efficacy Scale contains 10 items (eg, "I can constantly manage to solve difficult problems if I try hard enough"), with responses ranging from 1 (*not at all true*) to 4 (*exactly true*). The internal consistency and reliability are 0.76-0.90 and 0.80, respectively.

Life Satisfaction

The Chinese version of the Satisfaction with Life Scale [63] will be used to measure life satisfaction. This scale is a short 5-item (eg, "I am satisfied with my life") scale based on a 7-point rating scale that ranges from 1 (*strongly disagree*) to 7 (*strongly agree*). The Satisfaction with Life Scale has demonstrated a good reliability coefficient of 0.82 [63] and has been used in previous research using Chinese samples (Cronbach α=.84) [64].

Ill-Being

Depression, Anxiety, and Stress

The Chinese version of the 21-item Depression Anxiety Stress Scale [65] will be used to measure depression (eg, "I felt that I

lack something to look forward to"), anxiety (eg, "I felt that I was close to panic"), and stress (eg, "I found it difficult to relax") among adolescents. The respondents will be asked to rate the items using a 4-point combined severity-frequency scale that ranges from 0 (*not applicable to me at all*) to 3 (*extremely applicable to me*) based on their experiences related to each item over the past week. The Cronbach α for the depression, anxiety, and stress subscales is .83, .80, and .82, respectively, which indicates good reliability. The 21-item Depression Anxiety Stress Scale has been used in a previous study involving a Chinese sample [66].

Mood

The Chinese version of the Brunel Mood Scale [67] will be created based on the study by Terry et al [68] to assess the mood among Chinese students and adults. The Chinese version of the Brunel Mood Scale is a 23-item inventory with the following 5 negative mood dimensions: anger, confusion, depression, fatigue, and tension. Respondents will be asked to indicate their feelings (eg, angry, unhappy, or nervous) using a 5-point Likert scale that ranges from 0 (*not at all*) to 4 (*extremely*). All subscales have achieved good internal consistency and reliability (Cronbach α=.74-.85).

Physiological Outcome Measures

The physical health outcomes survey will include measures of blood pressure (BP), resting HR, body weight (BW), height, waist circumference (WC), and hip circumference (HC). BP will be measured using an automated BP monitoring device. The participants will be given a 10-minute rest before the measurement. The BP will be measured twice, with a 1-minute interval between the readings. Additional readings will be obtained if the BP measurements differ by >5 mmHg. The mean of the 3 consecutive readings will be used as the examination value. The resting HR will be measured through a wireless HR monitor that will be worn by the participants (Polar Electro Oy) for 1 minute after their 10-minute rest. BW and height will be measured using an electronic digital scale and a stadiometer, respectively. BMI will be calculated by dividing BW (kg) by height (m^2). The WC and HC measurements will be adopted from the study by Bacopoulou et al [69]. The WC and HC will be measured twice using an anthropometric tape while the adolescents stand erect and relaxed with their arms at their sides and feet positioned close together. The WC will be measured between the upper border of the iliac crest and the lowest border of the rib cage at the end of normal expiration. The HC will be measured at the widest part of the hip at the level of the greatest trochanter. For all the measurements, the tape will be positioned at a level that is parallel to the floor. Furthermore, the unit of measure will be in centimeters to the nearest 0.1 centimeter. The waist-to-hip ratio will be calculated as the ratio of the waist-to-hip circumference. All physical data will be recorded in the resting state at the baseline each week and at the end of training. The measurement for the physical health outcome assessment will be performed by a trained research assistant.

Data Analysis

Interim analysis will not be performed, and data analysis will only begin after the follow-up stage. The PI and trained research

assistants will have access to the final trial data set. Data will be analyzed using SPSS version 26. A missing value analysis procedure will be conducted to detect the missing values in the data file. The demographic characteristics of the participants will be investigated using the chi-square test for independence (for nominal variables) and 1-way ANOVA (for continuous variables). A Bonferroni post hoc test will subsequently be conducted for group comparisons. To examine the changes between and within groups for each outcome measure (ie, self-efficacy, mood, enjoyment, working memory, cognitive flexibility, inhibition, depression, anxiety, and stress), a 3 (before intervention vs after intervention vs follow-up) × 3 (aerobic exercise vs HIIT vs control) repeated-measure ANOVA will be conducted. A post hoc analysis will be used to confirm whether significant differences for any of the outcome variables exist among the groups. The Bonferroni method will be used to adjust the *P* values.

Declarations

All of the study procedures have been examined and approved by the Human Research Ethics Committee of the Education University of Hong Kong (reference number: A2019-2020-0167). Before the commencement of the study, oral assent will be obtained from the participating students and written informed consent, from their parents by a trained research assistant. A 6-digit number will be assigned to each participant and marked on all assessments to enable identity linkage among the pretest, posttest, and follow-up assessments. All the information obtained will be handled only by the PI and trained research assistants for research purposes. All data will be kept strictly confidential and will be identifiable by codes known only to the researchers. The signed consent forms and completed questionnaires will be stored separately. Entered data will be stored on a password-protected computer, whereas original, anonymized hard copies of the questionnaires will be stored in a locked office at the Education University of Hong Kong for 5 years after publication.

Results

This study was funded in 2021 by the Research Matching Grant Scheme through the University Grants Committee of the Hong

Kong Special Administrative Region Government. Ethical approval has been sought from the Human Research Ethics Committee of the Education University of Hong Kong. Study enrollment has been delayed owing to the COVID-19 pandemic. Participant recruitment will begin in January 2022 and continue through to April 2022. Data collection and follow-up are expected to be completed by the end of 2022. The results are expected to be submitted for publication in 2023. Knowledge exchange seminars and workshops will be held at the participating schools and the author's institution. The research findings will be presented at local and international conferences for large-scale public dissemination. The results of this study will be published in significant journals. The full protocol, participant-level data set, and statistical code will be made publicly available after the completion of the study.

Discussion

This project aims to examine whether aerobic exercise and HIIT can improve cognitive functions and well-being (eg, enjoyment) and reduce ill-being (eg, negative affect) among adolescents with low SES. Measures of subjective well-being indicators can be beneficial in examining the need for certain policies and measuring the outcomes of policy interventions. The positive findings of this study may yield a low-cost and effective intervention that enhances the overall mental health of adolescents, particularly of those living in low-income families. Despite these strengths, there are some limitations that must be considered in this study. It is anticipated that only participants with a high level of interest and motivation will enroll in exercise training. The study could be discontinued because of the current COVID-19 pandemic situation and some participants may drop out. To ensure adequate statistical power to detect statistical significance, a 20% dropout rate will be taken into account when estimating the initial sample size before the intervention. In summary, this study demonstrates the important role of regular exercise—during or after school—on the mental health of adolescents. Ultimately, we believe that such efforts will inspire policy makers to realize the benefits of physical activities at school and the importance of enabling students to integrate physical exercise into their lives.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by The Education University of Hong Kong-Committee on Research and Development.
[PDF File (Adobe PDF File), 312 KB - resprot_v11i1e34915_app1.pdf]

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Abbreviations

ANOVA: analysis of variance
BP: blood pressure
BW: body weight
CBT: cognitive behavioral therapy
CSSA: Comprehensive Social Security Assistance
DBT: dialectical behavior therapy
HC: hip circumference
HIIT: high-intensity interval training

HR: heart rate
PI: principal investigator
SES: socioeconomic status
S-PACES: Physical Activity Enjoyment Scale
WC: waist circumference

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Protocol

Connectivity-Guided Theta Burst Transcranial Magnetic Stimulation Versus Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Moderate to Severe Depression: Magnetic Resonance Imaging Protocol and SARS-CoV-2–Induced Changes for a Randomized Double-blind Controlled Trial

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Abstract

Background: Depression is a substantial health and economic burden. In approximately one-third of patients, depression is resistant to first-line treatment; therefore, it is essential to find alternative treatments. Transcranial magnetic stimulation (TMS) is a neuromodulatory treatment involving the application of magnetic pulses to the brain that is approved in the United Kingdom and the United States in treatment-resistant depression. This trial aims to compare the clinical effectiveness, cost-effectiveness, and mechanism of action of standard treatment repetitive TMS (rTMS) targeted at the F3 electroencephalogram site with a newer treatment—a type of TMS called theta burst stimulation (TBS) targeted based on measures of functional brain connectivity. This protocol outlines brain imaging acquisition and analysis for the Brain Imaging Guided Transcranial Magnetic Stimulation in

Depression (BRIGhTMIND) study trial that is used to create personalized TMS targets and answer the proposed mechanistic hypotheses.

Objective: The aims of the imaging arm of the BRIGhTMIND study are to identify functional and neurochemical brain signatures indexing the treatment mechanisms of rTMS and connectivity-guided intermittent theta burst TMS and to identify imaging-based markers predicting response to treatment.

Methods: The study is a randomized double-blind controlled trial with 1:1 allocation to either 20 sessions of TBS or standard rTMS. Multimodal magnetic resonance imaging (MRI) is acquired for each participant at baseline (before TMS treatment) with T1-weighted and task-free functional MRI during rest used to estimate TMS targets. For participants enrolled in the mechanistic substudy, additional diffusion-weighted sequences are acquired at baseline and at posttreatment follow-up 16 weeks after treatment randomization. Core data sets of T1-weighted and task-free functional MRI during rest are acquired for all participants and are used to estimate TMS targets. Additional sequences of arterial spin labeling, magnetic resonance spectroscopy, and diffusion-weighted images are acquired depending on the recruitment site for mechanistic evaluation. Standard rTMS treatment is targeted at the F3 electrode site over the left dorsolateral prefrontal cortex, whereas TBS treatment is guided using the coordinate of peak effective connectivity from the right anterior insula to the left dorsolateral prefrontal cortex. Both treatment targets benefit from the level of MRI guidance, but only TBS is provided with precision targeting based on functional brain connectivity.

Results: Recruitment began in January 2019 and is ongoing. Data collection is expected to continue until January 2023.

Conclusions: This trial will determine the impact of precision MRI guidance on rTMS treatment and assess the neural mechanisms underlying this treatment in treatment-resistant depressed patients.

Trial Registration: ISRCTN Registry ISRCTN19674644; https://www.isrctn.com/ISRCTN19674644

International Registered Report Identifier (IRRID):   DERR1-10.2196/31925

Introduction

Background

Major depressive disorder is the most disabling health condition in terms of years lived with disability [1] and has a life prevalence of approximately 13% of the general population [2]. Although antidepressants and psychotherapy are effective treatments for major depressive disorder, a number of patients do not respond to trials with ≥2 antidepressants [3,4]. These patients are categorized as patients with *treatment-resistant depression* (TRD), which is associated with increased rates of suicide, hospitalization, poor physical health, and increased health care costs [5].

Neuromodulation in TRD by means of transcranial magnetic stimulation (TMS) is cost-effective in comparison with standard care [6]. This approach attempts to directly modulate localized brain activity, by using an electromagnetic coil to target magnetic pulses to a specific region that in turn induce an electric current. Depending on the pattern of stimulation, this stimulation can modulate brain activity in either an excitatory or inhibitory manner [7]. The therapeutically desired activity modulation of specific brain regions also requires precise localization of the stimulation and understanding of its networks especially where the therapeutic target cannot be directly stimulated. It is also important to ensure that the selected brain region for stimulation is being stimulated by correctly determining its skull projections. This is currently done by using tape measures or electroencephalography caps. However, these measurements are prone to human error or differences in cap placement between sessions. Importantly, the variability in brain and skull anatomy of a population means that such

one-size-fits-all targeting approaches are not appropriate in the context of precision neuromodulation. In addition to such anatomical variation, advances in brain connectomics highlight substantial interindividual variability of functional brain networks that is expected to have a direct impact of network-mediated downstream effects from superficial TMS. There is also a potential for target misalignment across multiple treatment sessions. Therefore, it is important to find alternative procedures to TMS treatment target estimation that are reproducible and to also consider precision-based approaches.

Neuroimaging studies in depression have consistently demonstrated altered connectivity within, and between, canonical resting-state networks, such as the default mode, salience, and central executive networks, adding to our current understanding of the dysfunctional brain circuitry involved [8-11]. Importantly, the dorsolateral prefrontal cortex (DLPFC) and insula influence each other in a reciprocal fashion and are key hubs of the central executive and salience networks, respectively, meaning that dysfunction of such a loop would have greater effects on the networks. The United States Food and Drug Administration and National Institute of Health and Clinical Excellence approved TMS treatments in TRD target the left DLPFC, which likely exerts its treatment effect by modulating these deeper, connected brain regions and networks [12,13]. Importantly, to take into account the known interindividual variability in the tissue cytoarchitecture [14], and more pertinently, the functional connectivity (FC) of the DLPFC [15], individualized TMS targeting may be important for the efficacious delivery of treatment [13,16]. In addition, studies have shown that FC of the DLPFC can predict the clinical efficacy of TMS [13,17], that reproducible individual

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TMS targets can be created [16], and that treatment using this individualized targeting can improve the response rate above those reported in a recent meta-analysis of repetitive TMS (rTMS) treatments from approximately 45% to 50% to approximately 64% [18,19]. Recent studies provide further evidence of the strength of personalized TMS treatment targeting, with one nonrandomized trial observing an 86% remission rate in response to personalized and accelerated intermittent theta burst stimulation (TBS) treatment [20]. Further support for the importance of personalized neuromodulation comes from a small randomized controlled trial that shows improved efficacy the nearer the standard rTMS target was to an in silico determined connectivity-based personalized target [21]. In addition to creating personalized treatment targets for TMS, the use of neuroimaging in longitudinal studies of TMS provides an opportunity to both mechanistically evaluate the treatment effect on the intended treatment targets and to assess response prediction. A recent large-scale imaging study collated >1000 depressed participants' resting-state functional magnetic resonance imaging (rsfMRI) and using a data-driven canonical correlation analysis reported a biotype characterized by the connectivity between the insula and other brain regions that significantly predicted treatment response to TMS and was a stronger predictor of response than clinical measures alone [17]. Smaller studies have also provided evidence that baseline FC with the DLPFC can predict clinical efficacy [13,18]. Although there is growing evidence that brain connectivity patterns can predict treatment response, inconsistencies in the data demonstrate a clear need for further prospective investigation in a large, well-characterized sample.

The Brain Imaging Guided Transcranial Magnetic Stimulation in Depression (BRIGhTMIND) study [22] is a randomized, double-blind controlled trial comparing the cost-effectiveness, efficacy, and mechanistic effects of 2 neuromodulation approaches in TRD—standard the US Food and Drug Administration–approved rTMS [23] and connectivity-guided intermittent theta burst TMS (cgiTBS). Theta burst TMS corresponds to an alternative patterned form of standard rTMS that uses high (gamma) frequency pulses, repeating at lower (theta) frequency intervals. In this study, both standard rTMS and cgiTBS treatment locations on the head are determined in a repeatable and personalized manner based on magnetic resonance imaging (MRI) images obtained. However, the standard rTMS location is based only on the overall shape of the head, whereas the cgiTBS location is determined by the head shape, brain anatomy, and FC profile of the participant. Each participant is randomized at the first TMS session to either 20 sessions of rTMS or 20 sessions of cgiTBS performed daily for 4 to 6 weeks. Clinical and economic outcomes, including the primary outcome measure—the 17-item Hamilton Depression Rating Scale (HDRS-17) [24], are assessed by blinded research assessors at baseline, 8 weeks, 16 weeks, and 26 weeks. Clinical data are analyzed on an intention-to-treat basis. Further details of the clinical protocol have been published [22] and can be found in the clinical trials register (ISRCTN19674644). This paper describes the SARS-CoV-2–related changes to the study, including revised recruitment target, outcome measure and power calculation, MRI protocol, TMS target generation, interim baseline analyses, and mechanistic imaging outcomes for the BRIGhTMIND study.

Primary Objectives

The objectives of the imaging arm of the BRIGhTMIND study are to identify functional and neurochemical brain signatures indexing the treatment mechanisms of rTMS and cgiTBS and to identify imaging-based markers predicting response to treatment.

Primary Hypotheses for Mechanistic Imaging Study

The primary hypotheses for the mechanistic imaging study are as follows:

1. Treatment response, as measured using change in the HDRS-17, will correlate with posttreatment changes in DLPFC-dorsomedial prefrontal cortex (DMPFC) FC at 16 weeks.
2. Treatment response (HDRS-17) to TMS treatment can be predicted using baseline insula-DLPFC effective connectivity.
3. Connectivity-guided intermittent TBS treatment-related γ-aminobutyric acid (GABA) changes will be correlated with a reduction in HDRS-17 at 16 weeks.

Exploratory Aims for the Mechanistic Imaging Study

The exploratory aims for the mechanistic imaging study are as follows:

1. To identify imaging-based biotypes that predict treatment response in TRD patients
2. To further study the neural mechanisms underlying therapeutic efficacy by assessing interrelations of changes in complex brain network metrics with improvement of clinical symptoms
3. To determine the distance between the applied rTMS and TBS treatment targets with an in silico subgenual anterior cingulate cortex (sgACC) seeded DLPFC target, and its association with therapeutic efficacy (change in HDRS-17 at 16 weeks)

Interim Analyses of Baseline Data

Analysis of baseline MRI and clinical data will explore seven themes that will support and boost both the impact and inference of the main study outcomes. These themes are (1) treatment resistance, (2) comorbid anxiety, (3) cognitive impairment, (4) trauma, (5) medication and other confounds, (6) interlinking analyses, and (7) model building. Themes 1-5 will be driven by the testing of distinct hypotheses based on previous knowledge and literature. Themes 6 and 7 are exploratory as they are provided to allow expansion of the proposed analyses into further tests in different MRI modalities and measures, and to use any resulting findings from all the above themes into building a model-based brain signature of TRD. Given the limited literature published on TRD and the rich data set available from the BRIGhTMIND study, it is important that there is room to carry out both hypothesis-driven and exploratory analyses. All baseline analyses will remain blinded to treatment allocation (cgiTBS or rTMS) and trial outcomes (responder or nonresponder) until after the final database lock. The specifics

of these planned analyses can be found in the study by Cottam et al [25].

Methods

Ethics Approval

Ethical approval was granted by East Midlands Leicester Central Research Ethics Committee (ref: 18/EM/0232) on 30 August 2018.

Recruitment and Imaging Sites

In the initial setting, there will be 4 recruitment sites from across the United Kingdom National Health Services (NHS) (Nottinghamshire Healthcare Foundation NHS Trust, Nottingham; Northamptonshire Healthcare NHS Foundation Trust, Northampton; Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust, Newcastle; and Camden and Islington NHS Foundation Trust, London), which will deliver the TMS treatments locally. However, only 3 sites will perform imaging, as all Northampton participants will be scanned at the Nottingham site. The possibility of incorporating additional sites (either for recruitment and scanning or for recruitment only) will be kept open throughout the course of the BRIGhTMIND study and will be evaluated case by case, based on achieved recruitment. However, Northampton did not reopen to recruitment in August 2020 and was informed of the decision to close the site in December 2020 owing to low recruitment numbers. A new site is being opened in Oldham (Pennine-Care NHS Foundation Trust) in the summer of 2021 to increase recruitment. Both scanning and TMS treatments will be delivered locally at the Oldham site.

MRI Acquisition

MRI scans are acquired at 2 time points. First, a baseline scan is acquired within 14 days of the baseline assessment, after which treatment randomization occurs. Allocated TMS treatment is then initiated within 14 days of the MRI scan. The second MRI scan is acquired within 14 days of the 16 weeks follow-up assessment [22]. Both MRI scans will be carried out at the same site and using the same scanner platform, with the same list of images acquired at each time point.

The participants will undergo multimodal MRI at 3T. We will acquire a core protocol across all treatment sites consisting of a structural T1-weighted scan and an eyes-open blood oxygenation level dependent (BOLD) echo-planar imaging (EPI) rsfMRI scan with additional positive and negative phase-encoded images to enable distortion correction. For the mechanistic substudy, all sites will also acquire a diffusion-weighted scan (with an additional negative phase-encoded B0 image for distortion correction), whereas 2 sites (Nottingham and Northampton) will also acquire an arterial spin labeling (ASL) scan, and 3 sites (Nottingham, Newcastle, and Northampton) will acquire a Meshcher-Garwood Point Resolved Spectroscopy (MEGA-PRESS) magnetic resonance spectroscopy (MRS) scan. General descriptions of the scanning sequences are delineated in the next paragraph, with further

details available in Multimedia Appendix 1. A total of six scanners are used within the BRIGhTMIND study, and the details are as follows: Newcastle—Achieva dStream (Philips); London—Prisma (Siemens); Oldham—Achieva (Philips); Nottingham and Northampton will use the following three scanners (sequentially) over the course of the trial owing to a scanner upgrade carried out midtrial: (1) Discovery MR750 (GE Healthcare); (2) Ingenia (Philips); and (3) Premier (GE Healthcare). All sites are instructed to use 32-channel head coils for the study, and a 48-channel head coil will be used at the GE Healthcare Premier.

High-resolution T1-weighted images will be acquired using sagittal fast-spoiled gradient echo BRAVO (or equivalent) sequences with 1 mm^3 isotropic voxels covering the whole head from the vertex to the neck. rsfMRI images will be acquired with the eyes open using a fixation cross. All sites are instructed to use a gradient echo EPI sequence aligned with the anterior commissure-posterior commissure line, with acquisition covering from the vertex downward (repetition time [TR]/echo time [TE]=2000/32 ms; flip angle=77°; 35 slices; voxel size=3 mm^3; slice gap=0.5 mm; field of view=192×192 mm; interleaved bottom/up; 240 volumes; phase encoding direction=posterior>anterior). All rsfMRI images will have associated forward- and reverse-phase-encoded B0 images acquired to facilitate distortion correction. Importantly, these images will be acquired with the same image dimensions as the rsfMRI and will be acquired directly before the rsfMRI. Diffusion-weighted images will be acquired and aligned with the anterior commissure-posterior commissure line, with coverage beginning at the vertex and extending inferiorly (TR/TE=11,000/minimum ms; flip angle=90°; 55 slices; voxel size=2 mm^3; field of view=220×220 mm; 64 directions [B=1000]; 5 B0 images; phase encoding direction=anterior>posterior; sense factor=0). In addition, a reverse phase-encoded B0 image (posterior>anterior) will also be collected with all other parameters and coverage matched with the diffusion-weighted image acquisition to enable distortion correction. ASL on the Discovery MR750 (GE Healthcare) will be carried out using the vendor-supplied 3D-pseudocontinuous ASL sequence with whole-head coverage, and the participants will be instructed to keep their eyes open (TR/TE=4632/10.5 ms; inversion time [TI]=2025 ms; flip angle=111°; 36 axial slices; voxel size=1.875×1.875×4 mm; field of view=240×240 mm). Further ASL sequences on the Ingenia (Philips) and Premier (GE Healthcare) will be set up to replicate the original acquisition (see Multimedia Appendix 1 for details). MRS will be acquired via a voxel in the left DLPFC, which is placed to the best match as shown in Figure 1. The acquisition at both the Newcastle and Nottingham scan sites will be a MEGA-PRESS GABA editing sequence (voxel dimensions are 45×30×20 mm for anterior/posterior [A/P], left/right [L/R], inferior/superior [I/S] directions, respectively; TR/TE=2000/68 ms; 320 averages) acquired using the schema described by Mikelsen et al [26].

Figure 1. An example of the dorsolateral prefrontal cortex magnetic resonance spectroscopy voxel placement. A: anterior; L: left; P: posterior; R: right.
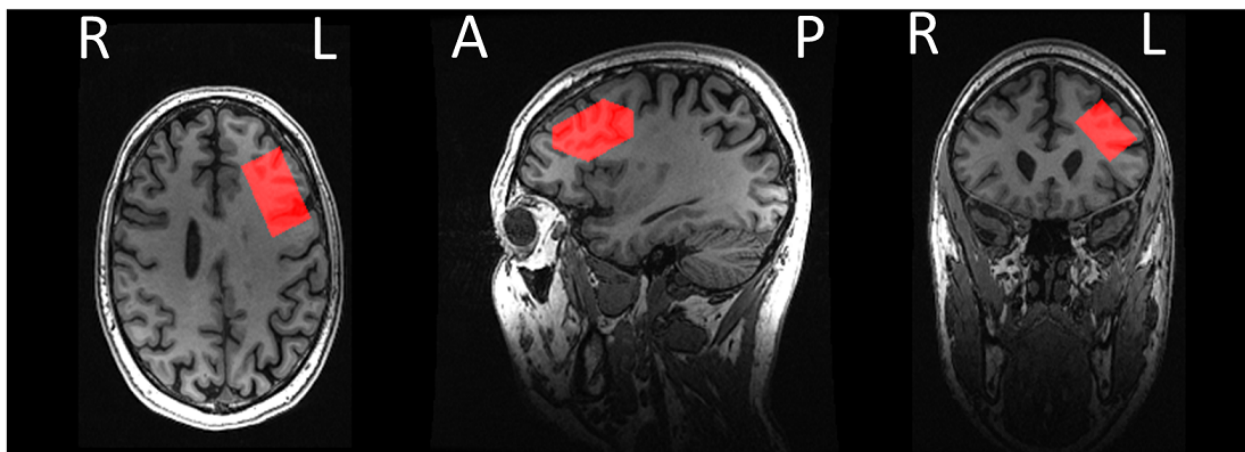
Image Archiving and Quality Control

Subject digital imaging and communications in medicine (DICOM) session files are uploaded onto an XNAT (Washington University School of Medicine) [27] database infrastructure for all data other than MRS data using anonymized subject numbers. Once the session is archived within XNAT, it is put into a quarantined state awaiting quality control (QC), and DICOM files are automatically converted into Brain Imaging Data Structure [28] NIFTI or JSON pairs for each scan using the dcm2bids-session v1.5 XNAT container, with T1-weighted images also undergoing defacing within this step. Defacing consists of the registration and application of a mask that removes the lower portion of the nose and the mouth and jaw to the T1-weighted image. Thus, allowing the nasion and ears to be used for TMS target generation. Then, the T1-weighted and BOLD rsfMRI scans are manually assessed using the MRIQC v0.11.0 [29] QC XNAT container. If both the T1-weighted and BOLD images within a session pass QC, then the session is removed from the quarantined state. T1-weighted image reports from MRIQC are assessed for and judged to pass QC if there is full head coverage and no visual artifacts or incidental findings. BOLD data MRIQC reports are checked for frame-wise displacements larger than 3 mm, average frame-wise displacement over 1 mm, image artifacts, or long-lasting intensity changes owing to motion in the carpet plot. If any of these are present, then the BOLD image fails QC. Note that only nonquarantined data are subsequently downloaded from the XNAT database for preprocessing and further analysis.

The MRS data are handled differently from the rest of the imaging data, as it is uploaded separately onto XNAT for participants whose structural T1-weighted and rsfMRI data have passed QC only. The QC for MRS data is carried out during preprocessing and is described later in this paper.

T1-Weighted and BOLD Image Preprocessing

Both structural T1-weighted and BOLD rsfMRI data are preprocessed with the SPMIC-BRC pipeline v1.2.6 [30,31]. This pipeline is based on tools from the following packages: Statistical Parametric Mapping v12 (SPM12 [32]), FMRIB Software Library (FSL) v5.0.11 [33], and Freesurfer v6 [34].

Structural T1-weighted images are first coarsely brain extracted using the FSL brain extraction tool (BET) [35] and their field of view is reduced by removing the lower head and neck using FSL *robustfov*. The original and brain extracted images are then nonlinearly registered to the MNI152 1-mm template [36] using FSL FMRIB's nonlinear image registration tool (FNIRT). The original FSL BET brain extraction is then refined by applying the produced nonlinear transformation to warp the MNI152 brain mask onto the subject's T1 image [37-39]. The resulting brain extracted image is finally bias-corrected and segmented into gray matter, cerebrospinal fluid (CSF), and white matter (WM) using FSL FMRIB Automated Segmentation Tool (FAST) [40]. The resulting WM and CSF probability maps are binarized at a tissue-probability threshold of 98% and then eroded using a spherical kernel with a radius of 2 voxels.

The BOLD rsfMRI images undergo EPI distortion correction by inputting the positive and negative phase-encoded acquisitions into TOPUP [41]. Then, they undergo between-volume motion correction (MCFLIRT 6DoF) and SPM12 interleaved slice-timing correction (bottom-up) [38]. The corrected BOLD image is subsequently smoothed with a 5 mm full-width half-maximum kernel using Smallest Univalue Segment Assimilating Nucleus (SUSAN) [42] and denoised with ICA-AROMA [43]. BOLD images are high-pass filtered at a frequency of 0.01 Hz after denoising. A transformation between the resulting BOLD image and the T1-weighted image is later computed using FSL *epi_reg*, and then combined with the TOPUP spatial distortion correction transformation. The resulting combined transformation is then inverted to create a nonlinear transformation from the T1-weighted to (original uncorrected) BOLD space. The previously computed binary WM and CSF masks are later warped into BOLD space using the T1-weighted to BOLD transformation to extract the WM and CSF time series from the BOLD data. To control for additional physiological or scanner-related noise, the WM and CSF time series are then regressed out of the rsfMRI time series.

Although the above pipeline will remain locked during the trial for the calculation of TMS target coordinates, any analyses carried out for final publication will seek to use further developed state-of-the-art pipelines to make the best use of the

data at the time. Thus, later versions of software or new tools may be incorporated into this pipeline and those detailed below.

MRS Preprocessing

MRS Processing

The MRS data will be processed using an in-house routine developed in MATLAB (MathWorks Inc) before metabolite quantification. All routines used will be made available to other researchers at the end of the trial via GitHub.

The GE Healthcare (P-file) MRS data will be coil-combined using the phase and maximum amplitude of the acquired unsuppressed water reference. Philips (.sdat or .spar) data are already coil-combined by the vendor software. Data will be split into 160 OFF and 160 ON spectra and eddy current corrected using the internal water reference. To minimize artifacts caused by subject motion or frequency drift, each spectrum will be frequency-and phase-corrected to the mean OFF spectrum using spectral registration [44,45]. Spectra with mean square error >3 SDs over the choline peak are automatically rejected as outliers [44,45]. The aligned ON and OFF spectra will subsequently be averaged to the 1 ON and 1 OFF spectra. The ON and OFF spectra will be aligned and subtracted to create the ON-OFF (difference) spectrum.

Metabolite Quantification

Unedited OFF spectra will be analyzed between 0.2 ppm and 4.0 ppm with linear combination model (LCModel; version 6.3-1H) [46,47]. Sequence-specific basis sets will be generated for each implementation of MEGA-PRESS in the study using density matrix simulations considering interpulse timings and radiofrequency pulses [48]. The OFF spectra will be used to quantify total *N*-acetylaspartate (tNAA=NAA+*N*-acetyl aspartylglutamate), total creatine (tCr=Cr+phosphocreatine), total choline (tCho=glycerophosphoryl choline+phosphorylcholine), mIns (*myo*-inositol), Glx (glutamate and glutamine), and taurine (Tau) levels. The edited ON-OFF MEGA-PRESS spectra will be analyzed in the range of 0.2-4 ppm with LCModel, using sequence-specific basis sets simulated using the same techniques as outlined for the OFF spectra.

Metabolite concentration values will be reported as ratios relative to tCr and Glx. In addition, water-scaled values, relative to the unsuppressed water signal, will be reported. For the latter, corresponding structural T1-weighted images will be segmented via SPM12 [49] into gray matter, WM, and CSF and aligned with the MRS volume using an in-house software. Water-scaled metabolite values will be corrected for partial volume effects and T1/T2 relaxation in accordance with the procedure by Gasparovic et al [50].

Initial QC criteria will be applied to reject data based on the raw spectral linewidth of the unsuppressed water<13 Hz [51] and also the signal-to-noise ratio of OFF spectra 3 SD below the mean for the study in line with recent consensus recommendations. The spectra will also be visually inspected for lipid, macromolecule, and subtraction artifacts by an MRS expert.

Identification of TMS Targets

cgiTBS Treatment Target

Once the BOLD rsfMRI sequence is preprocessed, an independent component analysis is performed on its volumes using MELODIC v3.15 [52]. The resulting z-scored components are filtered by zeroing values <1.96, and the component most correlated with a left central executive network (lCEN) Z-score map (derived from the lCEN network shared by Smith et al [53]; [component 13/20] thresholded at Z-score >1.96, and then manually masked to include only the cluster in the frontal gyri) is found. This most correlated component is subsequently masked with a left middle frontal gyrus (lMFG) region of interest (derived from the middle frontal gyrus from the Harvard-Oxford cortical atlas [54-57] thresholded at >35% probability to exclude the precentral gyrus, and secondarily masked to exclude voxels in the precentral gyrus and right hemisphere). Both the lCEN map and lMFG mask in the BOLD space are computed from the MNI152 space using a warp, which is the result of concatenating the MNI152 to T1-weighted and the T1-weighted to BOLD space transformations. Preprocessed BOLD images that have been previously fed into MELODIC are then fed into a bivariate first-order coefficient-based voxel-wise Granger causality analysis (GCA) using the rsfMRI Data Analysis Toolkit v1.8 toolbox [58] in MATLAB 2014a. GCA is used to compute the effective connectivity from the right anterior insula (rAI; 6-mm sphere centered on MNI voxel coordinates x=30, y=24, z=−14 from McGrath et al [59]) to the area within the MFG region of interest defined previously, as described by Iwabuchi et al [18]. Specifically, only the X-Y (rAI to lCEN) output is used to find the connectivity peak. The rAI mask in the BOLD space is computed in the same manner as the lCEN and lMFG masks. Finally, the cgiTBS brain target is defined as the peak of the most significant Z-score GCA cluster.

rTMS Treatment Target

The rTMS brain target is determined by taking the scalp F3 voxel coordinate in the MNI152 space defined in Tsuzuki et al [60] (x=−49.0, y=51.0 mm, z=40.0 mm) and computing the voxel in the brain parenchyma that is closest to it (ie, x=−41.0, y=43.0 mm, z=32.0 mm). This brain voxel is then nonlinearly projected into BOLD space by using a combination of the MNI152 to T1-weighted and T1-weighted to BOLD transformations.

Target Generation

To ensure that TMS treatment is administered as close as possible to the brain target point (computed as either a cgiTBS or rTMS target), the scalp projection and angulation of the TMS wand is computed. The MNI152 brain mask is first transformed into the subject T1-weighted space and then all the background voxels in the T1-weighted image are set to zero. Background voxels are considered to be voxels that are outside the transformed brain mask or have an intensity value below a certain threshold set by visual inspection. A 3D mesh model of the head is then created using Freesurfer *mkheadsurf* script with the processed T1-weighted image (converted into Freesurfer MGZ format) as input and 100 smoothing steps, and then

transformed into T1-weighted space using the *tkr2scanner* transformation matrix of the MGZ file. Note that, as the lower head and neck are previously removed from the T1-weighted

image, the resulting head model does not include enough facial features (such as the lips or chin) to uniquely identify the participant. Therefore, their anonymity is preserved (Figure 2).

Figure 2. An example of a generated head mesh.
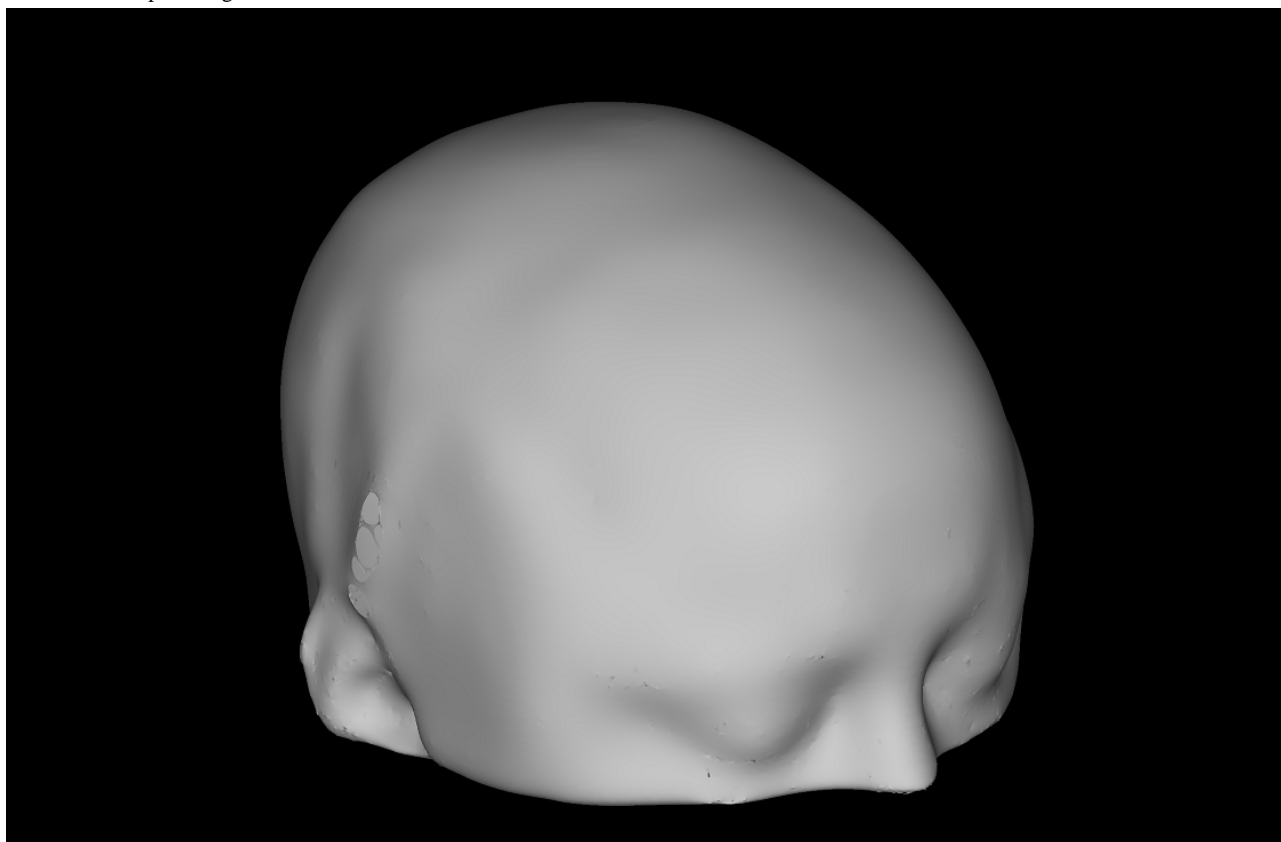
In the following stage, the nasion and both the left and right preauricular coordinates are manually annotated on the T1-weighted image. Then, the nasion and preauricular points on the head 3D mesh are defined as the vertices closest to the manually determined coordinates. This allows the construction of a nasion-left-right (NLR) coordinate system for the head mesh model, which is measured using the same units as the T1-weighted space (ie, mm). The idea behind the use of this coordinate system is that it is invariant to head positioning. The origin of the NLR coordinate system lies on the intersection between the line that passes through both preauricular points and the perpendicular line that passes through the nasion. The x-axis points toward the nasion, the y-axis points toward the left preauricular point, and the z-axis points toward the top of the head (Figure 3A). In order to convert coordinates in T1-weighted space into NLR space, the coordinates of the NLR origin in T1-weighted space are computed and the coordinates of the origin, nasion and preauricular points in NLR space are subsequently calculated as follows:

Here, correspond to the coordinates of landmark *L* in *S* space, and $\| \cdot \|$ is the L2 vector norm. Finally, given the 2 sets of 4 points, the optimal rigid transformation that maps T1-weighted space points into their NLR coordinates is computed using a Least-Squares approach [19,61]. This rigid transformation is then used to transform the cgiTBS and rTMS brain targets into NLR space. The treatment targets in the head mesh are then computed as the mesh point closest to its corresponding brain target. Finally, to determine the angulation of the TMS treatment coil, a coil coordinate system is created. In this coordinate system, the x-axis points toward the right of the wand, the y-axis points toward the front and the z-axis points upward (Figure 3B). The wand positioning must be such that the z-axis of the coil is normal to the head mesh at the target mesh vertex, and the projection of the y-axis of the coil onto the NLR xy-plane must form a 45° angle with the midsagittal plane (ie, the NLR x-axis), as depicted in Figure 4. Finally, to compute the rotation matrix that transforms coil coordinates into NLR coordinates, a procedure analogous to the one that transforms T1-weighted space coordinates into NLR coordinates is followed.

Figure 3. Nasion-left-right coordinate system (a) and coil coordinate system (b).
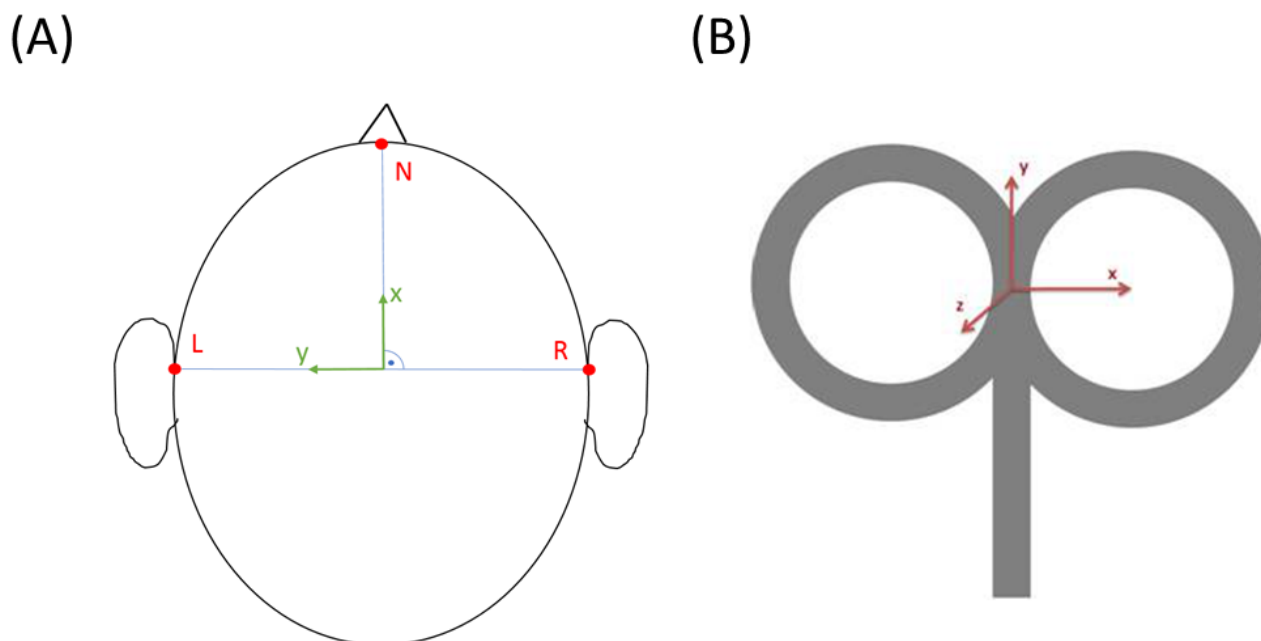
Figure 4. Transcranial magnetic stimulation wand positioning rule with respect to the nasion-left-right (NLR) coordinate system. The z-axis of the coil (in red) should be normal to the treatment target on the head mesh. The projection (in orange) of the y-axis of the coil (in green) into the NLR xy-plane forms a 45° angle with the midsagittal plane (NLR x-axis).
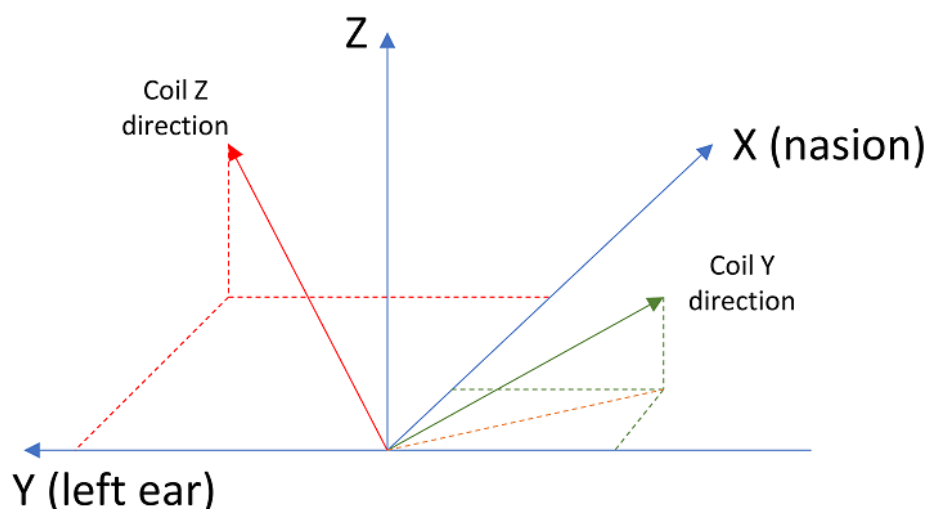
Treatment delivery on the BRIGhTMIND study will be performed using a 70-mm figure-of-eight coil (Ez Cool coil) and a Magstim Horizon Performance Stimulator with StimGuide Navigated TMS Package (Magstim Company). Therefore, the final step in the process is to generate a StimGuide compatible file with the computed treatment targets and rotation matrices in quaternion form [62]. The last QC step before sharing these calculated targets with the appropriate recruitment site is to visually assess the scalp surface on which the TMS stimulation angle is calculated. Targets are recalculated only if the scalp surface around the treatment sites is too noisy, which appears visually as bumps on the surface. The image threshold given is then increased iteratively until the scalp surface appears smooth.

Imaging Analyses on Mechanistic TMS Treatment Effects

Response Definition

Although the clinical trial is outlined in full in the former protocol paper [22], it is important to note that the clinical response within the BRIGhTMIND trial has been defined as a 3-point reduction in depression symptoms (averaged over all 3 posttreatment-time points at 8, 16, and 26 weeks, respectively) from baseline on the HDRS-17 [63]. All imaging tests outlined here will use this outcome as their variable for changes in depression symptoms.

Primary Mechanistic Outcomes

The primary mechanistic outcomes are as follows:

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1. Correlation of change in depression symptoms following TMS with changes in DLPFC-DMPFC FC at 16 weeks (post minus pretreatment)
2. Correlation of change in depression symptoms following TMS with baseline effective connectivity (as calculated for the cgiTBS target) between the rAI seed region and the DLPFC (defined as a 6 mm spherical region of interest centered on the subject's cgiTBS target coordinate)
3. Correlation of change in depression symptoms following TMS with cgiTBS treatment-related GABA changes (post minus pretreatment) at 16 weeks

Exploratory Outcomes

The exploratory outcomes are as follows:

1. Exploratory outcomes include, but are not limited to, evaluation of FC-based biotypes in the prediction of individual treatment response in TRD patients (25% change in HDRS-17 score from baseline to 16 weeks) [17] and to further study the neural mechanisms underlying therapeutic efficacy by assessing interrelations of changes in complex brain network metrics (including the use of graph analysis) with changes in clinical symptoms.
2. Exploratory outcomes include, but are not limited to, change in depression symptoms following TMS (HDRS-17 score post minus pretreatment) with baseline peak negative FC between the sgACC-left DLPFC and correlation of treatment response with distance between coordinates of the peak negative sgACC-left DLPFC FC and the calculated cgiTBS target.

Data Analysis

Clinical, demographic, and psychometric data will be compared between groups and conditions using the latest version of appropriate statistical software such as SPSS (IBM Inc) or R (R Foundation).

Imaging data will be analyzed using the latest versions of established toolboxes where possible, but as the T1-weighted and rsfMRI preprocessing pipelines have been defined to calculate TMS stimulation targets, this preprocessed data will also be used for further statistical analysis where appropriate. Toolboxes will include (but are not limited to) the following: FSL, SPM12, rsfMRI Data Analysis Toolkit, Brain Connectivity Toolbox, and LCModel for MRS data. Analysis of ASL and diffusion MRI data will be described in subsequent manuscripts as they are not used to create treatment targets, nor are they required to test the stated mechanistic hypotheses.

Study Amendments Because of SARS-CoV-2

Recruitment to the study was suspended on March 19, 2020, because of the SARS-CoV-2 pandemic. The study was reopened with a range of changes to protect participants and staff from SARS-CoV-2 on August 1, 2020, with recruitment at a slower permitted rate starting on September 1, 2020, at 3 of the 4 original study sites. The Northampton site was unable to restart, but another site at Oldham Greater Manchester has been opened to recruit for the study. Recruitment of the original sample of 368 participants was no longer possible within the resources and time-frame available.

In-person assessments were minimized owing to SARS-CoV-2 upon the study restart in August 2020, and as such, all assessments except the THINC-Integrated Tool (THINC-it; THINC-it Task Force [64]) task were carried out remotely either over the phone or via videoconference. THINC-it assessments were initially planned to take place at baseline and at the 8th, 16th, and 26th week in-person assessment. As these were no longer taking place in person, the THINC-it is now assessed only at baseline and 16 weeks, when the participant visits the center for their MRI scans. This was decided on to ensure that THINC-it assessments would remain consistent regarding both face-to-face instructions and the hardware used.

Using the expertise and independent advice of 2 independent committee monitoring and checking the progress of the study and in discussion with our funders who also sought external peer review, we changed the primary outcome measure from the binary variable of responder or nonresponder at 16 weeks (response was defined as a 50% drop or greater in the HDRS-17 from baseline to 16 weeks) to the mean change in the total score on the HDRS-17 across all follow-up time points (8, 16, and 26 weeks).

The National Institute of Clinical Excellence in its 2004 clinical guideline for depression defined a minimum clinically important difference in the total score on this scale of 3 points [65], which was reaffirmed in their 2009 guidelines [66]. We based our revised sample size on detecting an average difference of 3 points in the HDRS-17 at 8, 16, and 26 weeks, assuming an SD of 8 points based on our pilot study and a multicenter randomized controlled trial in chronic persistent depressive disorder led by the chief investigator [67], a correlation of 0.7 between the follow-up points (1 baseline measure with a correlation of 0.27 to the follow-up measures) and 20% loss to follow-up or drop-out, which was the average loss to follow-up across all follow-up points in the study as of January 31, 2021.

Under the assumptions mentioned above, a sample size of 266 participants will be required to achieve 89.3% power to detect the average difference of 3 points in the HDRS-17 at 8, 16, and 26 weeks at a 5% significance level (2-tailed); hence, 266 is the revised target for recruitment to the study. Recruitment of the sample will continue until January 31, 2022 and is limited by the resources available to the study. Given the uncertainties of recruitment to the study in the current pandemic, we note that under the same assumptions, a sample size of 232 would reassuringly still yield 85.1% power.

Mechanistic Power Calculation for the Study

If 266 participants are randomized into the study, we expect 116 participants to provide full data for the mechanistic substudy (DLPFC-DMPFC FCp; change at 16 weeks and HDRS-17 change at 16 weeks), based on the observed acquisition rate to date (92/210, 43.8% provided data for both). The remaining 56.2% (118/210) without full mechanistic substudy data are because of a combination of participants being randomized at the London site (where only baseline scans are carried out), loss to follow-up at 16 weeks for HDRS-17 score, and loss to MRI follow-up. If we allow for 5% further loss owing to poor imaging quality, this will give us a total of 120 participants to

assess the correlation of DLPFC-DMPFC FC change at 16 weeks and HDRS-17 change at 16 weeks.

A sample size of 120 achieves 96.3% power to detect a difference of −0.3 between the null hypothesis correlation of 0.2 and the alternative hypothesis correlation of 0.5 using a 2-sided hypothesis test with α=.05. The null hypothesis of 0.2 represents a very weak or weak correlation, whereas the alternative of 0.5 represents a moderate correlation [68]. The correlation between DLPFC-DMPFC FC change at 12 weeks and HDRS-17 change at 12 weeks in our pilot data was 0.58.

We must address 2 points regarding this aim. First, we previously had hypotheses 1 and 2 in reverse order, powering the substudy on the ability of the DLPFC-DMPFC FC change to discriminate between responders and nonresponders. The reason for moving away from this was because of the change in minimum clinically important difference criterion, such that by performing a correlation analysis, we assessed a noncategorized version of this test that removed the need to incorporate a response criterion but also improved statistical power owing to the use of the whole sample. Second, the proposed test assumes a weak correlation rather than no correlation. This approach was taken to make the test more robust against serial effects unrelated to treatment in the absence of a *no treatment* arm to the trial.

Regarding primary hypotheses 2 and 3, sensitivity analyses are presented to evidence that the revised sample size for the study will still allow for testing of these hypotheses. Sensitivity analysis based on a 1-tailed test with α=.05, 90% power, and a sample size of 232 for hypothesis 2 suggests a required effect size of $|\rho|=0.19$. This correlation of effective connectivity from the insula-DLPFC with changes in HDRS-17 at 12 weeks in our pilot data was −0.26. Sensitivity analysis following the same formula but with a lower expected sample size of 111 (as outlined for hypothesis 1) for hypothesis 3 suggests a required effect size of $|\rho|=0.27$. The correlation between GABA and HDRS-17 changes at 12 weeks in our pilot data was 0.68. Taken together, the study is expected to have the power to test the proposed hypotheses.

Results

The first participant was recruited on January 22, 2019, but recruitment was suspended on April 23, 2020, because of the SARS-CoV-2 pandemic. Recruitment began again in August 2020 and is ongoing. To date, 194 participants have been randomized for treatment.

Discussion

Neuromodulation via TMS has been shown to reduce the symptoms of TRD. However, using traditional identification of treatment locations, such as tape measurements or electroencephalography caps, may not be as effective as using personalized location estimation based on MRI. The BRIGhTMIND imaging substudy will assess the effectiveness and mechanistic effect of 2 variants of TMS, where treatment locations will be determined in a personalized manner using MRI. In addition, this study will evaluate whether treating a

FC-based location is more effective than treatment based on a standard F3 location. If this hypothesis is found to be true, it may serve as evidence of the importance of using precision medicine in mental health.

An important point within an imaging trial such as this is the QC and amalgamation of data from different imaging scanners and locations. Differences in acquisitions, scanner hardware, and geographic locations can lead to problems when combining data for analysis. To tackle these potential variations, this study has put in place standardized image acquisition protocols, QC protocols, and data analysis pipelines with all data analysis occurring through the lead center at Nottingham. The use of automated QC tools such as MRIQC (T1-weighted and functional MRI) allows investigators to make clear decisions on whether the data are of acceptable quality to enter analyses while minimizing the risk of bias [29,69]. After the data passes QC, we will create a locked analysis pipeline for the creation of the TMS targets, thus removing any user bias or effect of experimenter expertise on target calculation. For all non-TMS target coordinate-related analyses, these pipelines will be used as shown or improved upon with the advent of better software and processing tools to ensure that the end analyses remain state of the art.

To take advantage of the outlined image standardization and large data set, the study will perform data harmonization with the aim of minimizing statistical bias from any sites or scanner vendors in addition to performing all analyses at the Nottingham site. Relevant work has been carried out to assess various approaches with differing MRI modalities via the Enhancing Neuroimaging Genetics through Meta-Analysis consortium [70]. ComBat [71] is one such tool of choice [72,73], as it has been shown to be effective in harmonizing diffusion [74], cortical thickness [75], and fMRI measures [76,77] while retaining relationships with known confounders such as age and sex. However, this field of research is highly active and, as such, the final decision of the best approach will be made before the start of the analysis to take advantage of the best and most robust tools available at the time of analysis.

Although this trial aims to investigate the effect of precision MRI-guided TMS treatment, this precision must not be carried out at the expense of treatment tolerability, and thus, participant comfort. For instance, when the location of the calculated treatment site brings about adverse events, such as facial nerve twitching and jaw clamping, we follow the protocol set out by Morriss et al [22]. This involves three different steps—(1) move the coil 1 cm (coil to be kept within 2 cm of the original site); if discomfort persists then (2) reduce threshold; and (3) revert to F3 spot, ensuring that the allocated treatment type is used. This final location is then used for stimulation throughout the course of treatment with the aim of improving the participant experience and maximizing adherence and tolerability.

It is hoped that the sharing of such a detailed MRI study protocol provides clarity to the methods used for the BRIGhTMIND trial and, as such, will aid and accelerate future studies and replications. In addition, this transparency will lend greater weight and credence to the results of the trial upon its completion. An important factor when the study has the potential

to provide important insights into the mechanisms of TRD and   the effect of TMS treatment.

Acknowledgments

Conflicts of Interest

None declared.

Multimedia Appendix 1
Details of magnetic resonance scanning protocol.
[DOCX File , 1416 KB - resprot_v11i1e31925_app1.docx]

Multimedia Appendix 2
Peer-review report from the Medical Research Council - National Institute for Health Research (MRC-NIHR) - (NHS, UK) (1).
[PDF File (Adobe PDF File), 275 KB - resprot_v11i1e31925_app2.pdf]

Multimedia Appendix 3
Peer-review report from the Medical Research Council - National Institute for Health Research (MRC-NIHR) - (NHS, UK) (2).
[PDF File (Adobe PDF File), 366 KB - resprot_v11i1e31925_app3.pdf]

Multimedia Appendix 4
Peer-review report from the Medical Research Council - National Institute for Health Research (MRC-NIHR) - (NHS, UK) (3).
[PDF File (Adobe PDF File), 359 KB - resprot_v11i1e31925_app4.pdf]

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Abbreviations

ASL: arterial spin labeling
BET: brain extraction tool
BOLD: blood oxygenation level dependent
BRIGhTMIND: Brain Imaging Guided Transcranial Magnetic Stimulation In Depression
cgiTBS: connectivity-guided intermittent theta burst transcranial magnetic stimulation
CSF: cerebrospinal fluid
DICOM: digital imaging and communications in medicine
DLPFC: dorsolateral prefrontal cortex
DMPFC: dorsomedial prefrontal cortex
EPI: echo-planar imaging
FAST: FMRIB Automated Segmentation Tool
FC: functional connectivity
FNIRT: FMRIB's nonlinear image registration tool
FSL: FMRIB Software library
GABA: γ-aminobutyric acid
GCA: Granger causality analysis
HDRS-17: 17-item Hamilton Depression Rating Scale
lCEN: left central executive network
LCModel: linear combination model
lMFG: left middle frontal gyrus
MEGA-PRESS: Meshcher-Garwood Point Resolved Spectroscopy
MRI: magnetic resonance imaging
MRS: magnetic resonance spectroscopy
NHS: National Health Services
NIHR: National Institute for Health Research
NLR: nasion-left-right
QC: quality control
rAI: right anterior insula
rsfMRI: resting-state functional magnetic resonance imaging
rTMS: repetitive transcranial magnetic stimulation
sgACC: subgenual anterior cingulate cortex
SPM12: Statistical Parametric Mapping v12
SUSAN: Smallest Univalue Segment Assimilating Nucleus
TBS: theta burst stimulation
TE: echo time
TMS: transcranial magnetic stimulation
TR: repetition time
TRD: treatment-resistant depression
WM: white matter

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Protocol

A Mobile App for Wound and Symptom Surveillance After Colorectal Surgery: Protocol for a Feasibility Randomized Controlled Trial

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Abstract

Background: Surgical site infections (SSIs) are the most common nosocomial infection and occur in 16.3% of patients undergoing colorectal surgery at our institution (The Ottawa Hospital), the majority of which are identified after discharge from hospital. Patients who suspect having an SSI generally present to the emergency department or surgery clinic. Both options for in-person interaction are costly to the health care system and patients. A mobile app, how2trak, has proven to be beneficial for patients with complex wounds at our institution by facilitating at-home monitoring and virtual consultations.

Objective: This study aims to assess the feasibility of a randomized controlled trial to assess if how2trak can improve patients' experience and increase detection of SSIs after colorectal surgery while reducing patients' risk of COVID-19 exposure.

Methods: In this single-center prospective feasibility trial, eligible patients undergoing colorectal surgery will be randomized to either standard care or how2trak postoperative monitoring of their incision, symptoms, and ostomy function. Patient self-assessments will be monitored by a nurse specialized in wound and ostomy care who will follow-up with patients with a suspected SSI. The primary outcome is feasibility as measured by enrollment, randomization, app usability, data extraction, and resource capacity.

Results: This study was approved by our institution's ethics board on February 26, 2021, and received support from The Ottawa Hospital Innovation and Care Funding on November 12, 2021. Recruitment started June 3, 2021, and 29 were patients enrolled as of September 2021. We expect to publish results in spring 2022.

Conclusions: This study will determine the feasibility of using a mobile app to monitor patients' wounds and detect SSIs after colorectal surgery. If feasible, we plan to assess if this mobile app facilitates SSI detection, enhances patient experience, and optimizes their care.

Trial Registration: ClinicalTrials.gov NCT04869774; https://clinicaltrials.gov/ct2/show/NCT04869774

International Registered Report Identifier (IRRID): DERR1-10.2196/26717

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KEYWORDS

eHealth; mobile app; surgical site infection; colorectal surgery; app; surgery; infection; wound; surveillance; feasibility; randomized controlled trial; tracking; patient experience; COVID-19; transmission

Introduction

Background and Rationale

Surgical site infections (SSIs) are the most common nosocomial infection among surgical patients, occurring in 5.5% of surgical cases at our institution, The Ottawa Hospital [1]. Similar rates are seen at other centers across North America and Europe, with SSIs impacting 3%-5% of inpatient surgical cases and accounting for 20%-38% of nosocomial infections among surgical patients [2-5]. Patients undergoing colorectal surgery are disproportionately affected. A recent study at our institution found that 24% of patients undergoing colorectal surgery developed an SSI [6]. SSIs are associated with significant morbidity and mortality both in the short and long term. In the initial postoperative period, SSIs are associated with increased postoperative mortality, length of stay, and intensive care unit admission. In the long term, SSIs are independently associated with higher readmission and mortality rates compared to those without an SSI [1].

SSIs and a Need for Postoperative Surveillance

Approximately two-thirds of SSIs are defined as superficial, meaning they involve only the skin and subcutaneous tissues [5]. These SSIs are detectable by clinical exam; when identified early, they can be managed with wound management alone. However, approximately 57% of SSIs are diagnosed after discharge from hospital, when patients are no longer regularly examined by a clinician [7]. When comparing patients with SSIs detected after discharge from hospital to those with SSIs detected in hospital, the former are more likely to have an advanced infection at time of detection and experience poorer quality of life, greater physical limitations, and lower mental health component scores, as well as have increased outpatient and emergency department (ED) visits, hospital readmissions, and higher demand for diagnostic imaging [8,9]. The incidence and morbidity of an SSI can be reduced by regular clinical surveillance of the incision [10].

Mobile App Technology

Mobile apps are an effective and desirable method for assisting patients with self-monitoring for SSIs and other complications after surgery [11]. Photo-based mobile apps have been shown in multiple studies to be effective at detecting superficial SSIs [12-14]. This can also reduce a patient's need for in-person visits by facilitating virtual monitoring and virtual visits with a clinician. This is critical in the context of the COVID-19 pandemic, and could reduce ED visits and readmission in the postoperative period [15]. Finally, the postoperative period can be stressful and isolating for patients. Patients using mobile apps for surveillance after surgery have reported a greater sense of empowerment, as well as more engagement and satisfaction [16].

The Health Outcomes Worldwide how2trak (H2T) app is an example of a mobile point-of-care technology for wound surveillance. H2T has been shown to be an effective tool for postoperative monitoring after discharge from hospital following a cesarean delivery. However, this app has not been assessed among colorectal surgery patients, who represent a more diverse, comorbid, and older population than young females undergoing cesarean delivery [17]. H2T has been adopted at The Ottawa Hospital for wound monitoring in the vascular surgery patient population, and plans are underway to integrate it with the hospital electronic medical record system. H2T could potentially enhance postoperative monitoring and detection of superficial SSI but would require a significant change in workflow to the multidisciplinary care of wound complications. Therefore, its feasibility must be assessed prior to conducting a trial to assess its effectiveness in this population.

Objectives

This study aims to assess the feasibility of a randomized controlled trial where patients discharged from hospital after colorectal surgery are randomized to have virtual monitoring of their surgical incision(s), symptoms, and ostomy using the H2T app or to standard of care. The primary outcome is feasibility as measured by enrollment, randomization, H2T usability, data extraction, and resource capacity.

This is intended to inform the development of a definitive trial to establish if the H2T app enhances SSI detection, improves patients' experience, and reduces the risk of COVID-19 transmission compared to standard care.

Methods

Overview

This protocol was developed in accordance with the SPIRIT (Standardized Protocol Items: Recommendations for Interventional Trials) statement [18] and CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Onine Telehealth) reporting recommendations [19]. This study has been approved by the Research Ethics Board at the Ottawa Hospital Research Institute (20200596-01H).

Study Setting

This study will be conducted with the Ottawa Colorectal Group within the Division of General Surgery at The Ottawa Hospital, a multisite academic hospital in Ottawa, Ontario, Canada.

Trial Design

This is an unblinded feasibility randomized controlled trial. Eligible patients will be randomized 1:1 to receive virtual monitoring of their surgical incision, symptoms, and ostomy using H2T or to standard of care.

Eligibility Criteria

All patients being discharged from hospital after undergoing urgent, semiurgent, or elective abdominal surgery by a colorectal

surgeon at The Ottawa Hospital will be considered for participation in the study.

To be included in the study, participants must be ≥16 years of age, patients who are being discharged from hospital after undergoing semiurgent, urgent, or elective abdominal surgery by a colorectal surgeon at The Ottawa Hospital, and have provided informed consent to participate. Patients enrolled in other clinical trials will still be candidates for this feasibility trial.

Patients will be excluded if they are <16 years of age, have no access to or ability to use a mobile device, have no cellular data/Wi-Fi access, and/or cannot read and write in English.

Clinicians using the H2T app in this study will be considered study participants as well. They will be asked to complete the Modified Post-Study System Usability Questionnaire (PSSUQ) for Patients and Clinicians, a survey derived from the PSSUQ by Lewis and colleagues [20]. This survey addresses the experience of using the H2T app; their feedback regarding usability is fundamental for future improvement.

Informed Consent

The colorectal surgery team will notify the research assistant of all patients undergoing urgent, semiurgent, or elective abdominal surgery by a colorectal surgeon at The Ottawa Hospital who are potentially eligible for participation within 72 hours following the patient's surgery. The research assistant will then meet with patients by phone or in person to screen for eligibility, and proceed with the consent discussion, which will include the following: the nature of the trial, eligibility criteria, and the risks and benefits of participating. The research assistant will also assess their willingness to participate, and explain that their data may be included in a full-scale randomized controlled trial if completed as a vanguard study.

Clinicians who have used H2T during the study period will be contacted by email by the research assistant and will be invited to complete the Patient and Clinician Survey of Application survey. The completion of the survey will indicate their acceptance to participate in the study.

Interventions

Immediately after consent is obtained, eligible patients will be randomized 1:1 to two arms (Figure 1).

Figure 1. CONSORT flow diagram.
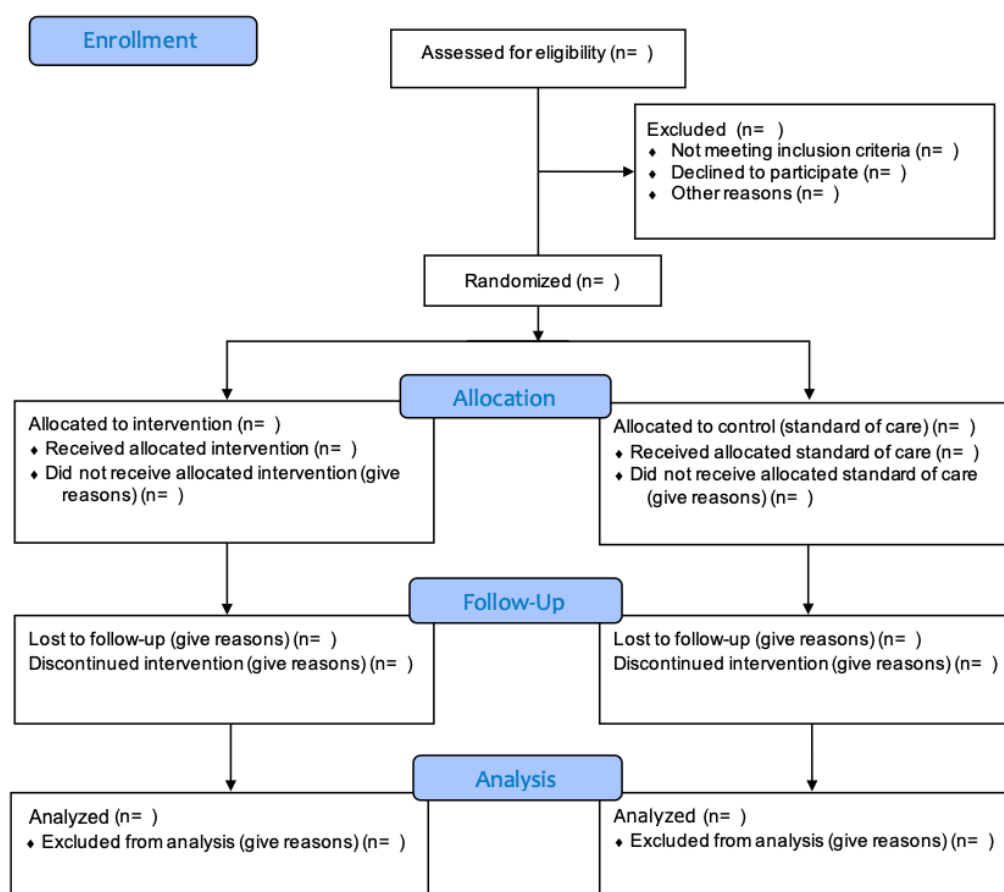
Intervention group patients will undergo virtual monitoring of their incision and symptoms using H2T. Early in their postoperative course, patients will be guided through developing a login and instructed on how to download and use H2T by the research assistant. In developing their login, patients will enter their full name and partial date of birth (MM-YYYY), which will be used as identifiers to link to The Ottawa Hospital data. Using the H2T app, patients will be asked to answer a series of questions (see Patient Application Questionnaire in Multimedia Appendix 1) and photograph their surgical incision on

postoperative day 3, 5, 7, 10, 20, and 30 through the app (see timeline in Table 1). Patient responses and photographs entered into the H2T app on the patient's mobile device will be reviewed within 72 hours by a trained Nurse Specialized in Wound, Ostomy, and Continence (NSWOC) [21] who will be trained to triage patients using the algorithm in Figure 2. If a concern is identified, the NSWOC will contact the patient to arrange a virtual visit using the H2T app or notify the surgery team (including colorectal surgeons and physician residents) in accordance with the algorithm, clinical discretion, and scope of practice. Patients will be reminded that it may take up to 72 hours to receive a response from the NSWOC; accordingly, if they have urgent concerns or emergency, they should present to the ED or call 911.

Control group patients will receive no virtual monitoring. No virtual monitoring is currently in place as part of standard of care after colorectal surgery at The Ottawa Hospital. Therefore, standard of care without any virtual monitoring was selected as the comparator.

Both groups will receive routine standard of care. Standard of care will involve a routine postoperative follow-up with the surgical team 4-6 weeks after discharge from hospital.

Patients and clinicians will complete the PSSUQ, a validated 16-item survey to assess the perceived learnability, efficiency, and errors of H2T, as well as user satisfaction with the app [20,22] (see Multimedia Appendix 1). Patients will also submit a survey to assess their satisfaction with their postoperative care at postoperative day 30 to assess their perceived experience of their postdischarge care using a modified version of PATSAT32, a validated questionnaire for patients undergoing gastrointestinal surgery [23,24] (see Multimedia Appendix 1). The intervention will be reviewed every two months by the investigator team and General Surgery Comprehensive Unit-based Safety Program team. H2T functionality will remain consistent throughout the study, with revisions made only in response to unexpected events.

Table 1. Participant timeline.

Timepoint	Study period									
	Visit with research assistant	Visit with research assistant	Intervention period (postoperative day 3-30)							Close-out
	$-t_1$	0-3	3	5	7	10	20	30		t_x
Enrolment										
Eligibility screen	✓	✓								
Informed consent	✓	✓								
Allocation		✓								
Interventions										
How2Trak virtual monitoring			✓	✓	✓	✓	✓	✓		✓
Control								✓		✓
Assessments										
Baseline comorbidities	✓	✓								
Health system interaction			✓	✓	✓	✓	✓	✓		✓
Postoperative outcomes			✓	✓	✓	✓	✓	✓		✓
Patient experience								✓		✓
App usability										✓

Figure 2. Nurse Specialized in Wound, Ostomy, and Continence (NSWOC) triage. Wound And Symptom Tracking After Colorectal Surgery Using How2trak (WATCH) study NSWOC workflow process. Urgent refers to a concern that requires immediate medical attention. ED: emergency department; H2T: how2trak; SSI: surgical site infection (based on the Centers for Disease Control and Prevention definition, see Patient Application Response suggestive of surgical site infection).
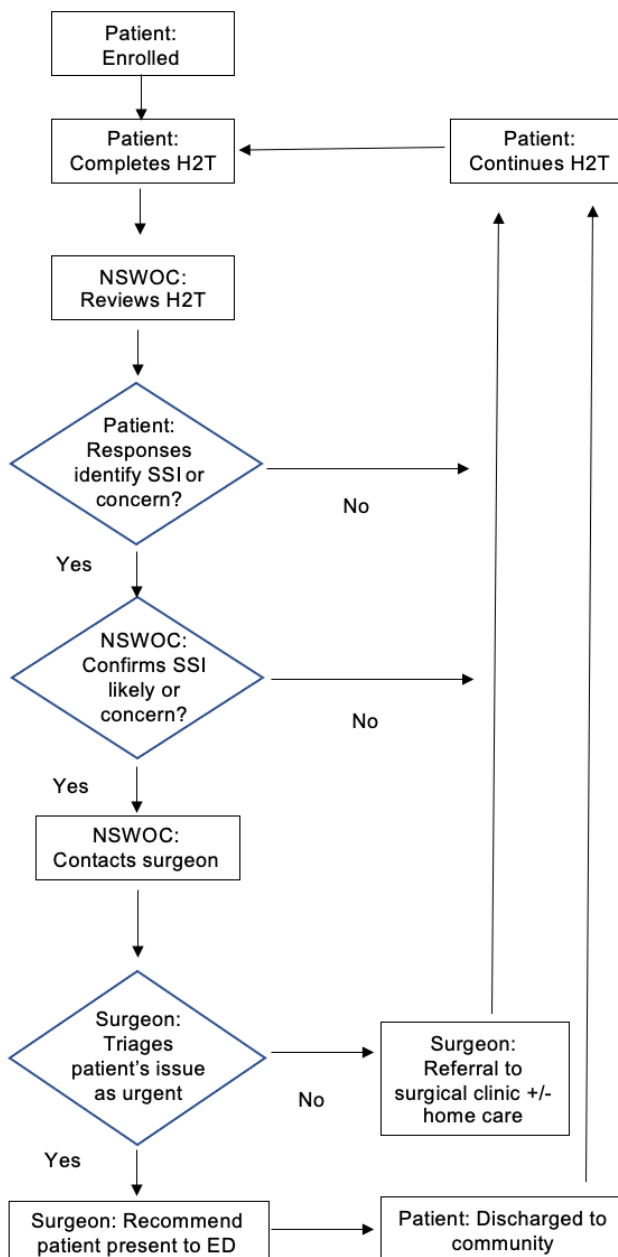
Strategies to Improve Adherence to the Intervention

Patients will receive notifications through the app to serve as a reminder each day that a photo and questionnaire are required. If no response is received, the research assistant will follow up with the patient by email and/or by phone. In keeping with the pragmatic nature of this trial, patients may request to withdraw from the intervention group at any time.

Outcomes

Primary Outcome: Feasibility

This study will assess the feasibility of a definitive trial by assessing specific outcome measures that will be determined to be feasible if all endpoints are met:

1. Capability for enrollment will be assessed to determine recruitment potential and an optimal sample size estimation for a full-scale randomized controlled trial, by measuring the following outcomes: proportion of patients screened, proportion of eligible patients consenting to involvement in this study, and proportion of recruited patients who are enrolled in the study.
   - Endpoint: 4 patients per month on average are enrolled in the study.

2. Feasibility of the randomization processes will be evaluated, including the proportion of patients randomized who receive the intervention.
   - Endpoint: 90% of patients enrolled are randomized to the intervention or control group.

3. How2trak usability, delivery, and compliance will be evaluated by assessing patients' and health care providers' perceived usability of the technology, as well as the number of questionnaires and photos completed by each patient during the postoperative period.
   - Endpoints: Patients completed, on average, 60% of self-assessments. The mean score of the H2T app in patient and clinician surveys is >2.

4. Feasibility of data extraction, measured by the proportion of participants for which all relevant outcomes of a full-scale randomized controlled trial were documented.
   - Endpoint: All primary outcomes of the definitive trial (see "Definitive Trial Outcomes" section below) are recorded for 80% of patients.

5. Resources and time required to conduct the feasibility trial will be assessed. In particular, the administrative capacity, expertise, skills, space, and time of the research team, the feasibility of the designated budget, and the compliance of interdisciplinary staff with the study protocol will be assessed.
   - Endpoint: The feasibility study is completed with the allocated interdisciplinary staff.

Definitive Trial Outcomes

The primary outcomes for a definitive trial collected in this study will compare the SSI incidence and severity of patients in the two study arms, as well as their experiences. An SSI is an infection that occurs after surgery in the part of the body where the surgery was performed. A superficial incisional SSI is an infection that involves only skin or subcutaneous tissue of the surgical incision and will be defined using the Centers for Disease Control and Prevention criteria [5].

Secondary outcomes for a definitive trial include hours of in-person interactions with the health care system (including readmissions to hospital, ED visits, and clinic visits), confirmed COVID-19 infection within 30 days after surgery, incidence of postoperative adverse events, and incidence and characterization of ostomy complications.

Statistical Analysis

Descriptive statistical analysis will be conducted using Microsoft Excel (version 16.16.19; Microsoft Corp) and RStudio (version 1.1463).

For the definitive trial, the following tests will be used to discern relationships between variables: two-sample Welch t test for normally distributed continuous variables, Kruskal-Wallis rank-sum test for data without normal distribution, and chi-square goodness of fit test for categorical variables. A P value of <.05 will be considered statistically significant.

Sample Size

There is no sample size for this feasibility study. It will be conducted over 6 months and we anticipate having 80 eligible patients over this time period.

Assignment of Interventions

After written informed consent is obtained, eligible patients will be randomly assigned to either the intervention or control group using a secure web-based randomization system at the Methods Centre of The Ottawa Hospital Research Institute. This study will be unblinded so no attempts at concealment of patients' allocation will be made.

Data Collection and Management

Data will be captured through the assessments and/or photographs in H2T and the hospital's electronic health information system (Epic). Data sent from H2T to The Ottawa Hospital—including patient identifiers to allow for merging with Epic data—will be transferred through a secure, access-controlled folder within Office 365. Once the data files are merged, they will be deidentified. Only research personnel will have access to the study data. A data monitoring committee will not be developed given the minimal risk and small sample size of this feasibility trial.

If a definitive trial is completed, we plan to incorporate the results of this study into the data collection of the trial.

Confidentiality

Data will be originally stored locally on patients' devices, encrypted, in a secure app sandbox of the H2T app. The H2T app will attempt to synchronize its internal database with the server's database whenever there is a need (ie, new information is created). Once the data are on the server, they will be retained with patient identifying information intact for a length of time (such as 6 or 10 years), as determined by the requirements of the jurisdiction in which the data is being collected.

The Ottawa Hospital data will be collected primarily from Epic using Workbench reports. Data from Health Outcomes Worldwide's encrypted servers will be securely transferred to the research team, who will merge it with data collected primarily from Epic using patients' names and partial dates of birth as identifiers (entered by patients when developing their login). A master list (containing the study ID and patient identifiers) will be accessible only to the researchers responsible for the analysis and will be kept separate from the main study data set in a secure, access-controlled folder on The Ottawa Hospital's Office 365 cloud. The Ottawa Health Science Network Research Ethics Board (OHSN-REB) and Ottawa Hospital Research Institute may review relevant study records (under the supervision of the investigator) for audit purposes.

Oversight and Monitoring: Adverse Event Reporting and Harms

Clinicians involved in the trial (surgical team and virtual care NSWOC) will monitor for adverse events and report them immediately to the Principal Investigator. The investigator team will report to the Research Ethics Board any adverse event that is deemed to be unexpected, related or possibly related to the investigational product or other study intervention/treatment/procedure or to participation in the research (ie, definitely, probably, possibly, or unlikely related) and that involves greater risk.

If the adverse event meets reporting criteria, the event will be submitted within seven calendar days of the team becoming aware of the incident using the OHSN-REB Reportable Events form. There are no plans for audits of the trial conduct.

Management Team

Principal investigators are RM (colorectal surgeon and quality improvement lead at The Ottawa Hospital) and HAS (general surgery resident, clinical investigator program graduate, and resident quality improvement lead). Coinvestigators include CHO (general surgery resident), JFC (Project Manager, ARC Innovation Center, Ottawa Hospital Research Institute), TM (NSWOC and advanced practice nurse at The Ottawa Hospital), and BR (internal medicine physician at The Ottawa Hospital), as well as two patient partners recruited to assist in trial design and analysis of results.

Results

This study was approved by the OHSN-REB on February 26, 2021, and accepted for The Ottawa Hospital Innovation and Care Funding on November 12, 2021. Recruitment started June 3, 2021, and as of September 2021, we had 29 patients enrolled. We expect to publish results in spring 2022.

Discussion

We anticipate this work will help us to better understand the feasibility of using mobile technology to optimize patients' care after discharge from hospital after colorectal surgery. Virtual postsurgery wound and symptom monitoring could enhance the patient experience, SSI detection, and reduce the risk of COVID-19 transmission. If this technology is feasible for our patient population and workflow, we plan to formally assess its effectiveness with a definitive trial. The H2T app has multiple functionalities, and this study could establish a framework for assessing its use in other domains including ostomy monitoring and patient education, as well as for patients undergoing other surgical procedures.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplemental materials.
[DOCX File , 50 KB - resprot_v11i1e26717_app1.docx]

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Abbreviations

CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
ED: emergency department
H2T: how2trak
NSWOC: Nurse Specialized in Wound, Ostomy, and Continence
OHSN-REB: Ottawa Health Science Network Research Ethics Board
PSSUQ: Post-Study System Usability Questionnaire
SPIRIT: Standardized Protocol Items: Recommendations for Interventional Trials

Protocol

Administration of Parenteral Vitamin C in Patients With Severe Infection: Protocol for a Systematic Review and Meta-analysis

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Abstract

Background: Severe infections are characterized by inflammation and oxidative damage. Ascorbic acid (vitamin C) administration may attenuate oxidative damage and, in turn, reduce vascular endothelial injury in pulmonary and systemic vasculature.

Objective: We aim to describe a protocol for a living systematic review that will evaluate the effectiveness and safety of parenteral vitamin C administration in adults with severe infections, including those with COVID-19.

Methods: We searched Ovid MEDLINE, Embase, CINAHL, the Centers for Disease Control and Prevention COVID-19 database, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov from inception to March 30, 2021, for randomized controlled trials evaluating parenteral vitamin C versus no parenteral vitamin C in hospitalized adults with severe infection. Eligible studies will include at least 1 arm involving any dose of parenteral vitamin C alone or in combination with other cointerventions and at least 1 arm not involving parenteral vitamin C. The primary outcomes of interest will include in-hospital, 30-day, and 90-day mortality. Title and abstract screening, full-text screening, data extraction, and risk of bias evaluation via a modified Risk of Bias 2.0 tool will be conducted independently and in pairs. We will perform random effects modeling for

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meta-analyses, in which study weights will be generated by using the inverse variance method. We will assess certainty in effect estimates by using the Grading of Recommendations Assessment, Development and Evaluation methodology. Meta-analyses will be updated iteratively as new trial evidence becomes available.

Results: Among the 1386 citations identified as of March 30, 2021, a total of 17 eligible randomized controlled trials have been identified as of September 2021. We are in the process of updating the search strategy and associated data analyses.

Conclusions: The results will be of importance to critical care physicians and hospitalists who manage severe infection and COVID-19 in daily practice, and they may directly inform international clinical guidance. Although our systematic review will incorporate the most recent trial evidence, ongoing trials may change our confidence in the estimates of effects, thereby necessitating iterative updates in the form of a living review.

Trial Registration: PROSPERO CRD42020209187; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=209187

International Registered Report Identifier (IRRID):   RR1-10.2196/33989

Introduction

Severe infections may be associated with intense inflammation and oxidative stress, which result in endothelial damage. Suspected or confirmed infection, together with a dysregulated host immune response causing acute organ dysfunction, as defined by the sepsis-related organ failure assessment (SOFA) score [1], defines sepsis [2]. Recent estimates from the Global Burden of Disease Study reported an estimated 48.9 million (95% uncertainty interval: 38.9 million to 62.9 million) incident cases of sepsis worldwide in 2017, along with 11.0 million (95% uncertainty interval: 10.1 million to 12 million) related deaths (19.7% of all-cause mortality worldwide) [3]. Interventions targeting the dysregulated host immune response and endothelial injury associated with severe infections and sepsis may improve patient-important outcomes [3-5]. For example, corticosteroids have been associated with improved survival in both sepsis [6-8] and severe COVID-19 [9-11].

Ascorbic acid deficiency, or vitamin C deficiency, has been reported in patients with severe infection [12,13], with preclinical data lending credence to the use of vitamin C in sepsis. Supplementation with vitamin C has been postulated to reduce vascular endothelial injury in pulmonary and systemic vasculature and reduce oxidative damage, and vitamin C has been postulated to act synergistically with glucocorticoids to suppress inflammation [14]. Due to the potential pulmonary effects associated with parenteral vitamin C and the preliminary evidence suggesting that vitamin C deficiency can occur in patients with SARS-CoV-2 infection [15], the World Health Organization (WHO) has prioritized parenteral vitamin C administration as a candidate treatment for COVID-19 as well [16].

Randomized controlled trials (RCTs) evaluating the effectiveness of vitamin C supplementation, either alone or in combination with other therapies such as corticosteroid and thiamine therapy, have yielded varied results. A systematic review in 2019 included RCTs of oral and parenteral vitamin C administration as monotherapy or in combination with other interventions in critically ill patients. The review found 9 RCTs

that showed no significant overall survival benefit (risk ratio [RR] 0.72, 95% confidence interval [CI] 0.43-1.20) and no significant differences in the risk of new infections, length of intensive care or hospital stay, or duration of invasive mechanical ventilation. The subgroup analysis revealed a possible survival benefit with intravenous high-dose vitamin C monotherapy (RR 0.21, 95% CI 0.04-1.05), but the certainty of the evidence was limited by a small number of trials, patients, and events [17].

Several recent RCTs have evaluated parenteral vitamin C in the context of various populations of patients with sepsis [18-20]. Our systematic review and meta-analysis will aim to assess the efficacy and safety of parenteral vitamin C administration as monotherapy or in combination with other therapies in adult patients with severe infection.

Methods

This protocol adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) standards (Multimedia Appendix 1).

Search Strategy

With the aid of a medical librarian, we searched the following electronic databases from inception to March 30, 2021: Ovid MEDLINE Daily and MEDLINE (from 1946), Embase (from 1974), CINAHL (from 1984), Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov (Multimedia Appendix 2). A combination of keywords and medical subject heading terms were used, as follows: *ascorbic acid*, *vitamin C*, *sepsis*, *septic shock*, *infection*, *multiple organ failure*, *critical illness*, *intensive care unit*, *severe illness*, *respiratory distress syndrome*, *parenteral nutrition*, and *intravenous administration*. No language restrictions were applied.

We also searched the US Centers for Disease Control and Prevention COVID-19 database from inception to September 10, 2021. Specifically, we imported all Centers for Disease Control and Prevention COVID-19–related articles into EndNote (Clarivate Analytics) and conducted keyword searches with the terms *vitamin* or *ascorb**. We will screen these studies to

identify eligible studies by using a predeveloped search filter. We will also include additional eligible studies, which will be identified by the review authors and clinical experts. We did not search grey literature, but we will include the conference abstracts and unpublished data that were retrieved in our searches (eg, unpublished data retrieved from ClinicalTrials.gov).

To maintain currency, we will adopt a living evidence framework and will update the search every 2 months.

Eligibility Criteria

We will include studies meeting the eligibility criteria described below.

Design and Population

We will include parallel-arm RCTs of adults aged ≥18 years with severe infection. Severe infection will be defined as the presence of suspected or microbiologically confirmed infection for which hospital ward or intensive care unit admission would be considered appropriate (ie, if feasible with available resources). We intentionally chose a liberal characterization of severe infection to include associated end-organ dysfunction (ie, sepsis [2]) and other studies in which organ dysfunction is not reported but patients are acutely ill and may still benefit from early treatment. We also chose this approach to account for the lack of intensive care units in many resource-limited settings [21] and variability in clinical practices across settings. Eligible studies may also enroll patients with severe infection involving at least 2 quick SOFA (qSOFA) criteria [22] or those meeting the WHO definition of sepsis (systolic blood pressure: <90 mm Hg) and 1 or more of the following: a pulse of >100 beats per minute, a respiratory rate of >24 breaths per minute, or abnormal temperature (<36 °C or >38 °C) [23]. We chose qSOFA criteria given feasibility of application across settings independent of laboratory criteria, despite imperfect discrimination of mortality in infected patients [24]. We will also consider the following studies to be eligible: (1) those in which at least 80% of patients meet our inclusion criteria for the population of interest and (2) those that include patients with severe organ failure, such as acute respiratory distress syndrome (ARDS), as long as outcomes are reported for the population with severe infection as the risk factor for ARDS.

Intervention

Trials with at least 1 arm involving the administration of parenteral vitamin C alone or in combination with other micronutrients and therapies will be included. Eligible studies will include those that administered doses of parenteral vitamin C above the very small doses that are typically seen in parenteral nutrition settings (100 mg/day), including high doses (>12 g/day), moderate doses (6-12 g/day), and low doses (<6 g/day). These dose cut points are arbitrary, but the use of 6 g to define the lower bound of high doses is consistent with a previous scoping review of adverse effects [25]. For studies using a weight-based regimen of vitamin C, we will use the mean patient weight to calculate a total daily dose. If this is not provided, we will assume that 70 kg is the mean weight. We will not exclude studies on the basis of administered cointerventions.

Comparator

At least 1 arm in included trials must not receive parenteral vitamin C; that arm may receive either placebo or active treatment. We will exclude studies that compare the same regimen of parenteral vitamin C with different cointerventions across multiple arms and studies that compare different regimens of parenteral vitamin C without an arm that lacks parenteral vitamin C administration.

Primary Outcomes

The primary outcomes will include in-hospital mortality, 30-day mortality, and 90-day mortality. We will include mortality data that are reported closest to the time points of interest.

Secondary Outcomes

The secondary outcomes will include the need for and duration of intensive care unit admission and invasive ventilation; the duration of hospitalization; the time to clinical improvement based on changes in the WHO 7-point ordinal scale for clinical status [26] (or another severity measure); changes in SOFA scores from baseline; stage 3 acute kidney injury, as determined by the Kidney Disease: Improving Global Outcomes criteria [27]; and the need for renal replacement therapy. Other secondary outcomes will be serious adverse events that result in the discontinuation of vitamin C, new hemolysis, new nephrolithiasis or clinically important oxaluria, and hypoglycemic episodes. The time point of interest for all secondary outcomes will be the 30-day follow-up or the closest available time point.

We will include studies meeting the eligibility criteria and reporting at least 1 primary or secondary outcome of interest. We will include grey literature and conference abstracts meeting other eligibility criteria.

Study Selection

Paired reviewers will screen identified citations at the title and abstract screening level based on predefined eligibility criteria. Potentially eligible citations will subsequently be reviewed at the full-text screening level by paired reviewers. Screening will be completed independently and in duplicate. Disagreements will be resolved by a third reviewer.

Data Extraction and Risk of Bias Assessment

We will extract data on study populations, interventions, comparators, and outcomes of interest as well as conduct prespecified subgroup analyses. Specifically, we will extract data on the following variables:

- Study-level characteristics: publication status, study design, and funding type
- Patient-level baseline demographic characteristics: country, median or mean age, proportion of males, and proportion of patients with renal disease
- Patient-level baseline clinical characteristics: primary infectious source (pneumonia vs intra-abdominal vs genitourinary vs other), proportion of intensive care unit–admitted patients, proportion of patients with confirmed COVID-19, illness severity score, proportion of patients needing renal replacement therapy, proportion of

patients needing vasopressors, proportion of patients with ARDS, proportion of patients needing basic supplemental oxygen modalities (including face masks, nasal prongs, noninvasive ventilation, and high-flow nasal cannulas), proportion of patients needing invasive mechanical ventilation, and mean or median serum lactate level

- Study-level intervention arm characteristics: description of regimen, number of patients randomized, total daily vitamin C dose, dosing level (as defined in the *Intervention* section), duration of treatment, cointerventions (including thiamine, corticosteroids, and other therapies) and associated doses and durations, route of administration, mean time from presentation or enrollment to the initiation of the intervention, mean fluid volume administered from admission or sepsis recognition to randomization, and mean fluid volume administered from randomization up to the first 24 hours postrandomization and received in first 6 hours of therapy
- Study-level dichotomous outcomes: outcomes reported, follow-up time (in days), number of participants analyzed, and number of events reported
- Study-level continuous outcomes: outcomes reported, follow-up time (in days), number of participants analyzed, measures and estimates of central tendency, measures and estimates of variability, and definitions used for time to clinical improvement outcomes (if applicable)
- Study-level subgroup analyses (see *Planned Subgroup and Sensitivity Analyses* section)
- Outcome-level risk of bias (RoB) assessment: dichotomous or continuous outcomes (1 evaluation per outcome) and assessment by domain, with justification

We will use a modified version of the RoB 2.0 tool, which was implemented in a recent systematic review [11], for related assessments in every eligible study. The RoB will be classified as "low," "probably low," "probably high," or "high" for the following domains: bias due to randomization, bias due to deviations from the intended intervention, bias due to missing outcome data, bias in the measurement of the outcome, bias in the selection of the reported result, and other biases. We will rate the overall RoB based on the highest risk attributed to any criterion.

Paired reviewers will extract data and evaluate the RoB of eligible studies independently and in duplicate. Disagreements will be resolved by consensus. Data extraction and RoB evaluations will be conducted by using predetermined forms.

Assessment of the Certainty of the Evidence

We will assess the overall certainty of the evidence for each outcome by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, based on the following domains: RoB, imprecision, inconsistency, indirectness, and publication bias. The overall certainty of evidence will be rated as "very low," "low," "moderate," or "high." We will consider rating down the certainty of evidence for the RoB domain based on a lack of blinding for subjective outcomes only. We will make judgments on imprecision by using a minimally contextualized approach. We will consider

any CI encompassing the null effect to be imprecise while taking into consideration important and trivial effects [28].

Statistical Analyses

We plan to conduct random effects modeling for our meta-analyses. All analyses will be performed in RevMan 5.3 (Cochrane Collaboration). Study weights will be generated by using the inverse variance method. We will present dichotomous outcomes as RRs and continuous outcomes as mean differences or standardized mean differences; these will all be presented with 95% CIs. We will assume a normal distribution for continuous outcomes and will convert interquartile ranges to standard deviations, as per the guidance from the Cochrane Collaboration [29]. We will use a web-based plot digitizer to obtain estimates only when outcomes of interest are presented graphically.

We will assess statistical heterogeneity among studies by using the I^2 measure, and inconsistency will be judged with GRADE assessments on the basis of the magnitude and direction of heterogeneity. We will assess publication bias via the visual inspection of funnel plots. This method will be supplemented by a regression test if at least 10 studies contribute to an outcome [30].

For each outcome, the primary analysis will include data from all studies meeting the eligibility criteria and reporting the outcome.

Planned Subgroup and Sensitivity Analyses

If sufficient data are available, we will plan the following subgroup analyses: (1) high-dose vitamin C versus moderate-dose vitamin C versus low-dose vitamin C (as previously defined; hypothesis: greater effects in the high-dose group), (2) vitamin C administration as monotherapy versus vitamin C administration in combination with other interventions (hypothesis: no differences in effects), and (3) treatment of patients with COVID-19 versus treatment of other severe infections (hypothesis: no differences in effects).

We will plan sensitivity analyses, which will be limited to (1) peer-reviewed studies published in full text and (2) low RoB studies.

Patient and Public Involvement

We do not plan to involve patients or public members in the conduct of this systematic review.

Dissemination

We plan to disseminate our study results through national and international critical care–focused and methodology-focused conferences. We also plan to publish our findings in a peer-reviewed journal.

Ongoing Updates

The review will be a living meta-analysis and will be iteratively updated every 4 to 6 months to incorporate emerging randomized trial evidence. Meta-analyses will be updated iteratively with the same frequency. When new evidence changes the certainty or direction of estimates for any primary

or secondary outcomes, we will disseminate subsequent iterations of our findings.

Results

Among the 1386 citations identified as of March 30, 2021, a total of 17 eligible RCTs have been identified as of September 2021. We are in the process of updating the search strategy and associated data analyses.

Discussion

Severe infections that result in hospital admission and organ dysfunction in sepsis are associated with significant global morbidity and mortality [3]. The COVID-19 pandemic has resulted in over 251 million COVID-19 cases and 5 million deaths [31]. Given the publication of recent trials and a variety of tested vitamin C regimens, an updated evidence synthesis regarding the efficacy and safety of parenteral vitamin C in this context is warranted. Our findings will inform clinical practices in hospitals for the management of severe infections, including COVID-19.

Our planned systematic review has a number of strengths. First, we will summarize evidence relevant to all severe infections for which hospitalization is required. Our findings will therefore be more applicable than those of recent reviews on vitamin C in critically ill patients in general [17]. Second, we will incorporate a number of recent landmark trials that have been published in the interim, including the CITRIS-ALI (Vitamin C Infusion for Treatment in Sepsis-Induced Acute Lung Injury) trial [18], VITAMINS (Vitamin C, Hydrocortisone, and Thiamine in Patients With Septic Shock) trial [19], ATESS (Ascorbic Acid and Thiamine Effect in Septic Shock) trial [20],

ORANGES (Outcomes of Metabolic Resuscitation Using Ascorbic Acid, Thiamine, and Glucocorticoids in the Early Treatment of Sepsis) trial [32], HYVCTTSSS (Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Sepsis and Septic Shock) trial [33], and ACTS (Ascorbic Acid, Corticosteroids, and Thiamine in Sepsis and Septic Shock) trial [34]. These trials will provide higher certainty estimates for our primary and secondary outcomes of interest. Third, we intend to create regular updates to produce a living systematic review that will provide updated estimates of effects as new trial evidence becomes available. Fourth, we have used a comprehensive search strategy that was developed with the aid of a medical librarian; have incorporated both published and unpublished data; have a predefined review, statistical analysis, and subgroup analysis plan in place; and intend to use the GRADE methodology to systematically evaluate certainty in effect estimates. Fifth, our summary of ongoing trials, which will be kept updated on an iterative basis, will provide a useful resource that contains upcoming and emerging evidence. Finally, we intend to share our data with any interested living network meta-analysis teams, so that evidence on parenteral vitamin C administration may be used to iteratively inform indirect comparisons to other treatments for severe infection, sepsis, and COVID-19.

In conclusion, this protocol describes the detailed methodology of a planned living systematic review and meta-analysis that will address the comparative efficacy and safety of parenteral vitamin C administration in patients with severe infections. The results will be of importance to critical care physicians and hospitalists who manage severe infection in daily practice, and they may directly inform international clinical guidance regarding the management of sepsis.

Authors' Contributions

AA, FL, and NKJA conceptualized the project and prepared the first draft of the systematic review protocol. All authors provided critical revisions and approved the final manuscript.

Multimedia Appendix 1
Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) checklist.
[PDF File (Adobe PDF File), 131 KB - resprot_v11i1e33989_app1.pdf]

Multimedia Appendix 2
Search strategy.
[PDF File (Adobe PDF File), 117 KB - resprot_v11i1e33989_app2.pdf]

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Abbreviations

ACTS: Ascorbic Acid, Corticosteroids, and Thiamine in Sepsis and Septic Shock
ARDS: acute respiratory distress syndrome
ATESS: Ascorbic Acid and Thiamine Effect in Septic Shock
CI: Confidence Interval
CITRIS-ALI: Vitamin C Infusion for Treatment in Sepsis-Induced Acute Lung Injury
GRADE: Grading of Recommendations Assessment, Development and Evaluation
HYVCTTSSS: Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Sepsis and Septic Shock
ORANGES: Outcomes of Metabolic Resuscitation Using Ascorbic Acid, Thiamine, and Glucocorticoids in the Early Treatment of Sepsis
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols
RCT: randomized controlled trial
RoB: risk of bias
RR: risk ratio
SOFA: sepsis-related organ failure assessment
VITAMINS: Vitamin C, Hydrocortisone and Thiamine in Patients With Septic Shock
WHO: World Health Organization

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Protocol

Geographical Disparities in Pooled Stroke Incidence and Case Fatality in Mainland China, Hong Kong, and Macao: Protocol for a Systematic Review and Meta-analysis

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Abstract

Background: Geographical variations in stroke incidence and case fatality in China have been reported. Nonetheless, pooled estimates in major Chinese regions are unknown.

Objective: This systematic review and meta-analysis aims to investigate pooled estimates of incidence and short-term case fatality of stroke in Mainland China, Hong Kong, and Macao.

Methods: Longitudinal studies published in English and indexed in PubMed/MEDLINE, Embase, CINAHL, and Web of Science, or in Chinese and indexed in SinoMed and CQVIP will be targeted. Articles reporting on adults living in China who experience first-ever stroke or die within 1 year from newly onset stroke will be included. The 95% confidence intervals of the event will be estimated using the exact method based on the Poisson distribution. The log incidence rates together with their corresponding log standard errors will be meta-analyzed using DerSimonian and Laird random effects models. Pooled case fatality rates will also be estimated using a random effect model. Time trends in pooled age-standardized stroke incidence and case fatality will be estimated. The heterogeneity of the included studies will be measured using the I^2 statistic and meta-regressions will be run to analyze the effect of reported covariates on found heterogeneity. Risk of bias will be examined using the Newcastle-Ottawa Scale. Publication bias will be tested using funnel plots and Egger tests. Sensitivity analysis will be run by risk of bias.

Results: This study was funded and registered in 2020. The systematic searches, study selections, and quality assessments were completed in July 2021. Data extraction and analysis and manuscript writing are scheduled to be completed by December 2021.

Conclusions: This will be the first study to provide regional differences in pooled estimates of stroke incidence with case fatality in Mainland China, Hong Kong, and Macao. This study will assist in addressing inequalities in stroke care across China.

Trial Registration: PROSPERO International Prospective Register of Systematic Reviews CRD42020170724; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=170724

International Registered Report Identifier (IRRID): PRR1-10.2196/32566

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Introduction

Background

Stroke is the leading cause of death in China, contributing to one-third of global stroke-associated mortality [1-3]. Compared to high-income countries, including those in North America, Australia, and western and central Europe, China has lower stroke prevalence but higher incidence rate and mortality [2,4]. An ongoing stroke surveillance program covering 31 provinces in China reported an annual increase of 8.3% in the incidence of first-ever stroke in adults, from 189 per 100,000 population in 2002 to 379 per 100,000 population in 2013, with ischemic stroke and hemorrhagic stroke having incidences of 335 and 44 per 100,000 population, respectively, in 2013 [5]. By contrast, comparing 1990 with 2010, age-adjusted stroke mortality rates in China dropped from 167 to 126.9 per 100,000 population [6]. Reflecting stroke-associated productivity costs, patients bear the highest financial burden of stroke, with an estimated 33% of Chinese patients falling into poverty after experiencing stroke due to functional disability and health services costs [7].

Regional variations in the incidence of stroke and stroke-associated mortality across China are continuously reported [3,8-10], showing a north-south gradient; high and low incidence rates are reported in northeast and southeast Chinese coastal provinces, respectively [8,9], with rates being 2.4-fold higher in northeastern provinces [11]. A total of 9 provincial-level regions (Heilongjiang, Jilin, Liaoning, Inner Mongolia, Beijing, Hebei, Ningxia, Tibet, and Xinjiang) form a so-called stroke belt, covering north and west China, with stroke incidence being twice as high as that documented in provinces outside this belt [10]. Disparities in stroke mortality rates are similarly reported in urban and rural populations [12]. Significant geographical differences in mortality-to-incidence ratios have also been observed. The mortality-to-incidence ratio in southwest China is 0.68, which is considerably higher than the ratio of 0.42 found in east and south China [2].

Gaps in the Literature

Considerable variations in the proportion of different pathologic types of stroke have been reported, with the proportion of intracerebral hemorrhage varying from 26.7% to 51.5% between Beijing and Changsha, which is a metropolitan city in central China [13]. Disproportionately higher rates of hemorrhagic stroke than ischemic stroke were reported in a 14-year study conducted in Changsha [14], which contradicts worldwide literature where ischemic stroke is reported at higher rates. By contrast, a nationwide study in 31 provinces showed that ischemic stroke was the major type of stroke in China, with the highest incidence rate being 166.9 per 100,000 population, constituting 70% of newly incident strokes [3]. Nonetheless, inconsistencies in stroke incidence continue to be reported across China [8], causing uncertainty regarding the real incidence rate among the Chinese population.

China is experiencing a decreasing trend in case fatality rates, with the overall rate of mortality per 100,000 population decreasing by 31% in urban or suburban regions and 11% in rural regions compared to 3 decades ago [15]. Although the proportion of patients with severe stroke admitted to best performing hospitals in China increased from 2007 to 2010, in-hospital case fatality following stroke hospitalizations dropped from 3.16% to 2.30% [16]. Underlying factors contributing to the downward trend of stroke case fatality in China may include improved treatments, broadened health care coverage, enhanced preventative campaigns, and public health literacy of stroke [15]. However, inconsistencies in stroke case fatality estimates have also been reported in China, ranging from 6.5% to 77.3% [8], which may have resulted from differences in inclusion and exclusion criteria used, resulting in samples that were not representative of the overall Chinese population diagnosed with acute stroke. Similarly, pooled estimates of the incidence of different types of stroke in China are currently unknown. Hence this systematic review (SR) and meta-analysis aims to estimate the pooled incidence and short-term case fatality of acute and nonrecurrent ischemic and hemorrhagic stroke in Mainland China, Hong Kong, and Macao. The evidence-based findings of the proposed study will inform policy making in stroke management and stroke prevention in China.

Methods

Study Registration

The protocol of this proposed study has been registered in the International Prospective Register of Systematic Reviews (PROSPERO): CRD42020170724.

Criteria for Study Selection

Definition of Stroke

This study will use the World Health Organization (WHO) standard definition of stroke: "rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin" [17]. Studies reporting the International Statistical Classification of Diseases and Related Health Problems (ICD) 10th version codes I60 to I64 and equivalent codes in earlier version will also be eligible for inclusion [18].

Inclusion and Exclusion Criteria

Inclusion Criteria

Studies that meet the following criteria could be included in the meta-analysis:

- Human adult populations (≥18 years old) experiencing an acute stroke or acute stroke-related death occurring within 1 year following diagnosis.

- Prospective or retrospective cohort studies reported in either English or Chinese.
- Study populations living in Mainland China, Hong Kong, or Macao.
- Sample size equal to or greater than 100 individuals. Studies reporting on less than 100 individuals will be regarded as case reports [19].

Exclusion Criteria

Studies that meet the following criteria could be excluded from the meta-analysis:

- Reporting on prevalent stroke or prevalent stroke-associated death. Admissions with acute stroke that occurred 48 hours after diagnosis will be considered as prevalent cases.
- Reporting on recurrent stroke or not clearly documenting past history of stroke.
- Reporting on transient ischemic attacks, silent cerebral infarcts, iatrogenic stroke, trauma-related or injury-related stroke, epidural hemorrhage, or central retinal artery occlusion.
- Case reports, case series, case-control studies, cross-sectional studies, studies with experimental or quasi-experimental designs, ecological studies, qualitative studies, abstracts without full text, comments, letters to the editor, newspaper articles or other non–peer reviewed grey literature, government reports, book chapters, reviews, and study protocols.
- Published before 1990 as before this year, computerized tomography (CT) and magnetic resonance imaging (MRI) were not widely used for stroke diagnosis in China [20].
- Data cannot be extracted.
- Denominators for estimating incidence and case fatality are not reported.
- No follow-up periods.

Other Considerations

Papers using the same data published in both English and Chinese will be included once. If multiple publications relate to the same study population, the study with the most complete data will be included.

Search Strategy

Electronic Searches

Systematic searches will target the following electronic bibliographic databases: PubMed/MEDLINE, Embase, CINAHL, Web of Science (for studies published in English), SinoMed and CQVIP (for studies published in Chinese). Subject headings, MeSH terms, keywords of incidence, and country will be searched in all fields, including the title, abstract, and full text. The searches of stroke and mortality will be limited to the title and abstract. The dates and numbers of matched studies of searches of all databases will be recorded. The search strategies for Chinese and English publications will be similar (Multimedia Appendix 1 displays the terms and keywords used in the search strategy)

Hand Searches

SRs on the topic, detected in the searches, will be hand searched for potentially eligible articles which were not identified in the aforementioned searches.

Data Collection

Selection of Studies

After removing duplicates, a team of researchers from La Trobe University, the Second Affiliated Hospital of Kunming Medical University, and Peking Union Medical College Hospital will follow the same screening process. Following the first screening, based on title and abstract, the full text of potentially eligible studies will be further screened. A total of 20% of the included studies in each step will be randomly and independently redone. Study authors will be contacted if additional details are needed for determining eligibility. All screened, excluded, and finally included articles will be reported in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) chart. This protocol was prepared in accordance with the PRISMA protocol (PRISMA-P) checklist.

Study Outcomes

Incidence of stroke will be measured as the number of new cases of stroke per 100,000 person-years. Short-term (1 month, 3 months, 6 months, and 1 year) case fatality will be reported as the ratio of the number of fatal cases to the total number of acute stroke cases. The Chinese standard populations over 3 decades, between 1990 and 2020, will be used to compute the age-standardized incidence and fatality rates for each historical period, when there is extractable data to do so.

Data Extraction and Management

Data will be extracted on the following covariates: date of publication, reporting language, authorship, regions under study, research design, sample size, time frame of the study, research setting (ie, community or hospital), information on the participants (age, sex, and smoking status), classification of stroke subtypes (ischemic or hemorrhagic), standard of diagnosis, and severity of stroke.

Risk of Bias Assessment

The quality and risk of bias (ROB) of all finally included articles will be examined using the Newcastle-Ottawa Scale [21]. This scale examines the ROB of observational studies using 8 items, grouped into 3 elements: the sample selection, the comparability of study groups, and outcome ascertainment. One asterisk is awarded to the study for each item within the elements of sample selection and group comparability, and 2 asterisks are assigned to comparability, with 9 asterisks indicating the highest quality. In this SR, the quality of each included study will be further catergorized as good, moderate, or poor according to the thresholds for transforming the Newcastle-Ottawa Scale into the Agency for Healthcare Research and Quality standards [22].

Disagreement Management

The coauthors will examine data extraction and quality evaluation independently. The level of agreement among reviewers will be estimated using the Cohen kappa coefficient. All inconsistencies in the screening process, assessment of the

ROB, and data extraction will be discussed to make the final decision on study inclusion or exclusion, and quality assessment.

Data Analysis

The exact method, based on the Poisson distribution, will be used to calculate 95% confidence intervals and standard errors of first-ever stroke. The incidence rates of disease will be expressed as Poisson means, estimated as the observed number of stroke events and probabilities relevant to the chosen confidence level, divided by time at risk. The log incidence rates together with their corresponding log standard errors, stratified by the 7 major Chinese geographical regions and 4 economic regions if there are enough data, will be meta-analyzed using DerSimonian and Laird random effects models [23]. Fixed effects models will also be considered. The pooled estimates will be age-standardized using the direct method, with the Chinese general population considered as standard. Case fatalities by region will also be meta-analyzed using random effect models. Region-specific analyses of pooled estimates of linear trends over time will be assessed using a chi-square test. The I^2 statistic will be used to assess the heterogeneity of included studies [24]. The effect of reported covariates (ie, sample size; research setting, whether community or hospital; severity of stroke; and age, sex, and smoking status of the participants) on the heterogeneity in estimates of incidence and mortality among different studies will be evaluated using meta-regression. Subgroup analyses will be conducted by region. Funnel plots and Egger tests will be used for evaluating publication biases.

All analyses will be done separately for ischemic, hemorrhagic, and total stroke. Sensitivity analyses will be run by study setting (ie, community or hospital), publication language, and ROB.

All analyses will be conducted using Stata/SE, version 15.1 (StataCorp LLC). Stata's metan command will be used to run the meta-analysis.

Results

The systematic searches, study selections, and quality assessments were completed in July 2021. Data extraction and analysis and manuscript writing are scheduled to be completed before December 2021.

Discussion

Pooled acute stroke incidence and case fatality rates in China are unknown. Reported estimates in the same or different regions vary considerably, making it hard to know the true incidence and fatality rates in the general Chinese population. Inconsistencies in these estimates may arise for various reasons [2,8]. Studies reporting incidence of stroke often use different diagnostic criteria, including definitions based on WHO criteria [25], Chinese National Stroke Conference criteria [8], or those based on ICD 9th or 10th codes [26]. Different methods of case ascertainment may also be used, which can lead to variations in incidence and case fatality rates. Examples of case ascertainment include neuroimaging (CT or MRI), medical records, self-reports, death registry data, and insurance claim

records. Furthermore, different reference populations for age-standardization are often used, for instance, the world standard population [8], the US population [8], or the Chinese population [27]. Discrepancies in case fatality estimates may also be caused by the inclusion of different etiological types of stroke, recurrent or first-ever stroke, different onset ages, different levels of severity, and different selection criteria of included patients. Moreover, in China, disease incidence is often measured using household survey methods that lack follow-up periods [3,28,29]. Such commonplace cross-sectional surveys, which are more suitable to measure prevalence and burden of disease rather than incidence of disease, can produce potentially biased estimates because of nonresponse bias, reporting bias, and sampling errors due to the exclusion of certain groups from the sampling frames [30].

In this study, several measures will be undertaken to minimize potential biases in using published incidence and case fatality estimates. The SR will abide by strict inclusion and exclusion criteria to ensure that the included cases are representative of the Chinese general population. Acute stroke will be restricted to first-ever cases, with studies enrolling cases after 48 hours from diagnosis being excluded. Only studies that report a clear follow-up time will be considered. Cross-sectional surveys over a period of time without prospective or retrospective follow-up of participants will be excluded. Age standardization will be based on the Chinese general population. Furthermore, the choice of 1990 as the earliest publication date will ensure the validity of case ascertainment as, after that year, CT and MRI became more widely used in China [20].

This SR has strengths, but it also has some potential limitations. Metropolitan and economically developed regions in the northern and eastern coastal regions are likely to be overrepresented as research data are less available from less developed regions in west China [10]. Although this SR aims to remove all duplicate studies, it is possible that studies in similar locations may be reporting data on overlapping samples. If the authors did not explicitly describe their included samples, the inclusion of overlapping samples is likely. This SR will not investigate the subtypes of ischemic and hemorrhagic stroke, although the incidence, case fatality, and prevention and management strategies of their subtypes vary significantly. This study will investigate all-cause mortality following first-ever stroke instead of stroke-related death; however, our SR will only focus on 1-year all-cause mortality, which is more likely to have been caused by the stroke event.

Striking inequalities are reported in both the availability and quality of health care in China. Disparities in regional Healthcare Access and Quality scores are consistent with differences in the number of medical doctors per 1000 population and the proportion of designated stroke centers among secondary and tertiary hospitals in different provinces in China [2]. Investigating the stark differences in stroke epidemiology in different regions of China will be an important step in understanding these geographical differences. Our SR findings have the potential to better inform and influence clinical practice and policy making to address the regional inequalities in stroke-associated health outcomes in China.

Funding

Authors' Contributions

FH，GM, and IB conceived the idea and formalized the design of this proposed SR and meta-analysis. FH, GM, LY, and HX prepared and finalized the search strategy. FH and GM analyzed and interpreted the data. All authors contributed to drafting this protocol paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Terms and keywords used in search strategy.
[DOCX File , 24 KB - resprot_v11i1e32566_app1.docx]

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Abbreviations

CT: computerized tomography
ICD: International Statistical Classification of Diseases and Related Health Problems
MRI: magnetic resonance imaging
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: PRISMA protocol
PROSPERO: International Prospective Register of Systematic Reviews
ROB: risk of bias
SR: systematic review
WHO: World Health Organization

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Protocol

Outcomes Following eHealth Weight Management Interventions in Adults With Overweight and Obesity From Low Socioeconomic Groups: Protocol for a Systematic Review

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Abstract

Background: Obesity is a complex health condition with multiple associated comorbidities and increased economic costs. People from low socioeconomic status (SES) backgrounds are more likely to be overweight and obese and are less successful in traditional weight management programs. It is possible that eHealth interventions may be more successful in reaching people from low SES groups than traditional face-to-face models, by overcoming certain barriers associated with traditional interventions. It is not yet known, however, if eHealth weight management interventions are effective in people living with overweight and obesity from a low SES background.

Objective: The primary aim of this study is to evaluate the efficacy of eHealth weight management interventions for people with overweight and obesity from low SES groups.

Methods: A systematic review on relevant electronic databases (MEDLINE, Embase, Emcare, and CINAHL) will be undertaken to identify eligible studies published in English up until May 2021. Using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement to guide the systematic review, two reviewers will independently screen, select, and extract data and complete a risk of bias assessment of search results according to predefined criteria. Studies that have investigated an eHealth weight management intervention within a low SES population will be included. Primary outcomes include weight, BMI, and percentage weight change compared at baseline and at least one other time point. Secondary outcomes may include a range of anthropometric and physical fitness and activity measures. If sufficient studies are homogeneous, then we will pool results of individual outcomes using meta-analysis.

Results: Searches have been completed, resulting in 2256 studies identified. Once duplicates were removed, 1545 studies remained for title and abstract review.

Conclusions: The use of eHealth in weight management programs has increased significantly in recent years and will continue to do so; however, it is uncertain if eHealth weight management programs are effective in a low SES population. The results of this systematic review will therefore provide a summary of the evidence for interventions using eHealth for people living with overweight and obesity and from a low SES background.

Trial Registration: PROSPERO International Prospective Register of Systematic Reviews CRD42021243973; https://tinyurl.com/2p8fxtnw

International Registered Report Identifier (IRRID): DERR1-10.2196/34546

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KEYWORDS

Introduction

Background

Overweight and obesity are associated with increased risk of developing common diseases that can cause premature death. These include type 2 diabetes, cardiovascular disease, liver disease, and some cancers and respiratory diseases [1]. There is also a bidirectional association between obesity and depression [2]. Overweight and obesity is therefore a complex condition conferring significant health, social care, and financial burden, which requires carefully designed countermeasures and interventions throughout the life cycle [3]. A person is currently considered overweight if their BMI (the ratio of mass in kg to squared height in meters) is ≥25kg/m^2, and obese if their BMI is ≥30 kg/m^2 [4]. Overweight and obesity is a growing health problem. Global obesity rates have more than doubled since 1980, with the mean (95% CI) BMI in the United Kingdom rising from 24.7 (24.4-25.0) kg/m^2 in 1986 to 27.1 (26.8-27.5) kg/m^2 in 2016 [5]. Tackling overweight and obesity is therefore an urgent public health emergency for policy makers, clinicians, and researchers, as well as the individual themselves [6,7].

Independent studies globally have confirmed that low socioeconomic status (SES) is associated with increased rates of overweight and obesity (eg, in China [8], the United States and France [9], and the United Kingdom [10]). Several parameters need to be assessed to measure SES including an individual's income, educational level, and occupation [11]. Other measures exist such as the Indices of Deprivation, used in England, which also includes exposure to crime, health, housing, and living environment domains [12]. These measures have been used to provide compelling evidence that deprivation is associated with worse health behaviors and outcomes; those who live in more deprived areas are more likely to engage in unhealthy behaviors (smoking, increased alcohol consumption) and less likely to engage in healthy behaviors (physical activity, healthy diet) compared with those in less deprived areas [13]. Thus, SES should be considered a confounding factor in studies determining the efficacy of weight management interventions if the intervention adopts behavior change approaches [6].

It is not surprising therefore that traditional behavior change interventions that target unhealthy behaviors in low SES groups have reported modest improvements in weight and physical fitness compared to people from higher SES. For example, meta-analyses estimated modest standardized mean differences (95% CI) between low-income groups and controls of 0.22 (0.14-0.29) following diet interventions, 0.21 (0.06-0.36) following physical activity interventions, and a relative risk of smoking following abstinence interventions of 1.59 (1.34-1.89) [14]. In a qualitative study of people delivering, receiving, and following an eating lifestyle change intervention in a low SES community, incorporation of diverse language/literacy, cultural origin, and the availability/cost of healthy foods and physical

activity options were important factors that could lead to more equitable success in weight loss [15]. This study acknowledged that not adapting interventions that are less efficacious for people with low SES would increase existing inequalities across SES groups. However, it also acknowledged that a dearth of literature is available with which to plan what to adapt (and how), and its results certainly help to address this by tailoring the service to multiple cultures and lobbying for fair local amenity access. What this welcome study did not include as a factor was any personal choice in the medium of weight loss interventions.

eHealth is defined as interventions delivered using computers, mobile phones, or similar media devices via internet websites/web applications; mobile or social network apps; email; or SMS text messaging [16]. It is possible that technological advances mean eHealth interventions can be offered as an alternative approach for low SES patients. Traditional weight management interventions typically require frequent face-to-face sessions. However, individuals from low SES have expressed barriers to physically attending health care appointments, which include stress arising from taking time off work, and excessive travel and childcare costs within limited personal budgets. It is therefore possible that eHealth options may be preferred by low SES individuals [17,18]. Prioritizing the use of technology may also help reach diverse groups that are often underrepresented in research and real-world interventions [19].

Ambitions for eHealth have been transparent in the UK National Health Service (NHS) over the last decade. NHS England's Five Year Forward View alluded to the health care opportunities afforded by the "information revolution" and "electronic glue" [20]. More recently, one of the NHS Long Term Plan aims was to increase the percentage of "digital access" options for services available for patients' care, with 100% of patients being offered a "digital-first" primary care consultation by 2023/24 [21]. There is also the acceleration of eHealth uptake in response to the COVID-19 pandemic, culminating in recent guidance from NHS England that 25% of all outpatient health consultations in secondary care should be offered remotely via telephone or video [22]. Given these ambitions and the eHealth evolution, there is no doubt the direction of travel for weight management interventions incorporates eHealth options. Although a large meta-analysis demonstrated that eHealth weight management interventions achieve statistically significant weight loss compared to controls [19], the analyses did not account for SES. Thus, it remains unclear whether eHealth options could lead to more equity in weight management intervention outcomes independent of SES.

Objectives

We propose to undertake a systematic review of the literature and determine what eHealth weight management interventions are offered and whether they are effective in facilitating weight loss and physical fitness and activity gains in people with low SES. The primary aim of this study is to first determine what eHealth weight management interventions exist in promoting

weight loss and improving physical activity and fitness for people living with overweight and obesity from low SES groups, and second evaluate their efficacy. The proposed systematic review aims to answer the following questions:

1. Are eHealth interventions effective in facilitating weight loss in people living with overweight or obesity from a low SES background?
2. Are eHealth interventions effective in facilitating improved physical fitness in people living with overweight or obesity from a low SES background?

Methods

Overview

This systematic review will be conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement [23]. The protocol has been reported according to the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) checklist [24] (Multimedia Appendix 1).

Eligibility Criteria

Eligibility criteria were structured using a PICOS (Population, Intervention, Comparison, Outcomes, and Study design) framework [25] (Table 1).

Table 1. Study eligibility criteria using the PICOS (Population, Intervention, Comparison, Outcomes, and Study design) criteria.

Criteria	Inclusion	Exclusion
Population	• Adults ≥18 years old with BMI >25 kg/m^2 • Low socioeconomic status	• Pregnancy or postpartum (within 3 months) • Any socioeconomic status other than low socioeconomic status
Intervention	• Weight management intervention delivered using eHealth technology	• Bariatric surgery • Medication-only interventions
Comparator	• N/A[a]	• N/A
Outcome	• Weight (kg), BMI (kg/m^2), and/or percentage weight change • A range of anthropometric and physical fitness measures	• N/A
Study design	• Experimental studies • Observational studies • Case studies/series	• Reviews • Secondary analysis

[a]N/A: not applicable.

Population

Adults aged ≥18 years who are living with overweight or obese (BMI ≥25 kg/m^2) at baseline and are from a low SES background will be included. Low SES will include either low educational level, low income, or low occupational status, or any combination of these [11] (Table 2). The term "low" will refer to less well paid occupational status, fewer years of academic study, and lower income or a similar social disadvantage [26]. Individual studies will need to have defined SES based on stated criteria to be included. Studies including adults and children may be considered if data reported for adults are recorded separately. All participants with comorbidities will be included due to known associations of overweight and obesity with other health conditions [27].

Table 2. Outline of domains that relate to socioeconomic status.

Domain	Explanation
Income	The earnings an individual or family receive from employment, generally compared against the nation's average earnings [28]
Education	An indicator for knowledge and involves the level of educational attainment, generally measured as the highest level of schooling achieved, such as primary, secondary, and tertiary education [26]
Occupational status	Involves the power, income, and educational requirements associated with the job role itself and the physical or hazardous demands related to that job [29]

Intervention Types

Studies will be included if their weight management intervention aims include weight loss, weight loss maintenance, and physical fitness, and/or physical activity increase. Intervention mechanisms will be included if they include those recommended by the National Institute for Health and Care Excellence (NICE) guidelines [30] for weight management programs and include behavior change, diet, and nutrition education, meal replacement interventions, physical activity advice, and activity and exercise.

Studies that involve one or more domain as outlined by NICE [30] will be considered for inclusion as previous literature has identified large variations in published eHealth interventions [16,19]. Interventions will be eligible if they include a single or range of eHealth technology to deliver content, which may be delivered via the web, mobile apps, mobile phones, computers, or other related devices that require participants to be engaged. We will exclude studies involving bariatric surgery or obesity medication only interventions.

Comparisons

No limitation will be imposed on the control group. Studies with or without a control group will be considered eligible.

Outcomes

The primary outcomes of interest are weight (kg) and BMI (kg/m^2) either in absolute or proportional terms. Secondary outcomes will include any anthropometric or fitness measures including (but not limited to) body composition, percentage change of lean muscle mass, VO_{2max} (maximum oxygen consumption), estimated VO_{2max}, predicted VO_{2peak} (volume of oxygen uptake during peak exercise), aerobic capacity, and physical activity levels. We have included a large range of outcomes to counter the expected large variation among studies. A combination of anthropometric measures and cardiorespiratory fitness measures have been considered to ensure a breadth of results are included. All outcomes will be included for data extraction if secondary measurement has been made in addition to baseline to evaluate the effect of the intervention.

Study Design

We will include experimental and observational cohort studies designed to describe and/or investigate the efficacy of eHealth interventions. Experimental trials will include randomized control trials (RCTs), controlled clinical trials, or cluster trials. Observational studies will include prospective and retrospective comparative cohort studies, and cross-sectional, case-control, or nested case-control studies. We will exclude review articles, secondary analysis, and case study articles.

Timing

There will be no restrictions on the length of follow-up of outcomes.

Setting

There will be no restrictions by type of setting as interventions will be by remote access.

Language

Only studies written in the English language will be included.

Search Strategy

Literature search strategies will be developed using medical subject headings (MeSH) and text words related to the eligibility criteria outlined (Multimedia Appendix 2). We will search MEDLINE, Embase, Emcare, and CINAHL electronic databases. Both subject header and free-text searches will be completed, using Boolean search techniques, based on our PICOS framework (Table 1). Weight management and eHealth search terms were based on a previously published systematic review [16]. The grey literature will be searched using OpenGrey [31], and completed master's and doctoral theses will be searched using E-Theses Online Service (EThOS) [32]. All databases will be searched from their respective inception dates.

Data Collection and Analysis

Study Selection

Two authors (JS and RMI) will complete the database searches using the search terms in Multimedia Appendix 3. Results from the database searches will be transferred to proprietary reference manager software (Endnote X8.0.1, Clarivate) and duplicates will be removed. Proprietary systematic review software (Rayyan Systems Inc) will be used by the same two authors to independently screen titles, abstracts, and full-text articles according to the eligibility criteria. Reasons for exclusion will be explained and discrepancies will be resolved by a third experienced reviewer (GDJ) if consensus cannot be reached by the two authors.

Data Extraction

Literature search results will be collated in an adapted data extraction form based on The Cochrane Data Extraction Form for RCTs and non-RCTs [33]. Extracted data categories are outlined in Textbox 1. Two authors (JS and RMI) will independently extract data, with any discrepancies settled by a third experienced reviewer (GDJ) if consensus cannot be reached by the two authors.

Textbox 1. Data extraction form checklist.

Source

- Reviewer name

- Review date

- Study title and authors

- Journal name

- Publication date

Eligibility

- Confirm eligibility for review

Methods: participants

- Setting (including country)

Methods: design

- Study design and duration

Methods: interventions

- Description of intervention (eg, diet/nutrition advice, physical activity, behavior change techniques)

- Length of intervention/follow-up

- Delivery details (type of eHealth, eg, internet-based, social media, mobile phone/app, online platforms, emails, texts)

Methods: outcomes

- Name and definition (eg, weight [kg], BMI [kg/m^2], and/or percentage weight change, a range of anthropometric and physical fitness measures)

- Time point measure

- Attrition rate

Results

- Number of participants randomized/allocated per group/analyzed

- Baseline characteristics (age, ethnicity, sex, weight, BMI, socioeconomic status)

- Summary data for each group at each time point

- Any adverse events

Quality

Two authors (RMI and JS) will independently assess the risk of bias using the Joanna Briggs Institute (JBI) checklist [34,35]. The article study design will influence what element of the JBI checklist we use, but it is anticipated that most included studies will be of cross-sectional design, therefore it is likely that the JBI Checklist for Analytical Cross Sectional Studies will be used. The JBI checklist uses a 3-point nominal rating scale, where a score of 0 is assigned for low risk of bias, 1 for unclear, and 2 for high risk of bias for each of the domains on the checklist. Overall, a high risk of bias will be concluded if a study returned a final rating of >50% of the total possible score. For example, the JBI Checklist for Analytical Cross Sectional Studies has 8 domains; therefore, a high risk of bias will equal a score of 8 or more. See Multimedia Appendix 4 for each JBI critical appraisal tool and related domains and descriptions. Disagreements between reviewers will be resolved by a third author (GDJ) if consensus cannot be reached.

Data Analysis

We will conduct a narrative synthesis on all available data, examining findings between and within studies following national guidelines [25]. The narrative synthesis will include an account of interventions (eg, eHealth), participants' characteristics, and outcomes.

If an adequate number of homogeneous studies in terms of participants, intervention, and outcomes are returned, the individual outcomes will be pooled quantitatively using a fixed- and random-effects meta-analysis.

Amendments

In the event that the protocol needs amending, we will provide dates of each amendment, describe the changes, and give rationale in the section.

Results

This study aims to determine the effectiveness of weight management programs delivered using eHealth for people living with overweight and obesity and from a low SES. Searches were completed on May 5, 2021, in the 4 selected databases and 2256 studies have been identified. Once duplicates were removed, 1545 studies remained for title and abstract review.

Discussion

The prevalence of people living with overweight and obesity has increased over time. Although eHealth has been an effective tool in weight management programs, it is not yet clear if eHealth weight management interventions are effective for people with low SES. The results of this systematic review will therefore provide a summary of the evidence for interventions using eHealth for people living with overweight and obesity and from a low SES. If the results are not definitive, the systematic review will identify where further research is required.

Acknowledgments

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) checklist.
[[DOCX File , 32 KB](#) - [resprot_v11i1e34546_app1.docx](#)]

Multimedia Appendix 2
Search terms using PICOS (Population, Intervention, Comparison, Outcomes, and Study design) criteria.
[[DOCX File , 15 KB](#) - [resprot_v11i1e34546_app2.docx](#)]

Multimedia Appendix 3
Database search overview.
[[DOCX File , 64 KB](#) - [resprot_v11i1e34546_app3.docx](#)]

Multimedia Appendix 4
Risk of bias assessment tools.
[[DOCX File , 30 KB](#) - [resprot_v11i1e34546_app4.docx](#)]

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Abbreviations

EThOS: E-Theses Online Service
JBI: Joanna Briggs Institute
NHS: National Health Service
NICE: National Institute for Health and Care Excellence
PICOS: Population, Intervention, Comparison, Outcomes, and Study design
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols
RCT: randomized controlled trial
SES: socioeconomic status
VO_{2max}: maximum oxygen consumption
VO_{2peak}: volume of oxygen uptake during peak exercise

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<u>Protocol</u>

Self-compassion Education for Health Professionals (Nurses and Midwives): Protocol for a Sequential Explanatory Mixed Methods Study

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Abstract

Background: A few recent studies have reported that having the ability to provide self-compassion can reduce health professionals' levels of anxiety and stress, the risk of compassion fatigue, and burnout, and it can generally improve their well-being. Therefore, there is evidence to support further research into the investigation and exploration of self-compassion education and training for health professionals.

Objective: This study aims to increase the knowledge and understanding of self-compassion and how this may enhance the health and well-being of health professionals.

Methods: The proposed research study will adopt a sequential explanatory mixed methods design. This study will be conducted in 3 phases. Phase 1 will use a pre-educational self-compassion questionnaire (web-based survey) to collect data from participants at 3 time points (before, immediately after, and after follow-up at 6-8 weeks) after they have attended a self-compassion education and training program. Phase 2 will use an interview schedule to explore the participants' views and experiences through a follow-up focus group or individual interview. Finally, phase 3 will include data integration and dissemination of key findings and recommendations.

Results: This study was approved by the Women's and Children's Health Network Human Research Ethics Committee and the Human Research Ethics Committee at the University of South Australia on June 26, 2021 (ID: 204,074). A scoping review was conducted to inform this research study (focusing on nurses and midwives). The preparatory phase was completed in April 2021. Phase 1 is expected to be completed by June 2022 and phase 2 will commence in July 2022.

Conclusions: The key findings from the data integration for this research project will provide in-depth details and insights to broaden the discussion about self-compassion and its influence on health professionals' health and well-being. Health professionals (nurses and midwives) may benefit from self-compassion education and training programs to improve their health and well-being.

International Registered Report Identifier (IRRID): PRR1-10.2196/34372

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Introduction

Background

Self-care relates to any activity undertaken to take care of oneself and encompasses physical, spiritual, emotional, and mental health. Self-care is well recognized to reduce levels of anxiety and stress and thus improve mood. Unfortunately, self-care is often neglected, and being kind and compassionate to oneself is overlooked. However, self-compassion has been embedded in Buddhist philosophy and meditation and has been practiced for over 2500 years. Self-compassion was defined as "being caring and compassionate towards oneself in the face of hardship or perceived inadequacy," [1]. Neff describes three interrelated elements of self-compassion: self-kindness, common humanity, and mindfulness [2]. Self-kindness involves warmth and an understanding for oneself when faced with difficulties in life and painful experiences and not being overly critical and judgmental of oneself. Common humanity involves recognizing that difficulties in life and painful experiences do not just happen to you but are a shared human experience. Mindfulness involves taking a balanced approach for negative emotions and neither suppressing or exaggerating these and a willingness to acknowledge these negative emotions with openness and clarity (mindfulness-awareness). Self-compassion is related to overall psychological well-being [3,4].

There is some evidence that when a person has high levels of anxiety and stress and history of depression, this is associated with low levels of self-compassion [2,5]. However, much of the research that has been undertaken has involved students as the population of interest and, more recently, military veterans [6]. It has been discussed that when a person has the ability to have self-compassion, they are more inclined to have good interpersonal relationships and experience a greater sense of self-worth and happiness compared with a person who has an impairment in self-compassion [7]. However, there appears to be limited research examining and exploring what self-compassion as a component of self-care is and its relationship with health and well-being for health professionals. Therefore, there is justification to undertake research to investigate and explore what self-compassion as a component of self-care means and the impact of education and training on health professionals. In this study (*You Matter: Finding Your Self-Compassion for health professionals' education*), the first group of participating health professionals will be midwives and nurses.

Significance of Self-compassion for Health Professionals

A few recent studies have reported that self-compassion can reduce the levels of anxiety and stress, risk of compassion fatigue, and burnout and can generally improve well-being [8-11]. For example, a cross-sectional study involving primary health care professionals was undertaken to assess the impact of self-compassion as a protective factor against burnout [10]. This study reported that low levels of self-compassion increase the susceptibility to burnout among primary health care professionals. In addition, self-compassion has been shown to increase health professionals' ability to manage their negative emotions and prevent negative consequences, such as burnout, compassion fatigue, and depression, when undertaking their roles and responsibilities [12].

Self-compassion has also been reported to be associated with sleep patterns and resilience; a study that included dieticians, nurses, physicians, social workers, and others showed that the quality of sleep and resilience were strongly correlated with both self-compassion and mindfulness [13]. This study reported that sleep disturbances were strongly correlated with perceived stress and poorer health, but this was reduced when mindfulness and self-compassion were practiced. Similar findings were reported for resilience and less stress, and improved mental health was associated with practicing mindfulness and self-compassion.

A study conducted in the United States recruited a diverse range of health professionals, that is, nurses, physicians, and social workers, who were asked to participate in three web-based modules of education and training that included: (1) gratitude, (2) positive words, and (3) loving-kindness and compassion meditation [14]. The findings showed that this education or training was associated with statistically significant improvements in gratitude, well-being, self-compassion, and confidence in providing compassionate care. Therefore, web-based education and training appear beneficial to a diverse range of health professionals but further research is required to confirm or refute these findings. Health professionals often work in highly demanding environments and situations and are also part of the community at large; therefore, they are exposed to both professional and personal stressors. Self-compassion education and training may improve awareness and increase the health professionals' ability to have self-compassion, which may act as a buffer against poor mental health and maintain their well-being and the ability to be compassionate with others.

Findings and Conclusions From a Scoping Review

A scoping review was conducted to assess the influence of self-compassion on midwives and nurses, and it reported that self-compassion appears to help reduce work-based stressors such as anxiety, compassion fatigue, and burnout in nurses and midwives [15]. This review highlighted that there is some evidence suggesting that self-compassion can improve caring efficacy [16], empathy [17], and emotional intelligence in nurses [18]. In addition, self-compassion can provide overall improvement in the midwives' and nurses' well-being and ability to provide compassionate care [19]. Positive components of self-compassion (ie, self-kindness, common humanity, and mindfulness) are generally associated with compassion satisfaction, job satisfaction, and better sleep quality in nurses [20]. Therefore, the influence of self-compassion on midwives' and nurses' health and well-being may be an important factor that has implications for future self-care strategies.

This scoping review concluded that self-compassion education and training may improve awareness and increase midwives' and nurses' ability to have self-compassion. Therefore, there is an urgent need to explore and investigate the influence of self-compassion on these health professionals, particularly midwives, as this review highlighted a lack of studies and that most studies were related to nursing.

Preparatory Phase

An educational workshop was developed from a literature search relating to self-compassion and health professionals, specifically focusing on midwives and nurses [15,21] and the primary researcher (MS) attending self-compassion education classes.

You Matter: Finding Your Self-compassion Workshop

The *You Matter: Finding Your Self-Compassion education workshop* has been piloted with clinical educators. Two workshops were held at the chief nurse's education rooms in Adelaide on November 3, 2020. Overall, 21 clinical educators who were members of the South Australia Practice Development Network and employed by South Australia Health attended the workshops.

The workshop aimed to increase awareness and ability for self-compassion.

The workshop objectives were as follows: to explore the benefits of self-care, to introduce the five ways to well-being, to demonstrate the links between compassion and self-compassion, to explore the three elements of self-compassion, to discuss the evidence relating to self-compassion, to dispel the myths surrounding self-compassion, and to develop some self-compassion strategies.

Workshop Evaluation

Before the Workshop

A total of 21 participants completed an assessment form to assess the baseline information. The assessment form included questions about what self-compassion was, what it meant to the participants personally and whether they had received any previous education for self-compassion. The participants were asked to complete the Self-Compassion Scale short version [22]. This scale consists of 12 statements to assess self-compassion. Data analysis of the responses to the 12 statements demonstrated a self-compassion mean score of 38.38 (SD 3.43), which indicates that the clinical educators had a moderate to low level of self-compassion. Therefore, this finding further supports the justification for providing self-compassion education to health professionals and teaching clinical educators to become trainers.

After the Workshop

Clinical educators who attended the workshop were invited to complete a workshop evaluation form. This evaluation confirmed that all clinical educators acknowledged the importance and value of compassion for self and others. Almost all the educators strongly agreed that the workshop provided them with a clear understanding of what self-compassion was and the strategies that could be used. The interactive workshop content helped them understand the underpinning philosophy and increased their awareness of the health and well-being

benefits of self-compassion. All educators reported that they would practice self-compassion in the future. A total of 10 participants confirmed that they would like to attend a *Train the Trainer* session to teach self-compassion care and strategies to other health professionals. Overall, this workshop met the educators' expectations at both personal and professional levels. The evaluation following the workshop provided evidence that the aims and objectives of the self-compassion workshop were achieved.

Clinical Educators to Become Trainers

The clinical educators who attended the *You Matter: Finding Your Self-Compassion* workshops and expressed an interest in becoming a trainer were given an opportunity to attend a *Train the Trainer* session. As a result, a *Train the Trainer* session was facilitated in July 2021. Two further training session were undertaken in October and November 2021. Approximately 8-10 clinical educators have been trained to facilitate the workshops.

Research Aim

The overall aim of the study is to increase the knowledge and understanding of self-compassion and how this may enhance health and well-being of health professionals. However, for this first study, we are focusing on health professionals who are nurses and midwives.

Specific Objectives

The specific objectives of this study are as follows: to find out and explore what self-compassion means to nurses and midwives; to find out what being compassionate to others means to nurses and midwives; to determine if there is an association between self-compassion and the levels of anxiety and stress, mood, and well-being; to provide education to develop self-compassion strategies; and to enhance nurses and midwives' skills for self-compassion

Research Questions

This study aims to answer the following research questions: (1) What does self-compassion mean for health professionals (nurses and midwives)? (2) What does compassion for others mean to health professionals (nurses and midwives)? (3) What influence will self-compassion education and training have on health professionals' (nurses and midwives) health and well-being? (4) Are high levels of anxiety and stress associated with low levels of self-compassion, mood, and well-being among health professionals (nurses and midwives)?

Methods

Study Design

This proposed research will use a mixed methods approach and undertaken in two stages: quantitative phase and qualitative phase.

A sequential explanatory mixed methods study will be conducted to investigate and explore the influence of self-compassion on health professionals' health and well-being. The sequential explanatory mixed methods study design was chosen to combine the strengths of both quantitative and

qualitative research methods to answer the research questions and meet this study's aims and objectives. This mixed methods approach will be guided and underpinned by a pragmatist worldview that focuses on a research problem and on how to answer a research question and address the aims and objectives of a research study [23]. Pragmatism uses an integrative philosophy that combines quantitative and qualitative research without restrictive methodological directions. This mixed

methods study provides a flexible and transparent approach to unexpected data findings [24]. In addition, the mixed methods approach will provide in-depth details and insights to broaden the discussion and strengthen the study's findings to answer the research questions, draw key conclusions, and identify further research areas [25]. The planned time to undertake this mixed methods study involving midwives and nurses will be 12 months. Further research is planned to involve other disciplines of health professionals on the completion of this initial study.

Conceptual Framework

A conceptual framework for this mixed methods study will include a philosophical stance and strategies that will underpin and guide the specific direction through which the research will be undertaken.

Philosophical Assumptions and Pragmatism

It is important to determine the most suitable philosophical assumptions for the mixed methods study, as it is considered the main foundation for research [26]. Pragmatism was chosen because this stance supports the use of both qualitative and quantitative research methods [27], and it appears to be the most appropriate philosophy for a mixed methods approach [26,28,29].

Pragmatism accepts the views of both postpositivists and interpretivists by using an integrative logic, linking and combining quantitative and qualitative approaches [23]. It uses an integrative philosophy that combines both quantitative and qualitative research without restrictive methodological directions. Therefore, these combinations of methods and ideas provide the best conceptual framework to address and provide reasonable answers to research questions through a mixed methods approach [26].

Strategies for a Sequential Explanatory Mixed Methods Design

This research study will adopt a sequential explanatory mixed method design, which consists of gathering data separately and sequentially into 2 phases [23]. Phase 1 involves quantitative data collection and analysis. Phase 2 involves qualitative data collection and analysis. The findings from these 2 phases will be combined and mixed for integration and final analysis. The adopted sequential explanatory design will be the best to answer the proposed research questions and draw broader conclusions. Phase 3 will be undertaken on completion of the data collection and analysis and will involve data integration, dissemination, and translation of findings and recommendations.

Methods to Describe Data Collection

Phase 1 will use a pre-educational self-compassion questionnaire (web-based survey), which includes 4 measurement scales. This questionnaire will be used to collect data from participants at 3 time points (before, immediately after, and after follow-up at 6-8 weeks) after attending the self-compassion education and training program. After collecting the baseline data from participants regarding their compassion, well-being, anxiety and stress, and mood, they will be invited to attend a self-compassion workshop. Participants will then be reminded to submit an immediate questionnaire and a follow-up questionnaire 6 to 8 weeks after attending the self-compassion workshop. Phase 2 will use an interview schedule to explore the participants' views and experiences. Participants will be invited to participate in either a follow-up focus group or individual interview (depending on COVID-19 restrictions) via the study website.

Phase 1: Quantitative Phase (Workshop Education and Evaluation)

This phase will include a web-based survey, a self-compassion workshop, an immediate evaluation, and a follow-up evaluation of the participants after 6 to 8 weeks of attending the self-compassion education and training program.

Aims and Objectives of the Web-Based Survey

The aim of the You Matter: Finding Your Self-compassion for Health Professionals (Nurses and Midwives) web-based survey (3 time point questionnaires) is to find out what being compassionate to oneself means to health professionals (nurses and midwives) and its influence on their health and well-being.

The primary objectives are to investigate and explore what self-compassion means and measure levels of self-compassion and well-being for registered health professionals with the Australian Health Practitioner Regulation Agency in South Australia (nurses, midwives) and to assess whether there is an association between self-compassion and levels of anxiety and stress, mood, and well-being among the health professionals (nurses and midwives).

Recruitment and Sample Size

Health professionals (nurses and midwives) residing and employed in South Australia will be invited to participate in the study (see Textbox 1 for the inclusion and exclusion criteria). An invitation will be sent via South Australia Practice Development Network, professional bodies, and social media outlets such as Facebook (Meta Platforms, Inc) and Twitter (Twitter, Inc). A dedicated study website with the domain name "https://compassionselfcare.org/" is being designed and will be used for all nurses and midwives to access and participate in the study [30]. In addition, advertisements will be distributed through local health networks in South Australia, including the following: Central Adelaide Local Health Network; Northern Adelaide Local Health Network (Lyell McEwin Hospital); Southern Adelaide Local Health Network (Flinders Medical Centre); Women's and Children's Health Networks (Women's and Children's Hospital); and Riverland Mallee Coorong Local Health Network.

Textbox 1. Inclusion and exclusion criteria for the study.

Inclusion criteria

- Qualified and registered health professionals with Australian Health Practitioner Regulation Agency working in the following roles:

  - Registered midwives

  - Registered nurses

- Residing and working in South Australia

Exclusion criteria

- Not qualified and currently not registered health professionals

- Working outside South Australia

Participants

A nonprobability convenience sample will be used in this study. Recruitment will commence with nurses and midwives as the first cohort of participants. Other health professionals registered with the Australian Health Practitioner Regulation Agency will be recruited later as the research project progresses, for which further ethics approval will be sought.

In South Australia, there are approximately 57,784 registered health practitioners as per the 2018-2019 registration statistics; of these, 678 (1.17%) are midwives, 32,361 (56%) are nurses, and 1854 (3.21%) have dual registration. A power calculation using a single-factor, repeated measures design estimated that a sample of 380 participants, measured at 3 time points, will achieve 95% power to detect differences before and after education using a Geisser-Greenhouse corrected F test at a .05 significance level (P=.05). Therefore, the study aims to recruit 400 health care professionals (nurses and midwives) to account for the potential loss to follow-up, with the intervention requiring completion of pre-, immediate, and posttest educational questionnaires.

Study Website

A specific study website is currently being designed to include detailed information about the study for nurses and midwives. A home page will introduce the research project and state its aims and objectives. Other pages will provide information related to participation in the study, ethical considerations, the research team, and the web-based questionnaires to complete. In addition, it will include an invitation for nurses and midwives to attend an educational workshop, a follow-up focus group or an individual interview (face-to-face, zoom, or telephone), and the instructions to contact the primary researcher (MS). Additional information will be provided at a later stage for future research involving other health professional disciplines and further workshops as the project progresses (the future studies will be part 2: managing emotions and conflict and part 3: ways to well-being).

Web-Based Survey (Questionnaires)

The website will provide a link to a web-based survey for participants to complete once they have clicked on the button expressing their consent to participate in the study. The web-based survey (questionnaires) will be hosted using the REDCap (Research Electronic Data Capture; University of South Australia) software from University of South Australia.

The following measurement scales will be included in the web-based survey:

- The Self-Compassion Scale short version (12-items) scale consists of 12 items related to self-kindness (2, 6 items), self-judgment (11, 12 items), common humanity (5, 10 items), isolation (4, 8 items), mindfulness (3, 7 items), and overidentification (1, 9 items) [22].
- The Warwick and Edinburgh Mental Well-Being Scale short version (7 statements) scale assesses the study population's mental and emotional well-being and psychological functioning, which describes feelings and thoughts (functions) [31].
- The Capture My Mood Scale—adapted version (5 items scale), with scores ranging from 1 to 5, is used to assess the mental health status [32].
- The State-Trait Anxiety Scale short version (6-items) [33].

The validity and reliability of these 4 scales have been previously assessed.

To determine the association between a health professional's prior anxiety and stress levels with their levels of self-compassion, a history of anxiety and stress will be assessed by including a specific and open-ended question asking the participating health professionals to provide further details. These questions will include the following: *Have you experienced high levels of anxiety in your life?Have you experienced high levels of anxiety when providing health care?Have you experienced stress at any time in your life?Have you experienced stress while providing health care?*

Compassion and Self-care Education and Training Workshop

This workshop will focus on facilitating and evaluating *You Matter: Finding Your Self-Compassion for health professionals*. Furthermore, 2 trained facilitators will run the workshops.

Recruitment of Participants

Approximately 400 health professionals (nurses and midwives) who have submitted the web-based survey (prequestionnaire) will be invited to attend workshops at the study sites (University of South Australia and South Australia Health). The workshops

will be undertaken for 6 months, and the number of participants will be between 10 and 12 per workshop.

Workshop Content and Components

A 3-hour workshop will be conducted and facilitated by 2 facilitators (1 clinical and 1 educator or trainer from University of South Australia). The workshop will cover self-compassion, research and evidence, dispelling myths, communication, self-care, befriending oneself, acknowledging and accepting negative emotions, and being compassionate to oneself. The workshop will also include time for refreshment and for completing an evaluation of the workshop.

The teaching materials will include a workbook, PowerPoint (Microsoft, Inc) slides, brochures, memo cards, and recommended reading materials. Several activities will include interactive group work, personal reflections, self-compassion exercises, and deep relaxation. Health professionals (nurses and midwives) who participate in the workshop will be given a certificate and awarded 3 points toward continuing professional development.

Posteducational Workshop Evaluation Questionnaire

The pre-educational workshop questionnaire (web-based measurement scales) will be completed again at the end of the workshop to evaluate the health professionals' responses after attending the educational workshop. This questionnaire will be provided as a hard copy or a web-based link at the study website. It will include measurement scales for self-compassion, well-being, mood, anxiety, and stress.

Follow-up Educational Workshop Evaluation Questionnaire

A member of the research team will contact the participants who attend the self-compassion workshop via telephone or email approximately 6 to 8 weeks after the workshop. The researcher will remind the participants to complete the final posteducational questionnaire (follow-up after test) through the study website to reassess their knowledge and ability for self-compassion. Completing the questionnaires for phase 1 will not take longer than 10 to 15 minutes.

Quantitative Data Analysis

Data from the questionnaires (3 time points) will be entered into SPSS version 26 (IBM Corp). Descriptive analysis will examine the participants' sociodemographic characteristics, such as age, level of education, years of experience, type of occupation and employment, and previous education related to compassion. Inferential data will measure correlations and statistical significance, and the chi-square test will be used to assess categorical data. Cronbach α and Pearson correlation statistical tests will be used to assess high and low levels, respectively, recorded by the measurement scales included in the web-based survey. Repeated measures analysis of variance will be used to examine and compare the differences in the variables before, immediately after, and after follow-up of the workshop (over 3 time points) and to see if self-compassion, well-being, and mood have increased and being maintained. Spearman correlation coefficient tests will be used to evaluate the strength and relationship between 2 or more variables

(anxiety, mood, self-compassion, and well-being). A biostatistician will be available to assist with the analysis.

Phase 2: Qualitative Phase

Focus Group and Interview

A subgroup of participants will be invited to either a follow-up focus group or an individual interview at 3 months (in person or web-based, depending on COVID-19 restrictions) after completing the post follow-up questionnaire. Upon completion of the questionnaire, a popup link on the study website will allow the participants to consent to be contacted by a researcher for an interview. Interviews will be conducted in a private room at the University of South Australia, Flinders University, or at one of the study sites.

An interview schedule, including prompts, will be used to guide the undertaking of interviews [34]. The interview guide will be developed from the literature evidence and the findings of phase 1. A purposive sampling technique will be used to recruit and represent health professionals (nurses and midwives) working in South Australia's metropolitan and rural regions. In addition, a selection criterion will be used to recruit the participants. A minimum of 2 participants will be recruited from different clinical practice areas. The opportunity to attend a focus group or an individual interview will be offered to the nurses and midwives or until data saturation is reached. Data from the participants' interviews will be recorded and transcribed verbatim. The participants who agree and consent to participate in a follow-up interview will be given an opportunity to cross-check their responses to the questions answered (guided by the interview schedule) at the end of the interview to confirm or refute that the researcher has recorded and interpreted their answers correctly. A summary of the verbatim data will be uploaded to the study website for all participants to access and read.

The transcripts will be analyzed until data saturation is reached and follow-up of participants will then cease. Data saturation is achieved when no new information emerges from the interview data [34-36]. Data saturation can be reached with a few participants (6-12) as well [35,37]. Finally, a thematic analysis will be undertaken and guided by the 6 stages of the thematic framework [38,39].

Qualitative Data Analysis

Approach Used

The thematic analysis will be used to evaluate the interview data using a reflexive approach. This method is used to identify, analyze, and report patterns or themes within the data. It organizes and describes data sets in detail and can be used to interpret various aspects of the research topic. The six-phase framework for conducting thematic analysis [38,39] will be used as described in the following subsections.

Familiarization With Data

The researcher will start listening and relistening to the audio and readings several times to gain depth and breadth of the data related to the topic studied and become immersed and engaged

with the data. During this phase, the researcher will start taking notes, marking ideas, and feeling curious.

Generating Codes

After becoming familiar with the data, the researcher will take notes and mark ideas, which would mean more details and engagement with the data. It will include focusing on, and making sense of, the data rigorously and systematically. The data will be organized under similar meanings and patterns to develop diverse codes to build themes.

Constructing Themes

After the data were coded and collated, the researchers will sort different codes into potential themes and collate all relevant coded data extracts within identified themes using codes. This will be achieved through building blocks or substantial patterns of meaning throughout the data and thematic mapping to visually explore the potential themes and subthemes. Themes should provide a coherent meaning and thread to answer the research question.

Revising Themes

The researcher will compile all coded data for each of the main themes and review them to ensure that the data are all connected and related to the main concept, as well as check the theme against the whole data set. This step will focus on an in-depth understanding of each theme's central concept and boundaries, including subthemes, overarching themes, and the overall theme story.

Defining and Naming Themes

In this phase, the researcher will ensure that all themes and themes' names were clear, concise, and comprehensive to represent the meaning of the whole data and were related to the research question.

Producing Reports

A final report will be written and will test how the themes work individually and in relation to the data set and the overarching concept. It will also involve revising the research questions, objectives, and the previous steps of coding and themes to ensure that these themes answer the research question.

Ethical Considerations

Ethical approval has been granted by the South Australian Health via the web-based research Governance and Ethics Management System and through site-specific applications for Women's and Children's Health Network Human Research Ethics Committee on May 26, 2021, as 1 of 5 designated study sites to facilitate workshops in metropolitan and rural hospitals and health service settings in South Australia. In addition, ethical approval has been granted by the Human Research Ethics Committee at the University of South Australia on June 26, 2021 (ID: 204,074).

The participants' identities and confidentiality were maintained throughout the research study. The participants will be informed about completing the questionnaires, attending a workshop, and conducting follow-up interviews.

In phase 1, the questionnaires will be coded to deidentify participants and linked to a participant's identity for reidentifying purposes to allow follow-up data to be monitored and analyzed.

In phase 2, if the participants wish to participate in an interview, this will be audiotaped for further analysis. Participants who attend an interview will be deidentified, and data findings will be nonidentifiable. Nonidentifiable findings will be published in peer-reviewed journals and presented at conferences.

There is no known risk or harm, that is, physical, psychological, spiritual, emotional, social or financial well-being, or employment, from participating in this study or publicizing its results or findings. A support protocol flowchart will guide the researchers to support any participant who is identified or who shows signs of anxiety or stress, and a well-being card will be given to participants with information on how to contact counseling services and the employment assistance program.

Informed Consent

Health professionals (nurses and midwives) will be able to access a participant information sheet (PIS) from the study website. The PIS will include information regarding the aim of the research, what the participation will involve, the workshop details, confidentiality, the consent process, and how the research information will be collected and used. The PIS will inform health professionals (midwives and nurses) that participation in the study is voluntary and that they can withdraw at any time. Participants will not be identified; they will be allocated a participant code number (ID). They can also contact the primary researcher (MS) at any time during the study for any further information. Participants will be required to give their consent and sign a consent form to participate in phases 1 and 2 of the study and to attend a *You Matter: Finding Your Self-Compassion* workshop.

Data Management Process

The data management process will be organized according to the University of South Australia guidelines and the My Data Management Plan Tool (University of South Australia). The participants' confidentiality will be maintained through a deidentified collection of data. The storage archiving of data is through software data stored on the web at the University of South Australia local server. Data files will be stored in at least two locations to reduce complete loss, including USB drives and personal laptops, and the data will be frequently backed up on the University of South Australia server. All soft copy data collected (questionnaires and interviews) during the study will be kept on a computer (password protected) to keep the research data confidential and limited to the research team. Hard copy data collection tools will be stored in a locked filing cabinet in a locked room in the Clinical and Health Sciences Unit, University of South Australia. Files within the folder will have a clear name so that the research team can find the related documents. These measures will be taken to ensure the security of information from misuse, loss, or unauthorized access while stored during the research project. The research data and records will be maintained for 5 years after publication. This storage of data requirements complies with the ownership and retention

of data policy as outlined by the National Statement on Ethical Conduct in Human Research. Regarding secure data destruction, the primary researcher will obtain written approval from the Executive Dean of the University of South Australia Clinical and Health Science Unit for secure destruction of the research data, the materials, and associated research records. This data material will be shredded and placed in secured document destruction bins. All data stored electronically will be deleted through a process of repeated overwriting of the documents and deletion from the server, ensuring that the contents cannot be recovered.

Results

Overview

A scoping review was previously undertaken to inform this research study, focusing on nurses and midwives [15]. The preparatory phase was completed on April 2021. Phase 1 is expected to be completed by June 2022, and phase 2 will commence in July 2022.

Integration of Quantitative Results and Qualitative Findings

Data integration requires an appropriate approach that knows when to combine results and investigate contradictory findings [40]. The findings from phase 1 will help develop and guide the undertaking of phase 2. The findings from phase 1 (quantitative) will be integrated and mixed with the findings from phase 2 (qualitative). This data integration will provide more in-depth and deeper insights into how self-compassion can influence the health professionals' health and well-being. Collecting the findings and analyzing data from both phases will lead to combined outcomes to draw acceptable conclusions.

The sequential explanatory design enables reporting the results from the 3 time point questionnaires, findings from the *your self-compassion* workshop, and the interviews to make general conclusions from the collective results or findings.

Phase 3: Dissemination and Translation of Findings and Recommendation

A project report will be written for any funding bodies, and a summary of the key findings and recommendations will be uploaded and accessible via the study website. The findings and recommendations of this mixed methods study will be disseminated through publications, conference presentations, and professional and social media platforms.

Discussion

Principal Findings

The previously undertaken scoping review concluded that self-compassion education and training can improve the midwives' and nurses' awareness and increase their ability for self-compassion. It suggests that there is a clear justification to undertake this research study by exploring and investigating the influence of self-compassion on midwives and nurses.

Conclusions

The key findings from the data integration of this research project will provide in-depth details and insights to broaden the discussion about self-compassion and its influence on health professionals' health and well-being. Therefore, the health professionals (nurses and midwives) would benefit from developing and designing self-compassion education and training programs to improve their health and well-being.

Conflicts of Interest

None declared.

Multimedia Appendix 1
External Peer-Review Report 1 by the University of South Australia, Clinical & Health Sciences.
[PDF File (Adobe PDF File), 114 KB - resprot_v11i1e34372_app1.pdf]

Multimedia Appendix 2
External Peer-Review Report 2 by the University of South Australia, Clinical & Health Sciences.
[PDF File (Adobe PDF File), 123 KB - resprot_v11i1e34372_app2.pdf]

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Abbreviations

PIS: participant information sheet

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Protocol

Digital Biomarkers for Supporting Transitional Care Decisions: Protocol for a Transnational Feasibility Study

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Abstract

Background: Virtual Health and Wellbeing Living Lab Infrastructure is a Horizon 2020 project that aims to harmonize Living Lab procedures and facilitate access to European health and well-being research infrastructures. In this context, this study presents a joint research activity that will be conducted within Virtual Health and Wellbeing Living Lab Infrastructure in the transitional care domain to test and validate the harmonized Living Lab procedures and infrastructures. The collection of data from various sources (information and communications technology and clinical and patient-reported outcome measures) demonstrated the capacity to assess risk and support decisions during care transitions, but there is no harmonized way of combining this information.

Objective: This study primarily aims to evaluate the feasibility and benefit of collecting multichannel data across Living Labs on the topic of transitional care and to harmonize data processes and collection. In addition, the authors aim to investigate the collection and use of digital biomarkers and explore initial patterns in the data that demonstrate the potential to predict transition outcomes, such as readmissions and adverse events.

Methods: The current research protocol presents a multicenter, prospective, observational cohort study that will consist of three phases, running consecutively in multiple sites: a cocreation phase, a testing and simulation phase, and a transnational pilot phase. The cocreation phase aims to build a common understanding among different sites, investigate the differences in hospitalization discharge management among countries, and the willingness of different stakeholders to use technological solutions in the transitional care process. The testing and simulation phase aims to explore ways of integrating observation of a patient's clinical

condition, patient involvement, and discharge education in transitional care. The objective of the simulation phase is to evaluate the feasibility and the barriers faced by health care professionals in assessing transition readiness.

Results: The cocreation phase will be completed by April 2022. The testing and simulation phase will begin in September 2022 and will partially overlap with the deployment of the transnational pilot phase that will start in the same month. The data collection of the transnational pilots will be finalized by the end of June 2023. Data processing is expected to be completed by March 2024. The results will consist of guidelines and implementation pathways for large-scale studies and an analysis for identifying initial patterns in the acquired data.

Conclusions: The knowledge acquired through this research will lead to harmonized procedures and data collection for Living Labs that support transitions in care.

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Introduction

Background

Transitional Care Study in the Context of the Virtual Health and Wellbeing Living Lab Infrastructure Project

Virtual Health and Wellbeing Living Lab Infrastructure (VITALISE) is a Horizon 2020 project funded by the European Union (under grant 101007990; April 2021 to March 2024), which brings together 19 partners from 11 different countries. The aim of the VITALISE project is the harmonization of services, methods, and procedures of health and well-being Living Labs, enhancing the interaction between multidisciplinary researchers among and beyond the consortium partners. For this purpose, joint research activities (JRAs) will be conducted by the VITALISE consortium. The JRAs will target rehabilitation, transitional care, and everyday life activities, bringing together researchers with diverse expertise across the Living Labs and creating innovation test beds based on harmonized infrastructures, data elements, processes, and research methods. This protocol describes the design of the JRA in the field of transitional care, exploring how information and communications technology (ICT) can act as a facilitator of the creation of big data to predict the risk of adverse events during transitions in care.

Transitional Care

Transition periods, most of the time, are related to vulnerable moments in the care of individuals who need to experience frequent transitions between settings, usually from hospital to home or rehabilitation centers and within hospitals from one unit to another. Poorly executed transitions from hospital to home or to rehabilitation centers can potentially result in readmissions, adverse events, patient dissatisfaction, low quality of life, or even death [1]. Approximately half of the patients that are discharged directly to their homes from the hospital are at risk of complications, such as falls, physical deconditioning, aspiration pneumonia, infections, social isolation, and depression because of factors not identified during hospitalization [2-4]. Transitional care is the term used to describe the coordination and continuity of health care to promote safe and timely transitions or *handoffs* between different locations or different levels of care within the same location that is used to minimize risks and improve patient and family experiences [5]. Transitional care includes, but is not limited to, discharge planning, follow-up and care support, patient and family education and supporting self-management, medication management, transfer of information, and shared accountability among providers of patient care [6].

As the provision of transitional care requires multifaceted efforts from the care institutions on both sides of the handoff, the prediction of high-risk patients to provide targeted intervention is of foremost importance [7]. The detection of patients at risk of adverse events or readmissions can guide prevention efforts and prompt proactive care [8] when combined with early treatment of risk factors. Kansagara et al [9] performed a systematic review of risk prediction models using administrative data, either retrospective or using real-time and primary participant data. The recent advances in artificial intelligence and machine learning have introduced computational methods and techniques to improve the prediction of readmissions, avoid the inclusion of *bad data,* and thus predict adverse events with greater precision. Studies have shown that a machine learning algorithm can have better performance for the prediction of readmissions by integrating different factors in the model than commonly used readmission measure scores alone. The potential of deep learning for the prediction of hospital readmissions has also been explored. Wang et al [10] used electronic medical records to predict readmission, whereas Min et al [11] and Xiao et al [12] explored the use of information available in electronic health records and deep learning modeling, which yielded promising results.

ICT can be a facilitator of integrated and coordinated care and can be used to capture biomarkers to develop risk profiles to tailor care to patient's needs, thereby mitigating future deterioration and optimizing interventions to improve function and participation. ICT can improve transitions in care by (1) standardizing and harmonizing assessment of patients' function and rehabilitation potential across the continuum of care; (2) exchanging information between interdisciplinary team members and patients or family members, strengthening collaborative care; (3) providing patient and family education and resources to identify services they can access at each point in the

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continuum of care; and (4) support quality improvement efforts by using data for program evaluation. On the assessment front, ICT tools can be used to provide additional information on a patient's function in an unobtrusive way that can potentially boost the prediction of readmissions.

Research has shown that data on a patient's mobility and functional status can predict successful transitions and the risk of adverse events. For example, mobility status is predictive of an increased likelihood that a patient will be discharged to home with better outcomes [13]. Assessment of patients' functional status may assist in identifying patients at risk for poor outcomes owing to lack of mobility and help describe and quantify patient function [14].

Harmonization of Real-life Environments Piloting

Precise predictions of future risk across transitions of care require large data sets to identify the interrelationships among biological, physical, social, and environmental factors. The collection of big data in real-life environment presupposes the exploration of the feasibility of data collection and the development of efficient data acquisition techniques and methodologies [15]. Especially in clinical settings, data may come from many disparate data sources and vary within the local context. Except for data collected from ICT devices, data collected from clinical assessments require special handling on how to be reported, the feasibility of collection from health care professionals, and the differences among health care systems. These challenges emphasize the need for transnational collaboration and harmonization that can on one hand, enhance the exchange of knowledge and technical infrastructure and on the other hand, the exploration of local context views on feasibility and health care systems.

This study helps address the aforementioned challenges for transitional care research through the involvement of Living Lab research infrastructures in 4 countries. Living Labs are defined as ecosystems that enable research activities in realistic environments that drive innovation with multidisciplinary stakeholders [16,17]. They also help adjust research in the local context through the access provided in cross-border real-life research infrastructures and end user populations. In that sense, Living Labs will be exploited with the aim of harmonizing technical infrastructure and outcomes collected by ICT toward supporting transitions of care. Following best practices for implementation science [18], we will develop tools to characterize the context in each Living Lab and to evaluate the barriers and facilitators to implementing ICT and collecting data [19]. The creation of similar sites and the collection of harmonized data sets, even when working with different tools (eg, different types of smartwatches) will support transnational

research and collaboration for transitional care around Europe and Canada.

Objectives

This study will combine data collected using ICT tools, patient-reported outcome measures, and clinical assessments that measure impairments, activity limitations, mobility, and participation of individuals with disabilities or complex chronic conditions to identify digital biomarkers that are related to patient mobility and functional status. This study aims to evaluate the feasibility and perceived benefit of collecting data across Living Labs in 4 countries and to harmonize the data to augment the capacity to perform big data analytics within each local context.

Feasibility across Living Labs include the following:

1. Test and evaluate harmonized infrastructures, data elements, processes, and research methods for transnational collaboration in real-life health care environments for research in transitional care.
2. Evaluate the feasibility to recruit and implement ICT to collect digital biomarkers.
3. Estimate initial patterns of correlation and ability of the data to inform health care transitions.

To inform future scale-up in clinical settings for collecting digital biomarkers, each Living Lab will explore ways of integrating observation of a patient's clinical condition, patient involvement, and discharge education in transitional care using a simulated hospital environment. Given this is in a simulated environment as compared with a real-world environment, it allows investigators to manipulate how and which ICT is implemented to inform the work in the other Living Labs.

Methods

Overview

The whole study will consist of three phases that will run consecutively at multiple sites: a cocreation phase, a testing and simulation phase, and a transnational pilot phase. This study is a multicenter, prospective, observational cohort study. The exchange of information among the phases is presented in Figure 1.

The cocreation will be the starting phase that will feed the other 2 but can also create insights that can be further considered in new cocreation sessions, if needed. The transnational pilot could lead to another testing and simulation phase if more data collection needs arise or to cocreation for the exploration of new insights. On the basis of the transnational pilot outcome, a scale-up protocol for big data collection in each Living Lab will be developed.

Figure 1. Overview of the information flow for the different phases of the study.
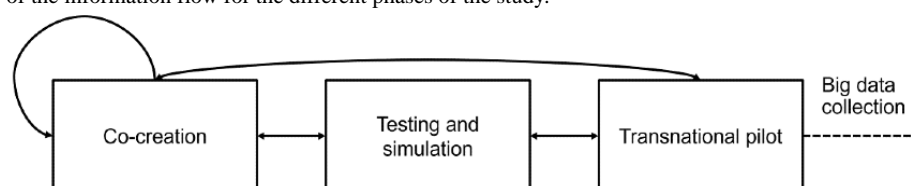
Participants and Recruitment Strategies

Different recruitment strategies will be followed for the cocreation, testing and simulation, and transnational pilot phases.

Cocreation will be conducted by each Living Lab; therefore, recruitment will be carried out at each of the stakeholder's community, including existing collaborations with hospitals and inpatient rehabilitation centers as well as community-dwelling older adults who have previously been hospitalized.

Convenience sampling will be used to recruit nursing students (n=10 per scenario) from the nursing bachelor's degree program at Laurea University of Applied Sciences for the testing and simulation phase. The simulation scenarios will be integrated into the study units, and a researcher and a lecturer in charge of the study unit will inform the students and ask the voluntary students to participate. Voluntary students will give informed consent to participate.

The recruitment process for the transnational pilot phase will begin during the hospitalization of the patient. The health care professionals who will be in charge of the study at each site will be responsible for recruiting the patients. The patient will be informed about the aims of the study and will be able to ask for any additional information. If they confirm their interest, they will sign the consent form. All participants enrolled in the study will undergo a screening evaluation to determine if they comply with the inclusion and exclusion criteria. The screening evaluation will include two standardized tests: the Clinical Frailty Scale and the Montreal Cognitive Assessment. More specifically, the following are the recruitment sites:

- Thessaloniki Active and Healthy Ageing Living Lab transitions Living Lab in *Hippokration* General Hospital of Thessaloniki targeting a total of 20 participants.
- The McGill–Université de Montréal Biomedical Research and Informatics Living Laboratory for Innovative Advances of New Technologies (BRILLIANT; herein referred to as the BRILLIANT platform) cohort, which will recruit 20 patients and their informal caregivers.
- LifeSpace infrastructure, for which the recruitment of a total of 15 patients will be carried out at hospitals in the Madrid region.

Study Population and Settings

The cocreation phase will run in different settings across Europe and Canada and will include various stakeholders, such as older adults (>65 years) who have been previously hospitalized, health care professionals, informal and formal caregivers, and family members.

Participants will be included in the transnational pilot study based on the inclusion and exclusion criteria presented in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- >65 years, living in the community, who are able to give informed consent
- Admission diagnosis to the hospital that includes one of the following multi-morbidities: stroke or brain injury, rheumatoid arthritis or osteoarthritis, or surgical postoperative patient
- Clinical Frailty Scale <4
- Montreal Cognitive Assessment >25
- Being hospitalized or having recently (within a week) discharged from hospital or inpatient rehabilitation

Exclusion criteria

- Severe cognitive disability (eg, not being able to communicate and understand)
- Severe physical disability (eg, tetraplegia)
- Terminal or severe illness with survival prognosis <18 months

Site and Infrastructure Description

The protocol describes a multisite study that will be performed in four different countries (Greece, Spain, Finland, and Canada). The infrastructures in which the study activities will be performed are described in subsequent sections.

Aristotle University of Thessaloniki—Thessaloniki Active and Healthy Ageing Living Lab Health Care Transitions Living Lab (Greece)

The Aristotle University of Thessaloniki (AUTH) Transition Living Lab includes the infrastructure, services, studies, and ICT tools that are used to study and support the transitions of a patient from long-term care facilities such as intensive care unit in hospitals or convalescence after surgery to another long-term care facility such as a rehabilitation center, nursing home, or patient's house. The AUTH Transitions Living Lab is located in *Hippokration* General Hospital in Thessaloniki, Greece, and consists of a home-like environment equipped with a small kitchen in one room and a bedroom and living room in the other. It is equipped with various ICT tools, including 3D depth sensors (Microsoft Kinect v3.0) for monitoring and analyzing gait patterns and posture, RGB cameras for gesture and activity recognition and emotion analysis, activity trackers, and biosignal monitoring. The collected raw data are analyzed and fused to provide higher level interpretable information to health care professionals. The Living Lab is governed by the Laboratory of Medical Physics and Digital Innovation of AUTH

in collaboration with the second Propedeutic Department of Internal Medicine.

McGill–Université de Montréal–Centre for Interdisciplinary Research in Rehabilitation of Greater Montreal (Canada)

Canadian hospital centers include infrastructure as part of the Centre for Interdisciplinary Research in Rehabilitation of Greater Montreal–BRILLIANT Community Mobility Rehabilitation. In the Centre for Interdisciplinary Research in Rehabilitation of Greater Montreal–BRILLIANT hospitals and rehabilitation sites, biomedical and health ICT technologies are being evaluated in health care and community settings that are part of the Living Lab network. The Living Lab infrastructure includes a laboratory space of approximately 15,000 sq ft that houses virtual reality research environments, motion caption cameras, haptic devices, wearable sensors, serious game environments, and training simulators. It also includes testing and student spaces, meeting rooms with break out spaces, integrated within the clinical settings. Community Living Labs benefit from meeting and testing rooms, debriefing spaces, and storage for equipment. The Living Labs will also benefit from shared personnel, coordinators, engineers, information technology specialists, and research assistants. There is also a dedicated health informatics team to develop digital health solutions. The Canadian Living Labs are located inside real clinical environments (hospitals and rehabilitation centers), which make them unique environments for constant experimentation and testing of the designed solutions. Although the primary link is with rehabilitation care, the space and network of patients, clinicians, and managers participate in studies across various domains such as transitional care, domotics, and acute care.

LifeSTech Living Lab (Spain)

LifeSpace (founded and formally known as Smart House Living Lab by LifeSTech) is an environment that presents an ecosystem approach that combines a wide range of knowledge and stakeholders to offer innovative and personalized solutions aimed at promoting improvement in health and services aimed at social well-being. Within this ecosystem, there is a laboratory for the generation of new knowledge and the creation of new innovative products and services. This environment demonstrates that smart living environments can contribute to and have beneficial effects on quality of life in terms of self-perceived quality of life, physical status perception, social engagement in active and healthy aging, and frailty. On the basis of the European Innovation Partnership in Active and Healthy Ageing Triple Win Strategy, a comprehensive evaluation oriented to data management will be created, designed, and promoted for the generation of global evidence around the three main pillars: quality of life, frailty, and training algorithms for early detection.

More specifically, more than 50 sensors and actuators, iterative robots, internet of things (IoT), and smart devices are distributed in the house. This distribution of *ubiquitous* devices is designed to allow the monitoring and testing of ICT applications, which capture data both within the controlled environment and associated users who actively participate and live at home in

the city itself to improve the quality of life and health of citizens, in particular offering gait capture that can, for example, analyze gait improvement to quantify a person's frailty and early detection of worsening trends because of disease progression or lack of performance of pharmacological treatment.

Laurea Simulated Hospital (Finland)

Laurea Simulated Hospital (LSH) provides a Living Lab environment for testing simulation scenarios. The testing process will be incorporated in nursing students' study units, and the students will practice the transition care process in a safe simulated scenario without causing risk for a real patient. LSH has the potential to be used for scientific validation of developed patient care methods, scenarios, and equipment. There are monitoring and control rooms for the instructors, and a separate debriefing room to be used during the scenarios for observation and after the scenarios for discussions. Simulated scenarios can be monitored in real time and video-recorded for debriefing and research purposes.

Centre for Research & Technology Hellas–Information Technologies Institute Near-Zero Energy Building Smart Home (Greece)

The Centre for Research & Technology Hellas–Information Technologies Institute near-zero energy building smart house is a rapid prototyping and novel technology demonstration infrastructure resembling a real domestic building where occupants can experience actual living scenarios while exploring various innovative smart IoT-based technologies with provided energy, health, big data, robotics, and artificial intelligence services. As the first smart near-zero energy building in Greece, it combines enhanced construction materials and intelligent ICT solutions to create a future-proof, sustainable and active testing, validating and evaluating of ecosystems. Data collection and assisted living infrastructure for the purposes of transitional care include IoT smart home sensors (eg, environmental, presence in a room, and appliance use), wearable sensors to capture physiological and lifestyle data, portable electroencephalography devices, robotics, digital coaches or avatars, and mobile apps. After data are collected and stored in an interoperable manner, intelligent data analytics, such as sensor fusion, are used to extract features, behaviors, and symptoms for assessment and care.

Data Collection

The data collected in this study will consist of qualitative data from the cocreation and testing and simulation phases as well as time series and clinician- and patient-reported outcomes from the transnational pilot phase. The data collection process and data sets are described in the following sections.

Cocreation Phase

In the cocreation phase, the objective will be to identify the tendencies of health care professionals, informal caregivers, and patients to use technological tools for collecting information to support their decisions on the transitional process. Possible questions that can be addressed during cocreation sessions are as follows:

1. What are the most important insights or information that a health care professional. informal caregiver, or patient should have about patients as they transition from one care setting to another (focus on hospital to home or hospital to rehab)?

2. Explore the most important expected outcomes of transitional care for a health care professional, informal caregiver, or patient.

3. Explore the experiences that a health care professional, informal caregiver, or patient has from previous transitions in care.

4. What are the needs or desires of health care professional, informal caregiver, or patient as they prepare for a transition and during the transition phase?

5. How can we deliver information to a health care professional, informal caregiver, or patient in an efficient way?

On the basis of the outcomes of the cocreation phase, we will create the first version of the template for reporting the collected data on the simulation and testing and transnational pilot phase. This phase will be used as a first step in defining the local context in the current clinical assessment and to evaluate the required effort from professionals to collect the harmonized data set.

Testing and Simulation Phase

Overview

Simulation-based research in the health care context can provide opportunities to investigate complex or rarely occurring phenomena, which would be challenging to capture in authentic clinical situations. Furthermore, simulation-based research is a safe approach, especially when vulnerable patient or client groups are involved. It also allows the triangulation of research data and enables patient-public involvement in research design and planning [20]. In the context of this study, simulation-based research will be used at the LSH among trainees and health professionals to explore ways of integrating observation of a patient's clinical condition, patient involvement, and discharge education in transitional care. The objective of the simulation phase is to evaluate the feasibility and the barriers faced by a health care professional, especially registered nurses (RNs), to assess transition readiness and investigate possible suggestions and directions for support systems. The participants in the testing and simulation phase will evaluate the suggested small-scale pilot, and changes might be applied based on the results.

Simulation scenarios focusing on transitional nursing care will be cocreated with nursing instructors and experts by experience. The scenarios will address (1) discharging a patient from a hospital ward to home and (2) transferring a patient from the emergency department to a hospital ward. The basic structure of the simulation scenario is described in the *Discharging a Patient From a Hospital Ward to Home* section; however, the details will be defined later based on cocreation.

Discharging a Patient From a Hospital Ward to Home

Once a physician has decided to discharge the patient and has delivered basic medical information concerning the operation and possible follow-up, an RN checks that discharge criteria are met using Airway, Breathing, Circulation, Disability, Exposure approach. The RN also administers the test battery that has been agreed upon for the small-scale pilot. The RN provides discharge education and instructions about the tasks that they need to perform at home. The RN will also be responsible for assisting the patient in properly placing the wearable devices and ensuring that the sensors work correctly.

Transferring a Patient From the Emergency Department to a Hospital Ward

The emergency department physician made the decision to transfer the patient to a hospital ward, where care will continue according to the physician's orders. The RN taking care of the patient is responsible for transferring the patient to the hospital ward and making appropriate preparations [21], which is to inform the patient, perform patient assessment using the Airway, Breathing, Circulation, Disability, Exposure approach, and check all the documentation and the physician's orders. An RN in the emergency department gives an oral handover following the Identify, Situation, Background, Assessment, and Recommendation structure to a ward nurse over phone. Identify, Situation, Background, Assessment, and Recommendation is a recommended systematic structure for handovers. It improves information exchange in transition care and promotes desirable patient outcomes and safety [22]. The ward nurse will also test the 3D cameras and app that is placed in the ward to monitor the patient and report on its usability and usefulness.

In both scenarios, a group of nursing students (n=10 per scenario) will play the roles of the patient and RN and act as observers. They will be trained for the roles (especially the patient) before the simulation. A simulation instructor, a researcher, and an expert with knowledge of the specific process will be observing the scenario.

After the simulation scenarios, a debriefing discussion with the student group will take place in the form of a group interview. Interview data will be analyzed using inductive content analysis. Students' feedback about the simulation scenarios in the form of structured and open feedback will also be gathered. Cocreation workshops will be organized after each simulation session. The aim of the cocreation phase is to develop both the simulation scenarios and the transition care process further. The participants of the simulation scenarios will facilitate the creation of new solutions and provide new insights through an iterative process.

Transnational Pilot Phase

The transnational pilot phase will involve the collection of longitudinal multiple time series and clinical data to conduct predictive analytics. The BRILLIANT platform [23] will be used as a reference point for the creation of predictive analytics and the future visualization of outcomes in the included rehabilitation information system (clinicians and patient or caregiver interface). An overview of the transnational pilot activities that will be performed is presented in Figure 2.

Figure 2. Transnational pilot stages.
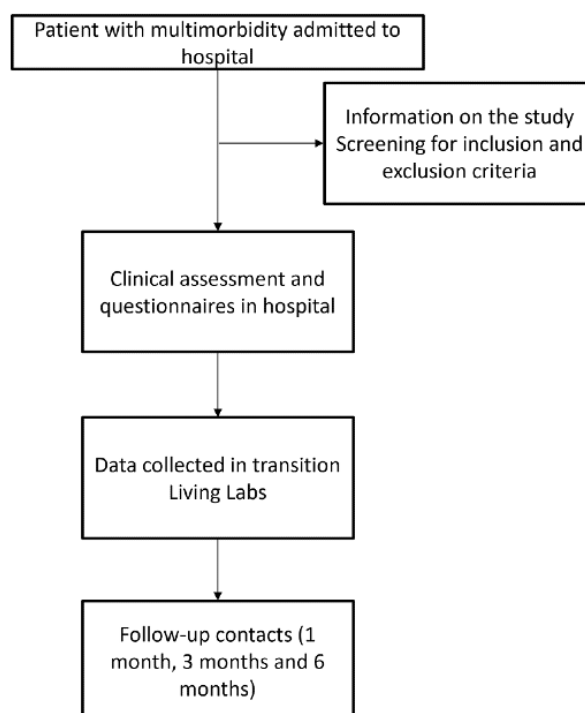
The data collection will take place in 3 different time frames, inside the hospital settings during hospitalization, during hospital discharge within transition Living Labs, and within 1 week after discharge. Table 1 summarizes the timing of the data collection.

During their hospitalization in McGill and AUTH clinical sites, a 3D depth sensor camera will be installed in the patient's ward to monitor the patient's movements in the bed. The smartwatches that are provided in the recruitment phase will monitor the patient's oxygen level, pulse rate, heart rate, sleep (heart rate variability details, daily oxygen saturation, and respiratory rate summary), stress (stress score and mindfulness), and blood glucose on a daily basis.

Before leaving the clinical settings (AUTH and McGill) or no more than 1 week after leaving the hospital (LifeSTech and CERTH), the patients will be asked to provide specific demographic features and prehospitalization history. Hospital charts will be used to identify the location of discharge after hospital and health professional–defined care plans. In addition, the patients will enter the transitions Living Labs in which they will remain for a few hours to perform specific measurements. To gather these data in an ecologically valid way, the participants will enter the transitions Living Lab infrastructure for 1 hour and will be asked to perform a morning routine that will include the patient rising from the bed, preparing breakfast, eating breakfast, spending some time watching television, reading a newspaper article or a small section of a book (they will be asked to read it out loud to capture linguistic features), and call a relative or a nurse on the phone. During these activities, the aforementioned sensors will perform measurements unobtrusively.

After discharge, the patient will have three follow-up contacts (1 month, 3 months, and 6 months). In these follow-ups, we will identify the following:

- The occurrence of readmissions within that period
- The occurrence of any adverse events
- The optimal care pathways that the patient was following
- Capture intervention that the patient has done (eg, physiotherapy)—type and intensity
- Participation and social inclusion
- Completion of questionnaires on symptoms, activity limitations, and participation in the BRILLIANT transitions of care platform

Table 1. Data collection.

Domain	Measurement tool	Hospital	Hospital discharge and Living Lab	After discharge
Demographic features	Questionnaire filled by a health care professional including gender, date of birth, level of education, employment status, income, living arrangements, and hospital insurance status		✓	
Patients' health record	Filled by the health care professional		✓	
Prehospitalization history	Including any previous hospitalization, period of hospitalization, and reason for hospitalization		✓	
Health status	EQ-5D-3L[a]	✓		
Health-related quality of life (physical, social, and emotional health)	SF-12[b] or PROMIS 29[c] (mapping tables between both exist)	✓		
Depression	PHQ-9[d]	✓		
Functional status	Lawton Instrumental Activities of Daily Living scale	✓		
Risk assessment	BRASS[e]	✓		
Physical activity	IPAQ[f] or AM-PAC[g]-Inpatient Basic Mobility Short Form Information	✓		
Speech features or linguistic analysis	Speech language pathology assessment	✓	✓	
Cognitive status	MoCA[h]	✓		
Quality of mobility or quality of walking and body posture measures	3D depth sensor cameras (Mentorage). Mentorage device can capture the person's skeleton		✓	
Gait features including steps, velocity, average distance	Smartwatch sensor		✓	✓
Biosignal measurements including heart rate and blood pressure	Smartwatch sensor	✓	✓	✓
Temperature	Thermometer	✓	✓	
Body weight and composition	Smart scale	✓	✓	
Direct time of treatment	Hospital system or manual measurement from health care professionals	✓		
Hospitalization measures	Number of procedures performed during hospital stay; number of hospital stays with ≥5 days; number of hospital admissions during the previous year; length of stay in hospital (days); and number of emergency department visits within 6 months	✓		

[a]EQ-5D-3L: EuroQol five-dimensional questionnaire.

[b]SF-12: 12-item Short Form Survey.

[c]PROMIS 29: Patient-Reported Outcomes Measurement Information System-29.

[d]PHQ-9: Patient Health Questionnaire.

[e]BRASS: Blaylock Risk Assessment Screening Score. [f]IPAQ: International Physical Activity Questionnaire.

[g]AM-PAC: Activity Measure for Post-Acute Care.

[h]MOCA: Montreal Cognitive Assessment.

Ethics and Data Management Considerations

Each partner institution involved in this study will submit an institutional review board application or ethical committee application according to the respective national regulations at the latest in December 2021. Informed consent will be obtained from all participants before data collection. The collected data will be exchanged among interested parties pseudonymized to perform a joint analysis. The exchanged data sets will be minimized, and partners will share the minimum amount of data needed to prevent potential risks. An access control list for user and data authentication will be created by each party, and a person responsible is already identified to keep the stored information safe.

Outcome Measures and Analysis

As the primary objective of this study is to evaluate the feasibility of collecting digital biomarkers within a real-life environment and Living Lab premises for transitional care, the outcomes will focus on the consensus on the activities and

collected data. The captured data will be accompanied by feasibility parameters across Living Labs, especially the number of recruits, time to complete assessments, and percentage of missing data. Qualitative outcomes will also be gathered from health care professionals to understand the effort and obstacles for gathering each measure. Mixed method analysis will be carried out by combining quantitative and qualitative data captured to arrive at a consensus on harmonized outcomes and methods.

As a secondary outcome, the initial data patterns will be explored. Descriptive statistics for sociodemographic and clinical characteristics of participants will be calculated, and statistical analysis will identify the correlation of collected digital biomarkers with baseline clinical assessments. A prediction algorithm using machine learning techniques will be created to explore the usability of information by health care professionals. The outcomes will feed and drive the big data collection protocol that will follow.

Results

In this study, each Living Lab governed by a different entity, will submit an ethical committee application according to the respective national regulations at the latest in December 2021. Recruitment for the cocreation sessions will be completed by February 2022, and the cocreation phase will run until April 2022. The testing and simulation phase will begin in September 2022 and will partially overlap with the deployment of the transnational pilot phase that will start in the same month. The data collection of the transnational pilots will be finalized by the end of June 2023. Data processing is expected to be completed by March 2024. The results will consist of guidelines and implementation pathways for large-scale studies and an analysis for identifying initial patterns in the acquired data.

Discussion

Study Significance and Future Research

This JRA protocol is 1 of the 3 JRAs that will be conducted during the Horizon 2020 project *VITALISE*, aiming at three different domains of health and well-being research: rehabilitation, transitional care, and everyday living environments. The main scope of this action is to create transnational collaboration opportunities, facilitating access to Living Lab research infrastructures for all European and international researchers. This specific JRA concerns the field of transitional care and addresses the issue of collecting information across countries that can guide and inform transitions of care. In particular, the described design focuses on the feasibility of using ICT tools for the creation of digital biomarkers and how they can be combined with data collected in clinical settings.

This study investigates the collection, integration, and combination of clinical and patient-reported outcome measures

with mobility and functional status automatically collected using ICT tools in real-world clinical settings. Digital biomarker, as a complement, enables continuous monitoring that can be collected remotely in real-life, ecologically valid environment [24]. A seamless assessment of the patient's health status combined with an investigation of the psychosocial factors and needs, experience, and desires of the different parties can create a multidimensional digital phenotyping that may play a role in improving our knowledge and response for successful transitions [25].

This study will act as a precursor for a large-scale study for the collection of big data on transitional care. The harmonization of procedures for data collection and the identification of obstacles will enable different parties to investigate the prerequisites for scaling-up. Multidisciplinary collaboration, including clinicians, engineers, data scientists, and informal caregivers, along with promising progress in big data collection and analytics, could further help to solve this complex puzzle of extracting meaningful indicators of transition care outcomes. A feasibility study is a crucial step that can help different actors understand the relative strengths and weaknesses of the proposed approach and plan accordingly a solution that can work effectively in real-world clinical settings [26]. The collection and validation of digital biomarkers should not be addressed as a one-time process but rather a longitudinal collection that incorporates adaptations and modifications [27].

With the collection of large-scale data, researchers will be able to identify digital biomarkers associated with mobility and functional status of the patient, which can help predict reduction in length of stay, readmissions, adverse events, and care pathways. Furthermore, the aim will be to evaluate the combination of information from various domains, namely impairments, activity limitations, mobility, and participation collected using ICT for the prediction of transition outcomes. That way, it can act as a facilitator to the execution of better and more effective transitions, with less readmissions and adverse events. The future direction is the development of a pragmatic clinical trial.

On a higher level, this study will allow the involved Living Labs to exchange knowledge and harmonize the technical infrastructure in a broader effort to harmonize the methods, services, and tools used across Living Lab initiatives in the domain of transitional care in real-life health care settings.

Conclusions

This study presents the design and implementation steps of a JRA that will be performed within the VITALISE project. The knowledge acquired through this research will lead to harmonized procedures and data collection for Living Labs that support transitions in care. In addition, this research contributes to the increase in capacity to perform big data analytics while accounting for each local context and across Living Labs.

Conflicts of Interest

None declared.

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Abbreviations

AUTH: Aristotle University of Thessaloniki
BRILLIANT: Biomedical Research and Informatics Living Laboratory for Innovative Advances of New Technologies
ICT: information and communications technology
IoT: internet of things
JRA: joint research activity
LSH: Laurea Simulated Hospital
RN: registered nurse
VITALISE: Virtual Health and Wellbeing Living Lab Infrastructure

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Protocol

The Use of a Computerized Cognitive Assessment to Improve the Efficiency of Primary Care Referrals to Memory Services: Protocol for the Accelerating Dementia Pathway Technologies (ADePT) Study

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Abstract

Background: Existing primary care cognitive assessment tools are crude or time-consuming screening instruments which can only detect cognitive impairment when it is well established. Due to the COVID-19 pandemic, memory services have adapted to the new environment by moving to remote patient assessments to continue meeting service user demand. However, the remote use of cognitive assessments has been variable while there has been scant evaluation of the outcome of such a change in clinical practice. Emerging research in remote memory clinics has highlighted computerized cognitive tests, such as the Integrated Cognitive Assessment (ICA), as prominent candidates for adoption in clinical practice both during the pandemic and for post-COVID-19 implementation as part of health care innovation.

Objective: The aim of the Accelerating Dementia Pathway Technologies (ADePT) study is to develop a real-world evidence basis to support the adoption of ICA as an inexpensive screening tool for the detection of cognitive impairment to improve the efficiency of the dementia care pathway.

Methods: Patients who have been referred to a memory clinic by a general practitioner (GP) are recruited. Participants complete the ICA either at home or in the clinic along with medical history and usability questionnaires. The GP referral and ICA outcome are compared with the specialist diagnosis obtained at the memory clinic. The clinical outcomes as well as National Health Service reference costing data will be used to assess the potential health and economic benefits of the use of the ICA in the dementia diagnosis pathway.

Results: The ADePT study was funded in January 2020 by Innovate UK (Project Number 105837). As of September 2021, 86 participants have been recruited in the study, with 23 participants also completing a retest visit. Initially, the study was designed for in-person visits at the memory clinic; however, in light of the COVID-19 pandemic, the study was amended to allow remote as well as face-to-face visits. The study was also expanded from a single site to 4 sites in the United Kingdom. We expect results to be published by the second quarter of 2022.

Conclusions: The ADePT study aims to improve the efficiency of the dementia care pathway at its very beginning and supports systems integration at the intersection between primary and secondary care. The introduction of a standardized, self-administered,

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digital assessment tool for the timely detection of neurodegeneration as part of a decision support system that can signpost accordingly can reduce unnecessary referrals, service backlog, and assessment variability.

Introduction

Worldwide, national dementia strategies emphasize the need for improving the diagnostic pathway at the point of primary care toward timely diagnosis. Currently, general practitioner (GP) clinical judgement of cognitive impairment is the basis of referral initiation to specialist services. Existing primary care cognitive assessment tools (eg, the General Practitioner Assessment of Cognition [GPCOG], the Mini-Cog, and the Six-Item Cognitive Impairment Test [6CIT]), are crude or time-consuming screening instruments which can only detect cognitive impairment when it is well established. Dementia is difficult to diagnose; in a study concerning false positive diagnoses, 60% of GPs misdiagnosed dementia [1]. More detailed tests deployed in secondary care are expensive and often physically and psychologically intrusive for the patient (eg, lumbar puncture). As a result, many false positives are identified in referred patients. A key limitation of existing screening tests is the lack of robust evidence to support them; few have been well validated in the populations for which they are intended.

Figure 1 demonstrates the dementia diagnostic pathway for patients. Patients who are referred by their GP are triaged. At the memory clinic, patients undergo 2 appointments; the first is typically conducted by a nurse and involves administration of a cognitive assessment. At the second appointment (the diagnostic clinic visit), conducted by a dementia medical specialist, the patient receives the outcome of the assessment (see "Outcomes" within Figure 1 for examples of typical outcomes).

Figure 1. Dementia diagnostic pathway for patients.
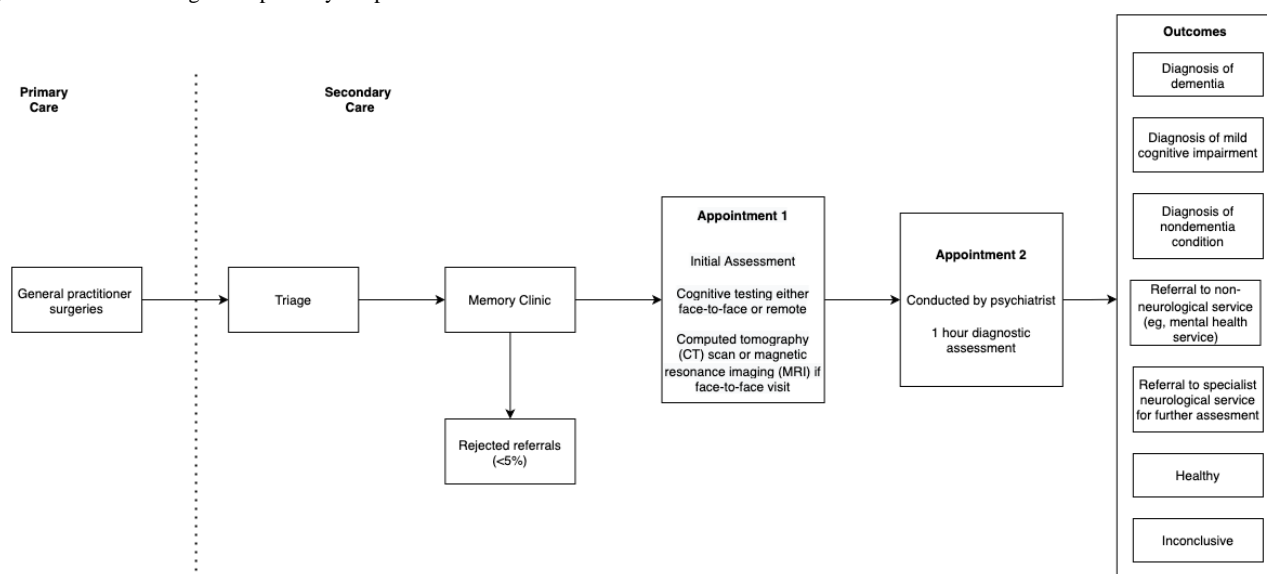
The COVID-19 pandemic has effectively brought clinical practice in the memory services to a standstill. Nationally, memory services have adapted to the new environment by moving to remote patient assessments to continue meeting service user demand while reducing viral transmission [2]. However, the remote use of cognitive assessments has been variable, while there has been scant evaluation of the outcome of such a change in clinical practice [3]. Emerging research in remote memory clinics has highlighted computerized cognitive tests, such as the Integrated Cognitive Assessment (ICA), as prominent candidates for adoption in clinical practice both during the pandemic and for post-COVID-19 implementation as part of health care innovation [4].

The ICA is a 5-minute computerized cognitive test based on a rapid categorization task that employs an artificial intelligence model to improve its accuracy in detecting cognitive impairment [5]. The ICA is self-administered and independent of language [6,7]. The value proposition of the ICA is that an accurate and sensitive tool for diagnosis will streamline the diagnosis of dementia by reducing false positive results from GP referrals and, therefore, minimizing the need for further, expensive and time-consuming assessments.

In order to address this challenge, we initiated the Accelerating Dementia Pathway Technologies (ADePT) study. The intention of conducting this study is to develop a real-world evidence basis to support the adoption of ICA as an inexpensive screening tool for the detection of cognitive impairment to improve the efficiency of the dementia care pathway.

The ADePT study is an ongoing multicenter real-world evidence study. The objective of ADePT is to deliver real-world evidence on practices and the economic case for ICA adoption in memory clinics for the assessment of cognitive impairment associated with dementia, Alzheimer Disease (AD), mild cognitive impairment (MCI), and similar diseases, including the assessment of preferred business models by comparing the accuracy of GP referrals against the ICA.

Methods

Ethics Approval

Health Research Authority and Health and Care Research Wales approval for this study was obtained in February 2020. The study is registered in the ISRCTN Registry (ISRCTN16596456).

Study Design

All participants are recruited among attendees at the National Health Service (NHS) memory services at the point of referral by their GP. The participants who do not have a formal diagnosis of a neurodegenerative disease are triaged as per usual clinical practice and are asked to complete the ICA in parallel with the diagnostic assessment. The aim of the clinical work package is to recruit 140 participants into the study.

The main study inclusion criterion is referral to the memory clinic by a GP. Patients recruited must be 55 to 90 years old. Potential participants must also be fully informed of and understand the objectives, procedures, and possible benefits and risks of the study and have the capacity to provide written consent.

Subjects that meet the following criteria will be excluded from the study cohort:

- Lack of capacity to consent to participation in this study
- Upper limb arthropathy or motor dysfunction that limits the use of a tablet computer

- Visual impairment severe enough to limit the use of a tablet computer
- Known diagnosis of dementia
- Already receiving cholinesterase inhibitors and/or Memantine

Study Procedures

Participants enrolled in the study will be required to attend 1 visit at a designated memory clinic or remotely at their home (Assessment Visit 1 [AV1]). Participants will be asked to complete the ICA. Prior to taking the ICA, participants will also be requested to view a short training video to assist them in completing the task successfully. After taking the ICA, patients will complete the following short questionnaires:

- Inquiry on stimulants, fatigue, and sleep: A questionnaire that assesses the participant's overall state. Questions revolve around recent intake of stimulants (eg, coffee or alcohol), sleep quality, energy levels, and mood. The questionnaire is used in conjunction with the ICA to determine whether any of these factors have had an impact on ICA performance.
- ICA Usability Questionnaire: A questionnaire that assesses the participant's views on their experience with the test to receive acceptability and usability feedback for the ICA.
- Cognitive Health Questionnaire: A questionnaire that assesses the participant's history of activities of daily living and physical and mental health comorbidities. The questions should ideally be answered by the informant (study partner) if available or by the participant if an informant is not present. The questionnaire is used in conjunction with the ICA to determine whether cognitive impairment detected by the ICA is due to MCI/dementia or other organic and/or treatable conditions.

Lastly, a brief medical history of the participants via electronic health care records will be obtained, mainly focusing on any cognitive tests that have been taken by the participants.

Participants will also be given the option to carry out a retest visit (Assessment Visit 2 [AV2]) whereby they are again given the chance to take the ICA test either remotely or face-to-face, complete a usability questionnaire, and respond to inquiries on stimulants, fatigue, and sleep. The overall study pathway for participants is detailed at a high level within Figure 2.

Figure 2. Accelerating Dementia Pathway Technologies (ADePT) study participant pathway.
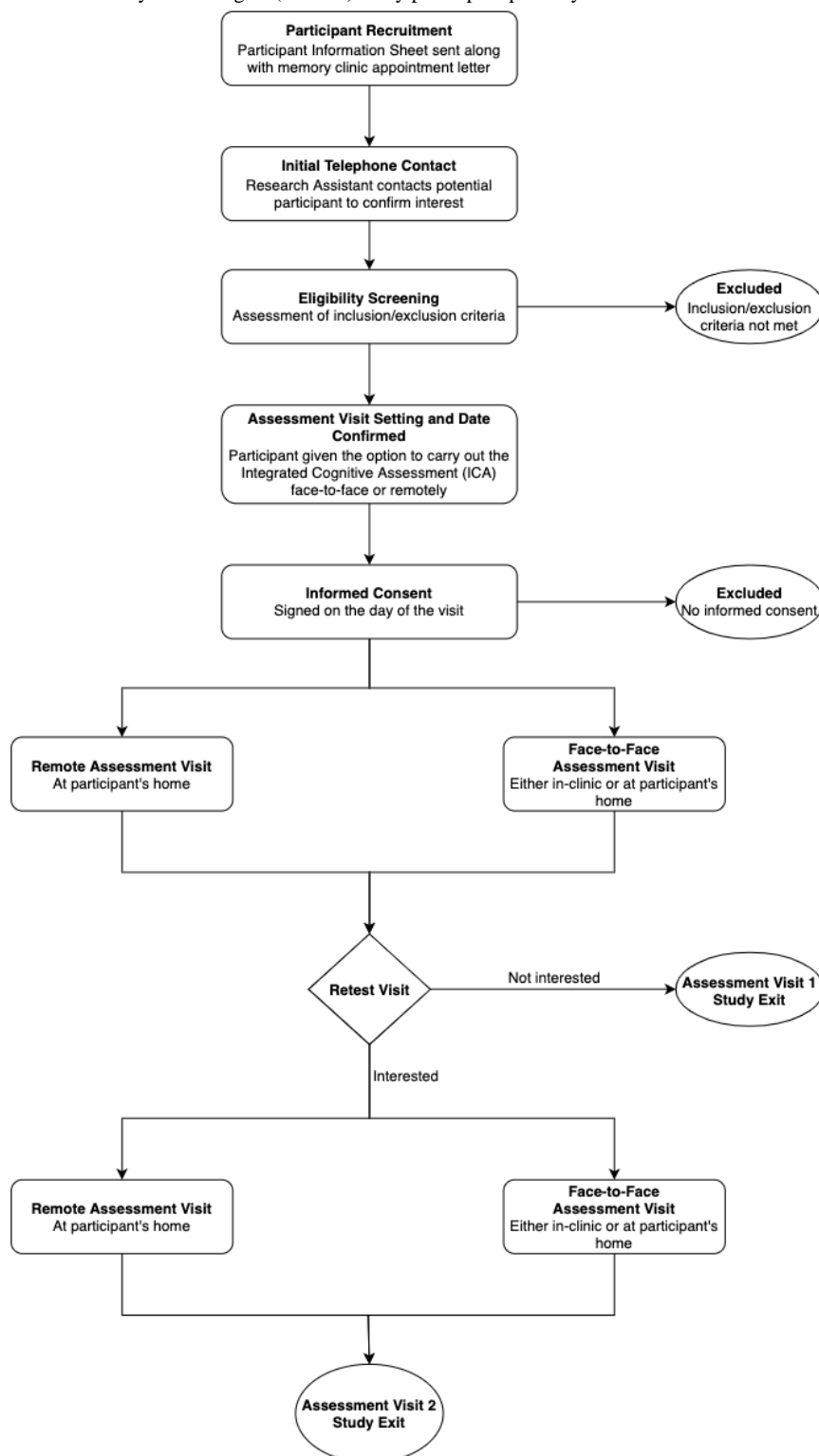
Data Management

The primary data sources are the Castor electronic data capture (EDC) system and the ICA portal. Castor EDC will be used to report all protocol-required information for each participant in the form of an electronic case report form. The participants of the study are not identified by name or initials on the electronic case report form or any other study documents to be collected by Cognetivity Neurosciences Ltd, but will be identified by a participant ID number. Data entry is performed by the researchers in the investigator sites, while data source verification is performed by the sponsor's clinical research associate.

The ICA portal is a secure portal where ICA results are uploaded. In addition, the participant's ID number and demographic details are also uploaded to the ICA portal, which allows linking of the ICA data to the Castor EDC data. Data entered in the iPad (Apple Inc) do not undergo source data

verification; however, the ID field and key fields which are common between the ICA and EDC undergo a data check by the data manager and queries are raised in case of discrepancy.

The secondary data source is source data, which includes any information in original records and certified copies of original records of participants, including medical history records as well as worksheets, which are usually used in order to record protocol-required information during the assessment of each participant (eg, usability questionnaires) prior to inputting such data into Castor EDC.

Data linkage and processing then takes place, from which metrics and data sets for analysis are generated. Such metrics include, but are not limited to, demographic breakdown (to track the distribution of age, years of education, and gender), a spreadsheet of key data fields used by the Medical Monitor to review data for a patient as well as site metrics on recruitment, queries and protocol deviations, lock and sign off, study exit, and adverse events.

Statistical Analysis

For the purposes of these analyses, patients referred to the memory clinic are divided into the following 3 groups, based on their memory clinic outcome: (A) those who receive a diagnosis of MCI or dementia, (B) those who are identified as healthy or receive a diagnosis of a brain or mental disorder other than MCI or dementia, and (C) those who receive an inconclusive diagnosis.

Participants with an inconclusive outcome after the memory clinic assessment are excluded from further analysis.

Participants in group A are counted as correct GP referrals. Participants in group B are counted as unnecessary or incorrect referrals.

Comparison with Specialist Diagnosis of MCI/Dementia

The metrics for GP referrals that will be calculated are the following:

- Total number of patients referred by GPs=A+B+C
- Proportion of necessary GP referrals (excluding inconclusive)=A/(A+B)
- Proportion of unnecessary GP referrals (excluding inconclusive)=B/(A+B)

Likewise, the following complementary metrics for the ICA will be calculated:

- Total number of patients the ICA would have referred
- Proportion of patients correctly referred by the ICA
- Proportion of patients incorrectly referred by the ICA
- Proportion of patients correctly not referred by the ICA
- Proportion of patients incorrectly not referred by the ICA

In a secondary outcome analysis, we will compare with specialist diagnosis of all types of cognitive impairment (those due to MCI, dementia, or other neurological or mental disorders).

Test-Retest Analysis

The test-retest reliability of the ICA will be analyzed by the following:

- Calculation of intraclass correlation coefficient to assess test-retest reliability across all participants
- Scatterplot construction and calculation of correlation coefficient between the initial and final assessment for all participants
- Construction of Bland-Altman plots for the initial and final assessment to assess agreement

Qualitative Data from Usability Questionnaire

Multiple choice responses from participants will be analyzed by calculating the proportion of participants who selected each option. Questions relating to frequency of tablet or mobile phone use will be used to assess familiarity with technology, in particular touch screen devices. The ease of understanding the ICA instructions and level of difficulty of the categorization task will be analyzed by calculating the proportion of participants who reported finding each of these steps very easy, easy, moderately difficult, difficult, or very difficult.

Procedures to Account for Missing and Spurious Data

Patients with inconclusive outcomes are excluded from our analysis. Other than that, we do not expect any other missing data regarding the calculations needed for primary and secondary outcome measures.

Health Economic Evaluation

The clinical outcomes described above and data gathered from surveys, in combination with NHS reference costing data, will be used to assess the potential health economic benefits of the use of the ICA in the dementia diagnosis pathway.

The inputs that are actively gathered as part of this study to be used for health economic modelling are the following:

- Comparison of ICA referrals with specialist diagnosis
- If the participant was referred to another secondary care team

NHS reference costing data (or other literature review) will be used to determine the cost of patient diagnosis considering the cost of the GP appointment and assessments performed at the memory clinic.

Based on the outcomes in the statistical analysis, we will compare the total costs and time saved if ICA was to be used by the GP for referral or at the entry to memory clinics to triage patients before entering the full diagnostic pathway.

Results

The ADePT study was funded in January 2020 by Innovate UK (Project Number 105837). The first patient visit was conducted in November 2020.

As of September 2021, 86 participants have been recruited for the study, with 23 participants also completing a retest visit. Initially, the study was designed for in-person visits at the memory clinic; however, in light of the COVID-19 pandemic,

the study was amended to allow remote as well as face-to-face visits.

The study was also expanded from a single site to 4 sites in the United Kingdom, based at the following trusts: Devon Partnership NHS Trust, North Bristol NHS Foundation Trust, Oxford Health NHS Foundation Trust, and Sussex Partnership NHS Foundation Trust.

We expect results to be published by the second quarter of 2022.

Discussion

In summary, the ADePT project aims to improve the efficiency of the dementia pathway at its very beginning and supports systems integration at the intersection between primary and secondary care. The introduction of a standardized, self-administered, digital assessment tool for the timely detection of neurodegeneration as part of a decision-support system that can signpost accordingly can reduce unnecessary referrals, service backlog, and assessment variability.

Remote assessments in the post-COVID-19 clinical environment are expected to form a core part of frontline service delivery as both services and their service user attitudes change while the use of smartphones and tablet computers is expanding in older adults [8]. Early identification is key as evidenced by the Prime Minister's Challenge in 2020 [9] and is now corroborated by the advent of novel disease-modifying treatments [10].

We hypothesize that the health economic benefits for such a decision support tool will overshadow the relatively low price of such a proprietary technology compared to pen and paper conventional tests that demand time and expertise most primary care practitioners may not have, in combination with limitations in their validity in prodromal dementia and invariable cultural and interpretation bias.

The main strength of this study is that it accommodates face-to-face and remote assessments as part of day-to-day practice in a memory service setting with minimal disruption to the pathway, while obtaining real-world data on participant experience and the acceptability of such a tool in a rapidly changing technological environment.

In the ADePT study, we investigate GP referrals to memory clinics, where GP colleagues have already made the clinical decision to refer to specialists. As a result, these cases may only be assessed as true or false positives based on prospective diagnosis of neurodegeneration or not. A more complete picture of the quality of primary care cognitive assessment would also require the study of true and false negatives (ie, those patients who were not referred to memory clinics by their GPs). This is a limitation of the study, albeit an unavoidable one as the latter would require multisite recruitment from GP surgeries and prospective participant follow-up which would be impractical. However, we expect that the ADePT results can inform a future longitudinal study in primary care.

To date, research on digital cognitive tests in primary care has been scant. A valid and acceptable tool can improve early diagnosis, provide timely interventions, enhance clinical and health economic outcomes, reduce burden on memory services, and foster interoperability and continuity of care throughout the patient journey in the dementia pathway. A remote assessment tool can also close the clinically important service gap that is the monitoring of disease progression both in already diagnosed patients and those with MCI. Monitoring of the latter patient group is particularly topical as there is no current service provision, as novel treatments are becoming available [10]. The ADePT project aims to provide appropriate evidence to support policy change to shape best practice guidelines in the dementia pathway. Finally, objective and consistent measurement of cognition for at-risk populations will support research and candidate identification in primary care for a disease that continues to take a toll on patients, services, and families.

Authors' Contributions

CK is the Medical Monitor for the Accelerating Dementia Pathway Technologies (ADePT) study. NT is Chief Investigator of the ADePT study.

Conflicts of Interest

SMKR serves as the Chief Scientific Officer at Cognetivity Neurosciences Ltd. CK serves as the Chief Medical Officer at Cognetivity Neurosciences Ltd. MHM is the Data Science Lead at Cognetivity Neurosciences Ltd. PA is the Clinical Trial Manager at Cognetivity Neurosciences Ltd.

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Abbreviations

6CIT: Six-Item Cognitive Impairment Test
AD: Alzheimer Disease
ADePT: Accelerating Dementia Pathway Technologies
AV1: Assessment Visit 1
AV2: Assessment Visit 2
EDC: electronic data capture
GP: General practitioner
GPCOG: General Practitioner Assessment of Cognition
ICA: Integrated Cognitive Assessment
MCI: mild cognitive impairment

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Protocol

A Mindfulness-Based Intervention to Alleviate Stress From Discrimination Among Young Sexual and Gender Minorities of Color: Protocol for a Pilot Optimization Trial

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Abstract

Background: Young sexual and gender minorities (SGMs) of color may face unique experiences of discrimination based on their intersectional positions (eg, discrimination based on both racial or ethnic identity and sexual identity). Emerging evidence suggests that mindfulness practices may reduce stress from discrimination and improve overall well-being among young SGM. Moreover, the omnipresence of smartphone access among racial or ethnic and sexual minority communities provides a method through which to administer mindfulness-based interventions among young SGMs of color.

Objective: This paper outlines the protocol of the Optimizing a Daily Mindfulness Intervention to Reduce Stress from Discrimination among Young Sexual and Gender Minorities of Color (REDUCE) study, a pilot optimization trial of a smartphone-based mindfulness intervention that was developed in conjunction with the Healthy Minds Program (HMP) with the aim of reducing stress from discrimination among young SGMs.

Methods: In total, 80 young (ages 18-29 years) SGMs of color will be enrolled in the study. The HMP is a self-guided meditation practice, and participants will be randomized to either a control condition or an intervention that uses a neuroscience-based approach to mindfulness. We will use the multiphase optimization strategy to assess which combination of mindfulness interventions is the most effective at reducing stress from discrimination among young SGMs of color. A combination of mindfulness-based meditation intervention components will be examined, comprising mindfulness-based practices of awareness, connection, and purpose. Awareness refers to the practice of self-awareness, which reduces the mind's ability to be distracted and instead be present in the moment. Connection refers to the practice of connection with oneself and others and emphasizes on empathy and compassion with oneself and others. Purpose encourages goal-making in accordance with one's values and management of behavior in accordance with these goals. In addition, we will assess the feasibility and acceptability of the HMP application among young SGMs of color.

Results: The REDUCE study was approved by the Institutional Review Board of New York University, and recruitment and enrollment began in the winter of 2021. We expect to complete enrollment by the summer of 2022. The results will be disseminated via social media, journal articles, abstracts, or presentations, as well as to participants, who will be given the opportunity to provide feedback to the researchers.

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Conclusions: This optimization trial is designed to test the efficacy, feasibility, and acceptability of implementing an application-based, mindfulness-based intervention to reduce stress from discrimination and improve well-being among young SGMs of color. Evidence from this study will assist in the creation of a sustainable, culturally relevant mobile app–based mindfulness intervention to reduce stress from discrimination among young SGMs of color.

Trial Registration: Clinicaltrials.gov NCT05131360; https://clinicaltrials.gov/ct2/show/NCT05131360

International Registered Report Identifier (IRRID): DERR1-10.2196/35593

Introduction

Minority Stress and the Health of Sexual and Gender Minorities

The term sexual and gender minority (SGM) comprises a broad range of identities related to sexual orientation and gender identity including, but not limited to, lesbian, gay, bisexual, and transgender individuals [1]. Many studies have documented that SGMs are faced with a multitude of health disparities, particularly within the emerging adulthood period (ie, ages 18-29 years) [2,3]. In particular, depression, anxiety, and suicidality continue to be disproportionately high throughout the emerging adulthood period among SGMs relative to older SGMs and non-SGMs [3]. Moreover, emerging adulthood is a key developmental period in which interventions designed to buffer the negative effects of stress on health may be particularly relevant, as emerging adulthood is characterized by rapid changes in psychological, social, and familial environments (eg, college) that greatly affect the development and maintenance of stress-coping mechanisms [4].

One pathway through which mental health disparities are posited to arise among SGMs is through sexual minority stress [5]. The sexual minority stress theory posits that sexual minority individuals experience many distal and proximal stressors related to the negative social valuation of sexual minority identity, resulting in exacerbated stress beyond the levels that people generally experience [5]. Over time, individuals may internalize minority stressors (eg, internalized homophobia), which in turn may contribute to poor mental health among SGMs [5]. Furthermore, SGMs who experience intersectional discrimination (eg, gender-based, racial- or ethnic-related, and sexual orientation–related discrimination) are more likely to report poorer mental health as compared with their White SGM and non-SGM counterparts [6-8]. Although the sexual minority stress theory also suggests that endemic structural-level processes contribute to the perpetuation of poor mental health among SGMs, it is imperative that interventions not only focus on reducing mental health inequalities at the societal level but also focus on reducing the *impact* of discrimination in the everyday lives of SGMs, particularly SGMs of color.

Researchers using daily diary methodologies have found that emerging adulthood SGMs who report more daily discriminatory experiences have more negative mood, poorer emotional states, and report more depressive symptoms and suicidal ideation on average than those who report fewer daily discriminatory experiences [9]. In addition, young SGMs of color who experience intersectional discrimination based on race or ethnicity, gender identity, or sexual orientation report more negative mood than young White SGMs [9].

Mindfulness and SGM Mental Health

Research suggests that increasing the practice of mindfulness may be useful for reducing the impact of daily stress on poor mental health among emerging adults who experience discrimination [10]. Mindfulness meditation is a practice that focuses on an individual's attention on the present moment, leading to reduced levels of stress [11]. Web-based mindfulness interventions among SGMs have been associated with lower levels of perceived stress compared with baseline readings in both men and women, as well as reduced sexual minority stress in SGM women [12]. Mindfulness interventions can also lead to increased individual resilience toward discriminatory experiences [13,14]. By allowing the SGM individual to disengage with the discriminatory experience by focusing on the present moment, negative feelings may be less likely to occur, which can lead to improved psychological well-being [13]. Past research provides evidence that mindfulness acts as a protective factor against the negative psychological effects of school-based victimization based on sexual orientation and age-based discrimination [14,15]. In particular, higher levels of mindfulness buffered the association between discrimination events and negative psychological outcomes, such as anxiety and depression [14,15]. Although there is a critical number of observational and intervention studies showing the effectiveness of mindfulness in reducing stress from discrimination and promoting well-being [16], the key features of mindfulness interventions that are the most effective, efficient, and scalable remain unclear. Thus, an approach to empirically examine the key features of mindfulness that are effective in reducing stress from discrimination among SGMs is imperative for creating culturally relevant and impactful well-being interventions for diverse populations of SGMs. In particular, there are three specific mindfulness-based practices, that is, awareness, connection, and purpose, that may lead to reductions in levels of stress and increased well-being.

Awareness through meditation promotes well-being through self-awareness, reducing the mind's ability to be distracted and instead be present in the moment, not allowing the mind to wander to negative thoughts that cause stress. Practicing awareness brings you to the present moment and allows you to become *aware* of your thoughts. Should the thoughts become

negative, awareness practice teaches individuals to let those thoughts wander without judgment. Furthermore, this practice teaches people to be present in the *current moment* rather than in thoughts regarding the past or the future [17]. The impact of awareness-based practice on mental well-being is supported by the overarching research literature [11,18]. For example, 1 study found that those who did not engage in awareness-based practices reported lower levels of happiness as compared with those who engaged in awareness-based practices [11]. Moreover, in another study of 717 students, Parto and Besharat [19] found that awareness was positively associated with mental well-being in their study sample. Thus, there is evidence to support that awareness is associated with positive mental health outcomes.

Connection through meditation supports empathy, compassion, and kindness in daily activities. The practice of connection emphasizes connections with oneself and with others. The mindfulness-based practice of connection with oneself highlights the need to be aware of oneself and one's emotions or feelings, to accept oneself owing to this awareness, and to orientate one's behaviors in conjunction with this awareness of oneself [20]. Moreover, mindfulness-based practices can also foster connections with others through *compassion* meditation, which begins with attention training and mindfulness, and goes on to contemplative practices with the goal of highlighting connection with others and self-compassion. Research shows that mindfulness-based self-connection is associated with well-being. Indeed, 1 study found that mindfulness predicted self-connection, which in turn was associated with increased well-being [20]. Moreover, previous work demonstrates that engagement in *compassion* meditations based on mindfulness and compassion is associated with reduced psychological distress and lower depressive symptoms [21,22].

Purpose through meditation encourages daily meaning in life through the encouragement of goal-making and behavior management in accordance with these goals [23]. The mindfulness-based practice of purpose allows emotions to be better regulated when an individual acknowledges the meaning in their life, leading to clearer values and persistence in the face of adversity. This practice guides overarching goals and daily behaviors by offering direction to oneself in alignment with one's goals and needs [23]. Much research documents the benefits of committing to the mindfulness-based practice of purpose. For instance, a systematic review found that meaning in life (ie, purpose) was associated with better overall physical health [24]. In addition, in a longitudinal study, Disabato et al [25] found in a sample of 797 adults that meaning in life predicted decreases in depressive symptoms over a 6-month period.

Conceptual Framework

Figure 1 displays the study's overarching conceptual framework. This framework describes how intersectional identities may lead to increased levels of stress and reduced well-being among young SGMs of color. SGMs of color possess multiple marginalized identities (ie, sexual or gender minority status and race or ethnicity). The possession of multiple marginalized identities, in turn, may lead to exposure to stigma and discrimination at the intersection of these identities (eg, they may experience discrimination based on both their gender identity and race or ethnicity). Exposure to stigma or discrimination may lead to increased stress levels in the form of minority stress, which may interact with other forms of stress (eg, chronic stress and financial hardship), which, in turn, may lead to poor mental health outcomes, including increased perceived stress and decreased well-being. However, the practice of mindfulness in the domains of awareness, connection, and purpose may buffer the negative effects of minority stress on perceived stress and well-being among young SGMs of color such that those who engage in these practices may experience improved mental health in the form of reduced perceived stress and increased well-being.

Figure 1. Conceptual framework.
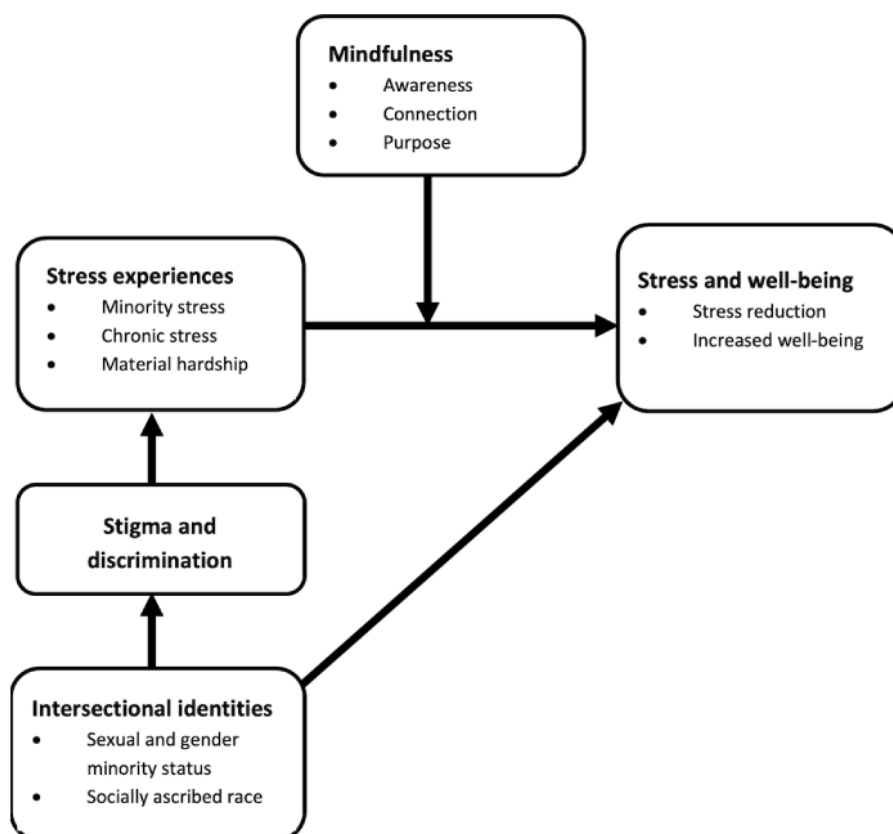
The Multiphase Optimization Strategy Framework

The primary goal of this study is to use an innovative optimization design (ie, the multiphase optimization strategy [MOST]) to evaluate different components of mindfulness interventions and the interaction between the components to build an effective, efficient, and scalable intervention to reduce daily stress from discrimination among SGMs of color. MOST is a systematic method for identifying the optimized combination of intervention components before testing an intervention in a resource-intensive randomized controlled trial (RCT) [26,27]. The MOST consists of three stages: preparation, optimization, and evaluation of the optimized intervention in an RCT. In this study, participants will be randomized into 1 of 8 conditions, and interventions will be administered using the MOST design. The participants will be randomized to at least one of the 3 intervention components of awareness, connection, and purpose for this optimization study, which comprises the 8 conditions. Each of these components is known to be effective in reducing stress and promoting well-being among populations that experience high rates of discrimination (eg, SGMs) [12-14]. These components will be administered via the Healthy Minds Program (HMP) app with the goal of examining which combination of components most effectively reduces stress from discrimination among racial or ethnic SGMs.

Study Objectives

In this study, the goal is to use the MOST to evaluate different components of mindfulness interventions and the interaction between the components to build an effective, efficient, and scalable intervention to reduce daily stress from discrimination among SGMs of color. The overall objective of this study is to

identify which combination of the three components (ie, purpose, connection, and awareness) meaningfully contributes to improvement in the primary outcomes of interest among SGMs, which are perceived stress reduction (ie, one's feeling about how stressed they are at a current moment) and improved well-being (ie, the state of feeling comfortable, happy, and healthy).

The aims of this study are as follows: (1) to assess the efficacy of the intervention components separately and in combination on mean change in stress and well-being among SGMs and (2) to determine the most effective intervention, based on the different combinations of the intervention components, which leads to the greatest reductions in perceived stress and the greatest improvement in mental well-being among SGMs. The 5-day period has been used in previous studies and demonstrates that mindfulness-based practice is effective at reducing stress over this brief period [28]. Furthermore, as a secondary aim, we will examine the feasibility and acceptability of the Reduce Stress from Discrimination among Young Sexual and Gender Minorities of Color (REDUCE) study. Feasibility and acceptability will be measured via retention rates and debriefing interviews, where we ask participants about their experiences with the study.

Methods

Setting and Participants

REDUCE is a single-site, pilot optimization study with the primary goal of assessing which component or components of a mindfulness-based smartphone app, the *HMP*, most effectively reduces the effects of stress from discrimination among young

SGMs of color. The study will use the MOST [26,27] framework to examine which combination of the well-being intervention components (ie, awareness, connection, and purpose; see the Intervention section) leads to the most optimal behavioral intervention. The *most optimal* behavioral intervention in this context is defined as one that yields the greatest improvement in mental health outcomes (ie, perceived stress and mental well-being) [29].

This pilot study will consist of 80 young SGMs (ie, between the ages of 18 and 29 years) who identify as a racial or ethnic minority (eg, Black or Hispanic). Participants will be randomized to 1 of 8 conditions (including a control condition; explained in detail in the Study Procedures section). The HMP app was developed by Dr Richard Davidson and others at the University of Wisconsin-Madison's Center for Healthy Minds in affiliation with the nonprofit Healthy Minds Innovations [30]. The HMP smartphone app is compatible with both the iPhone Operating System (iOS) and Android. The REDUCE study will be web- and smartphone-based, with study staff communicating with participants through Zoom (Zoom Video Communications), text message, phone, or email, depending on participant preference.

Participation in the study will last for 6 days, consisting of a web-based baseline survey (day 1), 5 days of self-guided practices completed through the HMP app (days 2-6), and 5 days of web-based daily diaries (days 2-6). In addition, we will collect data pertaining to feasibility and acceptability through a debriefing interview to be completed after completion of the 6-day study protocol. The Institutional Review Board of New York University at Washington Square has reviewed and approved this study (IRB-FY2020-4338).

Eligibility Criteria

Young SGMs of color who are aged between 18 and 29 years and who live in the New York metropolitan area will be eligible to participate in the study. The eligibility criteria were as follows: (1) be aged between 18 and 29 years; (2) must identify as a sexual minority (gay, bisexual, etc); (3) must identify as an underrepresented racial or ethnic minority (eg, Black or Hispanic); (4) must have an active smartphone and be able to access the smartphone 7 days a week between 6 PM and 6 AM the next morning; (5) must be willing and able to receive up to 6 text messages or emails per day; (6) must have consistent internet access 7 days a week between 6 PM and 6 AM; (7) must have the ability to understand, read, and speak English; (8) must reside in the New York metropolitan area; and (9) must be willing to provide written informed consent. We will exclude individuals who do not meet any of the eligibility criteria (eg, White participants).

Study Procedures

Recruitment

This study will focus on SGMs of color at the intersection of multiple marginalized identities (eg, race or ethnicity and sexual orientation). Participants residing in the New York metropolitan area (*n*=80) will be recruited using offline and web-based techniques, including the posting of flyers around New York City–based campuses (eg, New York University [NYU],

Columbia) and web-based listservs aimed at reaching young adult lesbian, gay, and bisexual (LGB) populations.

Screening

Interested persons will be directed to a web-based survey screener hosted on REDCap [31,32]. This web-based survey screener will provide a brief overview of the study to prospective participants. Prospective participants will be provided with contact information (ie, phone number and email) for both the principal investigator and laboratory at large, should they have any questions regarding the study objectives or protocol. Only those who are deemed eligible by the study screener (see the *Eligibility Criteria* section) will be contacted by the study staff. Ineligible responses will be kept on a file with a justification indicating why they were not eligible for the study.

Consent or Enrollment

If a prospective participant screens eligible through the web-based study screener, they will be contacted by trained study staff via email to schedule their informed consent session, which will take place over Zoom. During the informed consent session, trained study staff will first check identification to confirm identity and then go over the informed consent form with prospective participants. During this meeting, interested individuals will be given the opportunity to ask study staff any questions they may have to address concerns and to ensure comprehension among any and all prospective participants. The informed consent form will be programmed into REDCap, and all responses will be stored in a password-protected study folder separate from other study responses (eg, the baseline survey). Only trained study staff will have access to the REDCap responses.

Intervention

Randomization

After participants have provided written informed consent, they will be randomized into an intervention or control group using a randomization plan generator programmed into REDCap [31,32].

Optimization Study Design

The factorial design used for this study requires 8 experimental conditions, which were selected and presented in Figure 2. This design should not be considered an RCT because its purpose and logic are different. Although an RCT focuses on the direct comparison between interventions, the present factorial design does not directly compare interventions but rather identifies which components of each intervention are effective at reducing stress and promoting well-being. Following data collection, the main effects and interactions of all 8 conditions will be calculated to estimate efficiency. For instance, the main effect of awareness will be estimated by comparing the mean outcome across conditions 1 to 4 versus the mean outcome across conditions 5 to 8. To calculate the estimate of each main effect accurately, all participants will be included in an intent-to-treat (ITT) analysis. The factorial design does not use a traditional control group as it takes advantage of each factor having 2 levels, one of which serves as a control.

Figure 2. Proposed factorial design for phase 1 intervention optimization.
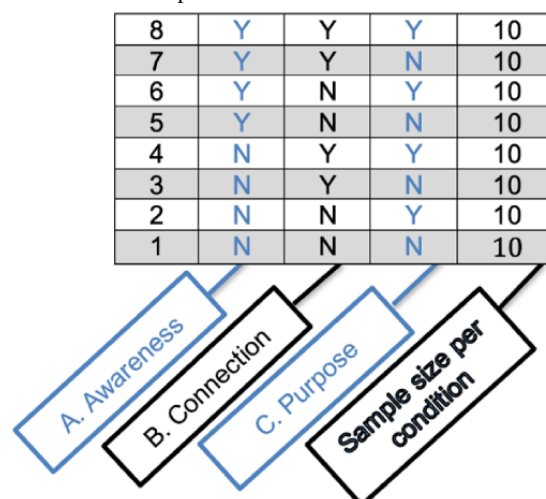
Intervention Content

The smartphone app used in this study, HMP, is grounded in neuroscience research [30]. The full HMP app is a self-guided mobile app (available via iOS or Android) that includes the four modules of awareness, connection, insight, and purpose [30,33]. The HMP app was designed by Healthy Minds Innovations, a nonprofit affiliated with the Center for Healthy Minds at the University of Wisconsin in Madison, Wisconsin. Mindfulness meditation is a practice that focuses on an individual's attention on the present moment, and past research has shown that this can lead to reduced levels of perceived stress [11]. The HMP app consists of prerecorded audio sessions that are designed to be completed over the course of the study (ie, over the 5-day diary period). Each unit is an average of 10 minutes in duration and includes both didactics and guided meditation practices. The participants could access a given unit after they have listened to prior units, and they could go back and replay units if desired. In this study, the app will be activated with a key code so that unit completion and playtime data can be logged for each participant. This study focuses on three aspects of well-being provided through the HMP app: awareness, connection, and purpose. In addition, there is an introductory exercise to mindfulness-based practice that is given to each of the study participants, which serves as the basis of the control group. Each of these components has been shown to reduce stress and promote well-being among populations that experience high rates of discrimination (eg, young SGMs) [34]. The 4 study components are described in detail in subsequent sections.

Introduction to mindfulness-based practice is a 5-minute self-guided introduction to mindfulness practice. This provides information pertaining to breathing and focus; however, information about the three pillars (awareness, connection, and purpose) is not provided during this session. This introduction is given to each intervention condition, and it is the only component given to the control group.

Given the literature demonstrating the benefits of awareness, connection, and purpose, there will be a total of 8 intervention arms for this study representing a combination of these 3 mindfulness-based practices. The eight intervention components are listed in Figure 2: (1) introduction only (ie, the control group); (2) purpose only; (3) connection only; (4) awareness only; (5) purpose and connection; (6) awareness and purpose; (7) awareness and connection; and (8) purpose, awareness, and connection. Daily self-directed mindfulness exercises are expected to last for an average of 10 minutes per day, depending on which intervention the participant is randomized to. However, those who are assigned to the control condition will listen to the introduction to mindfulness practice only and will not engage in self-directed mindfulness exercises each day.

Timeline

This study will take place over a 6-day period for each study participant, and the overarching study duration is expected to last 1 year. On the first day, participants will be randomized into 1 of the 8 conditions; complete the baseline survey; and complete the introduction to mindfulness activities or a combination of activities related to awareness, connection, or purpose depending on the randomization. To complete the baseline survey, participants will be sent a hyperlink to complete a baseline survey via REDCap. The baseline survey is expected to last 30-45 minutes. Constructs to be measured during the baseline assessment include, but are not limited to, perceived stress, perceived discrimination, depressive symptoms, and exposure to perceived microaggressions. See Multimedia Appendix 1 Table S1 [35-50] for a full list of the study measures collected during the baseline assessment. In addition, during the informed consent session, participants will be given information pertaining to the HMP app and how to access it. After completing their baseline survey on REDCap, participants will log in to the HMP app and complete their *introduction to mindfulness* exercise, which is expected to last 5 minutes.

On days 2-5, participants will complete their mindfulness activities, which will differ depending on randomization (see the *Intervention* section), which is expected to last between 5 and 15 minutes per day. In addition, participants will be sent a *nightly diary* survey via REDCap that ascertains information pertaining to stressful events and mood states experienced over the course of that day. Stressful events will be measured using the Daily Inventory of Stressful Events (DISE) [51], which is a 7-item questionnaire that ascertains experiences of stress on

that day. In addition, if they experienced a stressful event, the DISE asks a follow-up question regarding how stressful the event was for them on a 4-point Likert scale ranging from 1=*not at all* to 4=*very*. To measure mood, participants were given a modified version of the Positive and Negative Affect Schedule (PANAS) in the nightly diary [52]. The PANAS is a 20-item measure that asks respondents to rate how they have felt over the past week (eg, excited or nervous) on a 5-point Likert scale ranging from 1=*very slightly or not at all* to 5=*extremely*. For the purposes of the nightly diary, we modified the PANAS to reflect mood states over the current day. On day 6 of the study, participants will be scheduled for a debriefing session where they will be asked about their experiences in the study and remunerated.

Incentives

Participants will have the opportunity to earn up to US $47 for participation in the study, disbursed as a Visa gift card through Giftbit. The financial incentive structure is as follows: (1) participants will receive US $10 to complete their baseline assessment; (2) participants will also be compensated with US $3 for each daily diary completed over the 5-day diary period, up to an additional US $12; (3) participants will receive US $10 for competing their debrief interview. Thus, participants can earn up to US $47 for participation. In addition to the US $47, participants can also earn US $5 for every eligible individual that they recruit into the study who also enrolls.

Study Outcomes

There are 2 main study outcomes for this study, which are described in detail in subsequent sections.

Perceived Stress

Our first study outcome will be the perceived stress of the participants. Participants will be given the Perceived Stress Scale (PSS) [35,53] at both the baseline and follow-up assessments. The PSS is a 10-item measure used to measure the perception of stress over the past month. However, for the purposes of this study, we asked respondents to measure their perceptions of stress over the past day. Responses range on a 5-point Likert scale from 0=*never* to 4=*very often*. An example item is "In the last month, how often have you been upset because of something that happened unexpectedly" [35,53]. Items will be summed to generate a PSS score for both baseline and follow-up, with lower scores denoting less perceived stress over the last month. The Cronbach α for the PSS demonstrates high reliability among LGB adults (α=.92) [54].

Mental Well-being

Our second study outcome is related to the well-being of the study participants. Participants will be given the Satisfaction with Life Scale (SLS) [36] during both their baseline and follow-up assessments. The SLS is a 5-item measure used to measure an individual's overall well-being. Responses range on a 7-point Likert scale ranging from 1=*strongly disagree* to 7=*strongly agree*. An example item for the SLS is "The conditions of my life are excellent" [36]. Items will be summed to create a well-being score for both baseline and follow-up, with lower scores denoting lower well-being. The Cronbach α

for the SLS has demonstrated acceptable reliability among SGM populations (α=.83) [55].

Secondary Study Outcomes

Secondary study outcomes will include mood and stressful events, which will be analyzed via the 5-day nightly diary. Mood will be ascertained via the 20-item PANAS [56]. The PANAS measures positive and negative affect, and 10 items are given for each trait. The PANAS asks respondents to indicate the extent to which they felt a certain way over the past week; however, for the purposes of this study, we asked respondents the extent to which they felt a way over the past day (eg, interested or hostile). Responses lie on a 5-point Likert scale ranging from 1=*very slightly or not at all* to 5=*extremely*. The Cronbach α for the PANAS has demonstrated acceptable reliability for both positive and negative affect among LGB populations (α=.89 and α=.86, respectively) [57]. Exposure to stressful events will be measured via the DISE [51], which asks respondents whether they have experienced 1 of 8 stressors over the past day (eg, argument or disagreement with anyone). If a respondent indicates that they have experienced a given stressor, they are asked follow-up questions pertaining to stressor timing, intensity, perceived stress related to the stressor, resolution (yes or no), and stressor reappraisal. Responses for the follow-up questions lie on a 4-point Likert scale ranging from 0=*none at all* to 3=*very*.

Data Analysis

Univariate Analysis

Frequency tables and summary statistics will be calculated for each variable collected at baseline.

Main Study Outcomes Analysis

To assess efficacy, multiple linear regression will be used to estimate the effects of components on the mean change in stress (mean change in the PSS from baseline to follow-up) and well-being (mean change in the SLS). We will use an ITT approach for the analysis. Intervention components will be effect-coded to estimate the main effects and 2-way interactions of all 3 components. To select the optimized intervention, the research team will meet to determine the intervention components that demonstrate empirical evidence of efficacy the strongest or best of which will be considered candidates for the optimized intervention package based on procedures described by Collins et al [58]. Briefly, a component may be unselected if it interacts with another component to the extent that it undermines the effect of the second component.

Secondary Study Outcomes Analysis

Multilevel modeling will be used to examine if there are daily-level changes in positive and negative affect, as well as daily stressful events, given the participants' randomization. We will use an ITT approach for the analysis. We will examine whether there are daily-level changes in positive and negative affect and daily stressors by using a multilevel model that relates the repeated measures of positive and negative affect and daily stressors to the randomization assignment with time entered as a class variable to model potentially nonlinear patterns for 3 models. Furthermore, we will include covariates such as gender

identity within these analyses. For normally distributed outcomes, the model will be fit as a linear mixed effects model. For nonnormal outcomes, generalized linear mixed effects modeling will be used.

Power Analyses

For the primary outcomes of stress reduction and increased well-being at follow-up, we used the FactorialPowerPlan [59] package in the R software package to estimate the sample size needed for individual main effects of intervention components corresponding to a pretest–posttest correlation of 0.6, a medium effect size as standardized mean difference (Cohen d=0.50), given α=.05. A sample size of 80 provides 78% power.

Results

This project was funded in April 2020, and received institutional review board approval on April 27, 2020. After a delay owing to the COVID-19 pandemic, data collection commenced in February 2021. As of December 2021, 60 participants have been enrolled.

Discussion

This optimization trial is designed to test the efficacy, feasibility, and acceptability of implementing an application-based, mindfulness-based intervention to reduce stress from discrimination and improve well-being among young SGMs of color. We anticipate being able to identify which combination of mindfulness-based components is effective in reducing stress from discrimination. In addition, we will collect several indicators of feasibility and acceptability through retention metrics (eg, completion rates) and a qualitative debrief interview. Overall, this study has the potential to create a sustainable intervention for SGMs of color that uses an innovative mindfulness-based application.

Authors' Contributions

SHC conceived the study. SHC, SJ, and EG contributed to the design of the study. RT aided in the design of and implementation of the Healthy Minds Program app modules. EPW, NM, MB, MD, LG, OJ, and ZM drafted the initial manuscript and provided significant edits under the guidance of SHC, SJ, and EG. Each author has read and approved this manuscript.

Conflicts of Interest

RT is the Sr. Director of Research and Measures at Healthy Minds Innovation.

Multimedia Appendix 1
Description of scales used in the baseline assessment.
[DOCX File , 20 KB - resprot_v11i1e35593_app1.docx]

Multimedia Appendix 2
Peer review report from New York University, Institute of Human Development and Social Change.
[PDF File (Adobe PDF File), 265 KB - resprot_v11i1e35593_app2.pdf]

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Abbreviations

DISE: Daily Inventory of Stressful Events
EA: emerging adulthood
HMP: Healthy Minds Program
ITT: intent-to-treat
MOST: multiphase optimization strategy
PANAS: Positive and Negative Affect Schedule
PSS: Perceived Stress Scale
RCT: randomized controlled trial
REDUCE: Reduce Stress from Discrimination among Young Sexual and Gender Minorities of Color
SGM: sexual and gender minority
SLS: Satisfaction with Life Scale
SMS: sexual minority stress

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Protocol

Cocreating a Harmonized Living Lab for Big Data–Driven Hybrid Persona Development: Protocol for Cocreating, Testing, and Seeking Consensus

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Abstract

Background: Living Labs are user-centered, open innovation ecosystems based on a systematic user cocreation approach, which integrates research and innovation processes in real-life communities and settings. The Horizon 2020 Project VITALISE (Virtual Health and Wellbeing Living Lab Infrastructure) unites 19 partners across 11 countries. The project aims to harmonize Living Lab procedures and enable effective and convenient transnational and virtual access to key European health and well-being research infrastructures, which are governed by Living Labs. The VITALISE consortium will conduct joint research activities in the fields included in the care pathway of patients: rehabilitation, transitional care, and everyday living environments for older adults. This protocol focuses on health and well-being research in everyday living environments.

Objective: The main aim of this study is to cocreate and test a harmonized research protocol for developing big data–driven hybrid persona, which are hypothetical user archetypes created to represent a user community. In addition, the use and applicability of innovative technologies will be investigated in the context of various everyday living and Living Lab environments.

Methods: In phase 1, surveys and structured interviews will be used to identify the most suitable Living Lab methods, tools, and instruments for health-related research among VITALISE project Living Labs (N=10). A series of web-based cocreation

workshops and iterative cowriting processes will be applied to define the initial protocols. In phase 2, five small-scale case studies will be conducted to test the cocreated research protocols in various real-life everyday living settings and Living Lab infrastructures. In phase 3, a cross-case analysis grounded on semistructured interviews will be conducted to identify the challenges and benefits of using the proposed research protocols. Furthermore, a series of cocreation workshops and the consensus seeking Delphi study process will be conducted in parallel to cocreate and validate the acceptance of the defined harmonized research protocols among wider Living Lab communities.

Results: As of September 30, 2021, project deliverables *Ethics and safety manual and Living lab standard version 1* have been submitted to the European Commission review process. The study will be finished by March 2024.

Conclusions: The outcome of this research will lead to harmonized procedures and protocols in the context of big data–driven hybrid persona development among health and well-being Living Labs in Europe and beyond. Harmonized protocols enable Living Labs to exploit similar research protocols, devices, hardware, and software for interventions and complex data collection purposes. Economies of scale and improved use of resources will speed up and improve research quality and offer novel possibilities for open data sharing, multidisciplinary research, and comparative studies beyond current practices. Case studies will also provide novel insights for implementing innovative technologies in the context of everyday Living Lab research.

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Introduction

Virtual Health and Wellbeing Living Lab Infrastructure Project in Brief

The Horizon 2020 Project VITALISE (Virtual Health and Wellbeing Living Lab Infrastructure), funded by the European Union (EU; under grant agreement 101007990; April 2021-March 2024), unites 19 partners across 11 countries. VITALISE aims to harmonize Living Lab procedures and enable effective and convenient transnational and virtual access to key European health and well-being research infrastructures (RIs), which are governed by Living Labs. To do so, the VITALISE project itself follows a Living Lab procedure grounded on agile, user-centric, and multistakeholder-driven cocreation and testing approaches. A series of joint research activities (JRAs) in the fields of (1) rehabilitation, (2) transitional care, and (3) everyday living environments act as testing arenas for cocreating and validating the harmonized Living Lab procedures. Thematically, the JRA research protocol described in this study focuses on health and well-being research in everyday living environments among older adults.

Living Labs as an RI

The European Network of Living Labs (ENoLL), which is an international nonprofit association promoting and enhancing user-driven innovation ecosystems and is also the coordinator of VITALISE project, defines Living Labs as "user-centred, open innovation ecosystems based on systematic user cocreation approach, integrating research and innovation processes in real life communities and settings" [1]. A systematic literature review explored the key characteristics of the Living Lab approach and concluded that the definitions for Living Labs and their use vary significantly in the literature, whereas some common elements can be identified [2]. The Living Lab harmonization work conducted in the context of 15 health and well-being Living Labs across the Baltic Sea region acts as a starting point for this study [3]. In VITALISE, Living Labs are considered RIs. In regulation 1291/2013, the EU Parliament and Council of the EU define RIs as "facilities, resources and services that are used by the research communities to conduct research and foster innovation in their fields" [4]. RIs can be (1) a single-sited facility (ie, unified single body of equipment at 1 physical location), (2) distributed facility (ie, a network of distributed resources such as instrumentation, collections, archives, and scientific libraries), (3) web-based facility (ie, information and communications technology–based systems for scientific research), and (4) mobile facility (ie, vehicles design for scientific research) [5]. The everyday living environments in JRA case studies comprise (1) public outdoor (eg, natural parks and outdoor fitness areas) and indoor (eg, museum and sports hall) places and (2) private homes, day care facilities for older adults, and smart home Living Labs equipped with sensors and other technological devices.

Big Data as Dynamic Persona Enabler

Big data have been described as the *future of health care* as it may generate (1) better evidence for health care delivery; (2) improve data quality and access; (3) help drive better communication among patients, providers, and communities; (4) identify trends; and (5) provide better information for patients and authorities [6,7]. In the context of Living Lab–driven research and innovation activities, multiple opportunities for using big data approaches can be identified, including (1) comparative effectiveness research to determine clinically relevant and cost-effective ways to diagnose and treat patients; (2) identify needs, follow-on indications, and adverse effects, which otherwise would stay hidden; and (3) use real-time data for safety monitoring and event prediction [8].

Personas—hypothetical user archetypes created to represent a user community—have been argued to be a powerful technique in the early design process phases to define and prioritize requirements and user needs [9]. Nevertheless, no databases exist that represent the aging and chronic patient population in a holistic and deep way, making it difficult to create effective

personas [10]. The 3 primary ways to define personas include (1) qualitative personas, (2) quantitative personas, and (3) qualitative personas with quantitative validation, also known as hybrid personas [11,12]. Prior studies have identified various challenges regarding the creation and distribution of personas, including (1) the lack of knowledge of the technique, (2) lack of resources (time and funding), (3) sparse descriptions relying on too much on qualitative data, (4) small sample size, and (5) lack of first-hand user and patient data [13,14].

Owing to increasing popularity of big data and digitalization-driven opportunities, data-driven persona development has been suggested as a solution to create more reliable personas [12]. Therefore, VITALISE case studies focusing on everyday living environments adopt the hybrid big data approach and use various state-of-the-art technologies to collect real-time big data on top of the user-provided qualitative data. The possible technologies in case studies include, for example, serious games; mobile phone apps; user behavior monitoring with 3D depth sensors and red, green, and blue wavelength cameras; and sensor data. As each Living Lab and case study also have their own research priorities, there is a need to effectively manage big data collection to enable open data sharing between different Living Labs, which is one of the main outcome objectives of the VITALISE project. Prior studies have argued that a top-down approach is needed to achieve the effective management of big data [6]. Therefore, the proposed efforts regarding a harmonized research protocol for developing big data–driven hybrid personas have a justified foundation.

Objectives

The objectives of this study are described next. First, the aim is to collectively identify the most suitable methods, tools, and instruments to collect qualitative and quantitative data (ie, following a mixed methods approach) [15] among Living Labs in the context of big data–supported everyday living environment research. Second, by following triangulation principles [16], a group of small-scale case studies focusing on everyday living environment interventions will be conducted to evaluate the applicability of the selected methods, tools, and instruments in various real-life Living Lab environments, covering (1) applied- and solution-oriented and (2) use-inspired basic research settings [17]. Each case study intervention has specific research objectives, which are defined more specifically in the *Case Study Interventions for Phase 2* section. Third, a cross-case analysis regarding the challenges and benefits of using the proposed technologies, methods, tools, and instruments will be conducted to cocreate and define a harmonized research protocol for developing big data–driven hybrid personas. The aim is to reach a consensus regarding defined research protocols

among the case study Living Labs and external harmonization body, which is a wider community of stakeholders consisting of Living Lab researchers and practitioners, health care professionals, and policy makers.

Methods

Research Process Phases

Overview

A solution-oriented research paradigm covering (1) ex ante and engaging (ie, research activities before the case studies), (2) in situ and engaging (ie, research activities during the case studies), and (3) ex post and engaging (ie, research activities after the case studies) phases will be used as the overall theoretical framework for this study [18]. Among scholars and practitioners, there is no clear consensus on what are and how many stages there are in Living Lab research and innovation processes [19]. The different multistaged iterative Living Lab processes have very similar activities; however, the naming for the different phases varies [3]. By combining 2 prior studies' suggestions regarding Living Lab research process phases [3,20], the data collection phases for this study are given in the following sections.

Phase 1: The Ex Ante and Engaging

Phase 1 focuses on exploring the problem space by collectively identifying the most suitable Living Lab methods, tools, and instruments for health-related research conducted in everyday living environments [21,22]. The following research questions (RQs) have been defined for this phase:

- RQ1: What are the most potential data and big data collection technologies for health and well-being Living Lab research in the context of everyday living environment research?
- RQ2: What are the most potential methods, tools, and validated scientific instruments for health and well-being Living Lab research in the context of everyday living environment research?

On the basis of identified needs and opportunities, a joint research protocol will be cocreated to cover the interplay among the case studies and enable open data sharing among the case studies.

Phase 2: The In Situ and Engaging

Phase 2 focuses on experimentation by conducting a group of small-scale case studies in various Living Labs and everyday living environment interventions and settings, as presented in Table 1.

Table 1. Case study key interventions and data collection settings.

Case studies and key interventions	Virtual or auditive interaction	Sensor technology
Case study 1: Combination of distributed facility (participants homes) and virtual reality environments (ie, mobile phone coaching app)		
An 8-week training period to maintain social relationships and activities that could be at risk by the withdrawal from the workplace	Virtual coaching via mobile phone app	__a
Case study 2: Single-sited facility (smart home Living Lab) equipped with virtual reality environments (Windows-based software)		
Series of cognitive and physical exercises, including 1-hour yoga exercise	Measurement of financial capacity (banking game) and cognitive status (virtual supermarket game) as well as physical activity promotion via virtual coach by using app	Wristband sensors (Fitbit Charge 3 and Empatica E4) during all activities and Muse EEG[b] (InterAxon Inc) during the yoga exercise
Case study 3: Single-sited facility (measurement laboratory) equipped with virtual reality environments (Windows-based software)		
A total of 2 weekly sessions of 30 minutes during the 8 weeks training period focusing on physical and cognitive training	Windows-based software having combined physical and cognitive training (dual task) exercises	Motion capture via Kinect v2 (Microsoft)
Case study 4: Distributed facilities (sport halls, nursing homes, and outdoor training facilities) with mobile facilities (wearable sensors)		
Comprehensive physical fitness evaluation in a multistaged measurement track and recreational football playing (Spain) and outdoor fitness trail training (Hungary) for the 8 weeks period	In the case of COVID-19 restrictions, YouTube and WhatsApp group video calls will be used for virtual exercise coaching in Spain	Wearable activity sensors (SenseWear Armband [BodyMedia Inc] and Galaxy Watch 3 [Samsung Electronics])
Case study 5: Distributed facilities (museums) with various mobile facilities (wearable sensors and trackers)		
Explore the lived experience of the museum visit with the help of innovative technologies	Description of the museum exhibit items, including the audio version of the written information that accompanies the work and adaptive version of the information for people with disabilities	Eye-tracking glasses (Pupil Labs), smartwatch (Apple Watch or Fitbit inspire2), NIRS[c] system (Artinis Medical System), pressure sensitive walkway (Gaitrite, GAITRite), and APDM inertial sensors (APDM Wearable Technologies Inc)

[a]Sensor technology has not been used.

[b]EEG: electroencelogram.

[c]NIRS: near-infrared spectroscopy.

As a result, *data triangulation* using multiple data sources, *investigator triangulation* using >1 investigator, *theory triangulation* using multiple theoretical approaches to interpret the phenomenon, and *methodological triangulation* using multiple quantitative and qualitative data collection methods will be applied [16]. Each case study will generate quantitative big data derived from the case study interventions when using sensor devices or mobile phone apps. Furthermore, case study participants' user experience (UX) regarding their Living Lab experiment will be collected with a survey, including a group of harmonized questions across the case studies (quantitative data). In addition to testing the applicability of the suggested Living Lab and big data collection methods, each case study intervention has a specific health and well-being RQ and data collection method to evaluate either the effects of these interventions or their user acceptance. Each case study is defined more specifically in the intervention section.

Phase 3: The Ex Post and Engaging

Phase 3 focuses on collectively evaluating case study experiences from a Living Lab operator's point of view. A cross-case analysis grounded on semistructured interviews will be conducted to identify the challenges and benefits of using the proposed research protocols. The following RQ is defined for this phase:

- RQ3: On the basis of real-life case study experimentation, what are the key challenges and critical success factors for developing big data–driven hybrid personas?

Recruitment

Living Labs and Harmonization Body Recruitment

Regarding Living Lab RI harmonization objectives and RQs (RQ1 to RQ3), the unit of analysis is a Living Lab. The 9 VITALISE project Living Labs form the main sample group. The VITALISE project website provides links to Living Lab hosting organizations' home pages, where more detailed information about each Living Lab and its infrastructure is available [23]. Each Living Lab will indicate a dedicated contact person who will act as a key informant for RI harmonization–related research activities. Furthermore, this contact person can recruit additional experts from their Living Labs when needed. Thus, depending on the research activity, the number of representatives per Living Lab typically varies between 1 and 5 persons.

The external harmonization body members represent a wider community of Living Lab stakeholders comprising known Living Lab researchers and practitioners, health care professionals, and policy makers beyond the VITALISE project. Personal invitations are sent to persons matching the defined profile (ie, having extensive research, practical, or managerial

experience from Living Lab research, projects, or organizations). The harmonization body will comprise approximately 10 to 15 persons. Finally, the open access web-based cocreation event participants will be recruited by open calls distributed via the ENoLL and VITALISE project partner communication channels such as newsletters, social media accounts, and websites.

Recruitment for Case Studies

The following eligibility criteria are common in all case studies: (1) willing and interested to collaborate voluntarily in the study and conduct study-specific activities defined in the case study interventions that vary case by case, (2) conserved the ability to understand, (3) felt physically and cognitively able to take part in the particular case study (self-assessed), and (4) signed the consent for participation in the study and data processing (transfer of the collected data to an open access database is optional and does not imply exclusion from the study). Otherwise, the sample sizes, recruitment methods, and participant eligibility criteria vary among the case studies and are defined as part of the case study intervention descriptions.

Interventions for Phases 1 and 3

In the following sections, the interventions for developing and testing harmonized research protocols for big data–driven hybrid personas are defined based on the Template for Intervention Description and Replication checklist and guidelines [24].

Why

Lately, Living Labs have gained increased popularity among scholars and practitioners. Although the Living Lab community is already strong and continues to grow as singular entities, it still fails to provide and function according to unified and harmonized research processes that are easily accessible and exploitable by academia and industry researchers beyond the Living Lab internal researchers. As a result, there is a need to identify and test joint research protocols, methods, tools, and devices that could act as an effective and convenient interface to Living Lab infrastructures in various research settings, including everyday living environments research using big data approaches.

What (Materials)

The data collection methods, tools, and devices currently used by Living Labs will be collected via the following 3 different structured Microsoft Excel template files: (1) data collection devices, (2) validated scientific scales and questionnaires, and (3) Living Lab services, including prefilled service and method descriptions derived from the Product Validation in Health project's final report [3]. Guidelines for filling Microsoft Excel files are provided in a PDF document. The filled Microsoft Excel templates will also be used as background material and interview templates during each Living Lab interview. Summary reports (Microsoft Excel and Microsoft Word files) explaining the data collection summary results will be used to share information among all VITALISE Living Labs. The research protocols for each case study will be written as Microsoft Word documents using a structured format.

What (Procedures)

Phase 1: The Ex Ante and Engaging

First, by following written guidelines, each Living Lab will self-complete the provided Microsoft Excel files together with their core team members by adding new content or modifying the prefilled content. Second, structured interviews with each Living Lab will be conducted to deepen the understanding of each Living Lab's answers using the previously filled Microsoft Excel templates as an interview notes template. If certain questions remain unanswered during the interview, Living Labs will be requested to fill the missing information afterward directly to the interview notes template, which includes open questions. Third, 2 facilitated web-based cocreation workshops—1 with VITALISE Living Labs and 1 open access event during the ENoLL web-based conference—will be arranged to collect qualitative feedback and identify new Living Lab methods, tools, and services beyond the Microsoft Excel template lists. Fourth, research protocols for the case studies are cowritten and discussed in a series of web-based workshops and sending of the documents back and forth between the key researchers from each Living Lab.

Phase 2: The In Situ and Engaging

The detailed research protocol descriptions for each case study are provided in the follow-up *Case Study Interventions for Phase 2* section.

Phase 3: The Ex Post and Engaging

First, semistructured interviews (qualitative data) with VITALISE Living Labs will be conducted to identify the key experiences regarding case studies from a Living Lab operator's point of view. In the follow-up process, a series of facilitated cocreation workshops will be conducted to define a harmonized research protocol for developing big data–driven hybrid personas based on case study results.

Who Provided

Interviews and workshops will be managed and delivered by a small group of experienced Living Lab researchers (ie, 3 persons) taking part in the VITALISE project and having extensive experience in planning and implementing Living Lab research projects and protocols. Support personnel will be involved in the implementation of the study (eg, for note taking).

How

VITALISE Living Labs will be first instructed to fill Microsoft Excel file templates by each individual Living Lab team member and then self-arrange a face-to-face or web-based workshop where team members can collectively discuss and refine the Living Lab's responses. The follow-up Living Lab interviews will be conducted by 1 to 2 interviewers and 1 note taker in Microsoft Teams, Google Meets, or Zoom videoconferencing platform. Notes will be written interactively as the interview progresses, and the videoconference screen-sharing feature will be used to share the written information among all participants. Afterward, Microsoft Teams will be used for document and data sharing among Living Labs during the research process. Mentimeter, an interactive presentation platform, will also be

occasionally used for brainstorming during the web-based workshops.

Where

Owing to the long distances between the VITALISE Living Labs and the COVID-19 pandemic situation, all interviews and workshops will be arranged on the web using Microsoft Teams, Google Meets, or Zoom videoconferencing platforms. If the COVID-19 pandemic situation allows, face-to-face workshops will be organized as a part of the VITALISE project consortium meetings during phase 3.

When and How Much

During phase 1, each Living Lab's internal workshop where they collectively discuss and refine their existing Living Lab practice responses will occur once and is expected to take approximately 3 hours. If the time is not sufficient, Living Labs will be encouraged to keep as many workshops as required to properly fill the Microsoft Excel templates. Living Lab interviews focusing on deepening the understanding regarding each Living Lab's current practice will occur once and is expected to last approximately 2 to 2.5 hours. Living Lab interviews that focus on evaluating the key experiences regarding the case studies from the Living Lab operator's point of view will also occur once and are expected to last approximately 2 to 2.5 hours each. It is estimated that at least three (web-based) workshops with an estimated 3-hour duration each are needed to agree on the harmonized research protocols for developing big data–driven personas. After each workshop, a web-based voting procedure will be conducted to evaluate the consensus among Living Labs and harmonization bodies. The proposed research protocols will be modified until the voters reach a supermajority agreement (ie, at least a 70% acceptance rate). If an agreement is not reached during the first 5 iterations, the process will end, and disagreements regarding the research protocol and included technologies, methods, tools, and other scientific instruments will be documented.

Tailoring and Modifications

In principle, interviews and workshop interventions follow the same principles for all participants, and modifications are not preplanned. However, if a need to make modifications emerge, they can be made.

Case Study Interventions for Phase 2

Case Study 1: Digital Coaching App Impact on Self-efficacy and Well-being

Why

The general aim of this case study is to test the digital coach app of the Austrian Institute of Technology (AIT) by analyzing to what extent it can influence individuals' self-efficacy and well-being by motivating older adults to practice a healthy lifestyle. Moreover, the study will also assess the system's usability, learnability, and user acceptance. The monitoring of the effects of the coach app use may throw light on the capability of digital coaching in helping retirees maintain (and improve) social relationships and activities that could be put at risk by their withdrawal from the workplace. The study evaluations

will be set up in 2 different sites: Belgium and Austria. This multisite design will allow the evaluation of the AIT coach app in different social and cultural contexts.

To Whom (Sample Size and Recruitment)

A total of 40 persons will be recruited via the AIT (Austria) and LiCalab (Belgium) user panel databases. Social media channels and collaborations with local authorities will also be used. Key inclusion criteria include the following: for group A, older employees in good health (maximum approximately 3 years before retirement; work continuity during the study), and for group B, retired older people (retired for no longer than 3 years). For both groups, the availability of smartphones (Android version 8.0 or up, or iOS) was a key inclusion criterion. Key exclusion criteria include age <55 years and middle-to-severe constraints in mobility or cognition (self-assessed). For group B, care dependency (self-assessed) is also an exclusion criterion.

What (Materials)

Within the study, AIT's digital coaching app will be provided to the participants. The software used for the trials comprises a smartphone-based app and a server component providing the content and collecting the data. Communication between the front-end and back-end is established over the internet using secure communication channels. The back-end server runs within the facilities of the AIT's partner organization, ProSelf, to ensure privacy and security. No personal data will be stored in the cloud. A paper user manual will be provided to the participants to guide them through the first steps of installing, configuring, and using the app. Informed consent will be provided in paper form; questionnaires for collecting quantitative data will either be provided in paper form or as a link to a web-based questionnaire.

What (Procedures)

The study will follow a mixed methods design in which qualitative and quantitative data will be collected. To determine the effects of AIT's digital coaching on the 8-week term, 2 measurements (time point 0 [T0] and time point 1 [T1]) will be conducted using standardized tests. Thus, 2 face-to-face sessions will be scheduled with participants: 1 just before the beginning of the study and 1 at the end, after 8 weeks of use. Both qualitative and quantitative outcomes will be measured. At baseline (T0, before the start of the intervention), demographic data will be collected. The following outcomes will also be measured both at baseline (T0) and after the end of the intervention (T1): patient-reported outcome measures, including health and well-being (Short Form-36 version 2) and social life (Lubben scale), self-efficacy (General Self-Efficacy Scale-6), and patient-reported experience measures including, UX (User Experience Questionnaire [UEQ]) and basic health measures (eg, weight).

Who Provided

In this study, a multidisciplinary team comprising UX experts, clinical researchers (psychologists and researchers with experience in social sciences), and support personnel will be involved in the implementation of the study. All members hold relevant experience in EU health projects and eHealth research

and are experienced in planning, implementing, and analyzing clinical trials.

How

Within the study, AIT's digital coaching app will be provided to the participants. Participants will be provided with a link to install the app on their own smartphones. The app will be provided individually to all participants in the study.

Where

Sample group participants will be using their digital coach mobile app at their private homes in Austria and Belgium. This RI is classified as a combination of distributed (ie, private homes) and virtual (ie, mobile app) facilities.

When and How Much

The AIT's digital coaching app will be provided to the participants over a duration of 8 weeks. For data collection, 2 face-to-face sessions (each approximately 2 hours) will be scheduled with participants: 1 just before the beginning of the study and 1 at the end after 8 weeks of use.

Case Study 2: Net Zero Energy Buildings Smart Home Living Lab

Why

The aim of this feasibility and acceptability study is to evaluate the impact of physical and cognitive activity performance of older adults in a smart home Living Lab environment using a combined approach of virtual apps and several wearable sensors. This particular small-scale pilot study envisages showing us the benefits of specific types of physical and cognitive exercises combined with Living Lab technological advances. Moreover, the study will also analyze the extent to which it can influence individuals' self-efficacy and well-being by motivating older adults to practice a healthy lifestyle. The monitoring of the effects of the virtual coach app use may shed light on the capability of digital coaching for helping retirees maintain (and improve) social relationships and activities that could be put at risk by their withdrawal from the workplace. Yoga exercises, on the other hand, will provide evidence of how the body reacts by monitoring parameters such as brain activity and heart rate.

To Whom (Sample Size and Recruitment)

A total of 15 persons will be recruited by Aristotle University of Thessaloniki through the collaboration and research community for independent living. Participants comprise cognitively intact healthy older adults aged >60 years, with the absence of dementia, severe cognitive impairment, psychiatric diseases, and severe cardiovascular problems.

What (Materials)

Data will be collected using the following wearable sensors: Fitbit Charge 3, Empatica E4, and Muse EEG, resulting in physiological big data such as accelerometer, heart rate, and electrodermal activity during the interventions. Chairs will be used as props during the yoga exercises when needed. The following validated questionnaires will be used: (1) UEQ, (2) System Usability Scale, and (3) Unified Theory of Acceptance and Use of Technology, along with predefined key performance indicators will be used to measure the acceptability and usability

levels of the proposed protocols. The EuroQoL 5-dimensional 3-level questionnaire (Greek version) will be used to assess the participants' quality of life. The filled-in Microsoft Excel templates will also be used as background materials and interview templates during each interview. The research protocols for each case study will be written as word documents using a structured format.

What (Procedures)

Before cognitive and physical exercises, focus group sessions with beneficiaries and clinicians will be organized for recruitment purposes and participant profile data and end users' preferences and needs for the used technologies and interventions will be collected. The cognitive and physical exercises in a smart home Living Lab include the measurement of (1) financial capacity; (2) general cognitive status, memory, executive functions, and visuospatial functions; and (3) measurement of physical activity during virtual coaching and yoga exercises while participants are equipped with wearable sensors. After cognitive and physical exercises, focus group interviews will be conducted to assess participants' experiences regarding usability and acceptance of the performed activities and technologies.

Who Provided

A multidisciplinary team comprising Living Lab experts, health care personnel, and gym assistants will participate in the participant recruitment, exercise design, and safety standard definition. Focus groups and questionnaire administration will be managed by a well-coordinated group of experienced Living Lab researchers, with 4 to 5 people taking part in the VITALISE project and having considerable experience in planning and implementing Living Lab research projects and protocols.

How

Scheduled visits into a smart home Living Lab will be planned for each participant. All participants will attend all cognitive and physical exercises led by a virtual instructor (exercises 1-3) or a person (exercise 4) in the following order while wearing the Fitbit Charge 3 and Empatica E4 wristband sensors: (1) assessment of participants' financial capacity using tailored simulated Banking App [25], (2) evaluation of their general cognitive status, memory, executive functions, and visuospatial functions through the Virtual Supermarket app [26]—a simple virtual reality task running on tablet devices or PC for differentiating between MCI patients and healthy older adults, (3) implementation of the virtual coach application [27] for physical activity promotion and (4) applying a yoga session where participants will also wear the Muse EEG during the "body scanning" and "relaxation exercises" as part of the yoga protocol to obtain brain activity during these particular states. After cognitive and physical exercises, focus groups interviews will be conducted to assess participants' experiences regarding usability and acceptance of the performed activities and technologies.

Where

Cognitive and physical exercise interventions will take place in the smart home Living Lab environment equipped with various technologies described previously. Face-to-face focus

group sessions will be organized in meeting rooms for vaccinated individuals, whereas for the others, meetings will take place on web-based platforms such as Google Meets or Zoom videoconference.

When and How Much

Scheduled visits will be planned for each participant to visit a smart home Living Lab during the spring to summer of 2022. The cognitive and physical exercises will be conducted once, and their durations will be as follows: (1) simulated banking exercise for 5 minutes, (2) virtual supermarket exercise for 30 minutes, (3) virtual physical exercises coaching for 10 minutes, and (4) yoga sessions at a slow but gradually increasing pace, including breathing practice for 10 minutes, chair poses for 15 to 20 minutes, standing poses 10 to 15 minutes, floor poses 15 minutes, and a supine resting pose (Shavasana) for 10 minutes.

Tailoring

The interventions will be tailored for all 20 participants. Furthermore, the virtual app used during the interventions will be used in personalized mode to bring innovation.

Case Study 3: UX With Gradior Active for Physical Training Reinforcing Dual Task Performance

Why

The general aim of this case study is to test the Gradior Active prototype by assessing its usability, learnability, acceptance, and the overall experience of participants, especially in terms of how easy and pleasing it is to use or its perceived utility when embedded in active and healthy aging programs. Collection of UX during an 8-week program implementing the current Gradior Active prototype will be of most importance for the second objective, which is focused on performing a cocreation sprint to understand the challenges for optimizing the program and its implementation in real settings and services (eg, exploring ideal workflows). Ultimately, the case study results will be used to understand what is most important for the UX perspective and for developing big data–driven hybrid personas through the initially described harmonized research protocol.

To Whom (Sample Size and Recruitment)

A total of 30 older adults will be recruited through the INTRAS memory clinic and neuropsychological rehabilitation center customers. INTRAS has its own pre-existing testing panel of patients and participants in the active and healthy aging programs, as well as established groups of experts by experience (groups of older adults who, considering their motivations, participate in user-driven design and innovation processes). Participation will be voluntary and will follow best practices in terms of clear information in the information sheet and procedure and informed consent, accomplishing the General Data Protection Regulation, national regulations, and cognitive accessibility parameters. Participants will pertain to 2 groups of older adults aged >65 years: group A, comprising older adults with subjective complaints (for primary prevention), and group B, comprising older adults with mild physical impairment. Exclusion criteria will include participants with sensory or physical impairments that make it very difficult to use the devices (significant hearing or visual impairments) or any

nutritional disorder, psychiatric conditions, or neurological problems that make the person unable to participate in the study.

What (Materials)

In this study, Gradior Active will be provided to the participants. This is a system for physical and cognitive training that combines motion and cognitive activities with independent and unrelated purposes (*Dual Task*). It incorporates controlled physical exercises (aerobic, strength, balance, and flexibility exercises) using motion capture technologies (Microsoft Kinect). The software comprises a Kinect v2 (Microsoft), a computer and a good size screen or projector, and a server component providing the content and collecting the data.

The program provides step-by-step instructions for the participants, and the sessions will be performed with the support of an experienced professional (eg, clinical psychologist or neuropsychologist). In total, 2 to 3 units will be installed and configured in the INTRAS clinic facilities with the information technology team support. Informed consent will be provided in paper form; questionnaires for collecting quantitative data and UX diaries will be provided either in paper form or as a link to a web-based questionnaire. During the cocreation sessions, easy-to-use digital tools such as Kahoot! (Kahoot ASA) to facilitate social interaction and pleasing moments in the group will also be considered.

What (Procedures)

The study follows a mixed methods design in which qualitative and quantitative data will be collected. To determine the effects of Gradior Active on the 8-week term, 2 measurements (T0 and T1) will be conducted using standardized tests. Thus, 2 face-to-face sessions will be scheduled with participants: 1 just before the beginning of the study and 1 at the end after 8 weeks of use. At baseline (T0, before the start of the intervention), demographic data will be collected. The following outcomes will also be measured both at baseline (T0) and after the end of the intervention (T1): patient-reported outcome measures, including health and well-being (Short Form-36 version 2), social life (Lubben scale), Geriatric Depression Scale (GDS), Physical Status Scale (Rapid Assessment of Physical Activity), and (4) Borg Scale of Perceived Exertion; and patient-reported experience measures, including UX (UEQ) and usability and acceptance (System Usability Scale).

Who Provided

INTRAS counts with a multidisciplinary team comprising clinical researchers and technologists widely familiar with UX research and studies with digital health and well-being solutions and experts in the participatory methodologies that will be involved in the implementation of the study. All members hold relevant experience in EU health projects, eHealth research, and planning, implementation, and analysis of clinical trials. The study will be coordinated by a psychologist (panel manager), neuropsychologist (scientific coordinator), and gerontologist (project manager) with >10 years of experience in clinical services, (EU) health projects, eHealth research, user research, Living Lab research, and implementation and analysis of real-life tests.

How

The study evaluations will be set up in a single site in Spain with a quasi-experimental format without a control group, where each participant acts as their own control through the pre- and postdesign. The study is divided into 2 phases to accomplish the indicated aims. The first phase collects UX with the Gradior Active prototype during the 8-week testing period. The second phase will be focused on a cocreation sprint bringing the individual experience to a group discussion to understand what is linked to perceived value and opportunities for improvement based on value-driven brainstorming exercises (from the current prototype to ideal service offer). These interactive group sessions will include icebreakers, co-design methods, and adequate tools for the purposes. Testing sessions with Gradior Active will be performed individually and in a face-to-face format in the facilities of the Living Lab and INTRAS Clinic. The sessions will be supervised by an experienced therapist. Cocreation sessions will be conducted face to face and in groups. The sessions will take place with the support of 2 experienced facilitators in the INTRAS facilities. For both the stages and planned activities, COVID-19 safety protocols will be in place.

Where

A case study will be conducted in the INTRAS rehabilitation Living Lab in the neuropsychological rehabilitation center (with access to INTRAS care centers and memory clinics as ecologically valid environments for Living Lab activities).

When and How Much

In the first phase of the study, Gradior Active will be provided to the participants over a duration of 8 weeks, and participants will be oriented to perform 2 weekly sessions of 30 minutes under the supervision of experienced professionals. After the end of the intervention period, the same participants who previously tested the prototype will be invited to the 2 cocreation sessions (duration: 120 minutes).

Tailoring

Both the prototype testing phase and cocreation phase will be coordinated considering the participant's availability and other relevant conditions to participate (eg, transport logistics to attend the sessions). Testing sessions with the Gradior Cognitive intervention program will be supervised by an experienced professional who can intervene to provide support as required. In principle, pre- and postinterviews with assessment and workshop interventions follow the same principles for all participants, and modifications are not preplanned. However, if a need to make modifications emerge, they can be made.

Cross-country Case Study 4: Multidimensional Physical Fitness Testing Protocol for Aging Persons

Why

With older adults, functional independence is directly dependent on physical fitness. Aging is inevitably associated with the declining functions of systems and organs (heart, lungs, blood vessels, and skeletal muscles) that determine physical fitness. However, aging is a complex process involving many variables that interact with one another, for example, lifestyle factors, chronic diseases, and genetics. Relatively little is known about the physical fitness levels needed to maintain physical independence. Many studies have shown that measurements of physical performance can predict future mobility disability, institutionalization, and mortality. Studies have also shown a strong association between measurements of physical performance and self-reported mobility disability. However, most of these prospective studies used only a few measures of physical performance or were targeted at functionally limited persons; therefore, assessments have only limited value for counseling. Therefore, this case study will develop and test a physical fitness testing protocol for older adults in real-life settings in 3 countries: Finland, Spain, and Hungary.

To Whom (Sample Size and Recruitment)

In Finland, the sample group will comprise older adults aged >67 years. To recruit older adults with varying physical fitness levels, the following strategy will be applied: open calls to promote free of charge physical fitness level measurement as part of a research project will be published in local newspapers and social media channels in collaboration with the local city administration responsible for older adult services. Furthermore, the collaboration will be conducted with selected nursing home administrators to recruit participants with weaker physical fitness levels directly from nursing homes. It is estimated that approximately 200 to 400 persons will be recruited via open calls and approximately 50 persons from nursing homes. In Hungary, the sample group will comprise people aged >55 years. Social media, posters in outdoor trails and fitness parks, former contact lists, and snowball sampling will be used to recruit the participants. It is estimated that 30 to 50 persons will be recruited; however, because of dropouts during the training program, only 20 are expected to take part in the posttest. In Spain, the main target sample will be men and women aged between 60 and 80 years. of Participants will be recruited in collaboration with the city council of Gernika-Lumo, local nursing homes, and retiree associations. It is estimated that 20 to 40 people will be recruited from all collaborative organizations.

What (Materials)

Each participant will have to fill in an informed consent form before any measurements. Participant consent forms are tailored to meet the General Data Protection Regulation standards and local ethical requirements in Finland, Spain, and Hungary. A total of 2 similar score sheets will be created for the physical fitness measurements, 1 for the participant and 1 for the researchers. General reference values and the interpretation of the results will be presented after the measurement session. This material will also be displayed on the webpages for the participant to view later. Participants will also fill a self-completion quality of life questionnaire (World Health Organization Quality-of-Life) before the test and UEQ at the end of the test. The security of the participants in the event will be carefully designed and considered. A security plan has been developed and will be gone through for all participating event staff members. For the assessment or measurement, simple materials will be used, including stop watches, tape measures, chairs, hand weights (3 kg and 5 kg), and cones.

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Approximately 40 participants in Finland and all participants in Spain and Hungary will receive armband sensor devices (SenseWear Armband; BodyMedia Inc), which will measure their physical activity levels on a daily basis for 24 hours. During the measurement period, participants will also be keeping a diary. In Finland, other equipment will include a Jamar hand dynamometer (JWL Instruments), Tanita MC-780MA body composition analyzer, peak expiratory flow measurements (Mini Wright; Clement Clarke International), and a standout smart balance board (Smartifier Ltd). In Hungary, participants will receive information regarding the 8-week training program and related relaxation exercises. The training program uses a 1.5 km outdoor fitness trail with 19 physical exercise stations equipped with information boards, which show different variations in how to use the stations and how to get to the next station. In Spain, the Standout Balance Board and Xiaomi Miband 5 will also be used. A small group of participants will receive a smart wristband watch (Galaxy Watch 3), which measures the average daily activity performed on a 4-day basis. The training program will be based on recreational football playing.

What (Procedures)

The following physical fitness components will be covered in the physical fitness test in Finland and Spain: cardiorespiratory endurance, muscle strength and endurance, balance, agility, speed, flexibility, and body composition. After signing the consent form and filling the quality of life questionnaire (World Health Organization Quality-of-Life Scale), the participants will go through the following measurement points step by step in selected locations (ie, sports halls, nursing homes, fitness parks, and outdoor facilities): (1) 6-minute walk test or nonexercise cardiorespiratory fitness test, (2) handgrip strength test, (3) 30-second arm curl test, (4) 30-second chair stand test, (5) Smartifier balance board test, (6) 8-foot up-and-go test, (7) backward walk test, (8) 10 m walk test, (9) chair sit-and-reach test, (10) back scratch test, (11) height and body composition measurements, and (12) peak expiratory flow measurement. In Hungary, which is used as a control group, physical fitness will be measured by following a protocol defined in the senior fitness test manual [28]. After finishing the measurement track, participants will fill the UEQ, which also includes an open text box to propose improvement suggestions or give complaints about the testing procedure.

In Hungary and Spain, the physical fitness testing battery will be used to determine the baseline (T0, before the start of the training program intervention) and conduct the postmeasure (T1) at the end of the 8-week training program. Participants' daily activities will also be measured with the armband device for 4 days during the training period. In addition, in Spain, some of the participants will also use a smart wristband watch (Galaxy Watch 3). In Hungary, the training program will include outdoor training on fitness trails with 19 stations in a 1.5 km route. Feedback will be collected from participants after the training intervention. In Spain, outdoor training on recreational football will be performed in a network of distributed resources and public spaces. Feedback will be collected from participants after the training intervention.

Who Provided

In Finland, physiotherapy students will collect the materials under the supervision of experienced physiotherapy teachers and VITALISE project team members. The testing protocol will be introduced and trained for the students on a separate occasion before the measurement events. VITALISE project team members have extensive experience in planning and implementing Living Lab research projects and protocols in health and well-being research settings. In Hungary, Trebag staff will assist in the data collection of physical fitness tests with the guidance of an experienced and qualified leader. Outdoor fitness occasions will be facilitated by qualified coaches. In Spain, the Gaia staff will assist in data collection of the physical fitness tests, together with students of science degree in physical activity and sport from Deusto University, who will also assist in the fitness occasions.

How

During the measurement day in Finland and Spain, there will be an open access period when measurements will be conducted by following the walk-in principle. Participants will circulate individually from the measurement point to another, where they will receive instructions from students (physiotherapy or similar). After finishing the measurement track, participants will go to the meeting point where general reference values and the interpretation of the results can be self-read from the presented materials. At the meeting point, participants will also fill the UEQ questionnaire. In Hungary, the process will be similar; however, participants will be invited, and the measurement track will be based on a protocol defined in the senior fitness test manual [28].

The physical fitness testing protocol will be first run in Finland. Following this, modifications will be made to the testing protocol if needs for change are identified based on participant feedback. The same or revised protocol will then be used in Spain to collect cross-country data. In Hungary, a different protocol [28] will be used to get the baseline for UX and be able to compare how the extended measurement protocol influences the UX. At the end of the project, result comparisons regarding measurement day experiences will be made between the 3 countries and 2 different measurement protocols.

The participants receiving the armband device will be invited to a specific location (eg, university campus), where they will receive detailed information about the test and how to keep the activity diary. In Spain, some of the participants will also receive a Galaxy Watch 3 device, which is used for similar purposes as the armband device. In Finland, participants will keep the device for 1 day (24 hours). In Hungary and Spain, participants will keep it for 4 days (96 hours). Owing to the limited number of devices and device rotation, the measurement time will vary between participants.

In Hungary, outdoor training on fitness trails will be introduced by guided visits where participants can try to experience fitness station activities with the help of a qualified trainer. In the fitness stations, participants will perform exercises with their own body weight. At the stations, boards will show the planned, recommended tasks that participants can perform by 3 variants and how to get to the next station. Feedback collection and

postmeasurement (T1) will be conducted after 8 weeks of training interventions.

In Spain, outdoor training on recreational football will be performed in a network of distributed resources and public spaces. Owing to possible COVID-19 restrictions, web-based sessions will be organized if physical restrictions are in place, following 2 methodologies if needed: through live sessions with the instructors and through tutorials so the users could watch them at any time, which will be available on the Gaia Cluster YouTube account. For group web-based exercises (where users are at their homes), WhatsApp group video calls will be used. In these calls, the monitors will bring the classes home and give instructions so that the participants can feel part of the group again. Feedback collection and postmeasurement (T1) will be conducted after 8 weeks of training interventions.

Where

In Finland, the open access measurement day will be arranged in a big sports hall and in a few nursing homes. Participants participating in 24-hour measurements will perform their normal daily activities; thus, the location can cover home and various indoor and outdoor environments. In Hungary, the premeasurement day will take place at the Trebag premises and the Rákospalota Elderly Centre. The 8-week training program will take place at protected natural parks in Budapest, which are equipped with various fitness equipment. In Spain, the open access measurement day will be arranged in a public space in the Gernika-Lumo municipality and, possibly, in a nursing home as well. Participants participating in the 96-hour measurements will perform their normal daily activities; thus, the location can cover home and various indoor and outdoor environments.

When and How Much

The first measurement events in each country will happen for 1 or 2 days in spring to summer of 2022 at a spacious venue (eg, sports hall, gym, or similar space having enough space to establish the measurement track). Each participant will complete the measurement track once, which will take approximately 20 to 25 minutes in Finland and Spain and 15 to 20 minutes in Hungary. In Finland, the main measurement events will take place first, and smaller measurement events in nursing homes will take place soon after the main measurement session. Participants with armband sensor devices will keep the device for 1 day. In Hungary, after the measurement event, the outdoor fitness training program will start, and it will last for 8 weeks. Participants with armband sensor devices will keep it for 4 days. In Spain, outdoor physical interventions will last for 8 weeks after the measurement event.

Tailoring

Participants are expected to participate in all measurement points and preplanned activities; however, they can choose to take part in only a selected number of tests and activities, as participation will be voluntary. The physical fitness testing protocol will be first run in Finland. Modifications will be made to the testing protocol if needs for change are identified based on participant feedback. Thus, it is possible that, in Spain, a slightly modified version of the measurement track will be used. However, for each study participant, the track will be identical.

Cross-country Case Study 5: Characterizing the Interaction of the Effects of a Museum Visit on Mobility, Cognition, and Well-being in People With Stroke

Why

Although there are studies that have explored the impact of a museum experience on healthy older adults or individuals with acquired and degenerative neurological conditions [29-31], there is a lack of studies investigating the interaction of the effects of a museum visit on mobility, cognition, and the lived experience of individuals with stroke, as well as on older healthy aging adults using advanced technologies that measure mobility, cognition, well-being, and UX. To this end, this small-scale pilot aims to obtain measurements of mobility, cognition, and well-being of people with stroke and healthy aging individuals using innovative technologies to explore the lived experiences of these individuals as they participate in a museum environment. The collected data will be used to (1) study the feasibility of conducting a series of diverse measurements in a museum setting, (2) study the acceptability of such interventions in a museum setting, and (3) create a user model that can be adopted to describe people with disabilities visiting a museum in future big data collection.

To Whom (Sample Size and Recruitment)

In Canada, a total of 30 persons will be recruited via a patient contact list from a rehabilitation hospital and the Association Québécoise Des Personnes Aphasiques. In Greece, a total of 20 persons will be recruited via collaboration with the B Department of Neurology, AHEPA University Hospital. All participants will be aged between 55 and 85 years, have normal or corrected vision and hearing, and walk independently with or without technical aids. Group A will comprise 15 persons with stroke, including 6 with mild or mild to moderate aphasia in Canada and 10 people with stroke, including 4 with mild or mild to moderate aphasia in Greece. Group B will comprise 15 healthy controls for Canada and 10 healthy controls for Greece. For both groups, the key exclusion criteria will include (1) postural and balance disorders, (2) severe psychiatric disorders (excluding depression or anxiety), (3) recent history of alcohol or substance abuse, (4) general anesthesia within the past 6 months, (5) pain >2 on the visual analog scale, and (6) >10 on the GDS. In group A, participants with severe or global aphasia or scoring <20 in a mini mental state examination (MMSE) will be excluded. In group B, participants having a <26 score in MMSE will be excluded.

What (Materials)

The physical spaces of the museums (benches, stairs, exhibition halls, and vestibules), works of art (paintings and sculptures, casts, and antiquities), and audio guides will be used in the study. Furthermore, the following technologies will be used both in Greece and in Canada to monitor the participants before, during, and after their visit: (1) Pupil Labs eye-tracking glasses and (2) smartwatch (eg, Apple Watch or Fitbit 4). In Canada, additional materials will be used for monitoring, namely the (1) near-infrared spectroscopy (NIRS) system, (2) pressure sensitive walkway (Gaitrite), (3) portable force platform to measure body weight distribution and center of pressure oscillations, and (4)

APDM inertial sensors placed in the participants' thorax and tibia. Physical standardized test alternatives will be used in Greece to gather similar information. Specifically, the physical test battery will include (1) 10 m walk test, (2) Tinetti test, (3) Berg Balance Scale, (4) 30-inch chair stand test, (5) Timed Up and Go test, (6) 2-minute walk test, and (7) balance on 1 leg test. The following test batteries will be used for previsit profiling: (1) for cognitive status measurement, the MMSE or Montreal Cognitive Assessment, and (2) GDS. A neuropsychological evaluation will also be conducted before each session, specifically the (1), Rey Auditory Verbal Learning Test, Stroop Test, and Trail Making Test A+B; (2) Warwick–Edinburgh Mental Well-being Scale; (3) State-Trait Anxiety Inventory and visual analog stress; (4) Visual Analog Pain Scale; (5) Multidimensional Fatigue Inventory; (6) EuroQol-5 dimensions; and (7) Environment Quality and Satisfaction Tool.

What (Procedures)

The study will run in 2 sessions (session 1 and session 2), and session 1 will comprise 2 options based on the participants' profiles. The procedures that will be followed in each session are described below.

In session 1 (option A; participants with stroke and aphasia and half of the control participants), after signing the consent form, participants will be asked to wear the tracking and monitoring equipment (smartwatch, eye-tracking glasses, and headphones for audio guide). For each of the 3 chosen works of art, the participants will listen to the description of the work of art (audio version of the written information that accompanies the work), then listen to the adapted description, and answer some questions posed by the on-site assistant who will assess their experience.

For session 1, option B (participants with stroke and no aphasia and half of the control participants), after signing the consent form, participants will be asked to wear the tracking and monitoring equipment (smartwatch and NIRS cap only for Canadian participants). The participants of this group will be asked to walk twice through a predetermined circuit of 6 different works of art (painting or antiquities) and complete a guided tour. In each painting, participants will be instructed to (1) analyze each painting by focusing on the message or intention communicated by the artist, the symbolic meaning, and the composition of the artwork (ie, analytical condition); and (2) view the painting without analysis (ie, control condition).

In session 2 (all participants), participants will be asked to wear the tracking and monitoring equipment (smartwatch) and walk at their own pace on the predetermined tour of the spaces and the built environment of the museum (stairs, elevator, bench, chair, and toilet). Breaks will be provided as needed and requested by participants.

In both data collection sessions, the lived experience of individuals, as well as their opinions regarding the evaluations at the museum, will also be documented to understand the lived experience of all individuals involved.

Who Provided

Researchers from the study, as well as trained research assistants or students, will be present for each session at the museum and will be responsible for the placement of the various forms of technology on the participants and for all data collection.

How

All sessions will be held face to face, and only 1 participant will be tested at a time. After signing the consent form and completing the previsit testing batteries with a research assistant in a reception room, the participant and their caregiver or companion will go to the museum exhibit hall. Before the museum experience, participants will be equipped with the following devices: in session 1 option A, (1) smartwatch (Apple Watch or Fitbit), (2) headphones for the audio guide, and (3) eye-tracking glasses; in session 1 option B, (1) the NIRS cap for Canadian participants and (2) a smartwatch (Apple Watch or Fitbit); and in session 2, a smartwatch. In each session after the museum visit and the performed activities, the devices will be removed, and participants will return to the reception room, where a brief questionnaire Will be administered. The participants will receive a smartwatch that they will keep until they return in the following week for session 2.

Where

All testing in Canada will be performed at the Montreal Museum of Fine Art, Pavilion for Peace. In Greece, testing will be conducted at the Museum of Casts and Antiquities, School of Philosophy of the Aristotle University of Thessaloniki, Greece.

When and How Much

The measurement events in each country will happen for 1 or 2 days in spring to summer of 2022, with a 1-week period between sessions. Session 1 will last a total of approximately 1.5 hours, and session 2 will last approximately a total of 1 hour.

Analysis

During Phases 1 and 3

Inductive qualitative content analysis will be conducted to answer RQ1 to RQ3. First, an iterative open coding process will be conducted, and preliminary categorization will be generated to classify the raw data received from the Microsoft Excel file templates, interviews, workshops, and Mentimeter brainstorming. Next, the data will be grouped by reducing the number of categories by grouping similar technologies, methods, tools, and validated scientific questionnaires to identify alternative approaches to execute a certain research task. Finally, abstraction will be conducted to define the main categories and create possible subcategories under each main category. The popularity of the different technologies, methods, tools, and validated scientific questionnaires among VITALISE Living Labs will be identified by calculating frequencies and percentages. To evaluate the acceptance and consensus of the defined harmonized research protocols among VITALISE Living Labs and external harmonization bodies, an iterative web-based Delphi process will be conducted until a supermajority agreement is reached (ie, at least a 70% acceptance rate) [32].

Data Analysis Plans for Case Studies During Phase 2

The *main quantitative analysis approaches* will include descriptive data (eg, mean, frequency, and SD) to characterize

the participants' (sociodemographic variables) and summarize the results of the questionnaires. Chi-square tests will be used to detect the associations between the categorical variables when needed. To explore whether the outcomes of the interventions are significant, parametric (eg, paired and unpaired 2-tailed *t* tests, Pearson correlation, and 1-way analysis of variance) and nonparametric tests (Wilcoxon signed-rank test, Mann–Whitney *U* test, Spearman correlation, and Kruskal–Wallis test) will be conducted to investigate the possible research findings and future research directions. Case studies evaluating the impact of the intervention will include 2 temporal data collection moments, 1 before and 1 after the intervention period, to validate the changes that might occur. Standardized statistical tools will be used for data analysis, such as SPSS (IBM Corp) and Microsoft Excel. Sensor data analysis will be used by the sensor device–related software features, for example, for eye-tracking data or wearable sensor temporal activity data analysis, when case studies use them for data collection. The main quantitative analysis approaches include the inductive qualitative content analysis executed in phases 1 and 3. For case study 5, hermeneutic analysis of the phenomenon and content analysis of the photos will also be performed. For all cases, answers to the questionnaires will be extracted and triangulated with quantitative data.

Incentives

The VITALISE project consortium Living Labs will receive EU funding (under grant agreement 101007990; April 2021 to March 2024) for conducting the proposed study. According to the consortium agreement, each Living Lab is obligated to conduct such a study; therefore, funding is tightly interlinked with the delivery of the proposed study. Users' (ie, study participants) intrinsic and extrinsic motivations are key drivers of Living Lab research [33]. Prior studies have identified the following motivational factors that also create the foundation for the case study incentives [34]: (1) projects improving own health or are close to participants' health needs or interests; (2) projects helping the wider community and contributing to the common good; (3) contributions to formal acknowledgment instead of financial compensation or recognition by others; (4) knowledge seeking, curiosity, and being entertained; (5) desire to feel competent and self-determined; and (5) the possibility to test new innovative products and services. In addition to the abovementioned motivational factor–driven incentives, the following case study incentives will be provided:

1. Case study 1: Free of charge digital coaching mobile app training program for 8 weeks focusing on improving well-being and social participation in general and how to deal with challenges related to retirement; The monetary fees offered to compensate for the participation costs (eg, traveling) are €20 (US $20.90) to €40 (US $41.80) euros for Austrian participants and €15 (US $15.70) to €20 (US $20.90) for Belgium participants, and internet-connection will be reimbursed on request of participants

2. Case study 2: Free of charge measurement of personal physical fitness level and cognitive capability

3. Case study 3: Free of charge use of new services aimed at improving physical, psychological, and emotional health in 2 weekly 30-minute sessions for 8 weeks

4. Case study 4: Free of charge measurement of personal physical fitness level, including the ability to compare own results with the peer group; for Spain and Hungarian participants, free of charge training program for 8 weeks focusing on improving physical fitness

5. Case study 5: 2 museum tickets

Data Management and Ethics Statement

The VITALISE project will encapsulate multimodal data collection phases toward the development and evaluation of novel supportive interventions related to everyday living environments. As the individuals who will provide the data are the cornerstone of these data collection phases, special attention will be given to the compliance of the collection processes with ethical regulations and guidelines on research involving human beings, as well as on the safety of the sensors, tools, and devices involved, and the protection of personal and health data. Project deliverable *D1.2 First version of ethics and safety manual* constitutes a reference guide for the VITALISE investigators by reporting on the international, European, and national ethical regulations, device safety standards, and certifications. Deliverables will also include ethics management and data control actions and guidelines adopted by the consortium that will assist and monitor its compliance with the medical research regulations and guidelines. In addition, a thorough consent form template will be included and will be used by all partners according to their specific protocols.

Deliverable D1.2 presents the first plan for the VITALISE project scheduled data collection to be compliant with the reported regulations and guidelines and evaluates potential concerns early to be mitigated effectively through the proper management of ethical and data handling–related issues within each country and between different countries. The D1.2 deliverable will be publicly available after the completion of the European Commission review process (expected publication time will be by the end of 2021). It is highlighted that D1.2 is a living document that will be regularly updated throughout the project, leading to its final version (Deliverable 1.3) on project month 24.

Results

As of September 30, 2021, project deliverables *D1.2 First version of ethics and safety manual* and *D2.1 Standard Version 1*, presenting the state of the art for the Living Lab services, methods, and tools, have been submitted for the European Commission review process. Both deliverables will be publicly available after completion of the European Commission review process (expected publication time will be by the end of 2021). Both deliverables are living documents that are regularly updated throughout the project, leading to its final version by month 24. At the time of submission, the status of the VITALISE project is active, and materials for national ethics boards are being prepared. After receiving acceptance from ethics boards, participant recruitment for case studies will be started latest by June 2022. The study will be finished by March 2024.

Discussion

Harmonization Process Outcomes

The outcomes of this study enable Living Labs to exploit similar research protocols, devices, hardware, and software for interventions and complex data collection purposes when developing big data–driven hybrid personas. The harmonized protocols will speed up and improve the research quality and offer novel possibilities for open data sharing, multidisciplinary research, and comparative studies beyond current practices. Researchers will have wider, simplified, and more efficient access and services to Living Lab RIs, irrespective of location. This enables researchers to focus on the research itself instead of managing practical challenges. Economies of scale and improved use of resources across Living Labs have also been realized because of the less duplication of services and common development and optimization of operations.

Case Study Outcomes

Case Study 1

This study will allow a better understanding of how digital coaching can influence individuals' well-being and social participation by motivating older adults to practice a healthy lifestyle. Monitoring the effects of AIT's digital coaching app use may shed light on the capability of a digital coach for helping retirees maintain (and improve) social relationships and activities that could be put at risk by their withdrawal from the workplace. In addition, the results will also allow the optimization of the UX of deployed coaching mobile apps. By setting up this case study at 2 different sites, Belgium and Austria, specific results related to these different social and cultural contexts are also expected.

Case Study 2

The results of the randomized controlled trial will show that it is feasible to conduct a randomized controlled trial of yoga in a virtual and sensor-assisted Living Lab environment using the described protocol. Moreover, the collection of novel sensor data from the experiment is expected to provide insightful information about the physical and psychological status of the participants.

Case Study 3

The results of this study will allow the analysis of effectiveness, usability, and acceptance of the described Gradior Active intervention. It will state the pillars for evidence-based decision-making on investment in the upgrade and modernization of the prototype; at the same time, it will ensure a final co-design sprint with participants to orient the incremental development plans.

Case Study 4

The main results will focus on understanding older adults' physical fitness levels by defining and testing comprehensive testing patterns in a cross-country setting. Single test results with reference values exist; however, surprisingly, a wider understanding of older adults' fitness levels is lacking. From prior studies, it is acknowledged that the vast majority of the participants recruited via open calls will be persons with good fitness and functioning levels. Therefore, older adults with lower physical fitness will be recruited from nursing homes to also cover more fragile and less fit older adults. By combining the daily physical activity level sensor measures and physical fitness test results, novel and insightful information about the physical status of the participant can be verified. The perceived UX of the proposed comprehensive physical fitness level research protocol will be compared with a well-established but less comprehensive protocol. It is expected that there will be no significant differences regarding UX; therefore, in the future, a more comprehensive protocol should be applied to reveal a better understanding of the older adults' physical fitness levels. Furthermore, the pre- and posttraining period physical fitness levels will be compared in the cases of the Spain and Hungary case studies. These results are expected to reveal that the training program affects participants' physical fitness level as well as provide suggestions from participants on how to improve the training program.

Case Study 5

Although this study is exploratory, it is anticipated that museum visits will be associated with (pre and post) changes in mobility (endurance, navigation, posture, and balance) and cognition (attentional control and auditory comprehension in dual tasking) and will generate a well-being effect (positive experiential experience and decrease in anxiety state). Moreover, considering that museums or any public places solicit locomotor capacities (endurance, navigation, posture, and balance), it is expected that the visit will be associated with a greater variation in motor skill, cognition, and well-being in all our most vulnerable groups (stroke) compared with the control group. Finally, the environmental conditions and characteristics that do or do not influence the above variables will be identified. The latter may result in modifications that will favor inclusion and ultimate participation of aging individuals, especially those living with stroke and language limitations.

Conflicts of Interest

None declared.

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Abbreviations

AIT: Austrian Institute of Technology
ENoLL: European Network of Living Labs
EU: European Union
JRA: joint research activity
MMSE: mini mental state examination
NIRS: near-infrared spectroscopy
RI: research infrastructure
RQ: research question
UEQ: User Experience Questionnaire
UX: user experience
VITALISE: Virtual Health and Wellbeing Living Lab Infrastructure

A Technology-Based Intervention Among Young Men Who Have Sex With Men and Nonbinary People (The Conectad@s Project): Protocol for A Vanguard Mixed Methods Study

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Abstract

Background: In many parts of the world, including Brazil, uptake for biomedical interventions has been insufficient to reverse the HIV epidemic among key populations at high risk for HIV, including men who have sex with men. Young MSM (YMSM), particularly Black YMSM, have high HIV incidence, low viral suppression, and low preexposure prophylaxis (PrEP) uptake and adherence. Therefore, novel approaches to increase the HIV biomedical interventions uptake by YMSM are urgently needed.

Objective: We describe the Conectad@s Project, which aims to: (1) estimate the prevalence and incidence of HIV and other sexually transmitted infections, the onset of sexual risk behavior, and barriers to biomedical interventions among YMSM aged 18 to 24 years in Rio de Janeiro, Brazil; and (2) conduct a technology-based adherence intervention study to promote a rapid linkage of YMSM to HIV care or prevention, and support and sustain adherence.

Methods: A cross-sectional survey will be conducted with 400 YMSM recruited using respondent-driven sampling (RDS) adapted for social media-based sampling, preceded by a formative phase. HIV and sexually transmitted infections testing will be conducted, including early HIV infection biomarker detection. Behavioral, partnership, network, and structural measures will be collected through structured questionnaires. All individuals recruited for the survey will have access to HIV risk assessment, antiretroviral therapy (ART), PrEP, prevention counseling, and a technology-based adherence intervention. Those who accept the adherence intervention will receive weekly text messages via a social networking app (WhatsApp) for 24 weeks, with follow-up data collected over 48 weeks.

Results: The Conectad@s project has been approved by our local institutional review board (#CAAE 26086719.0.0000.4262) in accordance with all applicable regulations. Questionnaires for the RDS survey and intervention were developed and tested in 2020, formative interviews were conducted in January and February 2021 to guide the development of the RDS, and enrollment is planned to begin in early 2022.

Conclusions: The Conectad@s Project is a vanguard study that, for the first time, will apply digital RDS to sample and recruit YMSM in Brazil and rapidly connect them to ART, PrEP, or prevention counseling through a technology-based adherence intervention. RDS will allow us to estimate HIV prevalence among YMSM and measure HIV infection biomarkers in the context of the onset of risky behavior. The data will lay the groundwork to adapt and implement HIV prevention strategies, identify barriers to the earliest HIV infection diagnosis, immediate ART or PrEP initiation, and detect new clusters of HIV transmission.

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Introduction

Reported HIV cases in Brazil are increasing among gay, bisexual, and other men who have sex with men (MSM), particularly among the youngest, with a considerable disparity of infection for this population [1,2]. In 2020, 53% of reported male HIV cases were MSM [1]. Reported cases in Brazilian surveillance may be incomplete as MSM status is likely under-reported among men classified as heterosexual (30% of male cases) and those with unknown risk (14% of male cases) due to stigma [3,4]. National surveillance data show a 7-fold increase in the rate of HIV cases reported among Brazilian men aged 15-24 years between 2009 and 2019 [1]. A population-based survey in selected capital cities in Brazil found 18% HIV prevalence in MSM in 2016 [5], increasing from 12% seven years earlier [6]. In addition, MSM surveyed in 2016 were notably younger than those in 2009, while HIV prevalence rose [7].

Brazil was the first low-income/middle-income country to provide free antiretroviral therapy (ART) for HIV treatment, participate in clinical trials proving preexposure prophylaxis (PrEP) efficacy [8] and PrEP demonstration projects [9-12], and establish a national policy to provide PrEP at no cost within the National Public Health System (SUS). Nevertheless, uptake of these biomedical interventions has been insufficient to reverse or even slow the HIV epidemic among young MSM (YMSM).

Data from a national web-based survey of Brazilian MSM indicated higher HIV risk and lower use of biomedical prevention among YMSM aged 18-24 years compared to older MSM, including condomless anal sex, being unaware of PrEP, never testing for HIV, and not using PrEP [13]. Among 16,667 Brazilian MSM recruited in web-based studies, YMSM showed increased odds of binge drinking and condomless receptive anal sex and decreased chances of high perceived HIV risk [14]. Youth also had an increased probability of high-risk behaviors measured by the HIV Incidence Risk Index, even when adjusted by race, income, education, sexual orientation, steady partner, previous sexually transmitted infection (STI), and ever testing for HIV [15].

The data point to disparities for Black Brazilians, including late HIV diagnosis, not being on ART, low virological suppression rates, and low PrEP adherence [9,16]. Black Brazilians had over 50% increased odds of experiencing discrimination than White individuals, even after controlling for income, education, social status, and health problems [17]. In surveillance data, the proportion of HIV cases for Black and *Pardo* (mixed-Black) Brazilians rose from 51% to 63% from 2009 to 2019 [1]. MSM populations may face various forms of stigma, including internalized, perceived, experienced, and layered stigmas [18], and Black*/Pardo* MSM populations also face structural racism, which may increase their vulnerability to HIV infection in comparison to White MSM.

The Rio de Janeiro metropolitan area, with 13 million inhabitants and 22 municipalities, is the second-largest in the country and the 16th largest urban area in the world. Rio de Janeiro state accounts for 10% of HIV cases nationwide, 90% of them residing in the metropolitan area [1], where mortality due to HIV-related causes, particularly tuberculosis, remains persistently above the Brazilian mean [1]. The state also demonstrates high rates of late-stage HIV and death, which suggest poor engagement along the HIV care continuum, including late diagnosis, low ART use, and insufficient virologic suppression [1]. Emerging evidence points to resurging HIV among YMSM, including high case detection rates at HIV testing sites [19]. HIV prevalence among YMSM aged 18-24 years in Rio de Janeiro increased from 4.4% to 13.3% between 2009 and 2016 [20]. Drivers of HIV infection among Brazilian YMSM, likely to intersect in Rio de Janeiro, remain understudied and unaddressed. Therefore, we designed the Conectad@s Project, a respondent-driven sampling (RDS)-based study to specifically reach and engage YMSM in Rio de Janeiro, Brazil. Our primary aims are: (1) to estimate the prevalence and incidence of HIV and other STIs, the onset of risky behavior, and barriers to biomedical interventions among YMSM aged 18 to 24 years, and (2) to conduct a technology-based adherence intervention study to promote a rapid linkage of YMSM to HIV care or prevention.

Methods

The institutional review board of the INI-Fiocruz reviewed and approved this protocol on February 27, 2020 (#CAAE 26086719.0.0000.4262) in accordance with all applicable regulations.

Study Design

RDS has gathered robust samples of MSM in studies worldwide, including in Rio de Janeiro [5,6]. To reach and engage YMSM in Rio de Janeiro, Brazil, we will conduct an RDS-based study at the National Institute of Infectious Diseases Evandro Chagas (INI)-Fiocruz. The RDS will be adapted to include social media-based methods. The approach builds on research on young transgender women aged 15-24 years in San Francisco, United States [21]. Starting with initial "seeds" (ie, initial participants who start recruitment chains), successive waves of referrals will reach diverse social networks of YMSM. We anticipate that peer referrals through social media connections will particularly appeal to Brazilian YMSM who spend much of their time on mobile-based apps (eg, WhatsApp) and digital social media. Despite the discussion around the generalization of their data, RDS-based studies provide estimates of HIV risk among hard-to-reach populations [22] and allow the recruitment of these populations into longitudinal studies (ie, observational or intervention). Subsequently, we will offer all recruited individuals a prospective 48-week technology-based adherence intervention study to promote a rapid linkage of YMSM to HIV care or prevention and support and sustain adherence.

Eligibility Criteria

Individuals will be included if they (1) self-identify as men (cis or trans) or gender nonbinary, (2) report ever having engaged in anal sex with men or gender nonbinary persons with a penis, (3) are aged 18 to 24 years, (4) reside or spend most of the time in Rio de Janeiro metropolitan area, (5) did not previously participate in the study, and (6) possess an electronic referral coupon from a peer acquaintance participant. In this study, we collectively refer YMSM to young (18-24 years) cisgender men, transgender men, and non-binary or gender-nonconforming individuals. Exclusion criteria include individuals who self-identify as women (cis or trans).

Formative Phase

RDS-based studies require a formative phase to verify theoretical assumptions and identify logistical constraints and solutions [23]. These objectives are met through focus group discussions, key informant interviews, and pilot testing. The theoretical RDS assumptions are: (1) members of the population know each other as members, (2) social networks are interconnected within a few degrees of separation, (3) sampling occurs with replacement, (4) network size is reported accurately, and (5) people recruit approximately randomly from their network. RDS also depends on sufficient network density to make long recruitment chains [24]. Furthermore, the characteristics of social networks guide the selection of the number and type of "seeds." The formative phase also identifies potential "bottlenecks" (ie, social and physical barriers between networks) and variables to track "equilibrium" (ie, stability in sample composition as the chains grow). Other logistical questions include study site acceptability, transportation, online and social media apps for electronic referrals, safety, confidentiality, and appropriate incentives for participation and recruiting peers. In addition, the formative phase will inform the development and pilot testing of the questionnaire, as well as the refinement of the technology-based intervention.

The formative phase has already been conducted, comprised of two focus group discussions (aged 18-19 and 20-24 years) of up to 10 participants each and individual interviews with up to 20 YMSM. Group discussions and individual interviews lasted 1-2 hours. YMSM were referred from HIV clinics, LGBTQIA+ (lesbian, gay, bisexual, transgender, queer/questioning, intersex, and asexual/aromantic/agender) nongovernmental organizations, and peer counselors at Instituto Nacional de Infectologia Evandro Chagas, Fundação Oswaldo Cruz (INI-Fiocruz). We used a maximum variation sampling approach to include a diversity of participants by place of residence, race/ethnicity, and age [25]. Group discussions and individual interviews were audio-recorded with field notes captured by the interviewer. Files were transcribed in Portuguese and translated into English. Content analysis using transcribed content is underway and will focus on RDS theory, logistics, and strategies to improve the study. The study team will analyze qualitative data and discuss the preliminary results related to the density of the social network and logistics to reach a consensus on strategies to improve the implementation of RDS in this study. If social networks appear weak or diffuse, we will develop an additional seed recruitment plan and alternative approaches to improve recruitment based on the findings within a theoretical probability-based sampling framework. Questions raised during the formative phase will be incorporated into the RDS study instruments to be quantified. A chosen subset of participants (approximately 10) will pilot the questionnaire. Participants will provide feedback regarding comprehensibility, missing and unnecessary constructs, wording, and timing.

Sample Size and Power Calculation

Within an acceptable margin of error, the sample size of RDS surveys is powered to measure key indicators of HIV risk and prevention in the population of YMSM (eg, HIV prevalence, PrEP awareness, willingness to use PrEP, and never testing for HIV). Assuming a design effect of 2.0 (typical for RDS) [26] and a 95% CI, 400 participants are sufficient to measure RDS-adjusted estimates within SD 5% over a wide range of point estimates (ie, 5%-40%). For example, 400 participants could measure HIV prevalence at 5%, SD 2.1% or being unaware of PrEP at 39%, SD 4.7%. A sample size of 400 also provides 80% power at a 95% CI to detect significant odds ratios for effect sizes of 1.9 or greater for key outcomes (eg, HIV infection, PrEP awareness, and willingness to use PrEP) and predictor variables (eg, race/ethnicity, perceived HIV stigma, and family support).

Recruitment Methods

RDS sampling begins similarly to "snowball sampling" (ie, with purposively selected "seeds" from diverse social networks who then refer peers to the study). Peer recruitment on RDS differs from snowball sampling on key procedural and theoretical factors that enable better estimates of disease prevalence [22]. Seeds will be chosen for their connections to other YMSM, enthusiasm for the research, and belonging to different social circles. As with all other participants, the seeds must be eligible and undergo all study procedures. After completion, the seeds will be trained to recruit their peers using a digital coupon. This process will create a link between the recruiter and recruits, providing information needed for statistical adjustment. Digital coupons (Figure 1) will be shared on mobile apps and web-based texting platforms [25,27]. Digital referrals significantly increased recruitment of a cohort of transwomen aged 15-24 years in San Francisco, United States [21,25]. Upon presentation of a digital coupon to the study site, recruits will undergo similar procedures if eligible. The process will continue until the sample stabilizes on key characteristics ("equilibrium") and the sample size is met. RDS requires monitoring for "bottlenecks" (eg, chains that do not cross networks) and valid connection (eg, true acquaintances). The limited number of recruits per participant (typically 3) and incentives drive the propagation of long chains of referrals within and across social networks. Participants receive a "primary incentive" for their enrollment and a "secondary incentive" for each eligible participant they recruit. The value and type of incentives will be explored and determined in the formative phase.

Figure 1. Digital coupon for the Conectad@s Project recruitment. Legend: Coupon used by seeds to recruit peers to the project, with the name (Conectad@s) followed by "we are strong," inclusion criteria (18-24 years) and invitation to participate in the project only if coupon was received from a friend or acquaintance. Phone number and WhatsApp contact information to schedule an appointment are provided with a statement that scheduling is required.

HIV Diagnosis Algorithm

All participants will be tested for HIV using an HIV rapid test and antibody/antigen 4th generation serology. Participants reporting recent anal condomless sex (<30 days) with a negative HIV rapid test will be screened for acute HIV infection through HIV RNA viral load (VL) testing.

HIV Recency And Phylogenetic Testing

We will also test for recent HIV infection with the limiting avidity assay [28] to identify seroconversions occurring in the last few months. Recency data can help to identify possible transmission clusters and permit the calculation of HIV incidence by providing the timing of seroconversion [28]. The detection of acute infections may contribute to identifying active clusters of HIV transmission. HIV VL reaches high levels in the short period after infection, increasing the risk of HIV transmission. Recent HIV acquisition events will allow the characterization of drivers of new infections and avoid recall bias because remembering sexual partners once in the last few weeks is easier than over a longer time.

We will perform HIV phylogenetic testing on specimens with detectable HIV VL. Phylogenetic data will identify HIV strain types, ART resistance mutations, and clusters of transmission.

STI Testing

The incorporation of biomarkers for acute and recent infection, as well as STIs, may be particularly valuable among YMSM, where the onset of behaviors leading to infection is more recent.

We will evaluate STIs as markers of HIV sexual risk and causes of morbidity using nucleic acid amplification tests for oropharyngeal, urethral and rectal *Neisseria gonorrhea* and *Chlamydia trachomatis* (nontreponemal syphilis testing and if positive treponemal test), chronic hepatitis B (anti-HBs antibody, Hbs antigen, and total anti-HBc antibodies), chronic hepatitis C (anti-HCV), human papillomavirus testing and anal cytology. Participants diagnosed with STI will receive treatment according to Brazilian guidelines [29]. Participants screened positive for hepatitis B and C will undergo a complete diagnosis algorithm (ie, HCV viral load) [30] and will be referred to treatment. Participants without hepatitis B diagnosis and who have not been vaccinated will be referred for hepatitis B vaccination.

Behavioral, Partnership, Network, and Structural Measures

Trained staff will administer face-to-face questionnaires to participants using tablets. Due to the COVID-19 pandemic, all efforts will be undertaken to minimize SARS-CoV-2 transmission. Before study procedures, participants will be screened for COVID-19 symptoms, and visits will consider the safety of all participants and the study team. Our instrument will build upon questionnaires previously used for MSM in Brazil and the United States. Table 1 presents examples of measurements, hypotheses, and sources of questionnaires.

Biological data, particularly markers of recent HIV and STI infection, will permit closer linkage to the events, behaviors, partnerships, and social and structural conditions that lead to HIV acquisition. We will also identify whether there are infection clusters within specific racial/ethnic groups, as previously seen among Black MSM in the United States [31]. With robust biomedical markers of infection, we will be able to discern whether tight sexual networks constrained by racial bias and discrimination impact the spread of HIV among Black and *Pardo* Brazilians and whether this is a recent phenomenon or ongoing over the course of the Brazilian MSM epidemic.

Table 1. Behavioral, partnership, network, and structural measures for the RDS[a]-based study.

Timeframe	Level/domain	Examples of measures/hypotheses
Acute infection: within the last several weeks	Individual	Events of likely acquisition and transmission; missed opportunities for prevention; STI[b] co-infection.
	Partnership	Characteristics of most recent sexual partners (HIV status, disclosure, on ART[c], PrEP[d], and age) [32]; phylogenetic linkage.
Recent infection: within last 130-180 days	Individual	Missed opportunities for prevention; untreated STIs; HIV care cascade.
	Sexual network, with a focus on Black/*Pardo* Brazilians	Characteristics of recent sexual partners; age and racial mixing, with a specific focus on sexual networks of Black/*Pardo* Brazilians [31]; phylogenetic clustering; partner concurrency.
Long-standing infection: since the onset of risk or last HIV test	Previously undiagnosed	Missed opportunities for testing, linkage to care, experiences, and attitudes towards care providers.
	Previously diagnosed	Barriers to care, ART initiation, adherence [33-35], viral suppression; care cascade; care self-efficacy; perceived HIV stigma [36].
All (including and regardless of HIV status): since the onset of risk	Demographic	Racial disparities in risk, prevention, and care access (eg, race/ethnicity and socioeconomic status); homelessness, runaway; incarceration; digital health information.
	Risk and prevention	Onset of sexual risk, lifetime risk; substance use and chemsex [37]; HIV testing; internet use for sex (eg, apps); PrEP awareness, willingness, use [10,12,13,38]; knowledge and willingness to use new prevention technologies [39]; HIV perceived risk [40]; knowledge of HIV [41,42].
	Psychosocial, structural	Mental health [43,44], psychological distress, trauma [45], suicidality, and social support; testing, PrEP norms, and stigma [12]; peer support; family support; sexual orientation disclosure; experiences of discrimination [46,47], internalized homonegativity [48]; sexual compulsivity [49]; COVID-19 pandemic impact in personal life [50].
	Health and social welfare systems	Care-seeking and medical mistrust; health care participation; avoidance of care; perceived care access; "*Bolsa Familia*" (family grant or family stipend) program and other cash transfer programs; SUS[e] experiences; food insecurity [51]; political context; digital health experiences.

[a]RDS: respondent-driven sampling.

[b]STI: sexually transmitted infection.

[c]ART: antiretroviral therapy.

[d]PrEP: preexposure prophylaxis.

[e]SUS: Sistema Único de Saúde (Brazilian National Public Health System).

Technology-Based Adherence Intervention

All RDS participants will be invited to participate in a technology-based adherence intervention study. The intervention builds upon Health eNav, a text messaging HIV care linkage and retention intervention for young people living with HIV in San Francisco, United States, using an SMS-based platform to support ART adherence and provide HIV prevention counseling [21]. Based on a prior study, we anticipate 13% HIV prevalence [20] (N=52 individuals), 26 (50%) of whom will be newly diagnosed and 26 (50%) previously diagnosed (regardless of linkage to care). Therefore, we estimate that 65% (226/348) of HIV-negative YMSM, as previously described [15], will be interested and eligible for PrEP according to the Brazilian guidelines (eg, condomless anal sex, sex with HIV positive partner, and STI diagnosis in the last 6 months) [52].

HIV-negative participants enrolled in the intervention study will receive same-day PrEP, according to the Brazilian recommendations, plus a complete prevention package, including HIV/STI testing and treatment, counseling for HIV/STI risk reduction, hepatitis B vaccination, and condoms/lubricants distribution (Group 1: HIV-negative on PrEP). HIV-negative YMSM not eligible for PrEP or who do not accept PrEP may also be enrolled in the intervention study to receive the prevention package (including PEP, when indicated), risk assessments, and counseling (Group 2: HIV-negative not on PrEP).

HIV-positive YMSM enrolled in the intervention study will initiate same-day ART treatment according to Brazilian recommendations and will be further linked to care at the INI-Fiocruz HIV clinic (Group 3: HIV-positive on ART).

HIV-positive YMSM previously diagnosed and who initiated ART prior to inclusion will also be invited to the intervention.

All participants enrolled will receive weekly reminders for 24 weeks via WhatsApp, the most common SMS platform in Brazil. Automatic messages will include scheduled medication reminders, if applicable, and posts. Periodic feedback from participants will adapt and improve the approach. (eg, adjustments or modifications on the content of electronic messages). The weekly reminders will be personalized. Participants will be able to select the timing of reminders and choose between having explicit medication reminders or factoid messages (not specific to medication), such as LGBTQIA+ community events, health facts, or a combination of both types of messages. All messages sent will solicit a response, so we will have backend data (eg, time, date, message content, etc) on whether the message was received and reviewed by participants. For example, we may send a medication reminder text, such as "Did you take your medication today?" Responses will be recorded in our database, but more importantly, we will know whether the participant was exposed to the text message regardless of receiving a formal response.

After enrollment, follow-up visits will occur at 4 and 12 weeks and then quarterly (24, 36, and 48 weeks). Briefly, during follow-up visits, we will collect information on study outcomes, such as HIV seroconversion, PrEP continuum endpoints, and PrEP adherence (using dried blood spots for TFV-diphosphate concentration among HIV-negative participants); HIV viral load suppression among HIV-positive participants; and STI incidence among all participants. The intervention study baseline visit procedures are the same as those conducted during the RDS visit. A detailed schedule of events and procedures is depicted in Table 2.

Table 2. Schedule of events for the Conectad@s Project.

	RDS[a]/ Baseline	Week 4	Week 12	Week 24	Week 36	Week 48	Early Termination[b]	HIV seroconversion visit	Unscheduled visit
Questionnaires									
Behavioral, partnership, network, and structural measures	X	X	X	X	X	X	X	__c	—
Technology-based intervention: inclusion	X	—	—	—	—	—	—	—	—
Technology-based intervention: acceptability	—	—	—	X	—	—	—	—	—
Laboratory procedures									
HIV antigen rapid test	X	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X	X[e]
HIV RNAPool	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]		X[f]
HIV RNA viral load	X[g]	X[h]	X[h]	X[g]	X[h]	X[g]	X[g]	X	X[e]
CD4/CD8	X[i]	X[j]	X[j]	X[i]	X[j]	X[i]	X[i]	X	X[e]
HIV recency testing	X[i]	—	—	—	—	—	—	—	X[e]
HIV genotyping	X[k]	X[l]	—	—	—	—	—	X	X[e]
Urine (CT[m]/NG[n])	X	—	—	X	—	X	X	X	—
Oropharyngeal swab (CT/NG)	X	—	—	X	—	X	X	X	—
Anal swab (CT/NG)	X	—	—	X	—	X	X	X	—
Anal swab (HPV[o])	X	—	—	—	—	—	—	—	—
Anal cytology	X	—	—	—	—	—	—	—	—
Hepatitis B rapid test	X	—	—	—	—	X[p]	X[p]	X[p]	X[e]
Hepatitis B serology	X[q]	—	—	—	—	X[q]	X[q]	X[q]	X[e]
Hepatitis C rapid test	X	—	—	—	—	X[r]	X[r]	X[r]	X[e]
Anti-HCV	X[s]	—	—	—	—	X[s]	X[s]	X[s]	X[e]
RNA Hepatitis C viral load	X[t]	—	—	—	—	X[t]	X[t]	X[t]	X[e]
Treponemal syphilis rapid test	X	—	X	X	X	X	X	X	X[e]
Non-treponemal syphilis testing (VDRL)	X[u]	—	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[e]
DBS[v] (PrEP adherence assessment)	X[w]	X[w]	X[w]	X[w]	X[w]	X[w]	X[w]	X[w]	X[e]
Creatinine	X[x]	X[f]	X[f]	X[x]	X[f]	X[x]	X[x]	X[f]	X[e]
Complete blood count	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]

[a]RDS: respondent-driven sampling.

[b]Withdrawn or discontinued participants before the final visit.

[c]Not applicable

[d]Only for HIV-negative participants in a prior visit.

[e]If necessary.

[f]Only for postexposure prophylaxis use.

[g]Only for HIV-positive participants or HIV-negative participants with recent HIV exposition according to INI-Fiocruz guidelines (HIV acute infection screening).

[h]Only for HIV-negative participants with recent HIV exposition according to INI-Fiocruz guidelines (HIV acute infection screening).

[i]Only to HIV-positive participants or to participants with HIV rapid test, HIV RNA Pool or HIV RNA viral load positive result.

[j]Only to participants with HIV rapid test, HIV RNA Pool or HIV RNA viral load positive result, with negative HIV rapid test in a prior visit.

[k]Only HIV-positive participants ART naïve

[l]Only HIV-positive participants with prior ART use (before study initiation).

[m]CT: *Chlamydia trachomatis.*

[n]NG: *Neisseria gonorrhea.*

[o]HPV: human papilloma virus.

[p]Only for negative Hepatitis B rapid test at baseline.

[q]Only for positive Hepatitis B rapid test.

[r]Only for negative Hepatitis C rapid test at baseline.

[s]Only for positive Hepatitis C rapid test.

[t]Only for positive anti-HCV.

[u]Only treponemal syphilis rapid test.

[v]DBS: Dried blood spot.

[w]Only for participants using PrEP.

[x]Only for participants using PrEP or PEP.

Analysis Plan for the Technology-Based Adherence Intervention

We will measure exposure to the intervention, including the number of received and read WhatsApp messages during the 24-week intervention period. Intervention exposure and outcome data will be analyzed using multivariable logistic generalized estimating equations (GEE) with exchangeable correlation structures to account for repeated measures over time for each participant. GEE models will assess the association between intervention exposure measures (eg, receipt of intervention and intervention dosage) and primary outcomes related to the HIV care and PrEP continuum.

Results

To date, the Conectad@s Project has made significant progress despite the still ongoing COVID-19 pandemic. During 2020, we prepared the questionnaires for the RDS survey, intervention, and formative phase. We also discussed the best approach to move forward with the study in the context of the COVID-19 pandemic. The formative stage of the study started in January 2021. We conducted 20 individual interviews from January 12 to February 4, 2021, and three focus group discussions on February 4, 10, and 24, 2021. The study team prepared a COVID-19 plan that includes assessing COVID-19 symptoms, screening by phone prior to study attendance onsite before study visit, as well as a strong recommendation of facemask use and social distancing. Planned activities are indicated in Table 3.

Table 3. Planned activities for the Conectad@s Project.

Activities	2022				2023			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Formative phase analysis	x	—[a]	—	—	—	—	—	—
Dissemination of formative results	—	x	—	—	—	—	—	—
Manual of operations approval	x	—	—	—	—	—	—	—
Training	x	—	—	—	—	—	—	—
Investigators' meetings	x	—	—	—	x	—	—	—
RDS[b] survey and intervention enrollment	x	x	x	—	—	—	—	—
Follow-up for intervention	—	x	x	x	x	x	—	—
RDS survey analysis	—	—	x	—	—	—	—	—
Dissemination of RDS results	—	—	—	x	—	—	—	—
Intervention analysis	—	—	—	—	—	—	x	—
Dissemination of intervention results	—	—	—	—	—	—	—	x

[a]Not applicable.

[b]RDS: respondent-driven sampling.

Discussion

The Conectad@s Project is a vanguard study that will apply for the first time an RDS-based survey for YMSM in Brazil integrated with a technology-based adherence intervention. The results of the RDS survey will allow us to estimate HIV prevalence and incidence using recency testing and to measure HIV biomarkers near the onset of risky behavior among Brazilian YMSM. The intervention study will contribute to developing intervention-based adherence strategies to support

HIV care and prevention among a highly vulnerable population. Data will lay the groundwork to adapt and implement all strategies to identify the barriers to the earliest possible diagnosis, immediate ART initiation, PrEP uptake, and detecting new clusters of HIV transmission.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the Center for Scientific Review Special Emphasis Panel - RFA-AI-18-054 U.S.-Brazil Collaborative Biomedical Research Program (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 169 KB - resprot_v11i1e34885_app1.pdf]

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Abbreviations

ART: antiretroviral therapy
GEE: generalized estimating equations
INI-Fiocruz: Instituto Nacional de Infectologia Evandro Chagas, Fundação Oswaldo Cruz
LGBTQIA+: lesbian, gay, bisexual, transgender, queer/questioning, intersex, and asexual/aromantic/agender
MSM: men who have sex with men
PrEP: preexposure prophylaxis
RDS: respondent-driven sampling
STI: sexually transmitted infections
SUS: Sistema Único de Saúde (Brazilian Public health System)
VL: HIV RNA viral load
YMSM: young men who have sex with men

Protocol

Reducing Delays in Diagnosing Primary Immunodeficiency Through the Development and Implementation of a Clinical Decision Support Tool: Protocol for a Quality Improvement Project

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Abstract

Background: Primary immunodeficiencies (PIs) are a set of heterogeneous chronic disorders characterized by immune dysfunction. They are diagnostically challenging because of their clinical heterogeneity, knowledge gaps among primary care physicians, and continuing shortages of clinically trained immunologists. As a result, patients with undiagnosed PIs are at increased risk for recurrent infections, cancers, and autoimmune diseases.

Objective: The aim of this research is to develop and implement a clinical decision support (CDS) tool for the identification of underlying PIs.

Methods: We will develop and implement a CDS tool for the identification of underlying PIs among patients who receive primary care through a health care provider at the University of Iowa Hospitals and Clinics. The CDS tool will function through an algorithm that is based on the Immune Deficiency Foundation's 10 Warning Signs for Primary Immunodeficiency. Over the course of a year, we will use Lean Six Sigma principles and the Define, Measure, Analyze, Improve, and Control (DMAIC) framework to guide the project. The primary measure is the number of newly diagnosed PI patients per month. Secondary measures include the following: (1) the number of new patients identified by the CDS as being at high risk for PI, (2) the number of new PI cases in which immunoglobulin replacement or rotating antibiotics are started, (3) the cost of evaluation of each patient identified by the CDS tool as being at high risk for PIs, (4) the number of new consults not diagnosed with a PI, and (5) patient satisfaction with the process of referral to the Immunology Clinic.

Results: This study was determined to not be Human Subjects Research by the Institutional Review Board at the University of Iowa. Data collection will begin in August 2021.

Conclusions: The development and implementation of a CDS tool is a promising approach to identifying patients with underlying PI. This protocol assesses whether such an approach will be able to achieve its objective of reducing diagnostic delays. The disciplined approach, using Lean Six Sigma and the DMAIC framework, will guide implementation to maximize opportunities for a successful intervention that meets the study's goals and objectives as well as to allow for replication and adaptation of these methods at other sites.

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Introduction

Primary immunodeficiencies (PIs) are diagnostically challenging chronic disorders involving the immune system that lead to recurrent infections, increased risk for cancer, and autoimmune disease [1]. PIs may present at any age and manifest due to genetic predilection and environmental exposures [2].

Diagnoses of PIs are frequently delayed because of this clinical heterogeneity, knowledge gaps among primary care physicians, and continuing shortages of clinically trained immunologists [3-5]. These delays in obtaining care lead to increased mortality and morbidity as well as decreased quality of life [6-9].

PI diagnostic delays also cost a calculated $85,882 per patient [10] and contribute $40 billion in costs to the US health care system. It has been estimated that early diagnosis can save $6500 per patient [11]. Earlier identification of PI is critical for the following reasons:

1. To permit more appropriate management of the underlying condition. Immune globulin replacement and immunomodulators have demonstrated efficacy in reducing the frequency and severity of infections [12,13].
2. To enable more appropriate preventative health measures. Guidelines from the Advisory Committee on Immunization Practices (ACIP) and Infectious Disease Society of America (IDSA) state that immunocompromised patients, including those with PIs, have different requirements for vaccinations [14,15]. Identification of PIs enables more timely vaccinations and prevention of illness. Conversely, certain live vaccinations are contraindicated in certain types of PIs and should be avoided to prevent adverse events [16]. Finally, those with PI are at 1.4 to 1.6-fold increased risk for malignancy, with some estimates of prevalence of malignancy as high as 25% [17,18]. Therefore, a diagnosis of a PI significantly impacts screening guidelines for malignancy.
3. To prevent downstream diagnostic errors. Patients with a PI are more likely to present with atypical manifestations of infections that are less likely to be identified early on. Local infections are also more likely to become systemic, leading to increased morbidity and mortality [19]. Recognition of PIs enables providers to consider these diagnoses earlier and prevent further diagnostic delays. Studies also demonstrate that early diagnosis prevents further readmissions and improves Accountable Care Organization (ACO) scores [20].
4. To uncover diagnoses of family members. PIs are inherited conditions [21]. Identification of a proband in a family with immune deficiency enables family members who have compatible signs and symptoms to share information with one another.
5. To empower patients about chronic illness. A diagnosis of PI is empowering to patients and enables them to reach out to support systems. Studies have demonstrated that early

detection and diagnosis improves patient satisfaction and quality of life [22].

6. To address health disparities. PIs are more likely to affect patients in particular ethnic populations, including those of Middle Eastern descent [23]. Experts also voice concern that diagnostic delays disproportionately affect Black, Indigenous, and other people of color (BIPOC) and those with already reduced access to health care [24,25]. Additionally, PIs affect women in specific ways that amplify the downstream effects of diagnostic delays, including gynecologic and obstetric complications [26].

Methods

Objectives and Specific Aims

The objective of this study is to develop and implement a clinical decision support (CDS) tool for identifying patients with an underlying PI. The Jeffrey Modell Foundation has published a set of 10 warning signs for PIs for both adults and children [27]. We will adapt these warning signs to a CDS tool to help stratify the risk of a patient having an underlying PI. This CDS tool will enable primary care providers within the University of Iowa to refer patients to the University of Iowa's Immunology Clinic, and guide laboratory investigations prior to referral to ensure readiness prior to the visit.

Toward that end, there are two specific aims:

1. Identify the total number of patients who present to the University of Iowa General Internal Medicine, Pediatrics, or Family Medicine clinics with two or more warning signs of a PI over a 12-month period.
2. Refer at least 10% of these identified patients to a University of Iowa clinical immunologist for evaluation within 12 months of their initial presentation.

Rationale for the Intervention

CDS tools for PIs have not yet been developed and assessed in peer-reviewed literature. This intervention would represent the first attempt to address this critical need. However, we build upon several lines of evidence that bolster the rationale that a CDS tool is needed to identify PI patients:

1. A 2019 study of a large pediatric cohort of 185,892 patients revealed 2188 patients (1.26%) at medium to high risk for PIs [28]. The authors concluded that early identification of PIs in the 98 patients who were at highest risk within this cohort would represent an annual cost savings of up to $7.7 million.
2. CDS tools for identifying secondary immunodeficiencies, including HIV, have been developed. Although these methods are different and guidelines for implementation vary considerably, they add to the evidence of the feasibility of immunodeficiency screening of large populations [29].
3. Several CDS tools have been developed for tracking antibiotic usage, including at the University of Iowa [30]. The purposes of these CDS tools vary, but collection of

data about the frequency of use and type of antibiotic is vital in this proposal, further supporting the feasibility of our approach.

Settings and Target Population

University of Iowa Hospitals and Clinics (UIHC) represents the only comprehensive academic medical center within the state of Iowa. Between July 1, 2019, and June 30, 2020, there were 1,039,681 clinic visits, 32,872 inpatient admissions, and 50,468 emergency department visits. In the UIHC system, there are 77,779 patients that have a primary care provider in Family Medicine, General Internal Medicine, and General Pediatrics.

Patients with suspected immunodeficiencies are evaluated at the Allergy and Immunology Clinic located at the University of Iowa's clinics in Iowa City. If patients are determined to have an immunodeficiency, then they return to the Allergy and Immunology Clinic to obtain specialized care. Per year, there are 1863 half-day clinics staffed by 12 physicians serving 8963 patients. There are approximately 1684 patients with a diagnosis of a PI whose management is overseen by physicians and other practitioners in the Immunology Clinic. The average wait time to a new appointment is 5.46 weeks for adults and 13.16 weeks for pediatric patients.

Inclusion and Exclusion Criteria

Inclusion criteria include patients who receive their care from one of the General Internal Medicine, Pediatrics, or Family Medicine clinics through the UIHC system. Exclusion criteria include patients with an established secondary or acquired immunodeficiency, and patients with an established PI diagnosis.

Quality Improvement Framework

We will use Lean Six Sigma principles and the Define, Measure, Analyze, Improve, and Control (DMAIC) framework to implement this intervention. The Lean Six Sigma approach has been previously described in health services research literature as a methodology to improve health care delivery [31]. It combines two distinct process improvement methodologies: Lean and Six Sigma. The Toyota Motor Corporation initially developed Lean to improve manufacturing quality through the elimination of waste and creation of value for customers [32]. Lean complements Six Sigma, a data-driven management approach aimed at the elimination of defects and reduction of unwarranted variability [33].

Define Phase

In line with the DMAIC framework (Figure 1), we have begun defining the scope of the project. We have developed a project charter to articulate the problem at hand, our project goals, and customer requirements. The project charter also delineates the time frame for completion of tasks (Figure 2).

Additionally, to understand the needs of the customers, we are using Voice of the Customer to clarify experiences, expectations, and needs. We are currently conducting semistructured interviews with 20 patients with PIs to understand their experiences. EK, a core member of the team, is a patient with PI and is helping to formulate questions and analyze data.

Figure 1. The Define, Measure, Analyze, Improve, and Control (DMAIC) framework. CDS: clinical decision support; PI: primary immunodeficiency.

	Element of each step	Actions Performed by Core Investigators
Define 7/1/2021 – 7/1/2021	Problem statement	Project Charter was drafted, including a problem statement that articulated the background, specific needs, and aims of the project
	Goal statement	Articulated in the Charter: "Develop and implement a Clinical Decision Support Tool to identify the total number of patients who present to the University of Iowa General Internal Medicine, Pediatrics, or Family Medicine clinics with two or more warning signs of a primary immunodeficiency (PI) over a 12-month period."
	Project scope	Articulated in the Charter: "This Lean Six Sigma project will take place 360 days from start to validated solutions"
	Identification of project sponsor	The Associate Director of Biomedical Informatics Operations was identified and designed as the project sponsor
	Identification of process owner	The Primary Investigator was identified and designated as the process owner
	Primary impact measure	Articulated in the Charter: "The number of newly diagnosed PI patients per month"
	Secondary impact measures	1) Number of new patients identified by the CDS tool at high risk for PI 2) Number of new PI cases in which intravenous Immunoglobulin or rotating antibiotics are started 3) Cost of evaluation of each patient identified by CDS tool at high risk for PIs 4) Number of new consults not diagnosed with a PI 5) Patient satisfaction with the process of referral to Immunology Clinic
Measure 8/1/2021- 10/01/2021	Baseline operations	Chart review determined rate of newly diagnosed PI patients per month
	Impact data	Project charter updated regularly based on performance
Analyze 9/1/2021 – 2/1/2022	Run and control charts	The number of patients will be charted over time to determine stability of the process
	Time analysis	Determination of opportunities for earlier interventions for diagnosis
	Value-added analysis	Calculation of costs of diagnosis and identification of causes of inefficiency in diagnosis
	Voice of the customer	Semi-structured interviews with PI patients and care providers to better understand their perspectives and opportunities for further refinement so that the CDS
Improve 10/01/2021- 1/1/2022	Plan-Do-Study-Act cycles	At least three Plan-Do-Study-Act cycles will be performed
	Pilot results	Gaps between predicted and actual performance will be analyzed
	Failure Modes & Effect Analysis	Proactive determination of how the newly established process for identifying PI may create inefficiencies
Control 2/1/2022- 7/1/2022	Development of a control plan	A control plan will be drafted to summarize the process and take steps to ensure that the level of improvement is maintained and sustained
	Impact summary	A one-page impact summary will be drafted with simplified language and diagrams for dissemination within the institution
	Recognition of work accomplished	Results of quality improvement project will be disseminated locally at institutional grand rounds and nationally at annual conferences Celebration of short-term wins

Figure 2. Gantt chart outlining major phases of the study protocol.

	Phase	Start	Finish	Duration	2021						2022						
					Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul
1	Define Phase	7/1/2021	7/30/2021	22d	▬												
2	Measure Phase	8/2/2021	10/1/2021	45d		▬▬											
3	Analyze Phase	9/1/2021	2/1/2022	110d			▬▬▬▬										
4	Improve Phase	10/1/2021	3/1/2022	108d				▬▬▬▬									
5	Control Phase	2/1/2022	7/1/2022	109d								▬▬▬▬▬					

Measure Phase

During the Measure phase, we anticipate collection of data regarding our primary and secondary outcomes. The primary measure, as articulated in the project charter, is the number of newly diagnosed PI patients per month. We will measure the rate over the past 24 months to obtain a baseline, and then monitor it throughout the course of the protocol.

We will also measure the following five secondary measures:

1. Number of new patients identified by the CDS tool as being at high risk for PI.
2. Number of new PI cases in which immunoglobulin replacement or rotating antibiotics are started.
3. Cost of evaluation of each patient identified by CDS tool as being at high risk for PIs.
4. Number of new consults not diagnosed with a PI.
5. Patient satisfaction with the process of referral to the Immunology Clinic.

Administrative data will be used for the primary measure and secondary measures 1-4. For secondary measure 5, we will conduct semistructured interviews and surveys to obtain the Voice of the Customer.

Analyze Phase

Throughout the analyze phase, we will use the data being obtained as part of the Measure phase to assess the efficacy of the intervention and to guide modifications as necessary.

For quantitative data, we will construct both run and control charts. The specific type of chart will be dependent on the number of evaluated patients and specific outcome measures. For example, if the CDS tool is unable to find many patients with PI, then a T-chart may be more appropriate than an X-bar chart.

For qualitative data, we will continue to use Voice of the Customer. Once the CDS tool is implemented, we will conduct semistructured interviews with primary care providers to better understand their perspectives and opportunities for further refinement so that the CDS tool is more user-friendly.

For individual cases of newly diagnosed PI, we will perform more detailed analysis to recognize causes of diagnostic delays. We will use value-added analysis to calculate the costs of diagnosis and identify causes of inefficiency in diagnosis. Additionally, we will use time analysis to chronologically map out opportunities for earlier diagnosis. Both of these analyses will then be used to further refine the CDS tool.

Improve Phase

During the Improve phase, we will employ sequential Plan-Do-Study-Act (PDSA) cycles to refine the CDS tool to different settings, starting with Internal Medicine, then Pediatrics, and finally Family Medicine. The investigators will continue to use Voice of the Customer as a key Lean Six Sigma tool to guide these PDSA cycles.

Additionally, as we begin to finalize the CDS tool, we will use failure mode and effect analysis to proactively determine how the newly established process for identifying PIs may create inefficiencies and result in failures in diagnosis.

Control Phase

Toward the end of the quality improvement project, we will develop a monitoring and proactive response plan to sustain the improvement plan. Using those measures, we will establish a trigger level to ensure that new cases of suspected PIs are screened through the CDS tool. Additionally, with advances in the diagnosis of PIs, such as genetic testing, we will incorporate newer modes of evaluation into the CDS tool.

Finally, we intend on publishing our findings and presenting them at national meetings. Thorough documentation of the process, including this protocol, will be essential for transfer of knowledge to other settings and implementation in different settings.

Ethics Approval and Consent to Participate

This study protocol was submitted to the University of Iowa Institutional Review Board and determined not to be Human Subjects Research.

Results

As of July 31, 2021, this protocol has been funded by the Society to Improve Diagnosis in Medicine as a DxQI Grant. It has been determined to not be Human Subjects Research by the University of Iowa Institutional Research Board on July 13, 2021. Data collection will begin on August 15, 2021, and end on July 31, 2022. We intend on publishing results in winter 2022.

Discussion

While there have been tremendous advances in the modalities used to diagnose PIs, evidence of real-world interventions to better identify PI are largely lacking. To fill that evidence gap, this study protocol outlines a quality improvement initiative to

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help reduce delays in diagnosing PIs. To bolster the likelihood of success, we have designed our initiative in line with the principles of Lean Six Sigma and have structured it via the DMAIC framework.

We anticipate a series of challenges and have a comprehensive strategy to address these challenges as they arise. First, we have a screening algorithm (Multimedia Appendix 1) that has multiple redundancies for optionality if one method of obtaining data cannot be completed properly.

Second, we have a plan to accommodate increased volumes of patients who would need evaluation. Currently, there are 1863 half-day immunology clinics among 12 faculty members serving

8963 unique patients. The average wait time to a new appointment is 5.46 weeks for adults and 13.16 weeks for pediatric patients. The division has plans to expand with the hiring of 1-2 new faculty members over the coming academic year. Additionally, as allergy/immunology faculty are certified to see both adult and pediatric patients, flexibility can be arranged to accommodate incoming evaluations.

Third, the CDS tool will be implemented in a stepwise pattern through the clinics to assess its ability to achieve our stated specific aims. Therefore, we have the capacity to revise the tool accordingly as we recognize the specificity and sensitivity of elements within the algorithm in detecting cases of PI.

Acknowledgments

Authors' Contributions

BK, SZ, BD, ELKE, M Suneja, and M Swee contributed to the conceptualization of the study. BK, M Suneja, M Swee, and SZ designed the study protocol. BK, M Swee, and M Suneja drafted the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Primary immunodeficiency screening algorithm.
[DOCX File , 65 KB - resprot_v11i1e32635_app1.docx]

Multimedia Appendix 2
Peer review reports from the Society to Improve Diagnosis in Medicine.
[PDF File (Adobe PDF File), 299 KB - resprot_v11i1e32635_app2.pdf]

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Abbreviations

ACIP: Advisory Committee on Immunization Practices
ACO: Accountable Care Organization
BIPOC: Black, Indigenous, and other people of color
CDS: clinical decision support
DMAIC: Define, Measure, Analyze, Improve, and Control
IDSA: Infectious Disease Society of America
PDSA: Plan-Do-Study-Act
PI: primary immunodeficiency
UIHC: University of Iowa Hospitals and Clinics

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Protocol

A Text Messaging–Enhanced Intervention for African American Patients With Heart Failure, Depression, and Anxiety (TXT COPE-HF): Protocol for a Pilot Feasibility Study

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Abstract

Background: African Americans have a higher incidence rate of heart failure (HF) and an earlier age of HF onset compared to those of other racial and ethnic groups. Scientific literature suggests that by 2030, African Americans will have a 30% increased prevalence rate of HF coupled with depression. In addition to depression, anxiety is a predictor of worsening functional capacity, decreased quality of life, and increased hospital readmission rates. There is no consensus on the best way to treat patients with HF, depression, and anxiety. One promising type of treatment—cognitive behavioral therapy (CBT)—has been shown to significantly improve patients' quality of life and treatment compliance, but CBT has not been used with SMS text messaging reminders to enhance the effect of reducing symptoms of depression and anxiety in racial and ethnic minority patients with HF.

Objective: The objectives of our study are to (1) adapt and modify the Creating Opportunities for Personal Empowerment (COPE) curriculum for delivery to patients with HF by using an SMS text messaging component to improve depression and anxiety symptoms, (2) administer the adapted intervention to 10 patients to examine the feasibility and acceptability of the approach and modify it as needed, and (3) examine trends in depression and anxiety symptoms postintervention. We hypothesize that patients will show an improvement in depression scores and anxiety symptoms postintervention.

Methods: The study will comprise a mixed methods approach. We will use the eight steps of the ADAPT-ITT (assessment, decision, administration, production, topical expert, integration, training, and testing) model to adapt the intervention. The first step in this feasibility study will involve assembling individuals from the target population (n=10) to discuss questions on a specific topic. In phase 2, we will examine the feasibility and acceptability of the enhanced SMS text messaging intervention (TXT COPE-HF [Texting With COPE for Patients With HF]) and its preliminary effects with 10 participants. The Beck Depression Inventory will be used to assess depression, the State-Trait Anxiety Inventory will be used to assess anxiety, and the Healthy Beliefs and Lifestyle Behavior surveys will be used to assess participants' lifestyle beliefs and behavior changes. Changes will be compared from baseline to end point by using paired 2-tailed *t* tests. An exit focus group (n=10) will be held to examine facilitators and barriers to the SMS text messaging protocol.

Results: The pilot feasibility study was funded by the Academy for Clinical Research and Scholarship. Institutional review board approval was obtained in April 2021. Data collection and analysis are expected to conclude by November 2021 and April 2022, respectively.

Conclusions: The study results will add to the literature on the effectiveness of an SMS text messaging CBT-enhanced intervention in reducing depression and anxiety among African American patients with HF.

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Introduction

Background

Improving the mental health needs of African American patients with heart failure (HF) fits within the public health mandate to reduce health disparities based on race and ethnicity [1-3]. Screening for depression in all patients with HF is a recent public health directive [1]. However, screening without evidence-based interventions for improving mental health is inadequate and does not result in positive outcomes. Cognitive behavioral therapy (CBT) is a form of psychological treatment that has shown effectiveness in treating a wide range of mental health conditions but has also shown mixed results with some populations when used alone [4]. An intervention that is based on CBT, targets patients with HF, and is designed to reduce depression and anxiety is vital, given the well-established link among depression, anxiety, and mortality [5]. The purpose of our exploratory feasibility study is to adapt an evidence-based CBT intervention by using SMS text messaging boosters to reduce depression and anxiety in African American patients with HF. This project will impact the mental health care of racial and ethnic minority patients with HF by reducing depression and anxiety, thereby improving the health outcomes of this population.

More than 5 million people in the United States experience congestive HF [1,2], and it is the most common diagnosis in hospitalized patients aged over 65 years [2]. Further, in 1 in 9 deaths, HF is a contributing factor to mortality. Moreover, in one study with adult patients, racial differences were noted among young patients with HF (aged <50 years) [6]. More specifically, African Americans have a 20 times higher incidence rate of HF compared to that of White Americans [2,6], and among patients aged younger than 75 years, African Americans have the highest incidence of HF and often have an earlier age of HF onset [6]. The American Heart Association estimates that by 2030, there will be a 30% increase (from 2012) in the prevalence of HF among African Americans [2].

Depression has been found to be an independent risk factor for mortality in patients with HF [1,5]. HF, depression, and anxiety share pathophysiological mechanisms. The prevalence of depression and anxiety in patients with HF is about 20% to 40%, which is 4% to 5% higher than that of the general population [2,5]. In addition to depression, anxiety is also a predictor of worsening functional capacity, decreased quality of life, increased hospital readmission rates, and increased mortality [1,5-7].

Structural racism is a fundamental driver of health disparities among racial and ethnic minority patients with HF [8]. African Americans sometimes experience more severe forms of mental health conditions due to unmet needs and other barriers, such as distrust in the health care system, which can cause many African Americans to not seek mental health treatment [7]. These factors underscore the urgent need for an adapted intervention that improves the mental health outcomes of this vulnerable population.

Objectives

The proposed site for this study periodically screens its patients with HF for depression and anxiety during clinic visits and provides appropriate referrals to psychiatric services. However, the average wait time for the first psychiatric appointment remains high (116 hours), in part because 1 in 5 psychiatrists are not accepting new patients [9]. The provision of psychiatric care has been further impacted by the COVID-19 pandemic [9]. There is a lack of consensus on the best way to treat patients with HF, depression, and anxiety [3]. Some patients show improvement after taking medication, but medication does not have a significant benefit over placebos [5]. Psychotherapy may reduce depressive symptoms, but it does not affect disease outcomes [5]. One promising type of treatment—CBT—has been shown to significantly improve patients' quality of life and treatment compliance [10].

CBT Treatment

CBT is effective in treating insomnia, substance use disorder, schizophrenia, depression, anxiety, and anger in diverse patient populations, such as Hispanic and African American pregnant women, adolescents, and patients with HF. [11,12]. However, few studies have examined the effectiveness of SMS text messaging reminders for patients with HF [13-16], and even fewer have examined the effectiveness of CBT for African American patients with HF [17]. The implementation of interventions with HF patients is not a one-size-fits-all solution, and gaps exist in understanding how CBT can be an effective treatment for depression and anxiety in racial and ethnic minority patients with HF. The question that remains unanswered is as follows: how does implementing a prescriptive, case-specific, ethnic- and cultural-driven SMS text messaging–enhanced intervention for racial and ethnic minority individuals with HF, depression, and anxiety improve health outcomes? Our proposed pilot study will begin to fill this gap by examining the effect of SMS text messaging–enhanced CBT for a racial and ethnic minority population—African Americans with HF—to improve their physical and mental health outcomes.

Text Messaging–Based Interventions

SMS text messaging interventions can successfully modify adverse health behaviors. Compared to nonweb interventions, SMS text messaging interventions are effective in helping people with diabetes, cardiovascular disease, or prostate cancer achieve

positive behavior change outcomes and improve their quality of life [13-17]. African Americans are more likely than other ethnic groups to use devices such as mobile phones, making interventions that involve SMS text messaging more likely to be acceptable to this population [13]. This type of platform is not only affordable but also effective. SMS text messaging is particularly suited for this target group because little effort is required to receive the text reminders, and such reminders can be accessed at times that are suitable for study participants [15-17]. This type of intervention can help to bridge the gap between the socioeconomic disparity related to vulnerable populations and the delivery of health care [16]. The outcomes of mobile phone SMS text messaging–enhanced interventions include increased exercise time, increased knowledge of nutrition, increased participation in health care, and weight loss maintenance, of which all are factors associated with maintaining a healthy lifestyle and reducing depression and anxiety among patients with HF. One study used SMS text messaging to improve HF self-management (eg, eating a low-salt diet, engaging in physical activity, and measuring daily weight) in an African American population [17].

A sufficient number of studies have shown the efficacy of CBT as an effective treatment strategy for mild to moderate depression when it is augmented with other delivery modalities [18,19]. Few studies have used SMS text messaging to reduce depression and anxiety among racial and ethnic minority patients with HF [16,17]. To our knowledge, our pilot study will be one of the few to use a CBT-based intervention with SMS text messaging boosters to alleviate depression and anxiety symptoms among African American patients with HF.

Creating Opportunities for Personal Empowerment Intervention

The Creating Opportunities for Personal Empowerment (COPE) intervention consists of 7 brief, interactive CBT sessions that are evidence based, are readable at the sixth-grade level, and focus on empowering young adults to engage in healthy lifestyle behaviors, thereby improving mood and reducing depression and anxiety [11].

To our knowledge, we are the first to adapt the COPE intervention for use with SMS text messaging reminders to reinforce session content (Table 1). Our innovative study will result in a reproducible and scalable intervention for reducing depression and anxiety in ethnic minority patients with HF, thereby filling a needed gap in treatment for this population. We believe that this novel version of the COPE intervention, which is specifically designed for African American patients with HF (TXT COPE-HF [Texting With COPE for Patients With HF]), will have a synergistic impact on reducing the incidence of negative health care outcomes in this population.

Table 1. Examples of Creating Opportunities for Personal Empowerment sessions and proposed text message reinforcers to be sent (TXT COPE-HF [Texting With Creating Opportunities for Personal Empowerment for Patients With Heart Failure]).

Session	Content	Text message	Response examples
Session 1: Thinking, feeling, and behavior	Mindfulness activities	"What type of goal did you complete today?"	"Select & Send the # that matches your completed goal for today • 1=Exercising • 2=Journaling • 3=Healthy Eating • 4=Companionship • 5=Other (please list)"
Session 2: Self-esteem and positive self-talk	Positive messages	"Did you remember to remind yourself that you are important?"	"Type Y for Yes and N for No"
Session 3: Stress and coping	Responses to stress	"Which coping technique did you practice today?"	"Select & Send the # that matches your completed stress/coping technique for today • 10=Meditating • 11=Deep breaths • 12=Yoga • 14=Other (please list)"
Session 4: Goal setting	How to set goals	"Did you complete a goal or action step today?"	"Type Y for Yes and N for No"
Session 5: Effective communication	Guided imagery	"What positive self-control strategy did you use today?"	"Select & Send the # that matches the 1 completed self-control strategy for today • 15=Exercising • 16=Healthy Eating • 17=Companionship • 18=Praying/Meditating • 19=Other (please list)"
Session 6: Coping with stress	Coping skills	"What coping skill did you use today?"	"Select & Send the # that matches with 1 completed coping skill for today • 22=Listening to music • 23=Doing hobbies • 24=Having quiet time • 26=Reading • 29=Other (please list)"
Session 7: Last session	Reinforcement of skills	"Did you practice a positive coping skill today?"	"Type Y for Yes and N for No"

Specific Aims

The overall goal of our study is to improve health outcomes in African American patients with HF who experience mild depression and anxiety by adapting the existing COPE intervention for use with supplemental text messages. The specific aims for this pilot study are to (1) adapt and modify the COPE curriculum for delivery to patients with HF by using an SMS text messaging component to improve depression and anxiety symptoms, (2) administer the adapted intervention to 10 subjects to examine the feasibility and acceptability of the approach and modify it as needed, and (3) examine trends in depression and anxiety symptoms and conduct an exit focus group postintervention. We hypothesize that patients will show an improvement in depression scores and anxiety symptoms postintervention.

Theoretical and Conceptual Framework

Guided by cognitive behavioral theory, we plan to adapt the COPE curriculum for young adults for use with supplemental

SMS text messaging reminders to reach patients with HF and mild depression and anxiety (TXT COPE-HF). The COPE curriculum for young adults was adapted from other efficacious, cognitive-based, skill-building COPE programs directed at vulnerable populations (eg, racial and ethnic minority teens and pregnant women with depression) [11]. This intervention can be easily integrated into routine clinical care and support groups. On the basis of CBT, participants will be taught how to cognitively restructure their thinking when negative events and situations arise, as these tend to result in negative thoughts. Participants will learn how to restructure their thinking to create positive interpretations of negative events and situations, so that they feel better emotionally and behave in more healthy ways. Emphasis will be placed on how patterns of thinking impact behaviors and emotions (ie, the thinking, feeling, and behaving triangle). Goal setting for promoting healthy behaviors and problem-solving skills will be a part of the cognitive skill-building approach. We hypothesize that the TXT COPE-HF program will strengthen participants' beliefs about and confidence in their ability to engage in healthy lifestyle

behaviors and manage their negative emotions with text message booster reminders.

Methods

Research Design

This study will comprise a mixed methods approach. We will use the eight steps of the ADAPT-ITT (assessment, decision, administration, production, topical expert, integration, training, and testing) model to adapt the intervention (Table 2) [20]. The first step in this exploratory feasibility study will involve

assembling individuals to discuss questions on a specific topic. We will gather data from focus groups during 2 phases by creating an environment that encourages participants to discuss their beliefs, perceptions, and points of view on the COPE for young adults curriculum and its applicability to African American patients with HF [11]. In phase 2, we will examine the feasibility and acceptability of the SMS text messaging component along with its preliminary effects. The research team has experience in working with racial and ethnic minority populations, and one member has experience in adapting a curriculum for text message delivery.

Table 2. Applying the ADAPT-ITT[a] model to adapt the COPE[b] curriculum for use with SMS text messaging reminders.

Study phases and ADAPT-ITT model steps	Description
Phase 1	
Assessment	Conduct 2 focus groups with African American patients with heart failure (n=10)
Decision	Decision made to adapt the COPE curriculum for use with SMS text messaging reminders
Administration	Administer a theater test (trial) of text messages and analyze findings with 10 participants
Production	Produce draft 1 of the adapted TXT COPE-HF[c] program
Topical expert	Consult with a topical expert about the adaptations
Integration	Use feedback from the topical expert and create draft 2
Phase 2	
Training	Train research team on the study's outcomes and protocols
Testing	Pretest the TXT COPE-HF program with 10 participants, conduct an exit focus group and analyze the findings, make modifications based on feedback, examine trends in depression and anxiety scores, disseminate findings, and modify the program as needed

[a]ADAPT-ITT: assessment, decision, administration, production, topical expert, integration, training, and testing.

[b]COPE: Creating Opportunities for Personal Empowerment.

[c]TXT COPE-HF: Texting With Creating Opportunities for Personal Empowerment for Patients With Heart Failure.

Subjects

The sample sizes for phases 1 and 2 are based on our previous research on developing and pretesting text messages [21]. The participants in this study will be 30 African American patients with HF (20 patients in phase 1 and 10 patients in phase 2), and they will be recruited from a heart and vascular institute in North Carolina. For inclusion, phase 1 participants must be African American, be aged at least 21 years, understand what mobile phone SMS text messaging is, be diagnosed with HF, and speak and understand English. We will approach each African American patient who is treated at the heart institute about this study until we reach our desired sample size.

In phase 2, we will recruit African American patients with HF who meet the same inclusion criteria as those in phase 1 and have diagnoses of depression and anxiety. The participants in this group must have access to a mobile phone with SMS text messaging capabilities, so that they can access the TXT COPE-HF reminders.

An on-site staff member will answer questions from prospective participants, and the principal investigators' contact information will be available on the flyer. A previously used scripted protocol will be used to inform prospective participants about the study. If they choose to participate, we will obtain consent

on the first day of the study. The principal investigators will offer incentives for participation in the study, which we expect will help us attain and retain our sample. The compensation provided will be US $20 for the focus group participants (phase 1 and the exit focus group in phase 2) and US $20 for each completed TXT COPE-HF session in phase 2. The compensation amount is high because we aim to accommodate our population of patients with HF, who experience depression and anxiety and may tire easily.

Setting

Focus groups will be conducted at the proposed site for the study. Focus group meetings will be held at the heart and vascular institute, and parking will be accessible for study participants. The two principal investigators have experience in moderating focus groups. Focus groups will be held in a conference room at the heart and vascular institute (ie, while adhering to social distancing guidelines) or be conducted via Zoom (Zoom Video Communications Inc; patient's preference). The conference room offers access to computer equipment that the research team can use to display information from the COPE for young adults curriculum. The principal investigators will place audio recorders on a table in the middle of the room and use a flip chart to write down core ideas for adapting the COPE

curriculum for SMS text messaging–enhanced delivery and modifying it for African American patients with HF.

Instruments

The instruments and the reliability and validity values to be used in our pilot study are shown in Table 3.

Table 3. Instruments.

Study outcome	Instrument	Reliability values
Demographic characteristics (age, gender, income, level of education, and marital status)	Demographic survey	N/A[a]
Depression	Patient Health Questionnaire-9 (American Psychological Association, 2020 [22])	Cronbach α of .86-.89
Anxiety	State-Trait Anxiety Inventory (Spielbergere, 1989 [23])	Internal consistency coefficients of 0.86-0.95 and a test-retest reliability value of 0.65-0.75
Lifestyle beliefs	Healthy Lifestyle Beliefs Scale (Melynk et al 2014a [24], Melynk et al, 2014b [25])	Cronbach α of .91
Lifestyle behaviors	Health Lifestyle Behaviors Scale (Melynk et al, 2014b [25])	Cronbach α of .86
SMS text messaging	SMS text messaging plan	N/A

[a]N/A: not applicable.

Procedure

In phase 1 of our project, we will train a graduate assistant and research assistant with expertise in SMS text messaging and research methods on the details of the study. We will develop an interview guide with probes that are consistent with the literature and are based on CBT. We will adapt the curriculum based on the ADAPT-ITT model that was used in our previous research [20,21]. After we receive institutional review board approval, we will begin recruitment. We do not anticipate any difficulty in obtaining the sample for this project. At 1 month before the initiation of the focus groups, we will post a sign-in sheet at the heart and vascular institute. This sheet will be used to announce our study and will include our names and contact information. Potential participants will be instructed to contact us if they are interested in participating in the study. When we are contacted by 10 potential participants (ie, 10 for each focus group session), we will schedule a meeting and invite these potential participants by telephone to attend this meeting. Participants will be required to attend 1 focus group session, which will last 1 to 1.5 hours. As participants gather for each focus group, they will review and complete the approved consent form and demographic survey. Before the start of the formal session, we will conduct an interactive activity to allow participants to become acquainted with each other and with us. After the welcoming of participants and a discussion of the rules for interaction, the formal focus group process will begin. Data from the focus group sessions will be used to adapt the COPE curriculum for SMS text messaging–enhanced delivery to African American patients with HF. Dosage (number of texts), text message content, and whether messages are being read and understood will be determined based on the focus group's findings. In our previous study [16], we sent only 1 message per day, and participants were required to respond to the message with a 1-word response. We will use the TextMe app (TextMe Inc) to send the messages.

In phase 2, we will recruit patients with HF by using the same methods as those used to recruit the first group. We will administer the Patient Health Questionnaire-9 (PHQ-9), State-Trait Anxiety Inventory (STAI), demographic surveys, Healthy Lifestyle Behaviors Scale, and Healthy Lifestyle Beliefs Scale. We will invite 10 patients whose scores indicate mild depression (PHQ-9 scores: range 5-9) and anxiety (STAI scores: range 38-44) to participate in phase 2.

Phase 2 participants will receive daily SMS text messaging reminders (the number of reminders will be determined by the focus groups) after each session. After participants complete the seven sessions of the TXT COPE-HF curriculum, they will return for a follow-up exit focus group, during which we will readminister the surveys to examine trends in participants' depression and anxiety scores, perceptions of healthy lifestyle behaviors and beliefs, and perceptions about the SMS text messaging reminders. The incentive provided will be US $20 for each SMS text messaging–enhanced session (n=7) completed and US $20 for the exit focus group session that will occur after session 7 (a total of US $160 per participant).

Each focus group will be audiotaped. The principal investigators will provide the audio recording equipment that they own and have used in previous studies. The research assistant will monitor the equipment while the focus group sessions are in progress. The researchers will use a single moderator, 1 interview guide, and observation notes from each session to ensure reliability. The research assistant will transcribe the audiotapes verbatim, and the transcripts will be compared to the original audio recordings and corrected as needed to ensure data completeness and accuracy.

Data Analysis

The transcripts of the focus groups will be used as data for analysis. We will organize, store, and analyze the data by using NVivo qualitative analysis software (QSR International). The data analysis will begin with reading the transcribed interviews

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and listening to the audiotapes. The transcripts will be read multiple times by the research team to identify important phrases, paragraphs, sentences, and interactions. Analyses of the data will be conducted to categorize the responses according to a thematic topic guide (key components, group discussion responses, and delivery protocols). The principal investigators will read the data and compare their ideas to determine whether they have arrived at a consensus. Multiple meetings will be conducted until an agreement is met. Participants' responses will guide the discussion on how we can adapt the components of the COPE curriculum for SMS text messaging–enhanced delivery (TXT COPE-HF).

As this is a pilot feasibility study that will have a small sample size, we will only be able to examine trends in depression scores, anxiety scores, and healthy lifestyle belief and behavior scores rather than examine differences in outcome effects. One principal investigator will oversee the data entry, management, and analysis processes. She will analyze demographic,

feasibility, acceptability, and survey (PHQ-9, STAI, Healthy Lifestyle Beliefs Scale, Healthy Lifestyle Behaviors Scale, and the SMS text messaging evaluation plan) data by using descriptive statistics and 2-tailed t tests. The number of patients with HF who complete the SMS text messaging–enhanced intervention and their response rates in the session activities will be used as measures of feasibility. The number of participants who find the SMS text messaging–enhanced delivery method acceptable will be used as data for analyzing acceptability. Participants will be asked to comment on the overall text message delivery process by using a 4-point Likert scale ranging from 1 (strongly disagree) to 4 (strongly agree). We will enter quantitative data into SPSS version 28 (IBM Corporation) for analysis.

Time Frame

The project can be completed within 12 months. We anticipate no problems in recruiting at least 30 subjects for the proposed study (Table 4).

Table 4. Protocol timeline.

Month	Activities	Responsible person	Outcome
1-2	Phase 1: obtain institutional review board approval, recruit participants for focus groups, and obtain consent	RA[a], GA[b], PIs[c]	Focus group participants provide consent for phase 1
3-5	Conduct focus groups, transcribe and analyze data, and share data with consultant	PIs, RA, and GA	Feedback from topical expert on findings from the focus groups that can be used in the adapted curriculum
6-8	Adapt curriculum for SMS text messaging–enhanced delivery, conduct trial, consult with consultant, and recruit and obtain consent for phase 2	PIs, RA, and GA	Participants provide consent for phase 2 of the study
9-11	Phase 2: collect data, conduct exit focus group, analyze data, and prepare for the dissemination of findings	Topical expert (with whom the findings of phase 2 will be shared)	Feasibility and acceptability data for the project and the examination of data for identifying trends
12	Disseminate findings and write a final report for submission	PIs, RA, and GA (topical expert will be acknowledged or be a coauthor)	Manuscripts submitted to journals for publication and to research conferences for presentation

[a]RA: research assistant.

[b]GA: graduate assistant.

[c]PI: principal investigator.

Limitations

In this pilot feasibility study, we will have a sample of convenience, which may result in response bias. We are recruiting patients who own mobile phones or have access to one; hence, the findings may be different from those of patients who do not own a mobile phone. For future research, we may consider the inclusion of family members to assist patients who do not have access to a mobile phone or are not technologically adept. We also recognize that we are working with a population that may tire easily due to experiencing HF, depression, and anxiety. However, due to the enhanced SMS text messaging process, we hypothesize that patients will experience reduced depression and anxiety after the intervention, which may result in overall better patient outcomes.

Results

Institutional review board approval was delayed due to the COVID-19 pandemic but was obtained in April 2021. Recruitment will occur from August to November 2021, and data will be analyzed in spring 2022.

Discussion

In this paper, we describe a protocol for using text messages coupled with CBT to reduce depression and anxiety in African American patients with HF. This represents a first step in enhancing 2 intervention methods to improve the quality of life of an underrepresented group of patients with HF.

Acknowledgments

Conflicts of Interest

None declared.

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Abbreviations

ADAPT-ITT: assessment, decision, administration, production, topical expert, integration, training, and testing
CBT: cognitive behavioral therapy
COPE: Creating Opportunities for Personal Empowerment
HF: heart failure
PHQ-9: Patient Health Questionnaire-9
STAI: State-Trait Anxiety Inventory
TXT COPE-HF: Texting With Creating Opportunities for Personal Empowerment for Patients With Heart Failure

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Protocol

Coproducing Knowledge of the Implementation of Complex Digital Health Interventions for Adults with Acquired Brain Injury and their Communication Partners: Protocol for a Mixed Methods Study

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Abstract

Background: The Social Brain Toolkit, conceived and developed in partnership with stakeholders, is a novel suite of web-based communication interventions for people with brain injury and their communication partners. To support effective implementation, the developers of the Social Brain Toolkit have collaborated with people with brain injury, communication partners, clinicians, and individuals with digital health implementation experience to coproduce new implementation knowledge. In recognition of the equal value of experiential and academic knowledge, both types of knowledge are included in this study protocol, with input from stakeholder coauthors.

Objective: This study aims to collaborate with stakeholders to prioritize theoretically based implementation targets for the Social Brain Toolkit, understand the nature of these priorities, and develop targeted implementation strategies to address these priorities, in order to support the Social Brain Toolkit's implementation.

Methods: Theoretically underpinned by the Nonadoption, Abandonment, Scale-up, Spread, and Sustainability (NASSS) framework of digital health implementation, a maximum variation sample (N=35) of stakeholders coproduced knowledge of the implementation of the Social Brain Toolkit. People with brain injury (n=10), communication partners (n=11), and clinicians (n=5) participated in an initial web-based prioritization survey based on the NASSS framework. Survey completion was facilitated by plain English explanations and accessible captioned videos developed through 3 rounds of piloting. A speech-language pathologist also assisted stakeholders with brain injury to participate in the survey via video teleconference. Participants subsequently elaborated on their identified priorities via 7 web-based focus groups, in which researchers and stakeholders exchanged stakeholder perspectives and research evidence from a concurrent systematic review. Stakeholders were supported to engage in focus groups through the use of visual supports and plain English explanations. Additionally, individuals with experience in digital health implementation (n=9) responded to the prioritization survey questions via individual interview. The results will be deductively analyzed in relation to the NASSS framework in a coauthorship process with people with brain injury, communication partners, and clinicians.

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Results: Ethical approval was received from the University of Technology Sydney Health and Medical Research Ethics Committee (ETH20-5466) on December 15, 2020. Data were collected from April 13 to November 18, 2021. Data analysis is currently underway, with results expected for publication in mid-2022.

Conclusions: In this study, researchers supported individuals with living experience of acquired brain injury, of communicating with or clinically supporting someone post injury, and of digital health implementation, to directly access and leverage the latest implementation research evidence and theory. With this support, stakeholders were able to prioritize implementation research targets, develop targeted implementation solutions, and coauthor and publish new implementation findings. The results will be used to optimize the implementation of 3 real-world, evidence-based interventions and thus improve the outcomes of people with brain injury and their communication partners.

International Registered Report Identifier (IRRID): DERR1-10.2196/35080

Introduction

Terminology and Style

Coproduction of knowledge is a "process whereby professionals and those traditionally on the receiving end of their 'expertise' (eg, patients/service users/marginalized citizens) can collaborate with the goal of achieving outcomes that arguably cannot be achieved otherwise" [1]. This requires a shift in power [2,3] from the narrow profession of academia to the broader public, underpinned by an epistemological shift that values knowledge derived from experience as much as knowledge derived through research [1,3]. This "epistemic pluralism" is internationally espoused in the United Nations Educational, Scientific and Cultural Organization (UNESCO) Recommendation on Open Science [4] and underpins this study of the implementation of digital health interventions for adults with acquired brain injury (ABI) and their communication partners (eg, family and friends). To reflect this pluralism, this study protocol uses a nontraditional writing style in which the direct comments of coauthors with living experience of ABI, and of communicating with or clinically supporting someone with ABI, have been interleaved with traditional academic writing. This approach allows for the sharing of collective insights into research methods and conveys the equal importance of both experiential and academic knowledge.

Additionally, this protocol refers to the "living experience" of stakeholders, quoted in the present tense, as an equally valued commentary on the research methods. As author CR explains from their living experience of ABI:

> It is imperative to use vocabulary that empowers and increases the agency of a person whose life has been impacted by a brain injury, identifying with the tense in which they are experiencing their journey. One's language carries great weight, and with that, a responsibility to not wound, constrict or hold someone hostage to a traditionally perceived narrative of recovery. As such, using "living experience" can reflect the wisdom and expertise an individual possesses, and continues to build, as they move along their life journey.

Background

ABI, such as stroke or traumatic brain injury (TBI), commonly causes cognitive communication disorders, in which impairments in underlying cognitive skills lead to difficulties with communication [5]. These communication disorders can introduce challenges for a person's social participation and relationships [6], employment [7,8], and mental health [9], while the ABI remains a "hidden" or "invisible" disability [10]. Author BM describes from their living experience:

> If my TBI were to be a characterized in a word, it would be "isolation." People with brain injury often appear superficially "fine" with no head wounds or disfigurement, whereas in reality I lost the majority of my personality and capacity to relate to people for over half a decade.

Communities and close others of people with ABI also experience psychosocial, health, and economic burdens as a result of ABI [11-13]. The communication styles and skills of these close others can positively or negatively affect the communication skills of people with ABI [14-16]. Author BT observes from their living experience as a communication partner of someone with ABI:

> I found myself out of my depth and without the tools needed to be able to help my friend and communicate with him in such a way that would not add to his mental health issues relating to his new life with an ABI. I had to train myself to not say things to him that would emphasize that an error had been made due to his ABI. The medical, mental health and rehabilitation care is rightly all focused on the patient. However, when that person is moving towards coming home again, the carers that will be living on a day-to-day basis with the person with an ABI are not given the same level of support. A lot of the time during the months my friend was in hospital and rehabilitation could have been spent educating me on how I could best serve my friend, and a number of the mistakes I have made could have been avoided.

Therefore, communication partner training (CPT) to assist individuals interacting with people with ABI is considered best

practice in the management of communication disorders following ABI [17-19].

The current and future need for CPT exceeds global health care capacity to provide communication rehabilitation through qualified speech-language pathologists [20,21]. More than 135 million people worldwide currently live with an ABI [20], and this number is projected to grow continually [20,22]. To address this challenge of scale and equity in health care access, a novel suite of digital health interventions known as the "Social Brain Toolkit" [23] has been designed to enable adults with ABI, their close others and communities to access web-based communication training. The Social Brain Toolkit is being developed in Australia and will be available internationally.

The Social Brain Toolkit contains 3 interventions which leverage digital health functionalities and encompass established principles of CPT. First, "convers-ABI-lity" offers a web-based conversation skills training program for adults with ABI and their familiar communication partners (eg, family, partners, and friends). convers-ABI-lity converts the existing efficacious CPT programs of TBI Express [24] and TBIconneCT [25,26] into a bespoke all-in-one platform of self-directed web-based training and telehealth sessions with a speech-language pathologist. Second, "interact-ABI-lity" offers self-directed web-based CPT for individuals interacting with people with ABI, including paid support workers and the public. Finally, "social-ABI-lity" provides self-directed web-based social media training for people with ABI, to increase social connections for individuals who may have limited opportunity for interactions with communication partners. It aims to enhance social participation, social communication skills, and a sense of self or identity postinjury [27].

Digital health interventions such as the Social Brain Toolkit face many implementation challenges, including technological adaptability and complexity [28], cost [28,29], workflow impact [30], and long-term sustainability [29,31]. Addressing these complexities requires dialogue with potential end users early in the process of intervention design [32,33]. In addition, there is an ethical imperative for stakeholder involvement in the conduct of health care research [34,35]. The inclusion of "societal actors" in the research process has been enshrined internationally in the UNESCO Recommendation on Open Science [4] and the national Statement for Community and Consumer Involvement in Health Care Research in Australia [36]. The coproduction of research may facilitate research translation [36] and reduce research waste by ensuring that the research undertaken generates meaningful results for end users [37,38]. However, research systems and processes may be ill-equipped to support such collaboration [1,3,39]. Coproducing knowledge within these structures can be an extremely resource-intensive and politically and ethically fraught task [3,40], even without the additional complexity introduced by cognitive or communication impairments, such as those associated with ABI. Therefore, sharing of methodological knowledge and guidance on how to undertake this endeavor most effectively [37,38] is important to support future coproduction of research with people with ABI, their communication partners, and clinicians.

Aims

In this study, researchers, together with people with ABI, their communication partners, and clinicians, as well as individuals with living experience of digital health implementation, aim to coproduce an understanding of the implementation of the Social Brain Toolkit, to enable these interventions to reach their intended users and meet stakeholder needs in a feasible, scalable, sustainable, and acceptable manner. Specifically, this study has the following aims: (1) to obtain stakeholder prioritization of theoretically based implementation targets for the Social Brain Toolkit, (2) to understand stakeholder perspectives of these priorities, and (3) to collaborate with stakeholders to identify implementation strategies targeting these priorities.

Methods

Ethics

This research was ethically approved by the University of Technology Sydney (UTS) Health and Medical Research Ethics Committee (ETH20-5466) on December 15, 2020. Recruitment flyers included an invitation to email the researcher to express interest in the project. Communication partners, clinicians and industry or research experts were emailed a link to complete electronic participant information and consent forms. Participants with ABI were invited to provide informed written consent using accessible, plain English participant information and consent forms that were adapted to incorporate visual supports and explained via video call by a qualified speech-language pathologist using supported communication strategies [41]. Screening for the capacity to consent is described in the inclusion criteria (the screening protocol is also included as Multimedia Appendix 1) [42]. Participant demographic information is reported as an aggregate to preserve participant anonymity.

People with ABI and communication partners were reimbursed for their participation at the annual hourly rate recommended by Health Consumers New South Wales (NSW) [43]. To support the implementation of the Social Brain Toolkit, its developers sought to learn from the expert living experience of people with ABI, their communication partners and clinicians, as well as those who have implemented digital health interventions. From this paradigm, the individual experiential knowledge of these health care stakeholders is seen as valuable for the implementation of digital health interventions and can be valued by respecting, seeking, recording, and sharing it in academic publications, acknowledging this contribution publicly and personally, and financially reimbursing those who otherwise may not receive payment for this knowledge [38]. This reimbursement also aimed to minimize any undue burden of research participation. Potential participants were advised of this arrangement in the participant information form to facilitate decision-making around any potential economic burden of participation. This financial reimbursement was optional, and in some cases declined, with reasons including altruism and potential ineligibility for benefit schemes if any payment was received. The researchers respected these wishes. Of interest, there were procedural barriers to providing participants with direct payment via the university payroll, which would have

granted institutional affiliation as equals. These barriers included a lack of precedence, university requirements for participants to complete several modules of mandatory web-based induction training as staff, and taxation requirements. Therefore, researchers were requested to provide payment via electronic gift cards and could only maximize participant autonomy with their payments by providing a choice of retailer for the gift card. This may be seen as another example of a systemic structure within academia that is not readily suited to research coproduction. Author CR reflects from their living experience of both ABI and research participation that:

> Providing an option for an expert to choose between cash or voucher not only creates more equality; it also increases their individual agency, self-confidence and self-worth via their perceived value from the researchers, and most importantly pushes back against the narrative of being a consumer, and reduces their sense of being a burden but instead someone bringing significant value.

Finally, all participants received a certificate of appreciation for their participation, and for some participants, this was anecdotally expressed as the most meaningful acknowledgment.

As part of the ethical considerations of the study, participants were advised of the risks of emotional distress during participation and had opportunities to take breaks or seek support from the researchers or other psychological services. Emotional support was required by one participant, requiring vigilance and counseling skills within the small group format, which was aided by the clinical background of the facilitators. Author BM highlights that a focus group may be a participant's first encounter with another person with ABI. Individuals with living experience may therefore feel a range of emotions associated with their participation. For example, BM recalls it was "sad to see the variety of different stories of so many different people" who had this "shared devastation." However, BM believes this was also inversely "decentralizing" in a positive way, as such a group "provokes a feeling of unity" that we were "all here for the same thing."

Design

The coproduction of implementation knowledge in this study is part of a broader effort to involve stakeholders throughout the development of the Social Brain Toolkit (Figure 1). The development of the Social Brain Toolkit is led by author LT, a speech-language pathologist, clinical researcher, and Director of the Acquired Brain Injury Communication Lab [23] in Sydney, Australia, together with research team members, speech-language pathologists and authors EP, RR, MB, and MM, in collaboration with the technology vendor Changineers [44]. The project was jointly conceived and reviewed by stakeholders including people with ABI and their communication partners, community partners such as Brain Injury Australia, and funding partner icare NSW. This was a requirement for funding at project inception, and subsequent funding for this study and related studies [45]. These stakeholders have continued to participate in advisory and steering committees for the project, provided feedback on early prototypes, and will provide ongoing formative feedback on the interventions and their implementation [45]. Clinicians delivering convers-ABI-lity were included as associate investigators in the project. People with living experience of ABI, of being a communication partner, or of clinically supporting someone with ABI, are coauthors of this study protocol and will be included in the coauthorship of its results.

Theoretically underpinned by the Nonadoption, Abandonment, Scale-up, Spread, and Sustainability (NASSS) theoretical framework for digital health implementation [46,47] in both analysis and data collection protocols, this mixed methods study gives voice to the priorities and perspectives of 2 distinct cohorts: (1) a purposive, maximum variation sample of people with ABI, communication partners, and clinicians; and (2) a purposive sample of individuals with experience implementing digital health interventions for any health condition. The use of a complexity-based theoretical framework such as the NASSS [46] enabled the consideration and integration of the needs of multiple stakeholders, including clinician end users who will implement the intervention in complex, adaptive health care systems. People with ABI, communication partners, and clinicians participated in (1) an initial prioritization survey and (2) subsequent focus groups exploring these priorities. Individuals with experience in digital health implementation responded to the prioritization survey via individual interviews. Interview methods were used due to both limited participant availability and a need to balance homogeneity and heterogeneity in the focus groups, particularly in relation to power and differences and similarity of experience [48], as participants with experience implementing digital health were not required to have clinical or research experience in ABI specifically. The results of this group were analyzed separately to understand and compare these perspectives with those of potential end users.

Figure 1. Stakeholder involvement during the development of the Social Brain Toolkit.
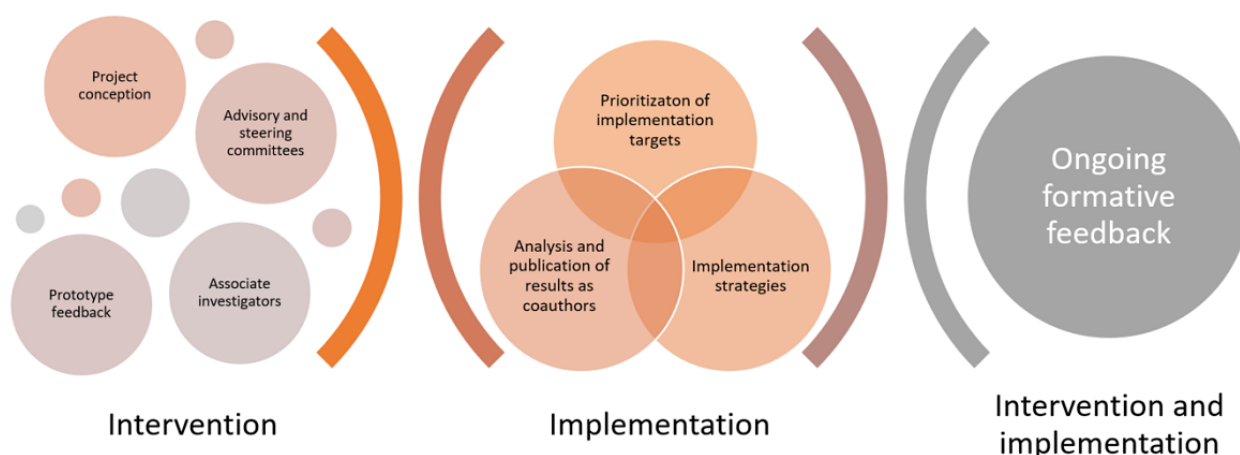
Participants

Inclusion and Exclusion Criteria

All participants had to (1) be older than 18 years and (2) have adequate English proficiency to participate in the study without the aid of an interpreter.

Participants with ABI were self-identified and could participate if they met the following criteria:

1. Had adequate capacity to consent to participate in the study. The capacity to consent was ascertained during a video call with a qualified speech-language pathologist according to our adapted consenting process protocol (Multimedia Appendix 1) [42], which includes relevant questions adapted from the University of California Brief Assessment of Capacity to Consent [42]. People with ABI unable to respond adequately to all 5 questions presented using supported communication strategies would be excluded from the study.
2. Were discharged from hospital.
3. Were ≥6 months post injury.
4. Were based in Australia.

The exclusion criterion for participants with ABI was a self-reported mild ABI or concussion in which minimal or no observable or self-reported changes in social communication function were present.

Communication partners of a person with ABI were self-identified individuals who (1) interacted at least once a week with a person with ABI, (2) had not sustained an ABI themselves, and (3) were based in Australia.

Recruitment of participants with ABI and communication partners was focused on participants based in Australia to reflect the Australian development context of the Social Brain Toolkit and because the available forms of reimbursement were only usable within Australia.

Clinicians were self-identified (1) as qualified and currently practicing allied health professionals (2) with a caseload of which at least 20% included people with ABI.

Research or industry experts in digital health implementation were required to have (1) a published, peer-reviewed academic track record in English concerning digital health implementation or delivery for any health condition or (2) a leadership position in digital health delivery in industry or the health care system, or (3) both.

There were no restrictions on any other factors (eg, gender or level of clinical experience), and maximum variation in these factors was preferred where possible.

Sampling

To obtain a purposive, maximum variation sample of people with ABI, communication partners, clinicians, and individuals with experience in digital health implementation, we distributed recruitment flyers tailored to each group via relevant organizational and researcher social media channels, organizational websites, and email distribution lists. Individuals with experience in digital health implementation were emailed directly through publicly listed contact information, such as web-based university researcher profiles or researcher networks.

The final sample (N=35) included people with living experience of ABI, of being a communication partner of people with ABI, of clinically supporting people with ABI, of implementing digital health, or a combination of these experiences (Table 1). Proportionally, the perspectives of people with ABI and their communication partners were prioritized by recruiting twice the number of health care stakeholders compared with clinicians, and by obtaining industry and research perspectives separately.

The authors of this study protocol include participants with living experience of ABI, of being a communication partner of a person with ABI, or of providing clinical care for people with ABI. Participants with ABI, communication partners and clinicians will also have the opportunity to participate as coauthors in the analysis, interpretation and write-up of the study findings.

Table 1. Participant demographic information reported as an aggregate to preserve participant anonymity (N=35).

	Adults with experience of ABI[a] (n=10)	Communication partners (n=11)	Clinicians (n=5)	Individuals with experience of digital health implementation (n=9)
Living experience	• 9 with living experience of ABI • 1 with living experience of both ABI and clinically supporting people with ABI	• 11 with living experience of being a communication partner of someone with ABI	• 5 with clinical experience supporting people with ABI as speech-language pathologists	• 8 with living experience implementing digital health interventions for any condition • 1 with living experience of both ABI and digital health implementation
Sex	• 7 male • 3 female	• 4 male • 7 female	• 1 male • 4 female	• 6 male • 3 female
Location	• Australia (as per inclusion criteria)	• Australia (as per inclusion criteria)	• 1 from the United Kingdom • 1 from the Netherlands • 3 from Australia	• 1 from Denmark • 9 from Australia
Education	• 1 with a graduate diploma or certificate • 4 with a bachelor's degree • 4 with a certificate or diploma • 1 with a high school certificate	• 1 with a PhD • 1 with a master's degree • 2 with a graduate diploma or certificate • 3 with a bachelor's degree • 3 with a certificate or diploma • 1 with a high school certificate	• 2 with a master's degree • 2 with a graduate diploma or certificate • 2 with a bachelor's degree	• 9 with a PhD
Age (years)	• 2 aged 25-34 • 4 aged 35-44 • 2 aged 45-54 • 1 aged 55-64 • 1 aged >65	• 1 aged 25-34 • 2 aged 35-44 • 2 aged 45-54 • 1 aged 55-64 • 5 aged >65	• 1 aged 18-24 • 2 aged 25-34 • 1 aged 35-44 • 1 aged 45-54	• N/A[b]
Time postinjury	• 9 participants >12 months • 1 participant <12 months	• N/A	• N/A	• N/A
Clinical experience	• N/A	• N/A	• 3 working for >10 years with 80%-100% caseload with ABI • 1 working for <5 years with 80%-100% caseload with ABI • 1 working for <5 years with 20% caseload with ABI	• N/A
Relationship to person with ABI	• N/A	• 3 friends • 3 partners • 5 family members	• N/A	• N/A

[a]ABI: acquired brain injury.

[b]N/A: not applicable.

Data Collection

Overview

People with ABI, communication partners, and clinicians each participated in (1) an initial prioritization survey and (2) subsequent focus groups discussing priorities identified in the initial surveys. Individuals with experience in digital health implementation participated in individual interviews that addressed the same initial prioritization questions. The following section reports data collection procedures, rationales, and reflections on these procedures from participant coauthors AS, MRW, LW, MW, and BM.

Surveys

Surveys included basic demographic questions, a Likert scale, an open-ended qualitative question for each domain of the NASSS framework, and an overall prioritization ranking of all domains (Multimedia Appendix 2). The inclusion of Likert scales and free-text responses was intended to capture the strength and nature of feeling participants may or may not have about each of the ranked items, enabling the complexity of the rankings to be understood, and if required, reflected in the time allocation of focus groups.

To enable stakeholders to access existing academic knowledge of digital health implementation [49], the survey was theoretically underpinned by the NASSS framework of digital health implementation [46] and underwent multiple rounds of piloting before administration:

1. An initial version of the survey was developed from a NASSS-based interview schedule [50], as applied to the Social Brain Toolkit [45]. This first version was piloted via a live audience poll during an in-person oral presentation of each NASSS domain to a range of funding and health care stakeholders.
2. On the basis of this pilot, a second version of the survey was developed, incorporating asynchronous video explanations of each domain, including large captions, slowed speech rate, and plain English. This version was piloted with 4 members of the research team (EP, RR, DD, and LT).
3. The video script and phrasing of the survey questions were further refined into a third version piloted with a speech-language pathologist with clinical experience in ABI, an informal carer from a culturally and linguistically diverse (CALD) background, and a usability engineer.
4. Their input was incorporated into the fourth and final version delivered to participants, in which videos and questions were made more concise, and survey usability was refined.

The final survey questions, including video transcripts, are included in Multimedia Appendix 2. Supporting videos explaining each question are available in Multimedia Appendices 3-9. Author MRW, who has living experience of ABI, notes "the video clips that were provided meant we were able to watch it repeatedly to get our ideas out." Clinician coauthor MW notes that the adaptations made to ensure the accessibility of surveys and videos reflects "the critical nature of these supports in enabling participants with unique needs secondary to ABI to be involved in this research." For participants with ABI, this survey was administered by a speech-language pathologist (MM) via video teleconference, using supported communication techniques [41].

Focus Groups

In the focus groups, stakeholders examined the top 4 stakeholder priorities from the NASSS framework [46,47], obtained via the prioritization survey ranking (Multimedia Appendix 2). The domains 1-4 received the highest scores from stakeholders. Therefore, domains 5-7 were excluded from further investigation, as they received the lowest scores.

A deductive analysis [51] of the qualitative survey data revealed a significant overlap between participants' discussion of domains 1 and 2 of the NASSS framework [46]. Therefore, focus group discussions for these 2 domains were combined, followed by a discussion targeting domain 4, and a discussion focused on domain 3 (see Multimedia Appendix 10 for a detailed time allocation).

On the basis of stakeholder priorities, the following plain English questions were posed to participants:

1. Domain 1: Who can use the Social Brain Toolkit (1) straightaway, (2) with support, or (3) would be unable to use it? How can we help and what supports can we provide?
2. Domain 2: Which device (ie, smartphone, tablet, desktop computer) would you prefer to use and why? How can we help/what supports can we provide to use the technology?
3. Domain 3: What is the value or benefit of the Social Brain Toolkit? Who should pay for the Tools? Who would you trust to tell you about the Tools (look online, a therapist or service, people with brain injury, research, organizations)?
4. Domain 4: How can we help the Social Brain Toolkit fit into your routine (ie, (1) doing a course by yourself, (2) doing homework, and (3) online video calls and appointments)?

Stakeholders with ABI, communication partners, and clinicians explored these prioritized questions during the focus groups. To coproduce knowledge of each of the above priority domains, author MM synthesized and presented the stakeholders with (1) relevant preliminary research findings from a concurrent systematic review underpinned by the NASSS framework [52] and (2) relevant qualitative data from the prioritization survey, based on deductive content analysis [51] using the NASSS framework [46] (Multimedia Appendix 10). All information was presented using visual supports and scaffolds via Microsoft PowerPoint (Microsoft Corporation) in plain English using supported communication techniques [41]. Author BM notes from living experience that the "acknowledgement and unhurried language" of these communication techniques allows "for more candid, useful answers." Author MRW also reflects "the slide meant you were able to understand what the study was all about."

The focus group method was selected as it allows participants to share and compare their experiences [48]. This rationale was corroborated by the experience of author AS, who reflects that:

> Participating as a member of a [focus] group (1) stimulated my thinking, (2) encouraged me to make a contribution to the discussion, (3) helped me evaluate my ideas by listening to other group members' responses to my suggestions, (4) provided me with immediate feedback and (5) helped build up my confidence.

For author AS, the benefits of participating in a focus group were that it "enabled me to appreciate some of challenges faced by others" and "to think more deeply about those challenges." Similarly, author MRW believes the "chance to listen to others' experiences and thoughts" was beneficial. Author LW, who has clinical experience supporting people with ABI and their

families, similarly reflects on the benefits of sharing in a focus group and hearing others' perspectives, while also feeling that it was important to "stay in the background so that those with living experience could do the core part of the talking and contributing given their expertise." This reflects the varied impact of difference or similarity of experience in focus groups [48] and may require proactive management by facilitators.

As focus groups require rapport among participants [48], time was allocated for personal introductions (Multimedia Appendix 10). For the groups that also met for collective discussions, author BM reflects that a full introduction of every participant could have contextualized each person's contribution in plenary discussions. Author AS reflects on the importance of this for disclosure in focus groups [48]:

> *This was the first time I had met the other participants. This lack of familiarity with fellow participants could have inhibited my contribution because I wasn't confident the others would interpret my contribution in the spirit it was intended.*

Author AS believes that a potential opportunity to informally meet other participants beforehand may have facilitated discussion in the focus group itself.

It is important to note that introductions were and are not straightforward for participants with ABI. Author BM highlights from their living experience that talking about an ABI can be very personal and difficult:

> *Depending on the personality and stage of recovery, I'd liken talking to a clinician about your TBI to something like...delineating to a stranger how you lost your virginity!*

This reflects the power imbalance that may affect disclosure [48] between a clinician and an individual with ABI. Therefore, BM advises the following:

> *To generate clearer, more candid answers from people with TBI, the researchers or clinicians are best served acknowledging the delicacy of the situation and reiterating how intense the gravity of a TBI is/was.*

Researchers also sought to convey this respect by advising participants that they were able to disclose as much or as little information as they felt comfortable, and researchers did not probe for details that were not volunteered.

Each focus group was 3 hours in duration. Author MRW notes that this required participants "setting time aside to do it, but it's like that with everything." Each hour included a break to mitigate fatigue. Author BM notes from their living experience, "It's usually an appreciated acknowledgement that working memory and attention spans are scarce with a TBI." Each hour of the focus groups included (1) a synthesis of survey and systematic review data for 1-2 domains and (2) small group discussions (see Multimedia Appendix 10 for a detailed time allocation). In author MRW's experience, "giving us something to concentrate on over a period of time meant we were able to think about it a lot more and get it sorted out in our own heads."

Focus groups were arranged based on participant availability to bring together as many participants as possible at a common time to share ideas. Participants received reminders, instructions, and an outline of the focus groups before participation. Author BM reflects that "follow up phone calls, gentle reminders" and "consistency and thoughtful language" were all "very much appreciated." There were a total of 7 focus groups (n=26) containing 3 to 6 stakeholders, each facilitated by 1 to 2 members of the research team. Author BM notes that "breaking the groups up to ensure there weren't too many contributions and noise at the one time" was helpful for participants with ABI, and author AS highlights the benefit of "having a group facilitator to assist." As data were collected and recorded using web-based video call software, researchers trained participants in how to use the software's mute and camera options. As video call "hosts," the researchers also familiarized themselves with the mute and camera functions to preserve participant privacy during scheduled breaks in the calls if needed.

Participant input from the first focus group (n=3) was incorporated into the information presented to a larger, subsequent session of 4 focus groups (n=17), where each focus group's insights were also recounted in plenary discussions in between the small group sessions (Multimedia Appendix 10). These findings were, in turn, shared for discussion with the 2 final groups (n=3 and n=3, respectively). This enabled sharing of insights among focus groups, in addition to the dialogue within each group, and the wider dialogue between researchers and stakeholders.

Data collection occurred entirely on the web via secure videoconferencing on Microsoft Teams (Microsoft Corporation). Participants with ABI had each used the software before during their initial screening, and all participants were provided with visually supported initial instructions on how to use the functions of the video call software. All participants were advised that they could log onto the call early to troubleshoot technology if needed. All participants were connected for the full duration of the focus groups without technical difficulty, with the exception of 1 participant whose participation was scheduled over 2 sessions owing to low battery. The focus groups were audio and video recorded using the built-in recording functions of the videoconferencing platform.

Interviews

Interviews with individuals with research or industry experience of digital health implementation used the same prioritization questions as the surveys (Multimedia Appendix 2) to enable discussion of multiple issues within a limited timeframe. Interviews were conducted individually and ranged from 1 to 2.5 hours in duration based on participant availability. Data collection was also iterative, with insights from prior focus groups and interviews included as conversation prompts in subsequent interviews. Data collection occurred entirely on the web, with interviews conducted via secure videoconferencing on Microsoft Teams and audio and video recorded using the built-in recording functions.

Analysis

Quantitative

Prioritization rankings, Likert scales, and demographic information from initial surveys were analyzed descriptively using Qualtrics (Qualtrics International) survey software.

Qualitative

Free-text survey responses were deductively analyzed [51] based on the NASSS framework [46] to enable qualitative data specific to stakeholder priorities to be extracted and shared in subsequent focus groups. All focus groups and interviews will be transcribed verbatim. To synthesize qualitative data and test the domains of the framework, author MM will deductively code interview data [51] against the NASSS framework [46] and lead an identical analysis of focus group data using a web-based codebook that will include the accessible videos, defining each domain to be coded (Multimedia Appendices 3-9). Deductive coding will be managed using Microsoft Excel 365 (Microsoft Corporation).

Rigor

This protocol details stakeholder prioritization according to the REPRISE (Reporting Guideline for Priority Setting of Health Research) guidelines for reporting research priority setting [38]. All interview and focus group participants were given an opportunity to add to their original contributions verbally or in writing for inclusion as original data. All focus group transcripts will be verified against the original audio or video recordings by at least one person originally present in that focus group. All interview and focus group participants will be given an opportunity to member-check preliminary interpretations of their input. A second author will verify a random 25% of the total codes from focus groups and interviews using the aforementioned codebook. For focus group data, this verification will be conducted by a coauthor who was present in that focus group as either a researcher or participant. Any discrepancies will be resolved via consensus discussion.

Evaluation

Stakeholder priorities and implementation strategies are directly informing the implementation of the Social Brain Toolkit. The outcomes of the implementation strategies will be investigated in a hybrid type 2 implementation–effectiveness study [53] of all 3 interventions in the Social Brain Toolkit [45].

Publication

Stakeholders with living experience contributed to, critically reviewed, and are therefore listed as coauthors in the publication of this study protocol. They are also coauthors in the analysis, interpretation, and publication of the study results. MM conceptualized and formalized this coauthorship process in the grant proposals for this study. MM is facilitating this collaboration by email, telephone, video call, and Microsoft Word (Microsoft Corporation), according to each author's communication preferences and accessibility requirements. In keeping with the UNESCO Recommendation on Open Science [4], researchers have obtained funding to enable both this study protocol and the forthcoming results of the contributions of participants to be available open access. Authors AS and MM highlight that journal requirements to include academic qualifications for the stakeholders coauthoring this protocol are artifacts of a system that prizes academic knowledge, which, although reported for transparency, may arguably be seen as less relevant than or even contradicting the value of living experience.

Results

Australian National Health and Medical Research Council Postgraduate Scholarship funding was granted in November 2019. UTS Center for Carer's research funding was granted in September 2020. icare NSW funding was received in November 2019. Ethical approval was received from the UTS Health and Medical Research Ethics Committee (ETH20-5466) on December 15, 2020.

Data were collected from April 13 to November 18, 2021. Data analysis is currently ongoing, with results expected for publication in mid-2022.

Discussion

Coproducing Implementation Knowledge

This implementation study combined (1) the experiential knowledge of people living with ABI, communicating with or clinically supporting people with ABI, and implementing digital health; with (2) academic knowledge in the form of current digital health implementation evidence and theory to (3) coproduce new implementation knowledge for 3 real-world interventions. As people with ABI, their communication partners, and clinicians are direct stakeholders in the development and implementation of digital health interventions targeting communication changes after ABI, there is an ethical imperative for their inclusion in intervention design, development, and delivery [35]. In the field of implementation science in particular, it is arguable that their input is essential for successful real-world implementation as early as intervention development [32] and while empirical data are still developing.

At the heart of this coproduction is a proactive exchange of power [2,3]. In the Social Brain Toolkit project as a whole, stakeholder involvement to date has included project conception, advisory input, feedback on prototypes, and the coproduction of implementation knowledge (Figure 1). In practice, this has required stakeholder input from multiple groups and individuals to varying degrees and at various times over the course of a multiyear program of research, commensurate with each stakeholder's autonomy and availability. For instance, within the present implementation study, some stakeholders did not accept the offer for coauthorship, instead preferring to participate in surveys and focus groups as a one-off contribution, whereas others are investing ongoing time and effort to coauthor this study protocol and its eventual results. The power to decide one's involvement in research can only begin when an opportunity is provided. Therefore, stakeholders can and should be given opportunities for involvement and contribution in research, which in some cases are opportunities that only researchers have the power to create or provide. For example, coauthorship of this study protocol required proactive invitation,

inclusion, and facilitation by researchers, thus giving power to stakeholders to decide whether they may or may not want to be involved in this way.

When researchers seek to redress the imbalance of power in research, it can *empower* stakeholders. As author AS reflects, his involvement "provided me with the opportunity to make a contribution to a worthwhile project, and improve my self-esteem." Author MRW reflects that:

> *Talking about my personal experience to someone who showed interest in my experiences - when some people might listen but won't take it on board - that encourages you to talk about your own experiences.*

Author MRW also reflects that "the encouragement that we got from [the researchers] and even other people with ABI and their communication partners was extremely encouraging." Author BM says:

> *Getting a voice and having your contributions valued by people in impactful positions is liberating. Researchers trying to understand the details of the TBI journey is emboldening.*

This protocol outlines the resource-intensive and politically and ethically challenging task of research coproduction [3,40] and how the consideration of cognitive or communication impairments, such as those associated with ABI, increased the complexity of the task. In this study, the facilitation of stakeholder involvement required proactive, premeditated support, including the investment of significant and ongoing time and effort to (1) guide stakeholders through the research process; (2) scaffold requests for input visually, verbally and in writing, according to individual communication preferences and accessibility requirements; (3) pilot and prepare resources in accessible, plain English with visual supports and supported communication techniques; and (4) secure grant funding in advance to reimburse participants for their expertise. The provision of these supports was necessary to affirm stakeholders' value and potential for input at each stage of an otherwise unfamiliar research process. Although MM, EP, RR, MB, and LT's backgrounds as speech-language pathologists and MM's background training in accessibility aided the development of accessible supports for participants, the aforementioned interest, encouragement, support, and respect that was appreciated by stakeholders are arguably universal hallmarks of effective and respectful communication and collaboration, achievable by, and expected of [36], all researchers. Likewise, the additional time, effort, and funding invested are not unique to the speech-language pathology profession. This time-cost may be counterbalanced by the way that stakeholder prioritization enables the reduction of research waste [37], in this case by enabling a focus on implementation domains that were of most importance to potential end users.

In this study, there were numerous time points and methods by which stakeholders contributed to the implementation of the Social Brain Toolkit. In addition to prioritizing implementation research targets, stakeholders were involved in the development of targeted implementation strategies to address these priorities. A subgroup is currently involved in the interpretation of these findings for publication as coauthors. Additional opportunities

for dialogue among stakeholders, and between stakeholders and researchers, were created by using collectively surveyed stakeholder priorities to inform focus groups, and cumulatively sharing each focus group's data in subsequent focus groups and interviews. This collaborative dynamic was important to foster not only for successful focus groups [48] but moreover because the purpose of the research was to coproduce implementation knowledge. Researcher MM reflects that although common goals were initially outlined in individual surveys and interviews, this could also have been reiterated in subsequent focus groups. Although plenary discussions naturally led to discussions regarding the collaborative purpose of the focus groups, author BM recommends that researchers proactively facilitate a collaborative dynamic by (1) prefacing focus group discussion with a concise and jargon-free explanation of "this is what we're doing, this is what your role is, and this why we're doing it," and (2) reminding participants "that the academic research goals are strictly aligned with the needs of TBI sufferers and their families, in that the research and collaboration is to build pathways that reduce problems and pain for TBI sufferers."

This collaboration toward a common goal is at the core of research coproduction. However, in author MM's experience, the time-limited nature of academic systems directly hinders research coproduction at every stage of research [1,3,39], as it inherently conflicts with the space and time required for the intensive and relational nature of effective collaboration. Yet stakeholder suggestions for the opportunity to build familiarity with other participants, and the need for researchers and clinical end users to discuss common goals clearly attest to this relational need.

Strengths and Limitations

This study demonstrates potential methods of engaging stakeholders throughout the implementation research process, from prioritization to authorship. In particular, we share how to retain theoretical rigor in implementation science while capturing the highly nuanced and complex reality of implementation from multiple stakeholder perspectives. However, there are several limitations to this study in relation to stakeholder representation. First, there was a minority representation of stakeholders outside Australia. Although the inclusion of English-speaking users in Australia reflects the initial development context of the Social Brain Toolkit, future studies may seek to explore international and CALD perspectives. In addition, although this study included similar numbers of communication partners as people with ABI, author MM observed that communication partners were most reticent to participate, and therefore underrepresented, in the publication stages of research. A particularly proactive effort was and may be required to give voice to this population specifically. Finally, although we sought to recruit clinicians, managers, and policy makers, clinical participation was solely comprised of speech-language pathologists. Although they are conceivably the most likely clinician to recommend, deliver, or support the implementation of the Social Brain Toolkit, the perspective of other clinical professions, as well as health care managers and policy makers, could have contributed to a more multifaceted understanding of implementation from a clinical perspective.

Conclusions

By making implementation theory directly accessible to multiple stakeholders and proactively facilitating a dialogue between stakeholder experience and implementation theory, we were able to coproduce new implementation knowledge to support the implementation of 3 real-world interventions, including targeted implementation strategies [45]. Author MW observes the following from a clinician perspective:

> *This paper, by its very nature, encourages reflection on the inaccessibility of research (both research processes and outcomes) to non-researchers and [this] work - towards breaking these barriers - is unlike anything I have seen before.*

To our knowledge, this is the first published coauthorship of implementation research with people with living experience of ABI, of being a communication partner of someone with ABI, and of clinically supporting adults with ABI. As a person with living experience of ABI, author CR believes:

> *Embedding of the experiential wisdom of people with living experience builds a more robust evidence base and foundations of trust which are required to occupy a shared space for innovation.*

Author CR concludes as follows:

> *[In this study, the researchers'] line of inquiry, pursuit of transparent feedback and desire for ongoing engagement in a relational, rather than transactional way, built a foundation of trust for how we might work together in cocreation. It is now for researchers to consume this new knowledge, reflect on it and act.*

Authors' Contributions

AS, BM, MRW, MW, BT, CR, LW, RM, and JCE contributed living, clinical, and caregiving knowledge of ABI and experience of research participation. BT is a carer of a person with brain injury. AS, BM, MRW, CR, RM and JCE are stakeholders with living experience of acquired brain injury. BM is also a Former World Boxing Association World Number 2, International Boxing Federation Super-Middleweight Champion, and Pan Asian Boxing Association Super-Middleweight Champion. MM conceptualized the study, selected the theoretical framework, designed prioritization methods, developed survey, interview and focus group materials, collected survey and interview data, and initiated and managed coauthorship with stakeholders. EP, RR, LT, DD, and MB provided feedback on survey design, and MM, EP, RR, LT, and DD collected focus group data. MM prepared the manuscript, and all authors critically revised it. All authors approved the final version of the manuscript for submission.

Conflicts of Interest

MM, EP, RR, MB, and LT are developers of the Social Brain Toolkit in collaboration with stakeholders. The authors declare no other conflict of interest.

Multimedia Appendix 1
Consent screening protocol.
[PDF File (Adobe PDF File), 225 KB - resprot_v11i1e35080_app1.pdf]

Multimedia Appendix 2
Prioritization survey.
[PDF File (Adobe PDF File), 4189 KB - resprot_v11i1e35080_app2.pdf]

Multimedia Appendix 3
Survey video for domain 1 of the NASSS as applied to the Social Brain Toolkit.
[MP4 File (MP4 Video), 85397 KB - resprot_v11i1e35080_app3.mp4]

Multimedia Appendix 4
Survey video for domain 2 of the NASSS as applied to the Social Brain Toolkit.

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[MP4 File (MP4 Video), 55037 KB - resprot_v11i1e35080_app4.mp4]

Multimedia Appendix 5
Survey video for domain 3 of the NASSS as applied to the Social Brain Toolkit.
[MP4 File (MP4 Video), 191379 KB - resprot_v11i1e35080_app5.mp4]

Multimedia Appendix 6
Survey video for Domain 4 of the NASSS as applied to the Social Brain Toolkit.
[MP4 File (MP4 Video), 90979 KB - resprot_v11i1e35080_app6.mp4]

Multimedia Appendix 7
Survey video for Domain 5 of the NASSS as applied to the Social Brain Toolkit.
[MP4 File (MP4 Video), 60353 KB - resprot_v11i1e35080_app7.mp4]

Multimedia Appendix 8
Survey video for Domain 6 of the NASSS as applied to the Social Brain Toolkit.
[MP4 File (MP4 Video), 74272 KB - resprot_v11i1e35080_app8.mp4]

Multimedia Appendix 9
Survey video for Domain 7 of the NASSS as applied to the Social Brain Toolkit.
[MP4 File (MP4 Video), 68440 KB - resprot_v11i1e35080_app9.mp4]

Multimedia Appendix 10
Focus group data collection.
[DOCX File , 17 KB - resprot_v11i1e35080_app10.docx]

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Abbreviations

ABI: acquired brain injury
CALD: culturally and linguistically diverse
CPT: communication partner training
NASSS: Nonadoption, Abandonment, Scale-up, Spread, and Sustainability

NSW: New South Wales
REPRISE: Reporting Guideline for Priority Setting of Health Research
TBI: traumatic brain injury
UNESCO: United Nations Educational, Scientific and Cultural Organization
UTS: University of Technology Sydney

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Protocol

Well-being of Canadian Armed Forces Veterans and Spouses of Veterans During the COVID-19 Pandemic: Protocol for a Prospective Longitudinal Survey

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Abstract

Background: The COVID-19 pandemic has resulted in significant changes to everyday life, including social distancing mandates, changes to health care, and a heightened risk of infection. Previous research has shown that Canadian Armed Forces (CAF) veterans are at higher risk of developing mental and physical health conditions. Veterans and their families may face unique social challenges that can compound with pandemic-related disruptions to negatively impact well-being.

Objective: This study aims to longitudinally characterize the mental health of CAF veterans and spouses of CAF veterans throughout the pandemic and to understand the dynamic influences of pandemic-related stressors on psychological health over time.

Methods: We employed a prospective longitudinal panel design using an online data collection platform. Study participation was open to all CAF veterans and spouses of CAF veterans residing in Canada. Participants were asked to complete a comprehensive battery of assessments representing psychological well-being, chronic pain, health care access patterns, physical environment, employment, social integration, and adjustment to pandemic-related lifestyle changes. Follow-up assessments were conducted every 3 months over an 18-month period. This study was approved by the Western University Health Sciences and Lawson Health Research Institute Research Ethics Boards.

Results: Baseline data were collected between July 2020 and February 2021. There were 3 population segments that participated in the study: 1047 veterans, 366 spouses of veterans, and 125 veterans who are also spouses of veterans completed baseline data

collection. As of November 2021, data collection is ongoing, with participants completing the 9- or 12-month follow-up surveys depending on their date of self-enrollment. Data collection across all time points will be complete in September 2022.

Conclusions: This longitudinal survey is unique in its comprehensive assessment of domains relevant to veterans and spouses of veterans during the COVID-19 pandemic, ranging from occupational, demographic, social, mental, and physical domains, to perceptions and experiences with health care treatments and access. The results of this study will be used to inform policy for veteran and veteran family support, and to best prepare for similar emergencies should they occur in the future.

International Registered Report Identifier (IRRID): DERR1-10.2196/34984

Introduction

Background

As of December 2021, over 1.8 million COVID-19 cases and 29,000 deaths have been reported in Canada [1]. To limit the spread of infection, the Canadian government has implemented, for example, social distancing protocols, lockdowns, school and nonessential business closures, travel restrictions, and social gathering size limits [2]. Both the virus that causes COVID-19 as well as restrictions associated with the pandemic have triggered various cascading stressors, including concerns related to contracting or spreading the virus, social isolation, changes in employment and/or financial stability, barriers to accessing supportive services, or a scarcity of these services. The widespread exposure to health threats and their multidimensional impact may lead to adverse mental health outcomes. Research conducted across countries revealed elevated rates of anxiety and depression throughout the pandemic [3,4]. More specifically, research has shown associations of symptoms of depression and anxiety with perceived threat of COVID-19 infection, social isolation, financial and occupational insecurity, and resource scarcity [5-7]. The impact of these pandemic-related stressors may be more detrimental to populations with increased vulnerability to mental illnesses, such as military veterans.

Epidemiological surveys consistently reveal that Canadian Armed Forces (CAF) veterans experience higher rates of mental and physical health conditions relative to the general Canadian population. These include posttraumatic stress disorder (PTSD), depression, and anxiety diagnoses, as well as chronic pain, arthritis, and high blood pressure [8,9]. Recent research has also found that the presence of prepandemic mental illnesses and medical conditions has been associated with greater risk of adverse mental health outcomes during the pandemic among the general population [4,10,11]. Thus, it is plausible that veterans exposed to pandemic-related stressors may be vulnerable to adverse psychological consequences. Additionally, the high rates of psychological and physical conditions in CAF veterans result in a strong reliance on physical and mental health care services relative to the general Canadian population [12,13]. Consequently, transitions and overload in health care sectors may disproportionately impose barriers to health care services and result in unmet health care needs among veterans; this may contribute to mental health concerns directly, or indirectly through worsening health conditions.

Another contributing factor to veterans' increased vulnerability during the pandemic involves their social networks and interpersonal relationships. Veterans frequently report feelings of loneliness and dysfunctions within their interpersonal relationships (eg [12,14]). Unprecedented government-imposed restrictions on in-person gatherings may further negatively impact veterans' recreational, occupational, and therapeutic activities. Indeed, research has underscored the associations between social isolation and elevated symptoms of depression and anxiety in the general public (eg, [15]).

Within the family context, there is evidence for existing relationship strain and disruptions between veterans and intimate partners, especially among veterans with mental illnesses [16,17]. The accumulation of stressors experienced throughout the pandemic may exacerbate psychological symptoms and amplify relationship strain for veterans and their spouses. Moreover, spouses of veterans are the most common source of unpaid caregiving to veterans [18], which can lead to significant caregiver burden and psychological distress [19,20]. Reductions in health services due to COVID-19 paired with associated exacerbations in pre-existing health conditions may result in additional responsibilities for spouses of veterans, further impacting relationship strains and psychological symptoms.

On the opposite side of the vulnerability continuum, veterans represent a unique population that has been specifically trained to demonstrate resilience in the face of adversity and extreme circumstances [21]. Despite the profile of vulnerabilities and risks, there is reason to expect that this population may adapt well compared to the general population. Research conducted in samples of veterans during the COVID-19 pandemic has revealed nonsignificant differences between veterans and the general population in levels of psychological symptoms [22,23]. However, these studies collected data at only a single time point during the pandemic, with specific samples (ie, only CAF veterans aged 55 years or older; only UK veterans) that may not generalize to all CAF veterans. Additional research is warranted to evaluate the long-term psychological impact of the pandemic and associated stressors on the mental health of veterans. This is especially important in light of theories that avoidance behaviors common to mental illnesses, including

PTSD, may be temporarily validated and reinforced [24,25]. These changes may lead to transient improvements in mental health that will create additional challenges when and if society returns to a prepandemic state.

The Current Study

This manuscript details the protocol for a longitudinal study aiming to capture the impact of the COVID-19 pandemic on the well-being of veterans and their spouses. We will assess a variety of psychological outcomes and determine how they fluctuate according to perceptions of social support, loneliness, family functioning, changes in health care delivery and access, disease status and precautions (eg, social distancing), occupational and financial insecurity, and demographics. Future publications from this study will explore the following: (1) the impact of the COVID-19 pandemic on psychological outcomes, with consideration for possible mechanisms of action such as the mediating and/or moderating roles of social support and loneliness or occupational and financial concerns on well-being, and (2) experiences, satisfaction, and psychological/well-being outcomes related to health care access and telehealth services.

Methods

Study Design

We employ a prospective longitudinal panel design using the secure web-based data collection platform Research Electronic Data Capture (REDCap), hosted by Lawson Health Research Institute. Participants completed questionnaires at baseline (from July 2020 to February 2021) and provided their emails for follow-up surveys to be completed every 3 months for a total of 18 months. The survey was conducted and will be reported according to the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) [26]. This study was approved by the Institutional Research Ethics Boards of Western University Health Sciences (WREM #115933) on July 16, 2020, and Lawson Health Research Institute (ReDA #10001) on July 17, 2020.

Participant Selection and Recruitment

Participants were recruited using a convenience snowball sampling strategy. Recruitment sources included a research participation recruitment platform (ParticipAid), emails distributed across professional and veteran group networks, social media advertisements, targeted media releases, and word of mouth. Recruitment channels directed prospective participants to the ParticipAid study webpage, which offered further information on the study procedures and directed eligible participants to the REDCap survey link. Eligible participants were at least 18 years of age, currently residing in Canada, and were CAF veterans or spouses (married or common-law) of CAF veterans at the time of baseline data collection. Eligibility was self-reported by participants via screening questions presented on the recruitment website, ParticipAid, and at the outset of the baseline REDCap survey.

Veteran participants' representativeness was monitored weekly throughout the recruitment period by comparing the sampling distributions against Canadian national databases on gender, age, and province of residence [27]. Recruitment efforts were adjusted accordingly to target underrepresented demographic segments (eg, through adjusting the target audiences in paid social media advertisements). No monetary compensation was provided to participants.

Data Collection

Survey Design and Administration

The online survey was designed in consultation with international research teams to evaluate the cross-cultural effects of the COVID-19 pandemic on veterans and their families. A drafted version of the survey was presented to the MacDonald Franklin Operational Stress Injury Research Centre advisory council comprising CAF veterans, spouses of CAF veterans, experts in veteran and military research, health care professionals providing treatment to veterans and military members, and other stakeholders engaged in the veteran community. The advisory council provided feedback and guidance on scale selection and relevance to issues faced by CAF veterans during the pandemic.

To cater to participant availability, participants can choose between two versions of the baseline survey: a short-form version (approximately 20 minutes) or a long-form version (approximately 30 minutes; Table 1). The short-form version consists of 9 measures, which contain between 171 and 240 items collectively (depending on conditional display logic), and is presented over 9 screens/pages. The long-form version consists of 15 measures, which contain between 221 and 312 items collectively (depending on conditional display logic), and is presented over 14 screens/pages. The long-form survey can be completed immediately at baseline or be returned to within a 6-week window after beginning the baseline measures.

After baseline, an automated follow-up survey is sent every 3 months for a period of 18 months to all participants who provided an email address for contact. The follow-up survey (approximately 30 minutes) consists of 13 measures, which contain up to 293 items collectively (depending on conditional display logic), and is presented over 13 screens/pages. To reduce participant burden, all survey versions (long-form, short-form, and follow-up) use conditional display logic to hide certain questions or modules that are not relevant (eg, hiding employment demographic questions at follow-up if their employment status did not change). Only eligibility-related questions require a response; all other items can be skipped. There is an option for participants to use a return code to change their responses once submitted. The surveys are offered in English or French based on participants' language preferences. Psychometrically validated French scales are used when available; otherwise, professional translations of the English scales, with certificates of translation provided, are used. Implied e-consent is collected at each data collection event (baseline and at each follow-up) by completion of questionnaires.

A team of 3 researchers was responsible for testing the technical aspects of the survey (eg, numeric validation, display of items and instructions, conditional display logic). Researchers tested the survey by assuming the role of hypothetical participants that systematically varied in all conditions on which conditional display logic is based (eg, "You are a Canadian Veteran **and a**

spouse and you choose the short version for now but complete additional measures after. You are a "key worker" in public safety and work full-time."). Automated processes, including emails for follow-up surveys, were systematically tested by the same researchers for all hypothetical scenarios.

Table 1. Data collection tools for short-form, long-form, and follow-up surveys.

Collection of assessments/domains	Short-form survey	Long-form survey	Follow-up survey
Demographics	✓	✓	✓
COVID-19 experiences/impact	✓	✓	✓
Health care access	✓	✓	✓
Social support 1 (Multidimensional Scale of Perceived Social Support)	✓	✓	✓
Social support 2 (Perceived Social Support Questionnaire)		✓	
Posttraumatic stress disorder (Posttraumatic Stress Disorder Checklist for the DSM-5)	✓	✓	✓
Depression (Patient Health Questionnaire-9)	✓	✓	✓
Anxiety (Generalized Anxiety Disorder Scale-7)	✓	✓	✓
Moral injury (Moral Injury Outcome Scale)	✓	✓	✓
Loneliness (University of California Los Angeles - Loneliness Scale)	✓	✓	✓
Alcohol consumption (Alcohol Use Disorders and Identification Test)		✓	✓
Family function (Family Assessment Device – General Functioning subscale)		✓	✓
Positive well-being (Mental Health Continuum – Short Form)		✓	✓
Chronic pain (Brief Pain Inventory – Short Form)		✓	✓
Social desirability (Marlowe-Crowne Social Desirability Scale)		✓	

Questionnaires

Demographics

Participants are asked to report their province of residence, age, gender, marital status, characteristics of area of residence (eg, city or rural area), education level, ethnicity, living arrangements (eg, whether living alone), and employment status including changes to employment during the pandemic (eg, change in work environment, hours worked, salary). Veteran participants are asked for their rank at time of release, branch of service, and length of service. Spouses of veterans are asked whether their veteran partner has a mental health condition and if yes, whether the condition occurred as a result of occupational service.

COVID-19 Experiences/Impact

Using items adapted from the CoRonavIruS health and Impact Survey (CRISIS) [28], participants are asked about their exposure to, infection with, and associated consequences (eg, hospitalization) of COVID-19 for self and family members. Participants are also asked about frequency of social contacts and time spent outside the home, perceived difficulties and stress related to physical distancing recommendations, changes to the quality of close relationships, concern over living situation and finances, media consumption, and an open-ended item to describe any concerns not otherwise addressed. Additional items created for this survey assess concerns relating to the pandemic (eg, on health, business, accessing essential goods), general mental health and stress of participants and their spouses, past-week COVID-19–related behaviors (eg, avoid public places, maintain social distancing), and impacts on work.

Response options vary by question and are rated on 4-point, 5-point, or 6-point Likert scales, with various yes/no options for COVID-19 exposure–related questions (eg, Yes, has positive test; Yes, medical diagnosis, but no test; Yes, have had some possible symptoms, but no diagnosis by doctor; No symptoms or signs).

Health Care Access

Participants are asked about whether they have had difficulties accessing health care and whether they have avoided health care with yes and no options (I haven't needed care; Yes; No; I don't know; Prefer not to answer), with respective questions about the specific types (eg, family doctor; dental care) and domains (mental health; physical health; both) of care. For each domain of care that was avoided or difficult to access, participants are asked about their past-week distress levels on a 5-point Likert scale ranging from 0 (not at all) to 4 (extremely). Participants are asked about their usage frequency and interest in telehealth prior to the pandemic for physical and mental health care on 4-point (usage) and 3-point (interest) Likert scales, as well as their current interest in receiving telehealth services (5-point Likert scale). Participants are also asked about telehealth experiences since the pandemic in terms of whether they have accessed it (yes/no), for which domain of care (ie, mental and/or physical, with an open-ended question to specify details), respective satisfaction with the telehealth services (4-point Likert scale), and an open-ended question for participants to indicate additional feedback on their telehealth experiences. Telehealth questions were derived from a University of Missouri quality improvement survey and other research exploring the

application of telehealth and telemedicine in various populations [29-32].

Mental Health Questionnaires and Moral Injury

Participants are asked about their symptoms of depression (Patient Health Questionnaire-9 [PHQ-9]) [33], PTSD (PTSD Checklist for the DSM-5 [PCL-5]) [34], general anxiety (Generalized Anxiety Disorder Scale-7 [GAD-7]) [35], alcohol consumption (Alcohol Use Disorders Identification Test [AUDIT]) [36], positive well-being (Mental Health Continuum-Short Form [MHC-SF]) [37], and moral injury expression using the Moral Injury Outcome Scale (MIOS) [38 and Litz, BT, unpublished data]. An additional item was added at the end of the PHQ-9, PCL-5, and GAD-7 for participants reporting the presence of at least one symptom on the respective scale to assess whether their symptoms are "directly related to the COVID-19 pandemic," "made worse or exacerbated by the COVID-19 pandemic," "related to traumatic events unrelated to the COVID-19 pandemic," or "not sure." An item was added after the AUDIT items to assess whether participants' alcohol consumption decreased, increased, or stayed the same relative to before the pandemic.

Social Support and Family Function

Participants are asked about their experiences with loneliness (University of California Los Angeles - Loneliness Scale [UCLA-LS]) [39], perceived social support (Multidimensional Scale of Perceived Social Support [MSPSS] [40], Perceived Social Support Questionnaire [F-SozU] [41]), and family functioning (General Functioning subscale from the McMaster Family Assessment Device Scale [FAD-GF]) [42].

Physical Health Questionnaires

Participants are asked about their symptoms of chronic pain using the Brief Pain Inventory-Short Form (BPI-SF) [43].

Social Desirability

Social desirability is measured using the Marlowe-Crowne Social Desirability Scale (MC-SDS) [44]. This instrument assesses whether participants exhibit a tendency to respond in a socially desirable, rather than truthful, manner. This instrument was included for psychometric analysis on measures in this study that have not yet been validated (eg, MIOS); the MC-SDS will be used to assess the discriminant validity of measures.

Data Management

Participant data are maintained in accordance with Western University and Lawson Health Research Institute institutional regulations pertaining to participant privacy and cybersecurity. Source data including electronic consent, patient identifiers (eg, email), and all questionnaire responses are stored on REDCap, which is securely housed behind an organizational firewall, and only accessible to approved investigators through an institutional login. Each participant is assigned a numerical code that is used to label and link source data. When exported from REDCap, all data are password-protected and accessible only to members of the research team. Data quality validation is performed directly through REDCap data entry forms by specifying acceptable numerical ranges, when applicable (eg, for age, and number of children living at home), and by using logic to hide

questions irrelevant to subsamples (eg, telehealth acceptability only assessed among participants indicating telehealth use). Details on missing data and attrition will be discussed alongside corresponding results in future publications.

Data Analytic Plan

Descriptive and Exploratory Analyses

Quantitative descriptive statistics will be used to examine sociodemographic characteristics including age, gender, ethnicity, income, education, occupation, and illness-related variables (eg, whether currently or formerly positive for COVID-19), as well as social, psychological, physical, and health care-related variables. These will include general descriptive analyses (means and standard deviations for continuous quantitative variables, relative frequencies for categorical variables), measures of internal consistency, and correlational analyses. Analyses will be performed on SPSS Statistics (version 28; IBM Corp) and RStudio (version 1.3). Qualitative, open-ended data, including participant descriptions of the impact of the COVID-19 pandemic on their health and well-being, comments about telehealth, and descriptions of morally injurious events, will be analyzed using content analysis. Data will be analyzed using NSR NVivo 11 software (QSR International). A minimum of two independent coders blinded to study hypotheses will code responses individually using both inductive and deductive approaches [45,46]. Themes will be explored, and identified and observed trends will be summarized.

Longitudinal Analyses

Data pertaining to psychological well-being and distress will be analyzed using latent growth modelling and mixed modelling methods to evaluate how psychological well-being and distress evolve over time. Longitudinal models will aim to identify predictors that influence individual trajectories of mental health and distress. Analyses will explore relations between mental health functioning in relation to social support and relationships, COVID-19–related variables, and health care access and satisfaction. Modelling and mixed modelling will be conducted using RStudio.

Results

Survey Completion and Representativeness

Baseline data were collected from July 31, 2020, to February 1, 2021. A total of 1538 eligible participants initiated the survey. Among those participants, 1047 were CAF veterans, 366 were spouses of CAF veterans, and 125 were both CAF veterans and spouses of CAF veterans. Most participants who initiated the baseline survey chose to complete the long-form survey version (1207/1538, 78.5%). Most participants who completed the short-form survey (140/206, 68.0%) indicated interest in completing the additional long-form questionnaires, with 55.0% (77/140) subsequently initiating those remaining questionnaires; this represents a conversion rate of 37.4% (77/206) of those prompted, and an overall increase of 6.4% (77/1207) in long-form survey data. See Figure 1 for the flow of participants from REDCap survey initiation to baseline retention for follow-up.

Figure 1. Participant flow for baseline completion rates. LF: long-form survey; SF: short-form survey.
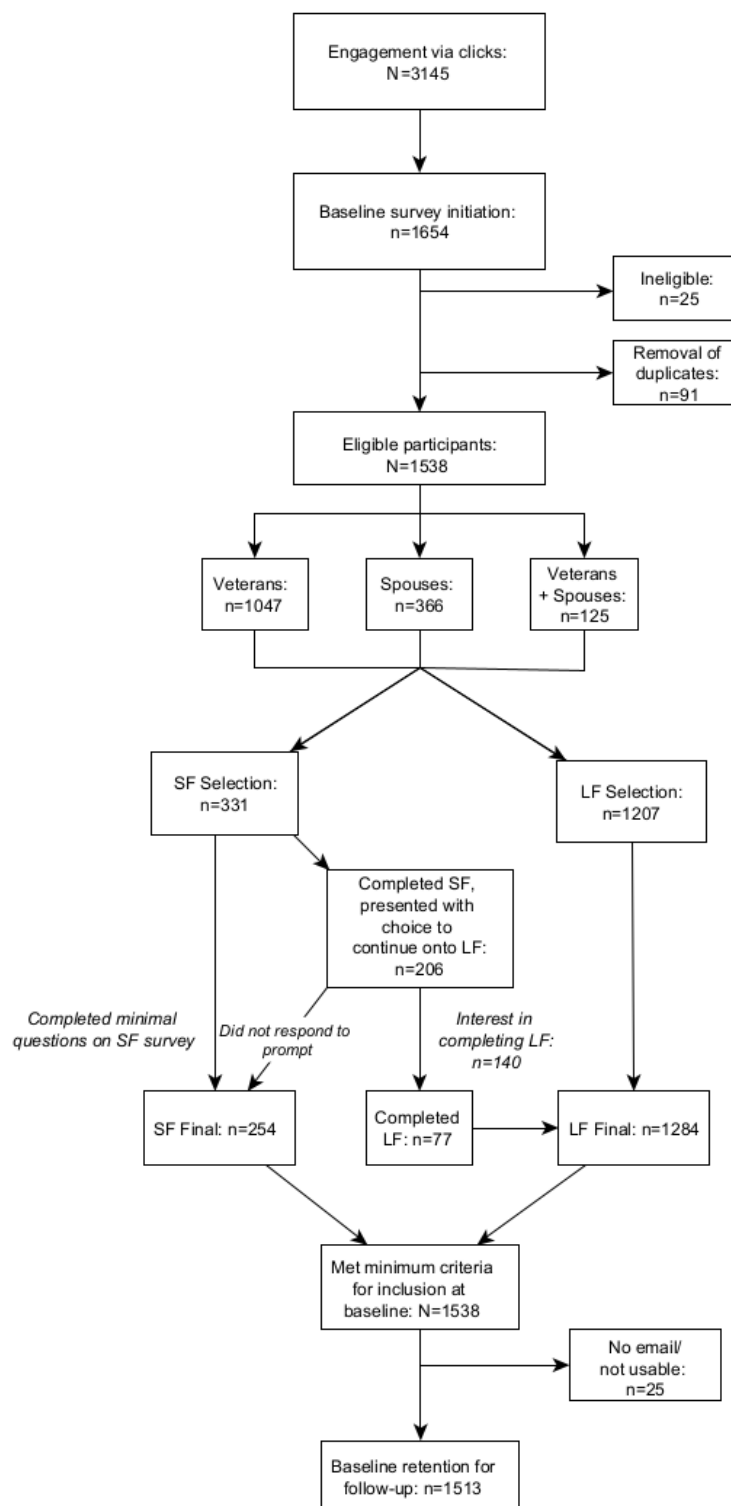
The veteran participants of our baseline sample were compared against national survey data of CAF veterans [27] using chi-square goodness of fit tests on distributions of age, gender, and province of residence by Canadian regions: Atlantic Provinces, Central Canada, Prairie Provinces, West Coast, and Northern Territories [47]. Overall, our veteran sample was largely similar to the Canadian veteran population in age, gender, and region of residence. Slight deviations from the national distributions were found in each variable, with absolute

percentage differences ranging from less than 1% to 11%. For age, absolute percent differences varied from less than 1% to 10%, with absolute differences greater than 5% observed in older age categories. Our sample had more participants in the 50-59 (+10%) and 60-69 (+6%) age groups, and fewer participants in the 80-89 (−10%) and ≥90 (−9%) age groups. Chi-square results revealed a significant difference in age distribution (χ^2_6=274.75, P<.001; Cramer V=.20, revealing this effect was small [48]). The absolute difference in proportions

of males and females between our sample and the national estimate is 11.0%. Relative to national estimates, females were overrepresented in our veteran sample ($\chi^2_1=136.07$, $P<.001$), with a medium effect size (Cramer V=.35). The absolute differences in proportions for region of residence varied from less than 1% (West Coast) up to 7% (Atlantic Provinces). The regional distribution of our participants differed from that of the national estimates ($\chi^2_3=44.49$, $P<.001$), with a medium effect size (Cramer V=.12).

Participant Data Retention

The median survey completion time varied by 11.5 minutes between the short-form (median 23.5 minutes) and long-form (median 35.0 minutes) versions of the survey. The percentages of participants completing each questionnaire at baseline varied according to whether participants completed the long or short version of the survey. The drop-off trend was similar between both survey lengths. For the long-form version, completion dropped from 100% at demographics to around 90% for the COVID-19 factors questions, with participation remaining above 80% for health care access, social support (MSPSS), and loneliness questions (UCLA-LS), before dropping to approximately 80% in the moral injury questionnaire (MIOS), and ranging between 70%-80% for the remainder of the questionnaires (PCL-5, PHQ-9, GAD-7, AUDIT, BPI-SF, FAD, MHC-SF, and MC-SDS). Participants who initiated the short-form version exhibited a similar trend. The rate of decline was steeper, particularly from the health care access questions to the MIOS questionnaire, with the completion rate of the full set ranging between 60% and 65% (Figure 2).

Figure 2. Completion rates of individual questionnaires at baseline. AUDIT: Alcohol Use Disorders and Identification Test; BPI-SF: Brief Pain Inventory – Short Form; F-SozU: Perceived Social Support Questionnaire; FAD-GF: Family Assessment Device – General Functioning subscale; GAD-7: Generalized Anxiety Disorder Scale-7; MC-SDS: Marlowe-Crowne Social Desirability Scale; MHC-SF: Mental Health Continuum – Short Form; MIOS: Moral Injury Outcome Scale; MSPSS: Multidimensional Scale of Perceived Social Support; PCL-5: Posttraumatic Stress Disorder Checklist for the DSM-5; PHQ-9: Patient Health Questionnaire-9; UCLA-LS: University of California Los Angeles - Loneliness Scale.
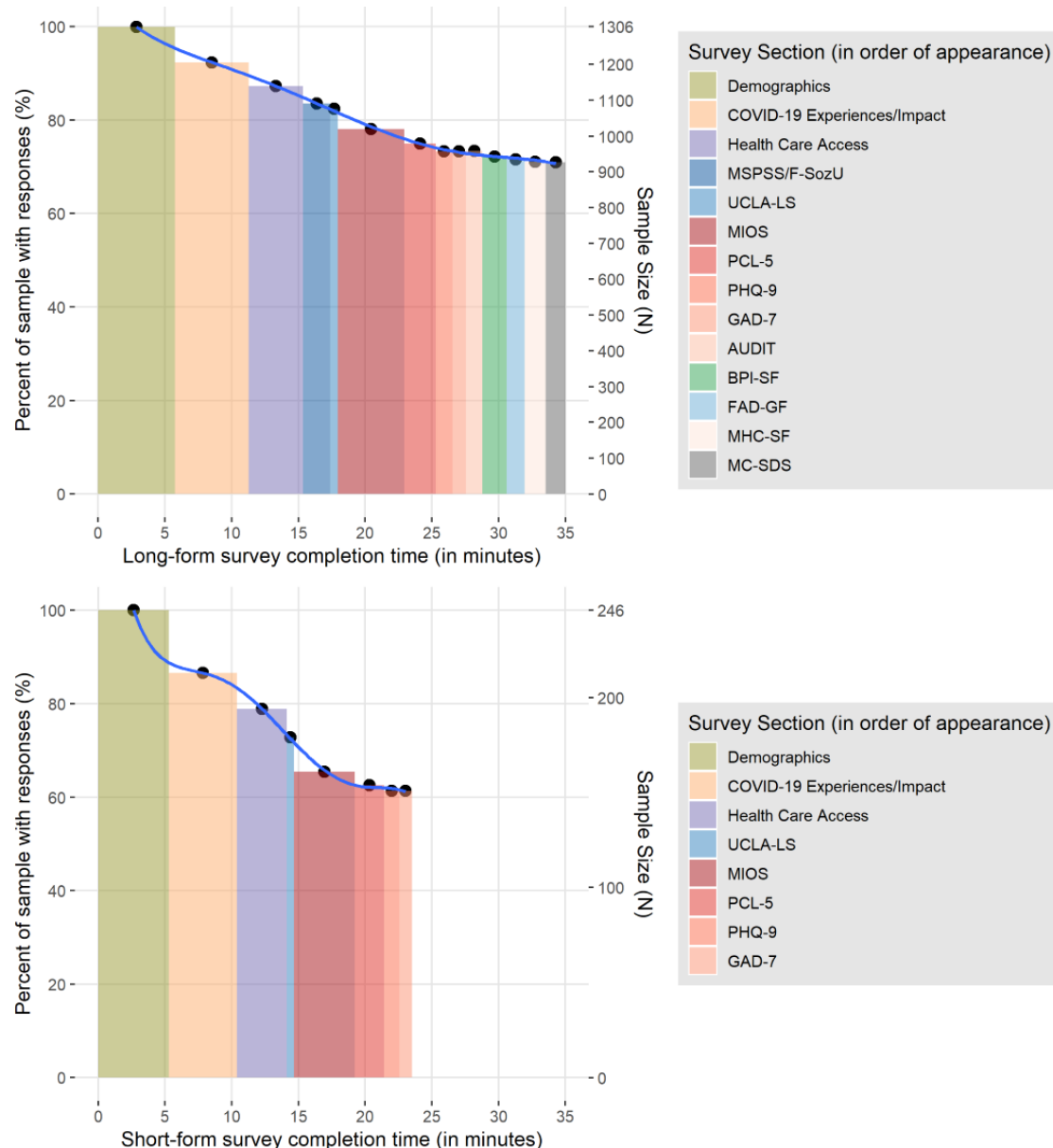
Based on the date of baseline survey initiation, participants receive system-generated notifications to complete their follow-up surveys every 3 months for a total of 18 months. The baseline retention with email addresses (N=1513) is being used as the reference point to evaluate participant retention and attrition during each of the follow-up periods. As of November 2021, a total of 831/1513 (54.9%) participants completed the 3-month follow-up, whereas 682/1513 (45.1%) missed the response window, and a total of 667/1513 (44.1%) participants completed the 6-month follow-up, and 846/1513 (55.9%) missed the response window. Data collection is ongoing into the 9-month and 12-month follow-up periods, with 683/1513 (45.1%) and 58/1513 (3.8%) participants missing the response window for each of these data collection periods, respectively. Participants missing the response window for follow-up time points will still be contacted for the next follow-up. Data collection over the full 18-month follow-up period is projected to end in mid-September 2022.

Discussion

This paper details the protocol for a longitudinal study evaluating the impact of the COVID-19 pandemic on the well-being of Canadian veterans and spouses of Canadian veterans. The use of convenience sampling and a flexible survey format yielded a large, cross-national sample of veterans and spouses. The longitudinal data gathered as part of this study will provide key insights in mapping out the long-term consequences of the COVID-19 pandemic and associated changes on dimensions of well-being among veterans and spouses. Our findings will contribute to the identification of vulnerabilities and protective factors that may enhance or reduce well-being in veterans and their spouses throughout the pandemic, and during similar emergencies should they occur in the future. Moreover, findings from this study will contribute to the optimization of health care for veterans and their families. A strength of this study is the comprehensive and rigorous development of the online survey. Given the wide-ranging implications of the COVID-19 pandemic, it is crucial to survey an exhaustive range of dimensions to understand their multifaceted and interactive impacts on well-being. Further,

this survey was developed with leading researchers and health care providers for veteran communities and was refined with feedback from veterans and spouses. The likelihood of feasibly capturing relevant experiences is high. The longitudinal design of this study is another important strength for several reasons. It is essential to capture data across several time points due to the evolving nature of the pandemic. Dynamic changes, such as fluctuating public health restrictions and regulations, waves of community outbreaks, and the progressive (and highly politicized) development of COVID-19–related research and vaccines underscore the value of longitudinal data collection. In addition, the pandemic will likely have complex indirect influences on veterans' and spouses' well-being through mediating roles of social support, social isolation, and/or financial insecurity. Finally, long-term monitoring is needed to capture lagged impacts of the pandemic on psychological well-being, which have been anticipated as society moves toward notions of a "new normal" [49].

There are several challenges associated with this study. These include maintaining a sizable response rate over the data collection period. Strategies were employed at the outset of data collection to achieve a large baseline sample size in anticipation of participant attrition. For example, both long-form and short-form survey designs were incorporated in this study to encourage participation among those who may have otherwise declined due to time constraints; the use of long-form and short-form survey versions has been successful in other longitudinal studies [50]. Ongoing retention strategies include sending reminder emails and tracking rates of attrition to monitor sample sizes during follow-up periods.

As of November 2021, data collection is ongoing, with participants currently completing surveys for the 9- and 12-month follow-up periods; data collection will be completed in mid-September 2022. This study offers a unique opportunity to characterize the impacts of the pandemic on veterans through both their own perspectives and through the lenses of their spouses. The results of this study will be used to inform policy and treatment planning to better support Canadian veterans and their families in the aftermath of the pandemic and during similar future events.

Conflicts of Interest

None declared.

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Abbreviations

AUDIT: Alcohol Use Disorders and Identification Test
BPI-SF: Brief Pain Inventory – Short Form
CAF: Canadian Armed Forces
CHERRIES: Checklist for Reporting Results of Internet E-Surveys
CoE: Centre of Excellence on Post-Traumatic Stress Disorder and Related Mental Health Conditions
CRISIS: CoRonavIruS health and Impact Survey
F-SozU: Perceived Social Support Questionnaire
FAD-GF: Family Assessment Device – General Functioning subscale
GAD-7: Generalized Anxiety Disorder Scale-7
MC-SDS: Marlowe-Crowne Social Desirability Scale
MHC-SF: Mental Health Continuum – Short Form
MIOS: Moral Injury Outcome Scale
MSPSS: Multidimensional Scale of Perceived Social Support
PCL-5: Posttraumatic Stress Disorder Checklist for the DSM-5
PHQ-9: Patient Health Questionnaire-9
PTSD: posttraumatic stress disorder
REDCap: Research Electronic Data Capture
UCLA-LS: University of California Los Angeles - Loneliness Scale

Protocol

Exploring Empathy and Compassion Using Digital Narratives (the Learning to Care Project): Protocol for a Multiphase Mixed Methods Study

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Abstract

Background: Digital stories—first-person, self-made, 2- to 3-minute videos—generate awareness, impart knowledge, and promote understanding on topics such as mental illness. Digital stories are a narrative-based art form often created by individuals without formal training in filmmaking to relate personal experiences. Somewhat like digital narratives, video testimonies created within the social marketing or fundraising campaigns of government agencies and private or public corporations aim to reduce the stigma of mental illness while supporting research and services. In video testimonies, personal stories are captured on camera by professional filmmakers. Sharing critical life events greatly benefits tellers and listeners alike, supporting catharsis, healing, connectiveness, and citizenship.

Objective: This study explores digital stories and video testimonies featuring mental illness and recovery in their ability to elicit empathy and compassion while reducing stigma among viewers.

Methods: Using mixed methods, phase 1 will involve a search of Canadian social marketing activities and fundraising campaigns concerning mental illness and recovery. Phase 2 will involve the organization of digital storytelling workshops in which participants will create digital stories about their own experiences of mental illness and recovery. In phase 3, a pilot randomized controlled trial will be undertaken to compare marketing and fundraising campaigns with digital stories for their impact on viewers, whereas phase 4 will focus on knowledge dissemination.

Results: Ethics approval for this study was received in March 2021. Data on the feasibility of the study design and the results of the controlled trial will be generated. This study will produce new knowledge on effective ways of promoting mental health awareness and decreasing stigma, with practical importance for future social marketing and fundraising campaigns. The anticipated time for completion within the 2-year study period includes 9 months for phase 1 (knowledge synthesis activities identifying social marketing and fundraising campaigns) and phase 2 (storytelling workshops), 11 months for phase 3 (feasibility assessment and data collection: randomized controlled trial), and 2 months for phase 4 (knowledge dissemination).

Conclusions: The knowledge generated will have practical implications for the public and for future social marketing and fundraising campaigns promoted by government agencies as well as nonprofit and for-profit organizations by enhancing our understanding of how individuals and societies respond to stories of mental distress and what prompts citizens to help others.

Trial Registration: ClinicalTrials.gov NCT04881084; https://clinicaltrials.gov/ct2/show/NCT04881084

International Registered Report Identifier (IRRID): PRR1-10.2196/33525

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Introduction

Background

Stories of human distress and struggle are shared daily through news stories and in social marketing and fundraising campaigns using digital formats, including videos [1,2]. Digital narratives are also created for public consumption by ordinary citizens with no formal training in filmmaking to promote awareness of different problems or realities [1]. Digital narratives and video testimonies aim to shape attitudes and stimulate empathy, compassion, and good citizenship among listeners [1,2]. Sharing moments and insights offered by personal experience is invaluable for tellers and listeners alike, promoting catharsis, healing, reconciliation, and social connection [3].

Researchers have studied the portrayal of mental health issues in various media (eg, television and newspapers) since the 1990s [4-7], identifying their impact as overwhelmingly negative. Media depictions abound with stereotypes of persons affected by mental illnesses as dangerous or violent, further contributing to their social marginalization and stigmatization [4-17]. In response, programs such as the Opening Minds campaign [18] have been created to encourage the dissemination of *good media reports* [19] that foster a more humanizing and hopeful understanding of the lived experience of mental illness and encourage help-seeking for mental health problems [20].

Although negative, media-generated portrayals of mental distress remain a serious cultural and social concern, new internet-based media forms offer a wider variety of perspectives [10,11], whether narratives created by government agencies and public or private corporations (video testimonies), or digital stories, a mix of images and text, and the visual arts of private citizens who use the internet to share personal experiences of mental illness as a way of promoting awareness [21,22]. Government or privately sponsored social marketing and fundraising campaigns use video testimonies to promote more positive perspectives, transforming the internet into an educational forum while eliciting financial contributions through organizational websites and social networking venues [23-28].

Preliminary evaluations report mixed results and raise many questions about the effectiveness of social marketing campaigns [29,30]. For example, the Cambridge intervention, which aimed to reduce discrimination against people with mental distress, succeeded in increasing public awareness of mental health issues through advertising to promote arts-based community interventions. However, the results were not sustained beyond the campaign, as has also occurred with other international initiatives [23]. Results of the Systematic Medical Appraisal, Referral, and Treatment Mental Health Project in India involving ≥2000 participants showed improved attitudes toward mental illness and reduced stigma around help seeking following a multimedia intervention that provided print information and a video on mental health [31]. The 2009 Opening Minds initiative of the Canadian Mental Health Commission also used media campaigns for public education on mental illness and stigma, with mixed results [26]. Moreover, the value of sharing recovery stories was not lost on those with lived experience who received training to perform a teaching role in the campaign [30,32]. Outcomes measured in terms of the attitudinal or behavioral intentions of listeners also showed success. The organizers agreed to create more focused, cost-effective, and sustainable grassroots public awareness campaigns following criticism that the Opening Minds campaign had not reached out to ethnic minorities or Indigenous people [29,30,33].

Another successful initiative, Bell Canada's annual *Let's Talk* antistigma fundraising campaign, takes on the stigma of mental illness while raising funds to support research and services. Video testimonies feature stories of celebrities such as Clara Hughes, a Canadian Olympic medalist who previously struggled with mental illness. In 2020, the campaign generated >154,173,435 *interactions* that contributed >CAD $7,900,000 (US $6,165,950) to mental health initiatives. Research showed a temporary increase in visits to mental health services among youth in Ontario, Canada, following the *Let's Talk* campaign [34]. However, this campaign has been criticized for using testimonies that tended to downplay oppressive conditions such as poverty, racism, and violence connected with mental illness [35,36].

Digital storytelling, that is, first-person, self-made, 2- to 3-minute narratives prepared digitally and shared on the web [20,37,38], are viewed by their creators as an opportunity for communicating emotions and thoughts and destigmatize sensitive and marginalizing personal issues while bringing hope and encouragement to others [38]. Storytelling is an age-old tradition that brings people together through shared knowledge and experience [3,39]. Digital stories or short movies that combine personal narratives and images are modern versions of this tradition [32] and an art form that combines emotional charge, authenticity, and simplicity [39,40]. Leading this grassroots movement [40] is the Center for Digital Storytelling, established in the 1990s to promote the creation of digital stories by citizens, from secondary school students to seniors, including those with no knowledge of media production techniques [38].

Given the lack of research on the impact of social marketing and fundraising campaigns [20,41] and the creation and dissemination of digital stories about mental illness by people with no film background, this study examines these 2 storytelling forms (video testimonies presented in social marketing and fundraising campaigns vs digital stories) in terms of their ability to elicit empathy and compassion. Individuals with lived experience of mental illness will be invited to create and share digital stories exploring difficult, vulnerable, and meaningful moments in their lives with full awareness and acceptance of any painful thoughts and feelings they experience. This process will enable them to see their experiences as part of the human condition rather than as personal, isolated, or shameful events.

Stories, Meanings, and Discourses

As Baldwin [3] describes, human beings are meaning-making creatures defined by and defining themselves through the stories they tell about themselves. Stories evoke emotions that can motivate changes in behaviors, attitudes, beliefs, and even the overall course of lives [3]. Stories bring together different realities, people, places, and times. Viewing stories from various epistemic and ontological standpoints reveals key elements: (1) stories are fluid, as people have many stories to tell and their experiential understandings change over time; (2) sharing stories fulfills the human need for connection; (3) listening to stories can be troubling, but listeners are not always ready to listen deeply; (4) how a life moment is recounted varies with individual experience; and (5) stories are generated by, and generate, discourse, inviting critical analysis [38,40]. Stories also use discourse voluntarily or involuntarily, and new discourses are generated in communicating experiences to others [42-44].

Empathy and Compassion

Empathy, a key concept, has both cognitive and emotional domains. Cognitively, empathy requires an understanding of another person's inner experiences, feelings, and perspectives regarding the outside world, whereas the affective domain involves entering the experiences and feelings of the other. The notion of *feeling with* another has been studied by phenomenologists contemplating how subject and object are enmeshed in prereflective existence [45]. Merleau-Ponty [46] described this as "the intertwining of my life with the lives of others, of my body with the visible things, the intersection of my perceptual field with that of others." Empathy has been criticized from a theoretical standpoint, notably in *On the Problem of Empathy* by the philosopher Edith Stein [45], where she questions whether it is truly possible to feel what another person is feeling.

Compassion, from the Latin *compati,* means *to suffer with.* Compassion, described as the capacity to feel distress for, and desire to alleviate the distress of, another person cuts across theological, philosophical, and psychological traditions [46]. The Dalai Lama defined compassion as "a sensitivity to the suffering of self and others, with a deep commitment to try to relieve it" [46,47], whereas psychological models and therapeutic practices recognize the concepts of compassion and self-compassion [46-49]. The model of self-compassion by Neff [48,49], inspired by Theravada Buddhism, emphasizes cognitive over motivational elements and comprises (1) awareness and openness to distress; (2) kindness; and (3) capacity to share experiences of distress with others without shame, as an act of common humanity. Another example, compassion-focused therapy by Gilbert [50], develops (1) genuine motivation to care for self and others, (2) sensitivity to distress and needs, (3) the ability to connect with one's pain to heal, and (4) tolerance toward distress in eliciting empathy and compassion.

Aims and Research Questions

Overview

This study explores digital stories and video testimonies about mental illness, particularly those focused on mental health recovery, and how these stories elicit empathy and compassion. The following three questions will be addressed:

1. How are mental and emotional distress depicted in video testimonies presented in social marketing and fundraising campaigns versus digital stories made by people without formal training in filmmaking?
2. What impact does digital storytelling have on its creators, as people willing to revisit difficult life moments and transform them into digital videos?
3. How do digital narratives (video testimonies and digital stories) elicit empathy and compassion among viewers?

Qualitative Research Methodology

Qualitative research methodology will be used to investigate all study activities related to digital storytelling, based on the following three research questions:

1. What is the value of digital narratives (video testimonies presented in social marketing and fundraising campaigns) and digital stories created by individuals for retheorizing empathy and compassion?
2. How do digital narratives (video testimonies in social marketing and fundraising campaigns) influence empathy and compassion? What emotions emerge when people engage with these digital narratives as viewers?
3. How do digital stories created by ordinary people impact empathy and compassion? What emotions emerge when people engage with digital stories as viewers?

Quantitative Research Methodology

A pilot randomized controlled trial (RCT) will be performed as a feasibility study to assess the impact of video testimonies (social marketing and fundraising campaigns) versus digital stories.

The specific quantitative research question is as follows: are digital stories made by people without formal training in filmmaking more effective in eliciting empathy and compassion among viewers than the digital narratives used in social marketing and fundraising campaigns?

Using the Thabane et al [51] typology for feasibility studies, we also developed questions to test (1) process, (2) resources, (3) management, and (4) the scientific basis of our RCT. Examples of questions related to feasibility of the RCT include the following:

1. Process: what were recruitment rates and refusal rates for participation; how was randomization conducted?
2. Resources: how much time was required to conduct each stage of the protocol? How much time was required to recruit participants (university students)? How adequate was the web-based platform (REDCap [Research Electronic Data Capture]; Vanderbilt University) for collecting data?
3. Management: what was the research team's capacity, expertise, and availability for completing the planned research activities? Were any important study variables omitted? Do the data show too much or too little variability?
4. Scientific basis: what were the reliability, validity, and trustworthiness of assessments used with the targeted population (university students) for this specific

intervention? What was the estimated intervention effect? What was the estimated variance of the intervention effect?

The primary focus of this pilot study will be to gather data on the feasibility of the RCT; however, the following primary and secondary hypotheses have been generated (Textbox 1).

Textbox 1. Primary and secondary hypotheses.


Primary hypotheses

- Change in empathy among participants using the Toronto Empathy Questionnaire [52]

- Change in compassion among participants using the Compassionate Love Scale [53]

Secondary hypotheses

- Change in positive emotions among participants using the Dispositional Positive Emotions Scale [54]

- Change in mental health self-stigma among participants using the Self-Stigma of Mental Illness Scale-Short Form [53]

- Change in public mental health stigma among participants using the Difference and Disdain Scales for Public Stigma [55]

Methods

Overview

This is a multiphase, mixed methods project that uses both qualitative and quantitative methodologies (Figure 1). Qualitative findings will be used to deepen the understanding of the quantitative results by (1) exploring differences between video testimonies and digital stories using discourse analysis and (2) conducting a thematic analysis of in-depth individual interviews. Phase 1 (months 1-9) will involve a preparatory search to identify Canadian social marketing and fundraising campaigns. Digital storytelling workshops (phase 2) will be held simultaneously, and in-depth interviews conducted before and after each workshop. In phase 3 (months 10-21), a pilot RCT will be undertaken, involving additional in-depth interviews. In phase 4 (months 22-24), knowledge mobilization will be conducted.

Figure 1. Learning to care project logic model.
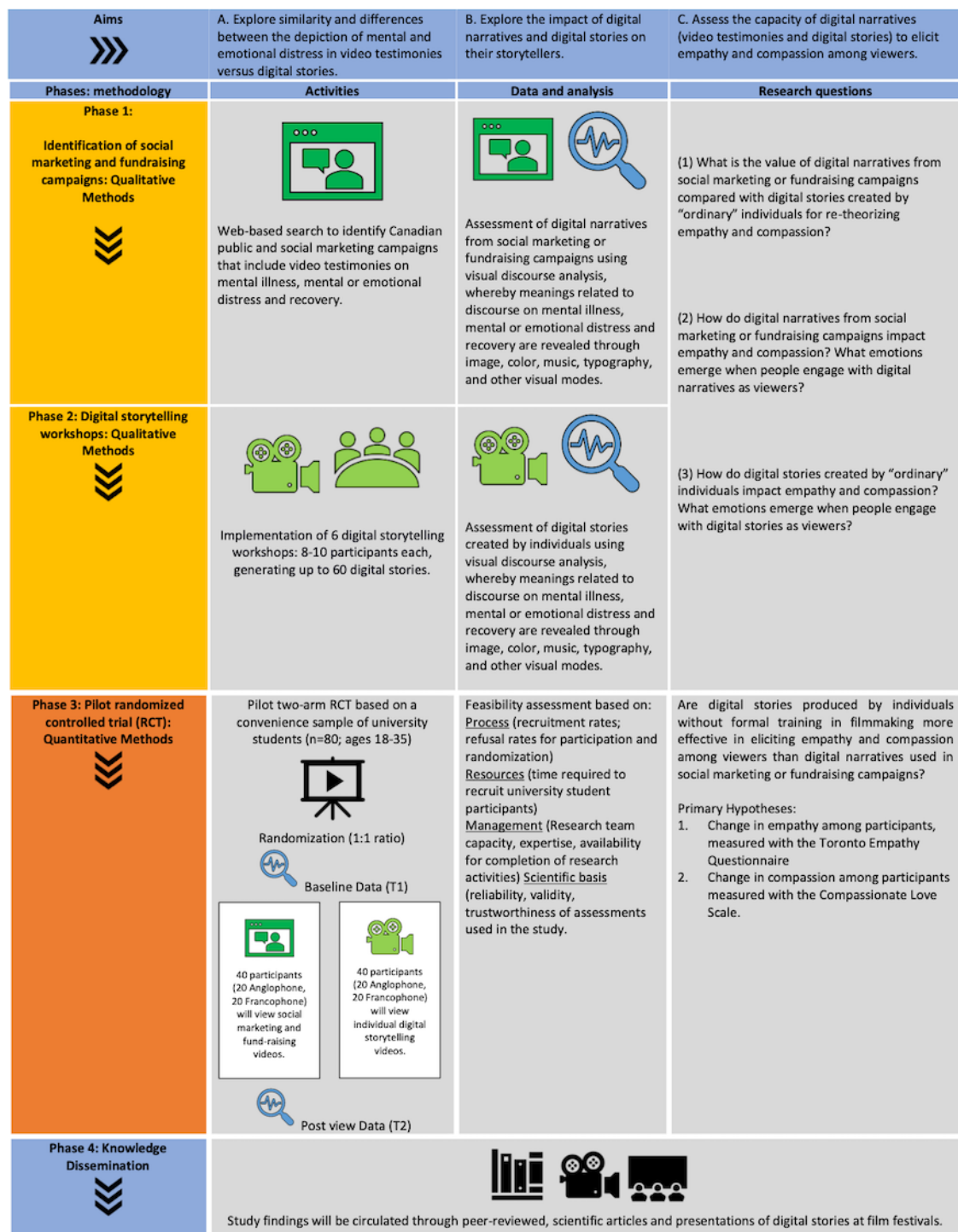
The Study Process and Outline

Phase 1: Identification of Social Marketing and Fundraising Campaigns

Knowledge Synthesis Activities Identifying Social Marketing and Fundraising Campaigns (Completed)

Canadian public and social marketing campaigns that include video testimonies on mental illness, mental or emotional distress, and recovery were identified using a web-based search engine (Google). The websites of organizations dedicated to improving mental health and well-being (eg, the Canadian Mental Health Association, Canadian mental health hospitals, and their associated foundations) were identified and searched for campaign materials. All video testimonies identified from these campaigns and organizational websites were collected and will be analyzed. The search was supplemented by a Google video search to locate other publicly disseminated video testimonies.

The searches were conducted from April to September 2021 to capture the most visible Canadian campaigns at the start of the study. Videos selected from each identified campaign included all the available first-person video testimonies, 1 to 5 minutes in duration, as well as television commercials and video advertisements in English and French. Campaign materials created as fact sheets involving substantial written text or image-based materials (eg, billboards, webpage advertisements, magazine advertisements, and slogans) were excluded. This study aims to gather 10 to 30 video testimonies for evaluation (phase 3).

Qualitative Discourse Analysis of Visual Materials and Interviews

The authors MF and SF will use visual discourse analysis [56,57] to assess the video testimonies (social marketing and fundraising campaigns) and digital stories created during the workshops (see the *Phase 2: Digital Storytelling Workshops* section). Discourse analysis appears to be an essential component in phases 1 and 2, which, in this phase, focuses on unpacking the meaning of texts, language, and other forms of communication in their social context [58]. Using this analytic method, visual data, video testimonies, and digital stories can be used to explore the construction of mental illness and recovery discourse in their digital forms [59]. In visual discourse analysis, image, color, music, typography, and other visual modes may be analyzed as languages [60-62], forming internally and externally coherent texts within the context in which they were produced [56]. Moreover, images and other visual modes may represent social relations between the producer, viewer, and represented object—an image vector of ideological positions [56]. The 3 perspectives from which visual content may be examined include contact (demand or offer), social distance (intimate, social, or impersonal), and attitude (involvement, detachment, viewer power, storyteller perspective on the story or video, equality, and representation power) [56]. The compositional meaning of images is analyzed through different systems: roles of the main character or protagonist and secondary characters in the video, information value (given or new, ideal or real, and important or less important), salience (achieved through size, color, and tone), and framing [56].

Following visual discourse analysis of the video testimonies (social marketing and fundraising campaigns) and digital stories, we will select the most suitable visual material for the RCT. A total of 2 homogeneous participant groups will be created to view the video testimonies and digital stories, respectively. The 2 groups will be similar in relation to illness experiences (eg, depression, anxiety, eating disorders, and psychosis) and language (English or French). The 3 dimensions for examining visual content (contact, social distance, and attitude) by Leeuwen [56] will be used as a guide to ensure similarity in the responses of the 2 groups regarding video testimonies and digital stories.

Phase 2: Digital Storytelling Workshops

Overview

MF will organize and facilitate the workshops. MF has previously implemented and evaluated a knowledge mobilization project using digital stories to explore care-seeking and access to care for psychosis. She will train 3 graduate students on digital storytelling practices. Workshop participants (aged 18-35 years) will be asked to create short, digital videos describing their subjective experiences of recovery from mental illness.

Recruitment

Social and community mental health services in Montreal and local universities will be contacted to promote, and host, 3-day digital storytelling workshops designed to produce a wide range of stories about recovery from mental illness that elicit emotions such as hope and compassion. Invitations to participate in the workshops will be posted (6 workshops: 8-10 participants each, generating up to 60 digital stories). Maximum variation sampling [63,64] will be used to determine participant composition in the workshops. Maximum variation sampling captures a wide range of perspectives by involving participants who represent a wide variety of identities, including gender, language, and sociocultural background, as well as different experiences of mental illness. Participants will be invited to an individual preworkshop meeting with the principal investigator where the subject matter for the stories (mental illness and recovery journey) and workshop structure will be explained.

Workshop participants (*storytellers*) will be invited to reflect on and depict moments involving emotions such as fear, shame, doubt, hope, courage, empathy, and warmth. Short digital videos created during each workshop will also be used for the evaluation of the study. The stories produced will remain the property of participants, who will each receive a media release form at the end of their workshop specifying if, how, and when their digital stories may be used. For this reason, we are soliciting the creation of approximately 60 digital stories for later use in the RCT. Workshop participants will be invited to a short interview before the workshop, and a longer interview soon afterward, to explore their experiences and story-sharing processes.

In-person workshops will be implemented based on participant availability and preferences. However, the workshops may also be implemented remotely for the duration of the COVID-19 pandemic to ensure participant safety. Specifically, participants will be offered a remote access option for involvement in the study (eg, preworkshop meeting with the principal investigator, screening, interviews, and data collection) using a secure, approved platform (Microsoft Teams). In addition, the web-based workshops will not operate under the full 3-day format, as originally planned, but will be split into short internet-based meetings, 3 hours each, and conducted over a 5-day period.

This project embraces *ethical practices in digital storytelling* [65]. The principal investigator and project coordinator will explain the consent form to participants at the preworkshop meeting, informing them of their rights, the purpose of the study, workshop structure and content, potential risks and benefits of sharing digital stories on the web, data collection processes and methods, and procedures for maintaining data confidentiality. Participants will have the opportunity to ask questions before signing the consent form. Written informed consent will be obtained from all the participants.

All workshop participants will participate in brief pre- and postworkshop interviews (n=60). Data will be analyzed thematically using a data-driven (inductive) approach rather than a theory-driven (deductive) approach. In this phase, the thematic analysis offers a useful method for examining the similarities and differences in the views of the research participants, generating rich insights. On the basis of a well-structured approach to handling data, thematic analysis is useful for producing clear, well-defined themes, subthemes, and relationships between them [55,66]. Following this approach, codes will reflect the discovered themes and meanings [67]. Braun and Clarke [66] guidelines for thematic analysis will be followed: (1) generating initial codes and searching for themes (collating codes into potential themes) and (2) reviewing and redefining themes.

Phase 3: Pilot RCT

Participants

A parallel 2-arm RCT design will be used to assess the impact of digital stories made by ordinary people compared with digital narratives used in social marketing and fundraising campaigns. A convenience sample of university students (n=80; age 18-35 years) from McGill University will be invited to participate in the pilot RCT, as a population comfortable with accessing web-based visual content and relatively easy to engage within the project timeline.

Sampling

The project coordinator will assess participant eligibility, obtain consent, and facilitate data collection (eg, log-in to the REDCap platform). Participants will choose an option for the screening and consent processes, whether in person, by phone, or video call using a secure platform (Microsoft Teams). Before seeking consent, the project coordinator will explain the consent form to RCT participants, informing them of the study objective, potential risks and benefits of participation, expected study duration, data collection processes, and methods and procedures for maintaining data confidentiality. Participants will be invited to ask questions before signing the consent form. Written informed consent will be obtained from all participants.

Randomization Procedure

Participants will be randomly assigned (1:1 ratio) to the social marketing or fundraising group (20/40, 50% Anglophone and 20/40, 50% Francophone participants) or the digital storytelling group (20/40, 50% Anglophone and 20/40, 50% Francophone participants) using the SAS, Stata, or R software. One of the arms of the pilot RCT will expose the participants to digital storytelling videos (intervention group), whereas the second arm will expose the participants to social marketing and fundraising videos (active control group). For both arms, sensitive content will be discussed with participants before screening of the videos so that certain content may be skipped over as needed.

The inclusion criteria for the study are as follows:

- Individuals of 18-35 years of age
- Individuals not currently treated in a hospital inpatient

The exclusion criteria for the study are as follows:

- Individuals outside the age range (18-35 years)
- Individuals currently treated in a hospital inpatient
- Individuals who attended a digital storytelling workshop and made a digital story used in the RCT

Methods of Assessment and Measurement

Participants will complete the first set of measures (time 1) before exposure to either study condition. Digital narratives will be assessed using a between-subjects design, in which each participant will view only video testimonies (social marketing or fundraising group) or only the digital storytelling videos (digital storytelling group). The system will record this information. Participants in each group will be exposed to a maximum of 10 video testimonies or digital stories. They will also complete standardized scales and a series of multiple-choice and open-ended questions regarding their perceptions of each digital video testimony or digital story. The duration of the survey will be 15 to 20 minutes.

Using a secure platform, a web-based survey comprising a variety of standardized scales, multiple-choice questions, and open-ended questions will be developed to assess video testimonies from social marketing or fundraising campaigns versus digital stories for their impact on empathy and compassion. The following scales will be used: Level of Familiarity scale (11-item questionnaire), which assesses the degree of contact with people living with specific diagnoses and will be used only before exposure to movies [68]; Toronto Empathy Questionnaire (16 items; Cronbach α=.79; test–retest reliability coefficient 0.73) [52]; Compassionate Love Scale (21 items; Cronbach α=.95; item-to-total correlations 0.46-0.81) [53]; Dispositional Positive Emotions Scale (5 items; Cronbach α=.80 [compassion subscale]; interscale correlation 0.44) [54]; Self-Stigma of Mental Illness Scale-Short Form (20 items; Cronbach α=.91) [69]; and Difference and Disdain Scales for Public Stigma (9 items) [70]. Examples of multiple-choice and open-ended questions are as follows:

- Why do you think this video was made? (response options: promote awareness, promote knowledge about services, promote knowledge about the organization, raise money, etc)
- How much control did the person in the video have over the story?
- How much control did the person in the video have over production of the video (eg, images music, etc)?
- How much control did the person in the video have over editing?
- How much control did the person in the video have over its dissemination or use?
- How much did watching these videos affect you?
- What was the most important thing you learned?

Data Management and Analysis

Mean group differences in scores on the selected measures from baseline to postintervention will be analyzed using repeated-measures analysis of variance, with intervention as the between-subjects factor and time the within-subjects factor, and with an interaction term (time and interaction group). To address feasibility questions, we will use descriptive statistics from standard operating procedures (eg, screening tools or data)

and data collected (eg, number of participants, recruitment rates, and refusal rates).

Phase 4: Knowledge Dissemination

The knowledge dissemination plan will use targeted strategies and tools to make findings readily accessible. Identified knowledge users include academics from multiple disciplines, government policy makers, organizational decision-makers, and the public. Findings will reach the academic community through presentations at international conferences and publications in peer-reviewed journals. Web platforms will be used to reach government policy makers, nonprofit or for-profit organizations, and other stakeholders, favoring content in the form of brief reports (French and English) and infographics. With participant consent, digital stories will be submitted for release at future public events, including short film festivals, to promote ongoing public dialog.

Trustworthiness, Validity, and Reliability

This study uses Lincoln and Guba [71] concept of trustworthiness, which is based on the following criteria: credibility, transferability, dependability, and confirmability. Credibility will be achieved using data collection triangulation and analysis. *Distinctive data collection activities will be implemented and a systematic search performed* to identify social marketing and fundraising campaigns (video testimonies) and analyzed using visual discourse analysis. Digital storyteller workshops will be implemented to generate digital stories that will be analyzed using visual discourse analysis. Interviews will be conducted with workshop participants to further investigate their experiences, and interviews will be analyzed using thematic analysis. At the end of each activity (data synthesis, implementation of workshops and interviews, and data analysis), the research team will hold a debriefing session on the research process, which will also increase credibility. Transferability, which refers to the generalizability of the qualitative inquiry and findings, will be operationalized through a detailed description of the methodological steps taken and an explanation of the process by which the definitive findings were generated and interpreted. To achieve dependability, the research team will document each phase so that the activities and decisions taken are transparent [71,72]. A logic model (Figure 1) describing the research process has been created to demonstrate dependability in the event of a study audit. According to Guba and Lincoln [73], confirmability, concerned with the grounding of interpretations and findings in the data, is established when credibility, transferability, and dependability are all achieved. As mentioned, the research team will rigorously disclose the reasons for the methodological and analytical choices made throughout the study [72].

To promote the validity and reliability of the RCT, this project has been registered, and CONSORT (Consolidated Standards of Reporting Trials) will be used to report the methodology and outcomes of the pilot trial.

Results

The study was approved by the research ethics board of the Douglas Hospital Research Centre, Montreal, Canada, in March 2021. The study design adheres to the CONSORT guidelines for reporting pilot RCTs [74,75]. Anticipated time to completion within the 2-year study period includes 9 months for phases 1 (knowledge synthesis activities identifying social marketing and fundraising campaigns) and 2 (digital storytelling workshops), 11 months for phase 3 (feasibility assessment and data collection: RCT), and 2 months for phase 4 (knowledge dissemination).

The short- and long-term objectives of the project are to (1) analyze how mental and emotional distress is depicted in social marketing or fundraising campaigns versus digital stories created by *ordinary* people, (2) implement a digital storytelling workshop in the community and create a collection of digital stories that capture emotional encounters involving compassion (eg, fear, shame, doubt, hope, courage, warmth, and genuineness), (3) assess the impact of social marketing or fundraising campaigns and digital stories created by *ordinary* people for viewer empathy and compassion, (4) explore the subjective experience of creating a personal story about mental and emotional distress in relation to theoretical formulations of empathy and compassion, and (5) explore the subjective experience of viewing digital stories about mental and emotional distress and compare this experience with the theoretical formulation of empathy and compassion.

Discussion

Principal Findings

Portrayals of mental distress are a matter of cultural and social interest as new media products become available to the public. Studies published since the 1990s overwhelmingly conclude that formal media depictions are biased, promoting the stereotypical view of people who undergo distress emotionally as mentally ill, dangerous, violent, or insane. Various agencies, organizations, and corporations are actively working to provide alternative stories or narratives to those presented in mainstream media by using video testimonies in social marketing and fundraising campaigns and, ultimately, by taking advantage of the internet. The impact of this work is underresearched. However, preliminary evaluations of social marketing campaigns report mixed results and raise questions about their effectiveness. In addition, the first-person narrative, prepared digitally and shared on the web, provides an alternative to mainstream media stories.

People are increasingly using digital videos to share their stories, viewing this as an opportunity to understand their emotions and thoughts and come to terms with disgrace around sensitive personal issues and marginalization while providing hope and encouragement to others. The proposed study explores digital stories, particularly stories of mental illness and recovery, and their ability to elicit empathy, compassion, and sense of citizenship among viewers.

Strengths and Limitations

This mixed methods study is the first to examine digital stories and video testimonies featuring mental illness and recovery in their ability to elicit empathy and compassion among viewers while reducing stigma.

The study will produce important knowledge on effective ways of promoting mental health awareness and decreasing stigma in the public, with practical application for future social marketing and fundraising campaigns.

Generalizability of the findings is limited to the Canadian and North American context, as the digital stories and video testimonies selected and evaluated in this study represent social marketing and fundraising campaigns in Canada or the testimonies of private citizens.

Conclusions

People are increasingly using digital videos to share their stories, viewing this as an opportunity to understand their emotions and thoughts and come to terms with disgrace around sensitive personal issues and marginalization while providing hope and encouragement to others. The proposed study will explore digital narratives, particularly those dealing with mental illness and recovery, and their ability to elicit empathy, compassion, and a sense of citizenship among viewers. The knowledge generated will have practical implications for the public and for future social marketing and fundraising campaigns promoted by government agencies as well as nonprofit and for-profit organizations by enhancing our understanding of how individuals and societies respond to stories of mental distress and what prompts citizens to help others.

Authors' Contributions

MF conceived the idea and devised the project and its main conceptual ideas, assisted by CM, JS, and SNI. MF and SF developed the first version of this manuscript, and CM, JS, and SNI provided editorial input.

Conflicts of Interest

None declared.

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture

Protocol

Dissemination and Implementation of a Google Apple Exposure Notification System for COVID-19 Risk Mitigation at a National Public University: Protocol for a Pilot Evaluation Study in a Real-World Setting

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Abstract

Background: As SARS-CoV-2, the virus that causes COVID-19, spread rapidly across the United States in the spring of 2020, institutions of higher education faced numerous challenges associated with minimizing risk of exposure to COVID-19 among their students, faculty, staff, and surrounding communities. This paper describes the protocol, South Carolina (SC) Safer Together, developed by Clemson University (Clemson) to design, deploy, and evaluate multi-level communication and dissemination and implementation (D&I) strategies in line with recommendations from governmental and educational agencies to mitigate the risk of exposure to COVID-19. Safer Together was enhanced by the addition of the Google/Apple Exposure Notification app, an alternative strategy to support a recommendation of COVID-19 testing outcomes: contact tracing, isolation, and quarantine.

Objective: This study aimed to (1) describe the content and intended audiences of D&I strategies used to deploy recommended COVID-19 mitigation strategies on a major college campus; (2) determine the reach, acceptability, adoption, and use of D&I strategies among target audiences among university students, faculty, and staff; and (3) characterize barriers and facilitators to the implementation and use of recommended mitigation strategies.

Methods: The study team incorporated elements of the Health Belief Model, the Technology Acceptance Model, communication and social marketing models, and the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework to identify and develop appropriate constructs and specific outcomes for inclusion in our approach to evaluate the communication, dissemination and implementation processes related to deployment of Safer Together at Clemson. A parallel convergent mixed methods design was used to (1) inform implementation strategies used to launch the program and (2) evaluate program reach, acceptability, adoption, and use guided by the RE-AIM framework. Data collection tools include surveys, data analytics–tracking, and focus groups or interviews with key stakeholders (students, employees, and university leadership).

Results: Rigorously studying both the dissemination and implementation of Safer Together in a national public university setting is expected to yield lessons that will be valuable at many organizational and governmental settings. On a local level, broad adoption and use of the Safer Together may help reduce COVID-19 transmission and keep the university "open." On a larger scale, lessons learned on how to influence student and employee behavior with respect to the use of a public health outbreak prevention tool including Safer Together may be applicable in future pandemic and outbreak situations.

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Conclusions: This study proposes a structured, theory-driven approach to evaluate dissemination and implementation strategies associated with the deployment of Safer Together in a university setting from the viewpoint of students, employees, and university leadership. Our results will inform future implementation of apps such as Safer Together at major state universities in SC.

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Introduction

Background

As SARS-CoV-2, the virus that causes COVID-19, spread rapidly across the United States in the spring of 2020, institutions of higher education (IHEs) faced numerous challenges associated with minimizing the risk of exposure to COVID-19 among their students, faculty, staff, and surrounding communities [1-3].

This paper describes the protocol used by Clemson University (hereinafter referred to as "Clemson") to design, deploy, and evaluate multi-level communication and dissemination and implementation (D&I) strategies in line with recommendations from governmental and educational agencies to mitigate the risk of exposure to COVID-19 and to assess D&I outcomes (reach, acceptability, adoption, and use), barriers, and facilitators encountered during this deployment from the perspective of multiple stakeholders.

Published guidelines of the Centers for Disease Control and Prevention (CDC) [4-7], the Equal Employment Opportunity Commission [8], the US Department of Education on the Family Educational Rights and Privacy Act [9], the Health Insurance Portability and Accountability Act [10], state and local health agencies and local governments, and various educational organizations such as the Chronicle of Higher Education [11] included these specific strategies for consideration by IHEs:

1. Opening in various formats (eg, virtual only or a hybrid of virtual and in-person classes) during the spring and fall semesters of 2020
2. Requiring entry screening prior to the beginning of each term
3. Implementing a universal screening testing strategy based on whether community SARS-CoV-2 was deemed moderate, substantial, or high
4. Assuring the availability of sufficient testing capacity
5. Consulting with local public health authorities
6. Implementing actions to support testing outcomes of contact tracing, isolation, and quarantine
7. Providing options to immediately separate students with COVID-19 and their close contacts by providing virtual learning options and self-isolation and self-quarantine rooms in residence halls or other housing facilities.
8. Providing support to students to manage COVID-19 symptoms, including medical care as necessary, as well as support managing emotional issues related to isolation or quarantine
9. Provision of alternative food service arrangements for students living on campus
10. Offering alternative teaching and work-at-home options for faculty, instructors, and staff who have COVID-19 or have been identified as a close contact, provided that they are well enough to continue working remotely, and
11. Considering the implementation of flexible sick leave and supportive policies and practices.

Clemson developed and implemented a plan that addressed each of these recommended strategies, in some form, in spring 2020.

Contact tracing is one typical and vital public health response to identify and isolate exposed close contacts (ECC) of known COVID-19 cases. The infectivity characteristics of SARS-CoV-2, the large proportion of very severe or deadly cases, and combined lack of specific treatment options for SARS-CoV-2 make it imperative to quickly isolate infected individuals and identify and track their ECC to reduce the odds of continued spread [12]. Moreover, for SARS-CoV-2, the incubation period is short (ie, 3-5 days); hence, chains of transmission must be recognized quickly in order to have an impact [12,13].

Implementing a timely contact tracing process is relatively slow, requires multiple calls to track down described contacts for interviews, and is labor-intensive. Simulation studies suggest the process is too slow to meaningfully limit COVID-19 spread [14]. In actual practice, reaching out to identified contacts is often unsuccessful [13,14]. Furthermore, the resulting data are flawed by memory biases, and many "contacts" never know that they were exposed.

To circumvent these issues, conventional contact tracing includes asking "cases" about where they were (ie, settings of potential exposure). While this information can be helpful in identifying ECC, information regarding the distance between persons and the total time of exposure gathered in this process often results in some individuals being considered as ECC when they actually had very limited or no exposure to an infected individual.

The time delays and personal recall limitations inherent in conventional contact tracing as well as the epidemiology and pathogenesis of SARS-CoV-2 provide a rationale for investigating novel approaches to control infection via contact tracing such as mobile apps [15].

To address the recommended strategy of implementing actions to support testing outcomes such as contact tracing, isolation, and quarantine, Clemson also took advantage of a novel partnership among the state public health authority for South Carolina (SC), the SC Department of Health and Environmental Control (DHEC), Google, and Apple.

In 2020, Google and Apple created the Google/Apple Exposure Notification system (GAEN), a novel mobile app to help governments and the global community accelerate the process of contact tracing [16]. Mutual agreements among the DHEC, Google, Apple, Clemson Computing and Information Technology (CCIT), and the Medical University of South

Carolina (MUSC) Biomedical Informatics Center branded GAEN as the SC Safer Together App (hereinafter referred to as "Safer Together"). Safer Together became part of an existing informational ecosystem at Clemson, which links test-ordering, test result–reporting, and case referral and management with exposure notification. Combined with deployment of other recommended strategies for COVID-19 mitigation, Safer Together was adopted as an efficient and privacy-protected approach to contact tracing (Figure 1). This system of notification, sharing of test results, and rapid access to testing or medical care when notified of exposure was expected to minimize contact tracing time and conserve campus resources.

Figure 1. Clemson University's information ecosystem for Safer Together.
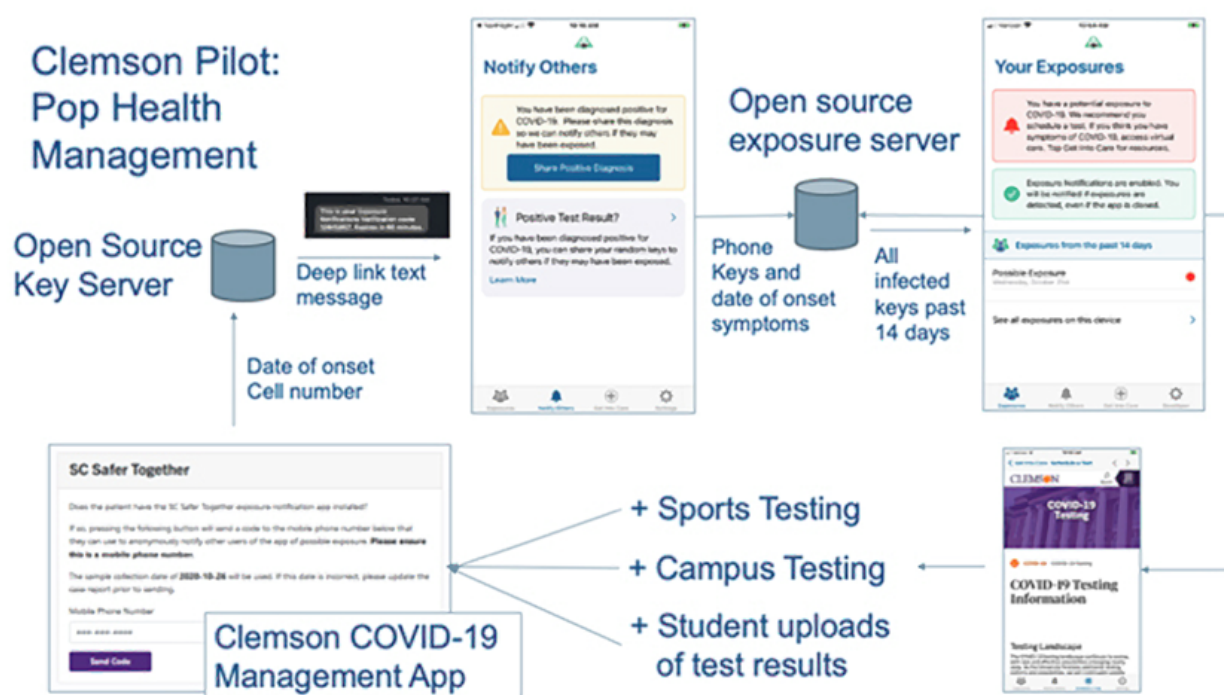
Safer Together interfaces with public health, clinical providers, and clinical laboratory systems as the source of official laboratory findings. Case managers at Clemson Redfern Health Center use an automated function to send the text message, which allows the Key Authorization Server to deliver a digital certificate to the user's cellphone. The cellphone user chooses whether they upload their test result to the exposure server.

To assure user confidentiality, each phone advertises itself using multiple keys that rotate over time to protect from malfeasants. If a match is found with another phone, the duration of exposure (total of 15 minutes at less than 6 feet over 24 hours) and the signal strength are evaluated by functions built into Safer Together and aligned with revised CDC guidelines for significant exposures [6,16].

When an exposure notification is triggered, the exposed individual can use the "get into care" tab for information on what to do next. Compared to conventional contact tracing based on "case" recollection, cellphone-based exposure notifications have the potential to inform individuals of exposures more quickly, to identify a more complete set of true contacts, and to better assess extent of exposure [12]. Additionally,

privacy-preserving Bluetooth technology promptly provides contacts with information regarding the frequency and intensity of lower-grade (shorter time, further distant) exposures, thereby empowering users to proactively measure their risks and take actions, which might safeguard their own health and public health, such as obtaining a test to determine their COVID-19 status or voluntarily quarantining.

Clemson operational units had concerns about whether their campus had sufficient beds and capacity to manage anticipated increases in quarantine facility requirements, based on Safer Together identification of ECC. A compromise plan was developed to conduct a limited pilot deployment of Safer Together for approximately 380 on-campus students living in 2 dormitories.

The first round of student messaging regarding recommended strategies and the use of Safer Together was initiated through Clemson Student Housing on October 28, 2020, to students in the two dormitories. On January 9, 2021, Safer Together was messaged and launched with all Clemson students in 2 waves, the first with students on campus and the second with all students regardless of residence.

Messaging for students was sent via email to explain Safer Together and its capacity to let students know if they had been exposed to someone with confirmed COVID-19, encourage them to download the app, link the app to the Healthy Clemson United as Tigers app, and understand what to do should she/he be notified of potential exposure. Students were also encouraged to participate in efforts to evaluate deployment strategies and learn about their acceptance and use of Safer Together (Figure 2).

Figure 2. Student messaging.

Given the small size of this pilot with students in only 2 dormitories and that on-campus isolation was not a burden to the university employees, Clemson's administration disseminated messaging about Safer Together to all Clemson employees on November 20, 2020, via an email asking them to download and activate Safer Together and advising them of the effort to evaluate Safer Together deployment strategies (Figure 3).

Figure 3. Employee messaging.

Employee Messaging

OUR Clemson
News and Events

Faculty and staff are invited to download and activate their personal health while helping keep the community safe.

SC SAFER TOGETHER, launched in collaboration with the Department of Health and Environmental Control (DHEC), Clemson and the Medical University of South Carolina, does not require personal information for use. Privacy-preserving Bluetooth quickly provides contacts with information about the frequency and intensity of exposures, empowering users to proactively measure their risks and take actions to safeguard their health.

When notified of a potential exposure, SC SAFER TOGETHER will provide steps to schedule a telehealth appointment, take a self-assessment or schedule a test.

For more information about how the app works, click here.

Downloading the app. and participating in the pilot program will also assist a team of Clemson researchers by allowing them to understand the app.'s adoption rate and impact on COVID-19 numbers on campus. Anonymous data will be used to understand how many downloads there are, its effects on the health care system and differences in exposure notification from traditional contact-tracing methods.

Clemson University Relations   **OURClemson@demson.edu**

Evaluation Process Infrastructure

The D&I team is composed of individual representatives of Clemson Public Health Sciences, Clemson Human Resources, Clemson Student Affairs, Clemson Housing, Clemson Strategic Communications, MUSC College of Medicine Department of Public Health Sciences, Clemson Redfern Health Center, and Clemson Strategic Communications. This team was responsible for developing the study protocol, gaining institutional review board (IRB) approvals at both Clemson and MUSC, developing surveys and focus group and interview guides, and coordinating all data collection with Clemson Human Resources, Clemson Redfern Health Center, and Clemson Strategic Communications.

The Clemson-MUSC Safer Together Implementation team was divided into three groups: D&I Research Group (11 members), Technology Design and Enablement (14 members), and Data Analysis (2 members).

The D&I Research Group includes 4 faculty members with expertise in D&I science and is responsible for all aspects of the evaluation study design.

The Technology Design and Enablement Group is composed of members of the MUSC Biomedical Informatics Center and Clemson CCIT. This team was responsible for developing Safer Together and coordinating all design components with systems at DHEC, Clemson Redfern Health Services, and relevant university service components.

The Data Analysis Group includes individuals from the Department of Clemson Public Health Sciences and the Department of Public Health Sciences at MUSC. This group was charged with creating and maintaining study-related databases and conducting analyses.

All teams met together weekly and, as needed, by team or group.

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Methods

Specific Aims and Objectives

The purpose of this mixed methods study is to (1) to characterize and evaluate communication and D&I strategies used to promote and support the use of Safer Together and (2) to examine implementation outcomes (reach, acceptability, adoption, and use), barriers, and facilitators encountered from the perspective of multiple stakeholders.

The study objectives are to:

1. Describe the content and intended audiences of multi-level dissemination and implementation strategies used to deploy Safer Together and other recommended mitigation strategies
2. Determine the reach, acceptability, adoption, and use of Safer Together among targeted audiences of university students, faculty, and staff, and
3. Characterize barriers and facilitators to implementation and use of Safer Together and recommended other mitigation strategies.

Evaluation Framework

Our D&I Research Group incorporated elements of the Health Belief Model (HBM) [17], the Technology Acceptance Model (TAM) [18], communication and social marketing models [19], and the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework [20] to identify and develop appropriate constructs and specific outcomes for inclusion in our approach to evaluating the communication and D&I processes related to the deployment of Safer Together at Clemson.

The HBM was used create questions for use in surveys and focus groups about HBM constructs such as perceived susceptibility, perceived severity, perceived benefits, perceived barriers, and self-efficacy [17].

The TAM measures intent to use a new technology by assessing perceived usefulness, perceived ease of use, compatibility, and self-efficacy of mobile health care systems [18].

Communication and social marketing models were used to create messaging and expected outcomes and to influence behavior by offering target market members (in this case students and employees) an attractive package of benefits and by reducing barriers that would otherwise encourage (or discourage) them from engaging in the behavior [19].

The RE-AIM model served as the guiding framework for measuring the D&I of Safer Together in our research setting [20]. The RE-AIM framework allows multiple measures at various setting levels while focusing on the measurement of "real world" D&I outcomes and processes. Table 1 provides a conceptual overview of the RE-AIM framework as applied to the evaluation of Safer Together.

Table 1. Conceptual overview of the Reach, Effectiveness, Adoption, Implementation, and Maintenance framework applied in Safer Together.

Framework concept	Reach	Adoption	Implementation
Outcomes	Number, proportion, and representativeness of students and employees participating in Safer Together	Number, proportion, and representativeness of settings and agents willing to initiate the Safer Together system	Extent to which the Safer Together system is launched, implemented, and used as planned
Data collection methods	Surveys and focus groups	Focus groups	Surveys, focus groups, and Data analytics tracking

Study Design

A parallel convergent mixed methods design will be used to (1) inform implementation strategies (ie, marketing, distribution, and education) used to launch the program and (2) evaluate program reach, acceptability, adoption, and use guided by the RE-AIM framework [21]. The three main data collection tools include surveys, data analytics–tracking, and focus groups or interviews with key stakeholders (students, employees, and university leadership). Table 2 contains a more comprehensive description of the RE-AIM framework elements, key questions to be addressed, and data to be collected.

Table 2. Evaluation matrix based on the domains of the Reach, Effectiveness, Adoption, Implementation, and Maintenance framework.

Framework domain	Students or employees	Health care providers	University leaders
Reach			
What proportion of eligible individuals were offered and then downloaded the Safer Together intervention?	✓	✓	
What percent of individuals seeking a COVID-19 test report actively using Safer Together?	✓	✓	
How did Safer Together use vary by individuals' demographic characteristics (eg, age, race, gender, student vs employee, faculty vs staff, and student residence location)?	✓	✓	
Effectiveness			
What number and percent of individuals seeking a COVID-19 test report receiving a risk exposure notification on Safer Together?	✓		
Were there differences in the time of the risk exposure notification between Safer Together and formal COVID-19 contact tracing methods?	✓	✓	
What was the effect of Safer Together on health care system outcomes (eg, work processes, organizational change, and interdisciplinary collaboration)?		✓	✓
Adoption			
What are the characteristics of setting and adopting Safer Together?		✓	✓
How well did Safer together fit with the values and expectations of stakeholders?	✓	✓	✓
How did the Safer Together system help Clemson University achieve their educational and practice missions during the pandemic?	✓	✓	✓
Implementation			
Was there sufficient leadership support and buy-in for the Safer Together system (predisposing)?	✓	✓	✓
What were the potential barriers to successful Safer Together implementation and use and how were they addressed (enabling)?	✓	✓	✓
What workflow adjustments were needed to streamline Safer Together into routines of daily life at Clemson University (enabling)?		✓	✓
What measures were needed to create readiness for Safer Together adoption, commitment, and buy-in by stakeholders (enabling)?		✓	✓
Did users perceive Safer Together as easy-to-use and useful (predisposing)?	✓	✓	✓
What were the confidentiality and data security concerns when adopting the Google/Apple Exposure Notification app and how were they addressed (enabling)?		✓	✓
Maintenance			
How did Safer Together use by stakeholders evolve over time?	✓	✓	✓
What efforts were needed to maintain the app participation rate and effectiveness?		✓	✓
Was the use of Safer Together sustained over time?		✓	✓

Study Setting

Clemson University, located in Upstate SC, is one of two land-grant universities in SC. Clemson was founded in 1889 and currently has 20,868 undergraduate students and 5538 graduate students. Clemson offers over 80 major and 90 minor areas of study and more than 130 graduate programs and maintains a 16:1 student to faculty ratio. As a major research university, Clemson was awarded US $106.3 million in research support in 2019-2020. A robust workforce of staff employees (n=4611), faculty employees (n=1742), and emeritus faculty (n=654), totaling to 6007 employees, supports all major initiatives and activities undertaken on and off campus.

Participants

A convenience sample of Clemson students, employees, and leaders involved in implementing or facilitating the use of Safer Together will be presented the opportunity to participate in this study. The inclusion and exclusion criteria for this study are shown in Textbox 1.

Textbox 1. Study inclusion and exclusion criteria.

Inclusion criterion

- All registered students and all employees (faculty and staff) of Clemson University

Exclusion criteria

- Being a nonemployee (eg, contractor)
- Not meeting the aforementioned inclusion criterion

Participant Recruitment, Enrollment, and Consent

Recruitment strategies for each group using social marketing and targeted messaging are detailed below. University representatives from the Student Affairs, Human Resources, and Strategic Communications units will participate as consultants on the D&I team to ensure coordination of efforts.

Social marketing and targeted messaging strategies will be deployed throughout the duration of the study, with specific emphasis on three time points: initial return of students to campus, start of the spring semester (and flu season), and late spring before completion of the academic year.

Given the "opt-in" nature of these user choices, and the fact that identifiable data are not available to the research team, the research team received a waiver of informed consent.

Members of the D&I research team and the Administration department at Clemson will not know whether any user activates or allows deidentified sharing of COVID-19 test results.

With respect to student and employee survey participation, anonymous surveys will be undertaken to obtain information related to student and employee use and perceived usefulness of Safer Together. Accordingly, the D&I Team received a waiver of informed consent for the anonymous surveys to be administered through the academic year.

With respect to focus group discussions addressed below, the D&I Team received a waiver of written informed consent. Verbal consent will be obtained from all participants after a study investigator provides a description of the purpose, procedures, and risks and benefits of the study.

Potential participants include university students, employees, and leaders. Potential participants will be approached through targeted communication avenues (eg, student housing listservs and student and employee newsletters). Our D&I Team will verify that participants meet the study eligibility criteria and approach them via electronic media or cellphone-based methods. Participants will be considered to have been enrolled when verbal consent is obtained in focus groups and acknowledged by moving forward to complete the electronic survey.

Implementation Strategies

Implementation strategies are designed to increase the uptake and use of the Safer Together App by students and employees.

Social Marketing and Targeted Messaging

Social marketing seeks to influence behavior by offering target market members (in this case students and employees) an attractive package of benefits and by reducing barriers that would otherwise encourage (or discourage) them from engaging in the behavior.

Key elements of social marketing include mutual fulfillment of self-interests, consumer orientation, segmentation (marketing to various subsets of the organization), and a marketing mix (product, price, place, and promotion) [19]. The study D&I team (including consulting representatives of Clemson's Strategic Communications, Student Affairs, and Human Resources units) will create targeted messaging based on social marketing principles to be delivered throughout the academic year 2020-2021.

The three major study time periods were the following: original back-to-school messaging in September-October 2020 timeframe, at the transition of semesters (and flu season) in the January-February 2021 timeframe, and spring break to the end of the academic year between March and May 2021.

The overall messaging campaign focused on (1) building a Clemson community partnership around COVID-19 infection control, (2) raising awareness about how exposure notifications can facilitate and supplement other public health efforts, (3) addressing privacy protections and security concerns, and (4) highlighting ease of use and voluntary participation.

Four main strategies were used for the campaign: (1) flyers were posted strategically across campus at the start of the semester; (2) presentations were made at key student, employee, and university leadership meetings; (3) email and social media

messaging were used to provide strategic messages over the course of the planning, early implementation, and maintenance phases, and (4) university-level messaging was delivered electronically via selected venues.

Branding for all materials and messages allows consumers to identify and connect with messages. The Basic Communication Model [19] elements were used to guide the selection of optimal communication channels, sources, and messages to fit the target audiences of students and employees. Messages were distributed

through highly visible channels and delivered by reputable sources (eg, Clemson leaders, staff, and student champions). Table 3 provides further details about each of these strategies.

Messaging was designed to influence student and employee behavior and prompt use of Safer Together. Specific behaviors include downloading the app, activating the app, sharing test results on the app, and pursuing COVID-19 testing if a user receives a Safer Together exposure notification.

Table 3. Sample activities, content, and purpose for marketing activities.

Planned schedule of marketing activities	Content	Purpose
Flyers posted strategically on campus	Highlight the Clemson University community partnership around COVID-19 infection control; brief overview of the app and how to use it; topics will cover benefits of contact tracing, how exposure notification can help, privacy protection, and how the app works	To increase awareness and acceptance of the app, address potential user concerns, and inform users how to use it
Presentations at key web-based employee and student meetings	Highlight the Clemson University community partnership around COVID-19 infection control; brief overview of the app and how to use it; topics will cover benefits of contact tracing, how exposure notification can help, privacy protection, and how the app works	To increase awareness and acceptance of the app, address potential user concerns, and inform users how to use it
Email/social media blasts	Highlight awareness at multiple levels of the university, colleges, and departments; garner student support and enthusiasm	To increase awareness and commitment at the university and department levels
University messaging 1 (via selected venues)	Highlight the importance of university commitment to curtail the spread of COVID-19; expand the readership to a variety of stakeholders	Increase awareness to a broad range of stakeholders; convey commitment from university leadership
University messaging 2	Brief overview of the app and how to use it; topics will cover the importance of the Clemson university community partnership for COVID-19 infection control; the benefits of contact tracing, how exposure notification can help, privacy protection, and how the app works	To increase awareness and acceptance of the app, address potential user concerns, and inform users how to use it
University messaging 3	Reminder about Clemson University community partnership for COVID-19 infection control and frequently asked questions about the app, and who to contact with questions about installing and using the app if an exposure occurs	To address problems users may be having in using the app via a series of frequently asked questions
University messaging 4	Brief stories of how the app has been successful when used in other places	To increase awareness of public health benefits of using the app
University messaging 5	Brief update on Clemson University's experience using the app and how it may help control the pandemic on campus	To increase buy-in regarding the app
University messaging 6	Reminder about Clemson University community partnership for COVID-19 infection control and engagement with the app again, repeating the brief overview	To provide a booster educational session to encourage continued use
University messaging 7	Messaging about not letting one's guard down during the spring break—continue protections and engagement with the app (spring break starts on March 15)	To increase buy-in regarding the app during vacation
University messaging 8	Message of thanks for participating in the app, with a brief summary of Clemson University's experience using the app	To debrief and increase buy-in

Study Flow and Data Collection Processes

Closer to the date of student return to the Clemson campus, the university initiated a series of messages to students and employees about Safer Together and this study. Messaging encouraged downloading of Safer Together to student and

employee cellphones, individual consent to activate Safer Together, and individual consent to share COVID-19 test results.

Students and employees selected through random sampling for COVID-19 testing, who present at the COVID-19 testing site at Clemson Redfern Health Center, will be asked questions as part of their registration process related to Safer Together. One

question asks if the individual has downloaded and activated Safer Together. A second question relates to whether the individual presented for COVID-19 testing primarily because of a Safer Together exposure notification alert.

Students and employees not selected through random sampling but presenting for COVID-19 testing at the COVID-19 testing site will be asked questions as part of their registration process related to Safer Together. One question asks if the individual has downloaded and activated Safer Together. A second question relates to whether the individual presented for COVID-19 testing primarily because of a Safer Together exposure notification alert.

Students and employees were asked to complete a one-time electronic anonymous survey administered by the D&I team to address framework measures. Key questions included assessments of the individual's decision to download and activate Safer Together, consent to record COVID-19 test results in Safer Together, and report whether they took some action in response to an exposure notification (eg, additional COVID-19 testing and quarantine). Additional questions assessed user experiences with the app and whether they found the app acceptable and easy to use. Among those who did not download the app, questions focused on factors influencing one's decision to not download Safer Together, including perceived barriers to downloading the app. All participants were asked questions about testing behaviors, perceived susceptibility to and severity of COVID-19, and individual sociodemographic characteristics.

At key points during the study, focus groups facilitated by the D&I team will be conducted with key stakeholders including students and employees (health care providers and university leaders) to address framework measures. Questions will predominantly address measures within the Adoption, Implementation, and Maintenance domains of the RE-AIM framework by using a structured interview guide. Focus groups will be completed virtually (on Zoom), last approximately 45-60 minutes, and be audiotaped for analysis.

Key leaders involved in developing, planning, and launching the Safer Together initiative were selected to complete individual interviews using a structured interview guide. Participants will include representatives from the information technology office, the Clemson Redfern Health Center, the communications office, the Healthy Clemson: United as Tigers initiative, dormitory housing, and the public health strategy team. Participants will be invited to participate in a 30-minute, audiotaped interview.

Using a team-developed implementation tracking log (Figure 4), the D&I Team monitored the completion, timing, and barriers faced in accomplishing planning, engagement, technology development, and messaging milestones. The log was competed at routine team meetings to assess completion of steps (with "yes" or "no" responses) and whether delays (eg, information technology, communication, university leadership, and engagement) were encountered.

Figure 4. Implementation tracking log. DHEC: Department of Health and Environmental Control; FAQ: frequently asked questions; IRB: institutional review board.

Implementation Events	Month	Delay?	Barriers Encountered	Facilitators Encountered	Notes	Notes-Implications
Submit IRB applications						
Build and engage core team members						
Designate team member roles						
Design study launch steps						
Finalize testing services						
Secure Clemson leadership support of plans						
Recruit key student stakeholders for pilot						
Secure IRB approval for modified protocol and data collection tools						
Train key stakeholders (e.g., student abassadors)						
Embed testing questions into Rymedi workflows						
Launch pilot program in dorms						
Invitation email to dorms						
Develop and submit scholarly study products						
Complete planning meetings						
Establish DHEC partnership						
Complete App Design						
Pretest App features						
Secure needed approvals						
Finalize App Name/branding considerations						
Complete tailored technology for ios						
Complete tailored technology for Android						
Complete technology testing						
Design FAQ's						
Engage key stakeholders for student stories						
Engage key stakeholders for employee stories						
Design student-facing messaging plans for pilot						
Design employee-facing messaging plans						
Secure needed approvals for launching messages through designated channels						
Prestest materials						
Flyers posted on campus						
Presentations deivered at key online faculty and student meetings						
University-level messaging delivered through Strategic Communications						
Launch social media blast phase I						
Launch social media messages phase II						
Launch social media messages phase IIII						
Ongoing evaluation of progress						

Primary Outcomes of Effectiveness

In this study, limited data are available for extraction by the research team from Safer Together, so most study measures are captured by alternative approaches. The four primary outcome measures are downloading the Safer Together app, activating Safer Together, activating sharing of COVID-19 test results in Safer Together, and responsive behavior to Safer Together exposure notification.

Participants Downloading Safer Together

The number and proportion of research participants who seek testing and those who complete the survey and download Safer Together will be delivered via the DHEC to Clemson CCIT. We will record this statistic on a daily basis and aggregate for periods prior to and after our social marketing targeted messaging.

Participants Activating Safer Together

The number and proportion of research participants who present for COVID-19 testing and claim that they have downloaded Safer Together and activated its exposure notification alert will be recorded.

Participants who consent to sharing COVID-19 results within Safer Together and the number and proportion of those who declare that they have authorized the sharing of COVID-19 results on Safer Together will be recorded. These data are not available from Safer Together and can only be assessed through surveys and focus groups.

Effect of Safer Together Exposure Notification Alert on Participant Behavior

The number and proportion of research participants who present for COVID-19 testing and claim that the primary reason for

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presenting for COVID-19 testing was a Safer Together exposure notification alert will be recorded.

Statistical Analysis

Sample Size

The survey was administered to a random stratified sample of 20% of Clemson employees (n=802) and students (n=4998), for a total sample size of 5790 individuals.

Analysis Plan

The analysis of our mixed methods approach will follow approaches for assessing and integrating findings from both a quantitative and qualitative perspective [21].

Safer Together overall use will be measured by a binary variable ("yes" or "no"). Univariate analyses for differences in app use via student demographics will be compared using chi-square tests and independent 2-sample t tests for categorical and continuous variables, respectively. Multivariate analyses will be performed using logistic regressions. Exposure notification time will be defined as the average of the time between an individual's recorded COVID-19 test (if positive) and notification of all contacts. Differences in exposure time between the two methods will be assessed using Kaplan-Meier estimators and Cox proportional hazard models.

The reach of each method will be measured as the number of contacts informed; differences will be assessed using independent 2-sample t tests. Upon presentation to health services, students will be asked whether they were notified of exposure through the Safer Together app, formal contact tracing, or other. Comparisons between Safer Together app tracing and formal contact tracing will be conducted using chi-square tests.

Transcriptions of digital recordings of focus groups and field notes will be analyzed to characterize app use experiences and barriers and facilitators to program delivery, adoption, and implementation. Analysis will be conducted using manual coding to identify, categorize, and contextualize patterns. We will use an initial codebook derived from the RE-AIM framework also allowing additional themes to arise directly from the data. Two independent coders will read and reread transcripts, outlining and organizing themes and subthemes; discrepancies will be resolved in team meetings. After completing qualitative and quantitative data analyses independently, we will use graphical matrix configurations ("joint displays") to integrate survey findings with qualitative data for data triangulation [21]. Qualitative themes will be supplemented by patterns identified in quantitative results guided by the RE-AIM framework.

We will use a team-based approach with individual and dual review of data and data findings with, as appropriate or needed, adjudication by a third party to interpret and translate results and determine D&I implications of our findings.

Ethics Approval

The protocol was approved by both the Clemson University IRB and the IRB-II-Medical University of South Carolina on September 11, 2020.

Results

Rigorous evaluation of both the dissemination and implementation of Safer Together in a national public university setting is expected to yield insights that will be valuable at many organizational and governmental settings. On a local level, broad adoption and use of the Safer Together may help reduce transmission of COVID-19 and keep the university "open." On a larger scale, lessons learned on how to influence student and employee behavior regarding the use of a public health outbreak prevention tool like Safer Together may be applicable in future pandemic and outbreak situations.

Discussion

This study proposes a structured approach based on the RE-AIM framework, to evaluate dissemination and implementation strategies associated with deployment of the Safer Together in a university setting from the viewpoint of students, employees and university leadership. The results of this study will inform future implementation of apps such as Safer Together at major state universities.

Authors' Contributions

CLM is the primary author and senior advisor. KRS is the secondary author and D&I advisor, and led quantitative tool development and analysis. RG is the Chair of the D&I Research Team and liaison with Clemson and MUSC information technology groups and with the Clemson leadership. LL is the lead bioinformatics team member. KBC is the senior author, developed the analysis plan, and is the lead qualitative analyst. The SC Safer Together Team includes Latoya Daniels, Kristin Donnelly, Leasa Evinger, Lesslie Graves, Corey Kalbaugh, Lior Rennert, Tara Romanella, and Heidi Williams.

Conflicts of Interest

None declared.

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Abbreviations

CCIT: Clemson Computing and Information Technology
CDC: Centers for Disease Control and Prevention
DHEC: Department of Health and Environmental Control
D&I: dissemination and implementation
ECC: exposed close contacts

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GAEN: Google/Apple Exposure Notification
HBM: Health Belief Model
IHE: institution of higher education
IRB: institutional review board
MUSC: Medical University of South Carolina
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
SC: South Carolina
TAM: Technology Assessment Model

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<u>Protocol</u>

Helping Patients Communicate With Oncologists When Cancer Treatment Resistance Occurs to Develop, Test, and Implement a Patient Communication Aid: Sequential Collaborative Mixed Methods Study

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Abstract

Background: Most cancer-related deaths result from disseminated diseases that develop resistance to anticancer treatments. Inappropriate communication in this challenging situation may result in unmet patient information and support needs. Patient communication aids such as question prompt lists (QPLs) may help.

Objective: This study aims to develop and pilot-test a specific QPL in the following two contrasting clinical contexts in France after cancer resistance has developed: triple-negative and luminal B metastatic breast cancer (MBC) and metastatic uveal melanoma (MUM).

Methods: A sequential study design with a mixed methods collaborative approach will be applied. The first step aims to build a specific QPL. Step 1a will explore oncologist-patient communication issues from oncology professionals' interviews (n=20 approximately). Step 1b will appraise information and support needs experienced by patients with MBC or MUM both quantitatively (n=80) and qualitatively (n=40 approximately). These data will be used to develop and pilot-test a QPL specific to patients with cancer experiencing initial or acquired resistance to treatment. We expect to obtain a core QPL that comprises questions and concerns commonly expressed by patients with resistant cancer and is complemented by specific issues for either MBC or MUM cancer sites. In step 1c, 2 focus groups of patients with any type of metastatic cancer (n=4) and health care professionals (n=4) will be conducted to revise the content of a preliminary QPL and elaborate an acceptable and feasible clinical implementation. In step 1d, the content of the QPL version 1 and implementation guidance will be validated using a Delphi process. Step 2 will pilot-test the QPL version 1 in real practice with patients with MBC or MUM (n=80). Clinical utility will be assessed by comparing responses to questionnaires administered in step 1b (QPL-naive historical control group) and step 2 (QPL intervention group).

Results: This study received grants in March and December 2019 and was approved by the French national ethics committee in July 2019. As of October 2021, interviews with oncology professionals have been conducted and analyzed (N=26 to reach saturation), and 39 and 27 patients with MBC and MUM, respectively, have been recruited.

Conclusions: A clinically and culturally tailored QPL is expected to facilitate patients' participation in consultations, improve oncologists' responses to patients' information and support needs, and thus foster patients' psychological adjustment to the diagnosis and follow-up of cancer resistance to treatment.

Trial Registration: ClinicalTrials.gov NCT04118062; http://clinicaltrials.gov/ct2/show/NCT04118062

International Registered Report Identifier (IRRID):   DERR1-10.2196/26414

Introduction

Background

Most advanced cancers eventually develop resistance to anticancer therapies, ultimately leading to the progression of the disease, symptom burden, and death [1]. Resistance may occur very early in the course of disease (often called *primary resistance*) or, in most instances, is acquired under long-term treatment exposure after a favorable initial response (secondary resistance).

Cancer progression, resulting from resistance to therapy, often indicates the onset of an advanced disease that will not be cured, although life expectancy may still be months or years with adequate treatment. This clinical situation represents a critical moment in the course of cancer care. Oncologist-patient communication is then particularly challenging. When resistance occurs, patient information on the severity of the disease, its prognosis, and the therapeutic options must be conducted with utmost subtlety. Patients are informed about alternative cancer treatments, expectations about their effectiveness, and side effects. This information is anxiety provoking, often eliciting the need for emotional support.

Information on prognosis and treatment outcomes is important for achieving a shared perception of the disease status and treatment goals between patients and oncologists [2-4]. A general population survey performed in 7 European countries indicates that 73% of citizens prefer to be informed in case of a poor disease prognosis (≤1 year to live) [5]. In the advanced cancer setting, most patients want a realistic understanding of their current condition and life expectancy; however, not all wish to receive exact or definitive time frames [2,6-9]. Oncologists have difficulty appraising patients' information preferences [10]. Information on prognosis is often lacking [11], and patients do not understand that the treatment provided is not likely to cure their cancer [12].

In addition, patients with advanced cancer do not participate as much as they wish during consultations [8,13]. Possible explanatory factors include patients forgetting questions, doubting the legitimacy of asking, expressing concerns indirectly, fear of the possible pejorative answer, and a lack of physicians encouraging their questions [14-16]. Patients may also present different needs and expectations, which depend on the time in their disease course [17] or factors such as their attentional coping style or sociodemographic background [10,18,19]. Discordance between the patient's and oncologist's perception of treatment aims and the disease timescale may result in medical decisions that do not align with life goals that are important to patients [20,21]. This leads to patients' greater psychological distress [22].

Patient-centered communication is the cornerstone of high care quality [23]. This allows physicians to better respond to patients' information and support needs. To this end, guidelines to improve communication skills of health care professionals are available in many countries [24-28]. Effective physician-patient communication may decrease patients' anxiety, sustain hope [29], and increase satisfaction with care [30-32]. Patient-focused communication aids have also been developed to complement physician communication skills training [18,30-32]. These interventions are designed to enhance patients' participation in the consultation and thus may increase physicians' awareness and timely accommodation of their needs and expectations [33-36].

Question Prompt Lists

Among patient-focused communication aids, question prompt lists (QPLs) [37-43] may help patients express their information and support needs according to their wishes. A QPL includes a structured list of questions given to the patient before the consultation. This intervention drives patients to more frequently ask questions and express concerns, especially regarding disease prognosis, and may enhance patients' recall of information and satisfaction with care [38,39,41,42,44-48].

Most QPLs that are already available address early cancers [39,49] or palliative care [41,50-52], specific clinical situations (eg, early breast cancer [53], esophageal cancer [54,55], and myelodysplastic syndrome [56]), care circumstances (eg, clinical trials [57,58]), and populations (eg, older patients with cancer [58] or cultures or ethnicity [53,59])

A QPL for oncology consultations taking place during the first treatment lines after cancer resistance has developed seems to be lacking. Such a QPL is expected to contain questions or concerns related to the following issues: disease severity, extent of spread, future course, medical tests, treatment options, course

of symptoms and side effects [60], likelihood of cure, primary goal of cancer care, expected treatment effectiveness and life expectancy [61], psychological needs [62], self-management [63], and cancer care provision and organization [64]. A QPL designed for advanced cancer care in Australia and adapted in the United States [37] and in the Netherlands [18] will serve as a basis.

In Western countries, a shift has been witnessed in models of care from a paternalistic to a patient-centered approach, tailoring information to patient preferences and wishes [65]. However, for example, little information exists on French patients' wishes to receive information on prognosis [56] and on the concordance between oncologists' information provision and the expectations of patients with cancer. In a previous study with patients receiving palliative care, we observed that addressing disease prognosis was seen as particularly difficult for clinicians [66]. The cultural adaptation of a QPL may be necessary not only in terms of content but also in terms of implementation modalities. Theoretically, QPLs are simple and cost-effective; however, their acceptability and implementation feasibility should also be verified cross-culturally. Therefore, optimal modalities and procedures of applying this tool in real oncology practice in France will also be explored and delineated. It is possible that a patient coaching or education group intervention may be needed as a complement.

Clinical Setting

The QPL will be developed in the following two clinical contexts, which are prone to cancer resistance, and contrasted in terms of epidemiology, life expectancy, long-term treatment options, and expected effectiveness: (1) triple-negative and luminal B metastatic breast cancer (MBC) and (2) metastatic uveal melanoma (MUM), both within the first 3 lines of anticancer treatment after treatment resistance has occurred.

Triple-negative and luminal B MBC represents approximately 15% and 50% of all breast cancer cases, respectively [67], and recurs with distant metastasis in approximately 30% of early-stage patients [68]. MBC is an incurable disease, with a median overall survival of 3 years and a 5-year survival rate of 25% [69]. Patients with MBC are generally followed by their oncologist for years, punctuated by occurrences of treatment resistance for which a new treatment regimen may be offered. This implies successive disclosures of the progressing disease and discussions of alternative treatment regimens [70].

Uveal melanoma is a rare cancer [71]. Up to 50% of patients with uveal melanoma develop metastases, mostly in the liver, within a median time of 2 to 3 years [72]. Once metastasis occurs, the median overall survival ranges from 9 to 12 months because of the lack of effective treatment options [73]. Most patients with MUM are referred to a medical oncologist after a multidisciplinary tumor board meeting. Medical oncologists then inform patients about metastatic progression and possible treatment alternatives. The dismal prognosis and rapid evolution of the disease are challenging aspects in the communication between oncologists and patients. A discrepancy in knowledge appears when the medical oncologist is aware of the patient's poor prognosis while the patient is still in good shape and does not expect such quick, fatal outcomes.

Objective

We propose an original design for the development of a complex intervention based on the Medical Research Council framework [74].

The specific aims are (1) to develop the content of a QPL for adults diagnosed with resistant cancer, who are still eligible for disease-targeted treatment, and (2) to pilot-test the implementation of this intervention in oncology consultations in a French cancer setting. During this process, the implementation will be prepared by investigating potential obstacles and facilitation strategies from the outset.

We expect to obtain a core QPL comprising questions and concerns that patients in the treatment resistance context might generally want to express at the oncology consultation. A common *core* QPL will be complemented with subsections containing specific issues for either the triple-negative and luminal B MBC or the MUM cancer sites.

Methods

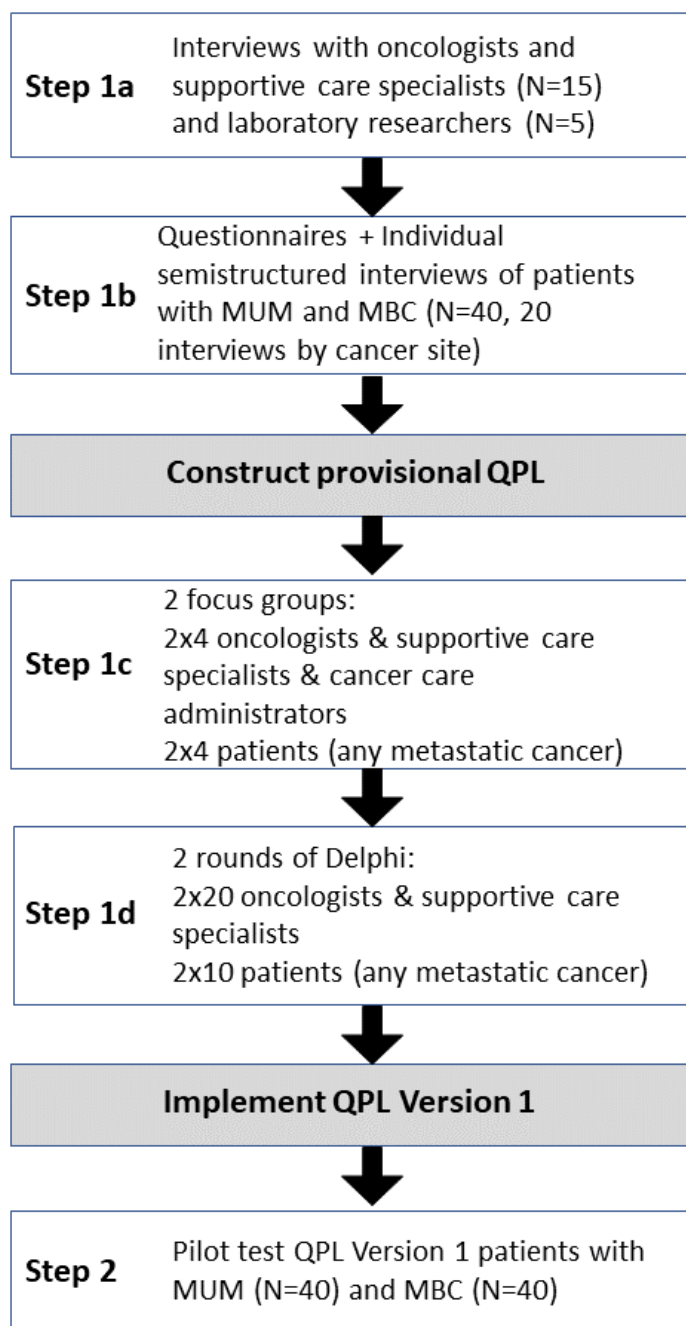### Patient and Public Involvement

This psychosocial study is embedded in an overall medical research program performed within the Institut Curie Integrated Cancer Research Site—*Site de Recherche Intégrée sur le Cancer*. In France, this framework is equivalent to a comprehensive cancer center and has been labeled by the French National Cancer Institute. This research program deals with treatment resistance in triple-negative and luminal B MBC and MUM. A patient and partner representative committee was created with the objective of fostering public debate and integrating patients' voices into research development, conduct, and dissemination. This committee was involved in the choice of the psychosocial study research question. Outcome measures were selected according to priorities, experience, and preferences. They found it particularly relevant and timely to address communication difficulties between the oncologist and the patient when treatment resistance occurs. Since 2017, their involvement has taken place at regular steering committees and brainstorming meetings. They provided feedback on this study protocol; the information and consent forms; and the content, format, and burden of the questionnaires.

Study Design

As shown in Figure 1 and Table 1, we will adopt a sequential design and mixed methods approach [75,76], evolving in successive steps and building on qualitative (individual and focus group interviews) and quantitative (standardized questionnaires, acceptability assessment, and Delphi process) data collection and analysis. It will involve the collaboration of adult patients with MBC or MUM, patients with any type of metastatic cancer (ie, *expert patient*, defined as "individuals with an experience of cancer diagnosis & treatment and educated knowledge of their disease and treatment trajectory" [77,78]), oncologists, supportive care specialists, cancer care administrators, and laboratory researchers dealing with cancer resistance [79].

Figure 1. Sequential study design. MBC: metastatic breast cancer; MUM: metastatic uveal melanoma; QPL: question prompt list.

Table 1. Sequential collaborative mixed methods approach.

Steps	Aim	Method	Sources or population
Step 1: QPL[a] development	To develop a QPL for the treatment of resistant cancer in 2 contrasting clinical contexts: MBC[b] (triple-negative and luminal B) and MUM[c]	• Mixed methods	Professionals and patients
Step 1a	To explore oncologist-patient communication issues (ie, difficulties, obstacles, and strategies) in the context of cancer resistance	• Individual interviews	Professionals, that is, oncology physicians, supportive care specialists, and laboratory researchers (from bench to bedside)
Step 1b	To explore communication difficulties and information and support needs that are experienced by patients with resistant cancer after an oncology consultation to initiate or follow a new disease-specific treatment after cancer resistance has developed	• Standardized questionnaires • Individual interviews	Patients with MBC (triple-negative and luminal B) or MUM within the first 3 lines after first cancer resistance[d]
Step 1c	To revise the content of a QPL developed for patients with advanced cancer and elaborate an acceptable and feasible clinical implementation, potentially facilitated by a coaching intervention	• Focus groups	Professionals and patients (any type of metastatic cancer)
Step 1d	To validate the content of a QPL preliminary version adapted to cancer resistance and the MBC (triple-negative and luminal B) and MUM contexts (version 1) and the implementation guidelines	• Delphi surveys	Professionals and patients (any type of metastatic cancer)
Step 2: QPL pilot testing	To pilot-test a QPL version 1: acceptability, feasibility, and potential clinical utility (effects)	• Standardized questionnaires (same as in step 1b)	Patients with MBC (triple-negative and luminal B) or MUM within the first 3 lines after first cancer resistance

[a]QPL: question prompt list.

[b]MBC: metastatic breast cancer.

[c]MUM: metastatic uveal melanoma.

[d]Patients in step 1b comprise a historical control group to which the patients provided with the preliminary question prompt list in step 2 will be contrasted.

Study Assessment and Procedures

The approval for the study was obtained from the French national ethics committee (ID-RCB: 2019-A01713-54). All patients will provide signed informed consent. The study, for which the acronym is HECTOR (Helping Patients Communicate With Oncologists When Cancer Treatment Resistance Occurs), is registered as NCT04118062 in ClinicalTrials.gov.

Step 1: QPL Development and Implementation Guidelines

Overview

Step 1 focuses on determining the QPL content, structure, and format, as well as the clinical implementation modalities. This step will allow the definition of the clinical setting of cancer resistance and the factors that may facilitate or impede patients' participation in oncology consultation. We aim to define a print brochure, along with a website and mobile app, offering a QPL perceived as attractive and satisfactory by patients and clinicians and that may be successfully used in the clinic (Table 1).

Interviews with patients and professionals will explore patient-oncologist communication issues in the context of cancer resistance. Moreover, study participants will be prompted to consider the relevance of a communication aid in the form of a QPL and complement this tool with patient coaching (ie, an intervention involving an interaction with a health professional or peer-support patient) and to prepare the operational implementation of this intervention in routine practice [80,81].

Step 1a: Oncologist-Patient Communication in the Clinical Management of Resistant Cancer

Individual semistructured interviews with oncologists, supportive care specialists, and laboratory researchers selected according to the inclusion and exclusion criteria listed in Textbox 1 started in July 2019.

Textbox 1. Professionals and patients' eligibility criteria included at each step of the study.

Inclusion criteria

- Professionals

- Oncology physicians (medical oncologist, oncology surgeon, radiation oncologist, and supportive care specialist), oncology laboratory researchers, and cancer care administrators

- Dealing with cancer resistance in solid malignancies

- Patients with metastatic breast cancer or metastatic uveal melanoma (MUM)

- Aged ≥18 years

- Diagnosed with resistant cancer

- Metastatic triple-negative or luminal B breast cancer or MUM

- Within the first 3 treatment lines after cancer resistance has developed

- Informed of cancer diagnostic and treatment resistance

- Patients with any type of metastatic cancer

- Aged ≥18 years

- With any type of cancer diagnosis

Exclusion criteria

- Professionals

- Physicians or laboratory researchers not involved in cancer resistance research

- Patients with metastatic breast cancer or MUM

- Unable to complete surveys in French

- Patients with any type of metastatic cancer

- Unable to participate in a group interview or complete a questionnaire survey because of physical, cognitive, or linguistic (French language) barriers

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A purposeful sample is planned to allow the obtaining of a variety of perspectives on the clinical situation of cancer resistance [82]. Snowball sampling (ie, inclusion by approaching further participants through initial ones) will identify participants in different oncology hospitals or departments (France) from participants initially interviewed in 1 cancer center (Institut Curie, Paris).

Laboratory researchers will be solicited because of their outlook and up-to-date knowledge of cancer resistance research; they will be susceptible to anticipate new therapeutic regimens and their clinical translations.

An interview guide comprising open-ended questions will explore the following three central themes: (1) the definition of drug resistance and cancer resistance; (2) perceptions of oncologist-patient communication when the patient is diagnosed with resistant cancer, initial or acquired, after 1 or several treatment regimens; and (3) perceptions of oncologist-patient communication difficulties, obstacles, and facilitating strategies in the clinical context. The expected sample size based on data saturation is approximately 20 participants (Table 2) [83]. The duration of each interview is estimated to be between 30 and 45 minutes.

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Table 2. Sample size by study population.

Population and data collection	Cancer resistance to treatment (before consultation)	
	Historical control (step 1; N=80)	QPL[a] (step 2; N=80)
Number of patients		
MUM[b] within the first 3 treatment lines after cancer resistance has developed		
Questionnaires	40	40
Individual interviews	20	—[c]
Triple-negative and luminal B MBC[d] within the first 3 treatment lines after cancer resistance has developed		
Questionnaires	40	40
Individual interviews	20	—
Number of professionals		
Oncologists or supportive care specialists or cancer care administrators		
Individual interviews	15	—
2 focus groups	8[e]	—
2-round Delphi	40[f]	—
Laboratory researchers		
Individual interviews	5	—
Number of patients with any type of cancer diagnosis		
Any cancer		
2 focus groups	8[e]	—
2-round Delphi	20[g]	—

[a]QPL: question prompt list.

[b]MUM: metastatic uveal melanoma.

[c]Not available (no individual interview in step 2).

[d]MBC: metastatic breast cancer.

[e]n=2×4.

[f]n=2×20.

[g]n=2×10.

Step 1b: Patients' Communication Experience and Information and Support Needs in the Oncology Consultation Dealing With Treatment Resistance

Overview

A cross-sectional assessment of patients' communication needs in the context of cancer resistance will then be performed. Patient enrollment started in January 2021 and will take place over 1 year.

Consecutive patients will be identified via lists of oncology consultation agendas in an oncology center (Institut Curie, Paris). If they respond to the inclusion and exclusion criteria listed in Textbox 1, they will be invited to participate in the study.

Patients' sociodemographic data (age, gender, educational level, and marital, parental, and professional status) and clinical data (date of initial diagnosis, disease recurrence and metastatic occurrence, stage, previous and current disease-targeted treatments, and supportive care interventions) will be collected

from patients or medical records to describe the study population.

Qualitative Assessment

Individual semistructured interviews will be proposed to a random subsample of these patients to specify in greater depth and detail the nature and temporality of communication experience, difficulties, and needs when confronted with cancer resistance.

On the basis of data saturation [83,84], an expected number of approximately 20 patients per cancer site will be interviewed no later than 1 month after they complete the questionnaires (Table 2).

The interview guide, comprising open-ended questions, will explore the following three central themes: (1) patients' actual experience of communication with the oncologist; (2) their expectations, preferences, met and unmet information, and support needs (retrospectively and prospectively); and (3) their opinions about a specific QPL to help them communicate with

oncologists. Individual interviews are estimated to last between 30 and 45 minutes.

Quantitative Assessment

Standardized questionnaires will be completed by patients to describe their unmet information and support needs while facing cancer resistance in the MBC and MUM settings. These questionnaires will also be used to obtain preliminary data, albeit limited to the potential clinical usefulness of the designed QPL. This will be performed by comparing responses from

patients at step 1b (QPL-naive group) with clinically similar patients at step 2 (QPL intervention group).

As information needs may depend on patients' characteristics [10,18], these outcomes will be assessed according to patients' sociodemographic (ie, age, gender, educational level, and marital status) and psychological correlates (ie, beliefs, preference for information, level of distress, and coping strategies). To address these outcomes and correlates, patients will be invited to complete standardized questionnaires, as detailed in Table 3.

Table 3. Standardized questionnaires.

Measures of QPL[a] potential clinical benefits	Factors assessed
Outcomes	
1 item of the PTPQ[b] [61]	• Satisfaction with the quality of information received about prognosis and treatment
EORTC QLQ-INFO25[c] information about the disease, medical tests, and treatments scales (items 31-43) and satisfaction with information items (52-55) [60]	• Perception of information received about the disease, medical tests, and treatments • Satisfaction with information
SCNS-SF34[d], Psychological (items 6-14 and 17) and Care and Support needs (items 18-22) [85]	• Perception of unmet psychological (eg, anxiety, fear of cancer spreading, and uncertainty) and care and support needs (eg, reassurance and sensitivity to feelings and emotional needs)
Correlates	
12 items of the PTPQ [61]	• Beliefs regarding the likelihood of cure, the importance and helpfulness of knowing about prognosis, and the primary goal of cancer care • Preference for information about treatment
HADS[e] [86]	• Anxiety and depression
Brief COPE[f] [87]	• Coping strategies

[a]QPL: question prompt list.

[b]PTPQ: Prognosis and Treatment Perceptions Questionnaire.

[c]EORTC QLQ-INFO25: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Information Module.

[d]SCNS-SF34: Supportive Care Needs Survey–Short Form.

[e]HADS: Hospital Anxiety and Depression Scale.

[f]COPE: Coping Orientation to Problems Experienced.

Patients' perception of prognosis and treatment will be assessed using the Prognosis and Treatment Perception Questionnaire (PTPQ) [61]. The PTPQ assesses beliefs regarding (1) the likelihood of cure, (2) the importance and helpfulness of knowing about prognosis, (3) the primary goal of cancer care, (4) preference for information about treatment, and (5) satisfaction with the quality of information received about prognosis and treatment (Table 3). This questionnaire has been translated into French and pilot-tested according to the European Organization for Research and Treatment of Cancer Quality of Life Group guidelines [88].

The perception of information received about the disease, medical tests and treatments, and satisfaction with overall medical information will be measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Information Module (EORTC QLQ-INFO25) scale [60]. The perception of unmet

psychological (eg, anxiety, fear of cancer spreading, and uncertainty) and care and support needs (eg, reassurance, sensitivity to patients' feelings, and emotional needs) will be measured by the Supportive Care Needs Survey–Short Form (SCNS-SF34) [85].

Additional patient information will include coping strategies (usual strategies when facing stressful life events) and distress (during the past week), as measured by the Brief Coping Orientation to Problems Experienced [87] and the Hospital Anxiety and Depression Scale [86] questionnaires, respectively.

Questionnaires will be completed within 2 weeks of the consultation; if not completed within this time-lapse, 1 reminder will be made by telephone. Questionnaires not returned after 1 month will be considered missing.

As indicated in Table 2, a sample size of 80 patients (40 patients by tumor site) is planned. Sample sizes up to 40 per group are

expected to provide estimates that are precise enough to assess the feasibility of QPL use and obtain preliminary clinical data for further randomized controlled trials of this tool [89].

Step 1c: Content and Implementation of the QPL in Routine Practice

From steps 1a and 1b, a core QPL comprising issues (ie, questions and concerns) commonly expressed by patients with resistant cancer, complemented by specific issues for either MBC or MUM cancer sites, will be developed. Issues to compose this QPL will be selected based on descriptive analyses of patients' responses to relevant items of the PTPQ, EORTC QLQ-INFO25, and SNCS-SF34 questionnaires. For example, if ≥50% of patients report that they received little or no information about the spread of their illness from the EORTC QLQ-INFO25 and are dissatisfied with the information provided, this issue will be prioritized while composing the QPL. Other issues will be similarly selected based on responses to items of the SCNS-SF34 (50% of patients reporting medium or high unmet needs) or the PTPQ (50% reporting that the quality of information on treatment options received from the oncologist was fair or poor). These quantitative data will be considered in conjunction with the qualitative interview data. A thematic content analysis will help identify issues that patients would like to address more frequently during oncology consultations dealing with cancer resistance.

Focus groups will be implemented to discuss the provisional QPL. On the basis of research on sample size calculation for the content analysis of qualitative interviews [83], we aim to conduct 2 focus groups of approximately 8 different participants each (patients with any type of metastatic cancer, oncologists, supportive care specialists, and cancer care administrators from various oncology centers or departments in France), approached through snowball purposive sampling. Participants will be identified from contacts of *expert* patients (patient university, Institut Curie *Site de Recherche Intégrée sur le Cancer* patient and partner representatives, and cancer patient associations) and oncology professionals (UNICANCER oncology professionals' network and French Association for Supportive Care—Association Francophone pour Soins Oncologiques de Support).

The group interview guide will address the following two central themes: (1) the appropriateness (adequacy, relevance, and importance for treatment resistance in oncology generally and in triple-negative and luminal B MBC and MUM specifically) and acceptability (satisfaction, anxiety-provoking, intrusiveness, irrelevance, and incompleteness) of the QPL content (questions, concerns or emotions, and narratives or testimonies), structure (logical order, length, and complexity), and format (paper, website, and app) and (2) the feasibility (obstacles and facilitating strategies such as complementary coaching, formal implementation blueprint, educational materials, and audit and feedback [90]) and optimal circumstances and procedures (when: timing of provision or access; where: hospital or home; how: text or video; who: coach or health educator expertise) for implementing the QPL in real-world clinical practice and ensuring its adoption and sustainability. The internationally designed QPL for patients with advanced cancer has been revised and further developed for the cancer resistance context by keeping, removing, or adding items according to their relevance and importance generally for treatment resistance in oncology and specifically for triple-negative and luminal B MBC and MUM.

Each focus group will be conducted via Microsoft Teams videoconference to facilitate participation and will last an estimated 90 to 120 minutes.

Step 1d: Content Validation With the Delphi Process

To facilitate the collection of individuals' feedback on the provisional QPL version, a 2-round web-based Delphi process [91] will be performed involving participants through snowball purposive sampling. Participants in the focus groups will be offered the opportunity to participate in the consensus method. Other eligible participants (see criteria in Textbox 1) will be solicited according to the same recruitment methodology as for the focus groups.

The Delphi survey assesses (1) each QPL item (instructions, questions, concerns or emotions, and narratives or testimonies) in terms of content appropriateness, formulation clarity, structure, format, and acceptability on a 5-point Likert agreement scale and (2) the feasibility of a complementary coaching intervention and implementation guidance.

The procedure comprises successive evaluations according to the following steps:

- Participants will indicate their level of agreement on the relevance and clarity of each proposed item of the QPL (ie, instruction sentences and questions or concerns) and implementation guidance (ie, ideas or sentences) using a 5-point Likert scale (ranging from 1=*strongly disagree* to 5=*strongly agree*). The overall length and clarity of the tool and guidance will also be assessed.
- Participants will comment and propose changes or additions to the QPL and guidance if required based on the following questions addressed to patients (professionals):

  What would you (your patients) have liked to ask?

  What questions do you (your patients) often not ask, that you (I) wish you (they) would ask?

- The research team will analyze the data obtained. It will then identify the issues on which there is consensus and make possible modifications and additions based on the participants' comments.
- Following the first evaluation, the modified items will be submitted to a second evaluation by participants who will be invited to rate each question, concern, or sentence on a 5-point Likert scale, and responses will be rated as *essential* or *important*; validation will be determined by an a priori threshold of ≥4.0.
- Following the second evaluation, QPL version 1 and guidance will be validated in its final version.

A total of 2 rounds of Delphi surveys administered via REDCap (Research Electronic Data Capture; Vanderbilt University) software will be performed, including 30 participants responding to the first survey on a first QPL version and then the second

survey on a QPL version revised from the initial survey responses and comments.

Step 2: QPL and Implementation Pilot Testing

The second step of the study pilot tests the QPL version 1 for its acceptability, feasibility, potential clinical utility, and sustainability. Consecutive patients (n=80) responding to the same eligibility criteria as in step 1b will be recruited. They will receive the QPL version 1 to prepare their subsequent oncology consultations, either a consultation during which the diagnosis of cancer resistance is communicated or in the course of a new disease-targeted treatment follow-up consultation. They will be invited to complete the same standardized questionnaires as in step 1b.

Additional questions will address the QPL acceptability in terms of uptake (the QPL has been read before the consultation), use (QPL items have been raised during the consultation), and patients' and clinicians' perceived helpfulness and satisfaction with this tool and its use in clinical practice.

Data Analysis

Qualitative Data

All interviews will be audiotaped, transcribed, and identified using an alphanumeric log. A thematic analysis will be conducted using the RQDA (R package for the qualitative data analysis) software (version 2.15.2; 2012-10-26). A total of 2 junior (JT and AR) postdoctoral health psychologists and 1 senior (AB) postdoctoral health psychologist will code the transcripts. The analysis of thematic content will allow both the frequencies of responses for each category to appear and the meaning of the responses associated with each category to emerge [92,93]. A coding grid will be constructed from 2 complementary processes; (1) a pre-established code based on the research objectives and the semidirected interview guide will be elaborated to create broad coding categories and subcategories, and (2) a third of the interviews will be coded, using an emergent coding method, to test and modify the grid. Following an iterative process, several rounds of analysis will be conducted to stabilize the coding sheet. Finally, double interjudge and intrajudge coding will be conducted to ensure the reliability and independence of coding.

A similar content analysis will be performed for focus group interviews, with coding based on themes related to the content, format, and clinical implementation guidance of the QPL.

Quantitative Data

Statistical analyses will be conducted using SPSS software (version 27.0; IBM Corp). Standardized questionnaires used in steps 1b and 2, and the Delphi surveys, will be analyzed descriptively in terms of missing data, response frequency, mean and SD, median, and range.

In step 1b, responses to items of the PTPQ, EORTC QLQ-INFO25, and SCNS-SF34 will determine the prevalence of communication needs in the cancer resistance setting and thus help prioritize communication issues to compose the QPL.

The step 1b group (QPL naive) will comprise a historical control of patients from step 2 (QPL intervention group). Quantitative data collected from standardized questionnaires at step 1b will be compared with the data collected at step 2. Patients will be consecutively included in steps 1b and 2; therefore, they are expected to be clinically similar; however, sociodemographic and clinical data between these groups will be compared to check their similarity. Bivariate analyses of outcome measures will be performed to preliminarily assess the potential clinical usefulness of the QPL. Bivariate analyses will also be performed to explore patients' satisfaction with information and support needs in relation to their sociodemographic and psychological characteristics (distress and coping strategies) in step 2 samples, overall and by cancer site.

Results

This study received grants from the Ile-de-France CancerôPole (2019-1-EMERG-14-ICH-1; March 2019) and from the *Fondation de France* (2019 number 00101610; December 2019) and was approved by the French national ethics committee in July 2019. As of December 2020, to reach data saturation, 26 oncology professionals' interviews have been conducted and analyzed. As of October 31, 2021, a total of 40 and 31 patients with MBC and MUM have been recruited, 20 and 20 have been interviewed, and 39 and 28 have completed questionnaires, respectively.

Discussion

Principal Findings

This protocol describes a study using an innovative, sequential, mixed methods approach and involving patients as well as oncology professionals to collaboratively develop a QPL for cancer resistance in the French cultural context.

This study will be undertaken in 2 clinical settings prone to cancer resistance and contrasted in terms of epidemiology, life expectancy, long-term treatment options, and expected effectiveness. The resulting QPL is expected to comprise core issues related to the cancer resistance context to which specific issues will be added if needed, according to the tumor site. The core QPL is expected to be applicable in other advanced cancer contexts.

QPLs seem effective in raising patients' asking questions [38,42,94]; however, a complementary coaching intervention may be needed to further patients' support [95,96,97]. Coaching is the provision of nondirective support by an individual (either in-person or remotely eg, by telephone or the internet) [98]. It is expected to help patients assess their information needs (ie, about treatment options such as disease-targeted treatment [standard or experimental], best supportive care, watchful waiting, and their benefits and harms) [18], prepare and rehearse questions [33], express their concerns or emotions [99], and prioritize issues to discuss during the consultation.

This study's sequential collaborative mixed methods approach is innovative; the following methodological aspects are expected to be fruitful. First, a triangulation of perspectives is foreseen as it involves patients, clinicians, and researchers, and thus a better grasp of the specific realities of oncology consultation communication in resistant cancer care.

Second, the quantitative and qualitative data collection approaches are complementary, and the results will be sequentially and iteratively integrated. In-depth interviews with different protagonists who are experts in cancer resistance at their own level are expected to increase the appropriateness and acceptability of the tool. Considering the modalities and procedures of tool implementation from the outset is also meant to promote its adoption in routine practice. Focus group discussions and exploratory quantitative analyses will help decide for whom, when, and how the QPL will be implemented in clinical routine.

Third, the quantitative assessment allows the assessment of the specific information and support needs that are experienced when faced with cancer resistance. These data may be compared between 2 groups: before (step 1b) versus after (step 2) the availability of the QPL. This will offer initial information on the clinical utility of the tool tailored to cancer resistance in the French cultural context.

Owing to consecutive sampling, information will be available about the number of patients willing to use the QPL and the number of oncologists who will engage in its use during consultations [92]. Furthermore, the resulting QPL will be pilot-tested on outcomes such as patients' beliefs about primary cancer treatment goals or satisfaction with the information provided about prognosis and treatment, which are important [93] and previously lacking effect measurement of QPL use [2].

Finally, focus group discussions will specifically elicit collaborative work. The reactions and proposals of various appropriate persons [100] will help prepare the modalities of QPL use in routine practice and promote its long-term adoption [101], that is, the tool use in real-world clinical practice [102]. Moreover, the Delphi process aims to reach consensus among patients and oncology professionals on a QPL version 1 and explicit guidance for clinical implementation [103,104]. We anticipate that these persons will have diverging views and opinions about the tool [91]; thus, a consensus will have to be developed.

This protocol has several limitations. The methodology described herein is an innovative but long process. It may not be systematically applied as a new clinical context in need of a QPL. However, this study offers the opportunity to reveal unnecessary steps and thus indicate an optimized process for future research.

We focus on the communication between oncologists and patients; however, other oncology professionals such as nurses or psychologists may also play an important role in responding to patients' information and support needs; therefore, further research is needed to address their specific role in addressing these needs. In addition, patients' relatives may also present their specific information and support needs and may interact with the patient when facing this information. The QPL may also be useful to them, as such or adapted, and this must be evaluated.

The assessment of patients at step 1b and step 2 of this study is cross-sectional; therefore, we also need to consider that information is not collected on the same individual patients over their evolving needs and information processing.

Dissemination

A clinically and culturally specific QPL complemented, if necessary, by a coaching intervention is expected to facilitate patients' participation in oncology consultations to improve oncologists' responses to their information and support needs. This tool allows patients to control the provided information according to their wishes and thus respects their potential ambivalence and need for hope. Digital health interventions provide patients with evidence-based interventions through software apps. The availability of QPLs through these technologies is increasing [55,105,106]. Digital health interventions are easily accessible to patients from their homes through mobile devices or websites. Studies suggest that they are cost-effective, increase uptake by patients and clinicians, and provide clinical benefits [107]. Therefore, this French-adapted QPL will be available not only in paper form (brochure) but also as an app (MyCurie app) and on the institutional website. It will contain information about the purpose, interests, and modalities of use of the brochure or web document. Moreover, studies have shown the importance of clinicians' endorsement of the tool, encouraging its use by patients; therefore, particular attention will be given to an implementation guide that recommends communication about this tool during the consultation. Patient and partner representatives of the Institut Curie will be invited to attend the local public and scientific conferences planned to communicate about this study. They will be solicited for their feedback on articles to disseminate results nationally and internationally through popular or scientific journals.

Conclusions

This research proposes an original methodology to adapt and further develop a QPL for patients with resistant cancer and enable its implementation in the French cultural context. It is expected to facilitate patients' expression of questions, concerns, and emotions and, in that way, improve oncologists' responses to their information and support needs. Clinically, this study will also improve the understanding of patients' and clinicians' experiences, difficulties, obstacles, and strategies in discussing prognosis and treatment options in the first anticancer treatment lines after cancer resistance has developed. Methodologically, it will be possible to infer an efficient method for designing and guiding the implementation of communication aids for patients with advanced cancer.

in the overall study process as patient and partner representatives of the Institut Curie. The authors would also like to thank Léonore Robieux, Leila El Mellah, and Mathilde Torsdorf for their help with the design and initial draft of this research project.

Authors' Contributions

Conflicts of Interest

None declared.

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Abbreviations

EORTC QLQ-INFO25: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Information Module
HECTOR: Helping Patients Communicate With Oncologists When Cancer Treatment Resistance Occurs
MBC: metastatic breast cancer
MUM: metastatic uveal melanoma
PTPQ: Prognosis and Treatment Perception Questionnaire
QPL: question prompt list
REDCap: Research Electronic Data Capture; Vanderbilt University
SCNS-SF34: Supportive Care Needs Survey–Short Form

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Protocol

Military Injuries—Understanding Posttraumatic Epilepsy, Health, and Quality-of-Life Effects of Caregiving: Protocol for a Longitudinal Mixed Methods Observational Study

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Abstract

Background: Veterans with posttraumatic epilepsy (PTE), particularly those with comorbidities associated with epilepsy or traumatic brain injury (TBI), have poorer health status and higher symptom burden than their peers without PTE. One area that has been particularly poorly studied is that of the role of caregivers in the health of veterans with PTE and the impact caring for someone with PTE has on the caregivers themselves.

Objective: In this study, we aim to address the following: describe and compare the health and quality of life of veterans and caregivers of veterans with and without PTE; evaluate the change in available supports and unmet needs for services among caregivers of post-9/11 veterans with PTE over a 2-year period and to compare support and unmet needs with those without PTE; and identify veteran and caregiver characteristics associated with the 2-year health trajectories of caregivers and veterans with PTE compared with veterans without PTE.

Methods: We conducted a prospective cohort study of the health and quality of life among 4 groups of veterans and their caregivers: veterans with PTE, nontraumatic epilepsy, TBI only, and neither epilepsy nor TBI. We will recruit participants from previous related studies and collect information about both the veterans and their primary informal caregivers on health, quality of life, unmet needs for care, PTE and TBI symptoms and treatment, relationship, and caregiver experience. Data sources will include existing data supplemented with primary data, such as survey data collected at baseline, intermittent brief reporting using ecological momentary assessment, and qualitative interviews. We will make both cross-sectional and longitudinal comparisons, using veteran-caregiver dyads, along with qualitative findings to better understand risk and promotive factors for quality of life and health among veterans and caregivers, as well as the bidirectional impact of caregivers and care recipients on one another.

Results: This study was approved by the institutional review boards of the University of Utah and Salt Lake City Veterans Affairs and is under review by the Human Research Protection Office of the United States Army Medical Research and Development Command. The Service Member, Veteran, and Caregiver Community Stakeholders Group has been formed and the study questionnaire will be finalized once the panel reviews it. We anticipate the start of recruitment and primary data collection by January 2022.

Conclusions: New national initiatives aim to incorporate the caregiver into the veteran's treatment plan; however, we know little about the impact of caregiving—both positive and negative—on the caregivers themselves and on the veterans for whom

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they provide care. We will identify specific needs in this understudied population, which will inform clinicians, patients, families, and policy makers about the specific impact and needs to equip caregivers in caring for veterans at home.

Introduction

Background

Epilepsy is a substantial concern among United States service members and veterans (hereafter referred to as *veterans* as service members ultimately become veterans). Among post-9/11 veterans, prior studies have found a prevalence of epilepsy of approximating 10.6/1000 [1]. In particular, posttraumatic epilepsy (PTE), which occurs following a traumatic brain injury (TBI), is more common among veterans who served during Operation Enduring Freedom or Operation Iraqi Freedom (post-9/11) because of the higher incidence of TBI and blast injuries compared with earlier conflicts [1-3]. The annual cost of epilepsy care in the United States has been estimated at US $12.5 billion [4], with higher costs for those newly diagnosed, those with seizures refractory to anticonvulsant medication treatment, and those with comorbid health conditions [5,6]. Indirect costs (eg, caretaker's time away from work) comprise most of the total cost of epilepsy care [7,8]. Estimates of caregiver-related costs based on self-report are high [9].

Poorly controlled epilepsy is associated with injury, disability, mortality, and poor quality of life [10-15]. Veterans with epilepsy have also reported role limitations caused by impairments related to physical, mental, emotional, and social functions [16,17]. Of the post-9/11 deployed veterans, 11% to 23% experienced TBI, most of which were mild TBIs (mTBIs) [2,18-21]. Even among those with mTBI, the risk of developing PTE is elevated (adjusted odds ratio 1.28, 95% CI 1.07-1.53) [1]. With hundreds of thousands of veterans exposed to mTBI, even a small elevated risk has the potential to impact thousands of individuals, caregivers, and families.

Our understanding of epilepsy and the impact of PTE in post-9/11 combat veterans is limited. Data from the Department of Veterans Affairs' (VA) comprehensive TBI evaluation have shown that veterans with PTE have significantly higher cognitive, affective, somatosensory, and vestibular symptom burdens than those with mTBI only. A survey-based study found that veterans with PTE had significantly lower quality of life, social support, and family resilience scores compared with those with epilepsy, mTBI, and control participants with neither TBI nor epilepsy [22]. Given the relatively young age of post-9/11 veterans, the costs of care (both personal and financial) may profoundly affect the lives of these veterans, their caregivers or families, and the health care systems on which they depend for care.

Informal caregivers—family and friends who provide assistance for people living with chronic health conditions or disabilities living in the community—in general, have significantly higher levels of stress, depression, and lower levels of physical health than noncaregivers [23-25]. Although positive effects of caregiving have been reported [26], caregiving can negatively influence caregiver health, and these effects are likely unique to specific caregiver populations. The effects of caregiving for veterans with PTE are understudied. Qualitative interviews indicated that caregivers experience stress, anxiety, and secondary posttraumatic stress disorder because of frequent *seizure or suicide watch* when caring for a veteran with PTE. These data suggest unmet needs for support and services owing to a lack of tailored programs and support for veterans with PTE and their caregivers. Most prior studies that have assessed the dyadic relationship between caregivers and care recipients have focused on children with epilepsy; therefore, assessments of the quality of life for veterans with PTE and their caregivers are needed.

The available evidence regarding military caregiving suggests that these caregivers may experience a health decline for a longer period than any other caregiver population [27-29]. The young age and long life span of veterans with TBI, PTE, and other catastrophic injuries make this population unique in light of the existing literature, which has focused on family caregivers of patients in hospice or patients with a diagnosis of cancer, dementia, Parkinson disease, Alzheimer disease, and other diseases or disabilities [30-32]. The full range of experiences and needs of caregivers of veterans with TBI in general and of those with PTE in particular has not been fully explored. For example, other researchers have highlighted the need to understand family and relationship quality [33], caregiver resilience [34], and positive aspects of the caregiver experience [35] to support veterans with TBI and their caregivers.

Given these gaps in knowledge, the purpose of this study is to longitudinally examine factors associated with quality of life and health outcomes for veterans with epilepsy or PTE and their caregivers. To develop appropriate interventions to improve health outcomes for veterans and their families, we must understand the veteran-caregiver dynamics.

Hypotheses and Objectives

On the basis of the existing literature and our preliminary studies, we hypothesize that caregivers of veterans with PTE encounter unique challenges in their caregiving role, resulting in more intense caregiving and a higher burden than caregivers of other post-9/11 US veterans, including those with TBI only or nontraumatic epilepsy (NTE). Furthermore, we hypothesize that caregivers of veterans with PTE and associated epilepsy comorbidities (eg, depression and headache) have a higher

burden and poorer health than caregivers of veterans with PTE but without associated comorbidities. Therefore, we expect that the health and burden trajectories of caregivers of veterans with PTE will differ from caregivers of veterans without PTE and that there will be distinctions between these groups based on whether the veteran has associated comorbidities. Finally, we hypothesize that the caregiver's burden and own health trajectory will influence the health status of the veteran at baseline and their health trajectories during follow-up.

This study will evaluate the health, well-being, and quality of life of veterans and their caregivers with the following aims: (1) describe and compare the health and quality of life of veterans and caregivers of veterans with and without PTE; (2) evaluate the change in available support and unmet needs for services among caregivers of post-9/11 veterans with PTE over a 2-year period and compare supports and unmet needs with those without PTE; and (3) identify veteran and caregiver characteristics associated with the 2-year health trajectories of caregivers and veterans with PTE compared with veterans without PTE.

Methods

Conceptual Framework

This study is guided by a biopsychosocial model of caregiving [36] and the Military and Veteran Caregiver Experience Map [37]. Figure 1 [36,37] is an adaptation of the Military and

Veteran Caregiver Experience Map developed over the course of several years by the Elizabeth Dole Foundation and military and veteran caregiver (MVC) stakeholders [37] and Raina's synthesis of theoretical frameworks for the impact of caregiving [36]. The model posits that baseline characteristics (ie, social and economic status, family structure, cultural support systems, and veteran health and wellness) influence the caregiver's ability to meet the new demands of caregiving, which may lead to caregiver stress or strain depending on the extent to which their current identity and roles are altered by caregiving requirements. Over time, the caregiver may shift priorities and seek help within current social or family circles or the health care system and may develop new coping skills. When the caregiver is unable to shift priorities or obtain the needed support within social relationships or the health care system, there is a negative impact on caregiver well-being, continued dysfunction, and diminished veteran, caregiver, and family function, which can then lead to a negative impact on baseline influences and a negative spiral of health and well-being. When the caregiver is able to adapt or cope with new roles and responsibilities, there is a positive impact on veterans, caregivers, and family well-being, as well as a positive impact on baseline characteristics with a positive spiral for health and well-being for veterans, caregivers, and families. Survey and ecological momentary assessment (EMA) data collection will obtain data that address each component of this model and use modeling techniques to explicate the trajectories of veteran and caregiver health or well-being and quality of life.

Figure 1. Study conceptual framework modified and adapted from Raina et al [36] and the Military and Veteran Caregiver Map [37].
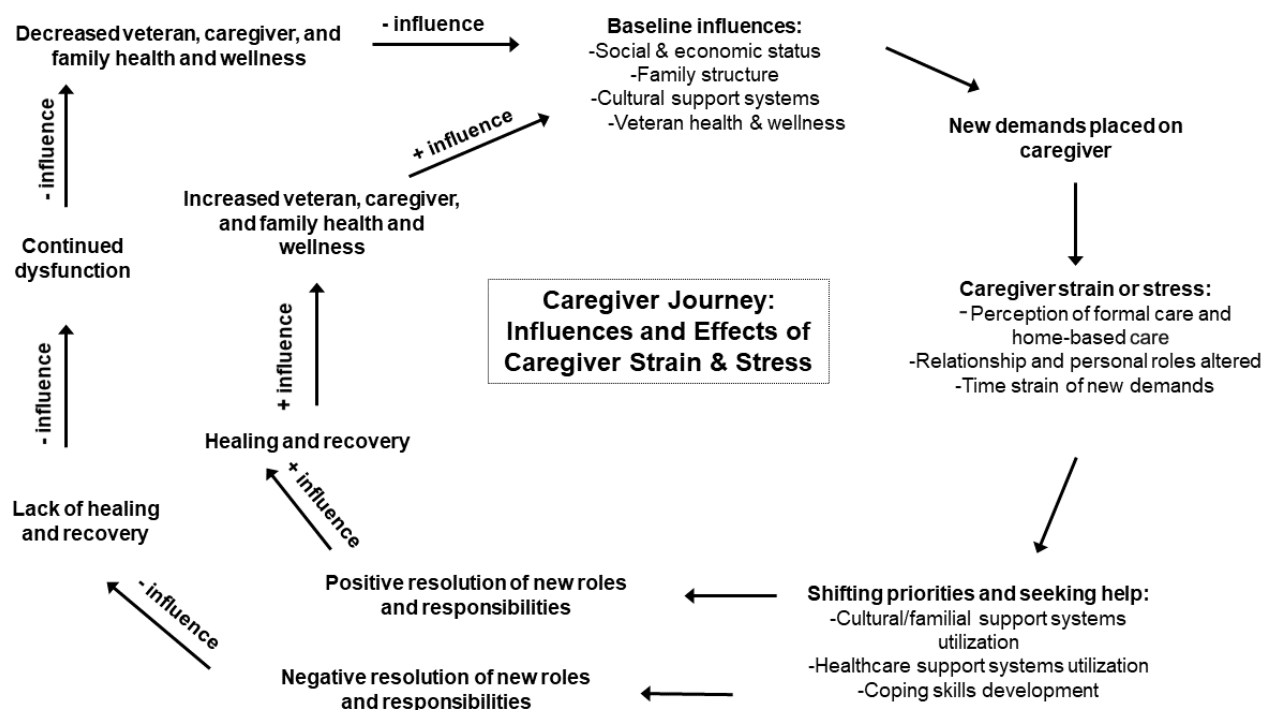
Study Design

We will conduct a prospective cohort study of the health and quality of life among 4 groups of veterans and their caregivers: (1) PTE, (2) NTE, (3) TBI only, and (4) neither epilepsy nor

TBI. We will recruit participants from previous studies of PTE or TBI and MVC outcomes conducted by Dr Pugh and Dr Delgado; specifically, we will sample from among respondents who agreed to be contacted for future research studies. Data sources will include existing study data from these prior projects

supplemented with primary data collected for this study in 2 forms: (1) survey data collected at baseline; (2) daily brief reporting using EMA [38] over the course of 30 days, with the option to continue this data collection for up to 2 years; and (3) qualitative data collected via interviews.

Service Member, Veteran, and Caregiver Community Stakeholders Group

We established a Service Member, Veteran, and Caregiver Community Stakeholders Group for this study, which consists of 3 veterans with the goal of having 1 with TBI, 1 with epilepsy, and 1 without TBI or epilepsy, and 3 caregivers of veterans with TBI or epilepsy. We recruited locally using existing relationships and used state and national service members, veterans, and caregiver organizations as recruitment sources (eg, Wounded Warrior Programs, American Red Cross' Military and Veteran Caregiver Network, and Iraq and Afghanistan Veterans of America). This group will help identify special issues in addressing veteran and caregiver needs and ensure that our approach is consistent with community needs and values. Members will receive stipends for their participation. We will consult with the community stakeholders to finalize the veteran and caregiver surveys and EMA items, and we will discuss findings with them to assure our interpretation of the results resonate with their experiences and understanding of living with and providing care to veterans with TBI and PTE. Full community stakeholders group meetings are planned quarterly throughout the study period.

Study Population

We will recruit veteran and caregivers for this study from among a group of participants who agreed to be recontacted from the Veterans Posttraumatic Epilepsy Study (VPES; 189/210, 90% response rate in follow-up interviews), the pilot TBI Caregiver Study, and the Military and Veteran Caregiver Health and Well-being (MVCHW) study. We will request participation from the primary caregiver for VPES participants, veterans for the MVCHW, and recontact both veterans and the primary caregiver from the pilot TBI Caregiver Study. The group of veterans with neither TBI nor epilepsy includes people with primary mental health comorbidities or devastating diseases such as amyotrophic lateral sclerosis. These groups will allow us to examine variations in caregiver burden, stressors, resources used, and unmet needs based on epilepsy and comorbidity patterns.

Inclusion and Exclusion Criteria

As we are recruiting from 3 prior studies, the inclusion criteria and sampling frame for each of these studies vary slightly and are summarized below.

The VPES included veterans who were deployed in support of post-9/11 conflicts and received ≥2 years of VA care between fiscal year 2002 and fiscal year 2014 with at least one of those years after 2007, when VA began mandatory TBI screening. *Epilepsy* was identified using our validated algorithm (International Classification of Disease-9 or -10 diagnosis of epilepsy or convulsion and subsequent use of antiseizure medication) [1], with subsequent validation by medical chart abstraction. TBI was identified using the International Classification of Disease-9 or -10 algorithm developed by the Armed Forces Health Surveillance System [39], and self-reported lifetime TBI history based on the Ohio State TBI Identification measure [40]. Veterans with PTE, NTE, TBI, and controls (veterans with neither epilepsy nor TBI) were randomly selected for survey administration. Only those veterans who responded and agreed to be recontacted for future research and also reported having a caregiver were included in this study (269/326, 82.5% reported having a caregiver).

The MVCHW study recruited participants using email invitations sent out by MVC support organizations such as the Elizabeth Dole Foundation and Hearts of Valor in April 2017. Although no denominator was provided to the study team, 476 individuals responded and completed the web-based survey within a 3-month period without any incentive. Caregivers self-reported the types of conditions for which they provided care.

The pilot TBI Caregiver Study invited 186 veterans who were diagnosed with penetrating TBI (per the Armed Forces Health Surveillance System algorithm) and their caregivers via email. Upon validation of TBI severity using the Ohio State TBI Identification measure [40], it was found that all had moderate or severe TBI. Of the 186 invites, 66 (35.4%) veterans and caregivers responded, and 65 (34.9%) dyads agreed to be recontacted for future research.

For this study, we will use data on TBI and epilepsy history to classify all veteran-caregiver dyads into 1 of the 4 study groups. Only caregivers aged >18 years will be included. Although we will inquire about caregiving provided by children, we will not engage minors in the study.

Sample Size

We expect to achieve a response rate of 75% given that we will sample from among veterans who have already participated in a study and expressed a willingness to be recontacted. We also expect a high participation rate among caregivers, as the veteran has already participated and presumably will have told the caregiver about the study. We plan to enroll 97 veterans with PTE, 45 with NTE, 323 with TBI only, and 145 with no PTE and no TBI and their caregivers, totaling 610 veterans and 610 caregivers. Table 1 shows the number of participants in each of the 4 study groups.

Table 1. Anticipated sample size from each recruitment source study, assuming a 75% response rate (N=610).

Recruitment source	Number of veterans, n (%)				
	With posttraumatic epilepsy (n=97)	With nontraumatic epilepsy (n=45)	With TBI[a] only (n=323)	With no epilepsy and no TBI (n=145)	Total (N=610)
Veterans Posttraumatic Epilepsy Study	42 (43.3)	43 (95.6)	88 (27.2)	37 (25.5)	210 (34.4)
Military and Veteran Caregiver Health and Well-being Study	36 (37.1)	2 (4.4)	204 (63.1)	108 (74.4)	350 (57.3)
Pilot TBI Caregiver Study	19 (19.6)	__b	31 (9.5)	—	50 (8.2)

[a]TBI: traumatic brain injury.

[b]Respondents in this category were not included in the study.

We plan to compare veterans or caregivers of veterans with PTE to those with (1) NTE, (2) TBI only, and (3) no epilepsy and no TBI. We anticipate adequate statistical power for planned analyses using the survey data. For example, we have >80% power to detect a 2-point difference between veterans with PTE and those with NTE, the minimum size considered clinically meaningful for the Veterans RAND 12-Item Health Survey, with an SD as high as 4.25, even if we account for the correlation between veterans and caregivers (assumptions: cluster size of 2, intraclass correlation coefficient of 0.8 between veterans and caregivers, and α=.05) [41]. We assume similar variability among caregivers and therefore also anticipate adequate power when comparing the experiences of caregivers of veterans with PTE and NTE. We may not have adequate power to detect differences between groups when making comparisons based on health trajectory groups, given that we anticipate 3 groups, 2 of which may be moderate to small. However, our qualitative analysis will allow us an additional perspective in comparing PTE and NTE.

Sampling

We will collect survey data from both veterans and caregivers following the Dillman Tailored Design Method for mail and web-based surveys to minimize nonresponse errors [42]. This approach involves a combination of data collection strategies to achieve a higher response rate. Our specific strategy will involve either mail or email, depending on what contact information we have for the veteran and caregiver, and is outlined in Figure 2.

To encourage participation, we will provide an incentive of US $25 for the baseline survey and US $2 per response for the first 30 days of EMA data collection. In addition, we will offer incentives for the remainder of the 2-year EMA period by entering participants in a drawing for 5 US $500 gift cards and 10 US $100 gift cards per quarter for veterans and caregivers. This approach was used in a previous study and improved response rates by over 60% (from 30% to 48%).

Figure 2. Process for contacting potential study participants based on Dillman Tailored Design Method for mail and web-based surveys.
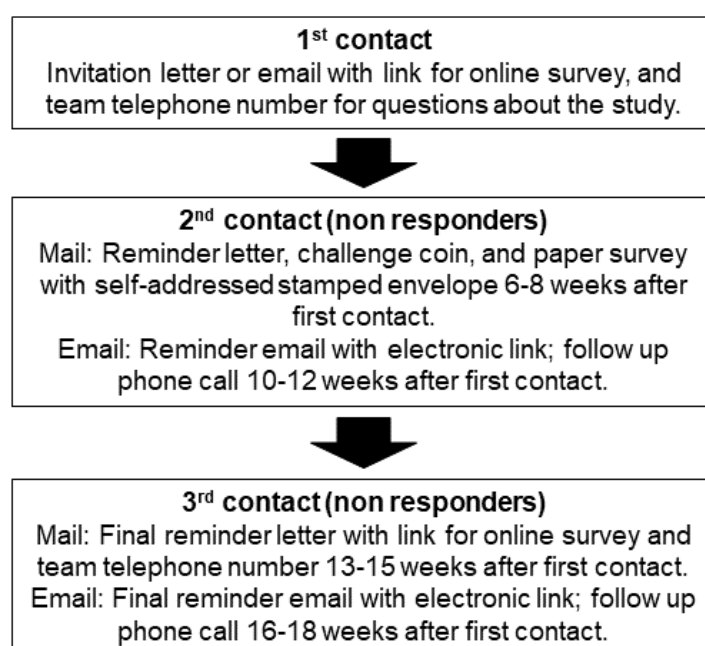
Data Collection

We will collect survey data from both veterans and their primary caregivers at baseline. Our caregiver survey was modeled based on the RAND Military Caregivers Study [23], the Behavioral Risk Factor Surveillance System (BRFSS) Caregiver Module [43], and the National Alliance for Caregiving survey [44]. The goal is to develop a comprehensive survey that assesses various aspects of the respondent's health, quality of life, and service needs in a reasonable amount of time (≤30 minutes). The Service Member, Veteran, and Caregiver Community Stakeholders Group will review the baseline survey and recommend changes before it is fielded. Veterans and caregivers who complete the baseline survey will be invited to participate in EMA data collection for up to 2 years.

We will mail or email information on how to use the LifeData EMA platform to those who agreed to participate in the EMA. Participants will also be given contact information of study personnel who can assist the participant with the platform setup. Once set up, each participant will receive approximately 2 prompts daily to respond to for 30 days. The EMA will capture different measures daily. Participants can also add information to the EMA platform on concerns or unmet needs at any time using a *pull* mechanism where they initiate the data collection at the time of their choosing. Participants will receive US $2 per assessment completed for 30 days and also be eligible for drawings of larger incentives for continued EMA participation. The EMA platform (LifeData) is Health Insurance Portability and Accountability Act compliant and includes iOS, Android, and web-based platforms that can be used depending on the preference of the participant [45].

We will conduct qualitative interviews based on extreme variation sampling of results from early EMA data. Our descriptive phenomenological approach will be guided by the following research questions: (1) (Veteran) What are the epilepsy and TBI characteristics (ie, exposure, mechanism, and history) of veterans in a subsample of the cohort? (2) (Caregiver) How do veteran caregivers experience and perceive health, and what are the characteristics and unique factors that affect their overall health?

The goal of the qualitative component of this mixed methods study is to describe the insights and experiences of participants and to identify important elements of caregiving in this particular group that will help develop strategies for preventive care.

Measures

Overview

We will classify veterans as having epilepsy or TBI using procedures consistent with the International League Against Epilepsy [46]. Two of the source cohorts were identified using VA health system data (VPES, TBI caregiver), where epilepsy was identified using a reliable epilepsy algorithm [1] and confirmed using medical chart abstraction; lifetime TBI was identified using the Ohio State University TBI Identification measure [40]. TBI severity and frequency is defined using the Ohio State University TBI measure, and PTE is defined as probable and possible PTE based on the US National Institute of Neurological Disorders and Stroke PTE screening measure.

The third cohort includes the MVCHW cohort. Veterans from this study will complete PTE and TBI screening measures to have the same reliable classifications.

The primary method of assessing comorbidity, medical, and psychiatric conditions over time will be self-reported by veterans and their caregivers using survey and EMA methods. Although self-reported conditions have some limitations, studies including the BRFSS, the Millennium Cohort Study, and the Large Health Survey of Veterans routinely use these measures to gauge population health [47-49]. Whereas sensitivity varies by condition, the specificity was >80% for all conditions included in the BRFSS [47]. Sensitivity and specificity are higher when longer periods of observation in medical records are used [48]. Thus, this method is appropriate for this prospective observational study. We will also validate PTE, TBI, and baseline health status using measures in our baseline survey. This will enable us to classify respondents as having probable or suspected PTE (or TBI).

Baseline Survey

We will measure caregiver burden using the short version of the Zarit Burden Interview, a 12-item caregiver inventory [50]. Responses for each item will be measured using a 5-point Likert scale ranging from 0 (never) to 4 (nearly always), with scores summed to create an overall burden score. A score >16 on caregiver burden has been shown to reflect a clinically significant burden, which will be used as a dichotomous measure of high overall burden in this study. The National Alliance for Caregiving survey developed a level of care index that combines information about the number of activities of daily living and instrumental activities of daily living a caregiver performs with the amount of time a caregiver spends providing care [44]. We will use this measure to represent caregiving intensity in this study.

We will use the Veterans RAND version of the Medical Outcomes Survey Short-Form, a 12- item survey, to measure physical and mental health among both veterans and caregivers [51]. Each item will be rated on a Likert scale ranging from 0 (worst) to 4 (best). We will transform the scores using standard-based scoring [52]. A difference of 2 to 3 points is considered clinically important [53]. We will also use the presence of self-reported comorbid conditions (eg, chronic health conditions, pain, substance use disorder, and posttraumatic stress disorder) to evaluate veteran and caregiver health status and changes in health over time.

We will use the 4 items from the BRFSS Healthy Days Core Module to evaluate the quality of life [54]. These items assess overall health (from poor to excellent) and the number of days in the past month on which the respondent's physical and mental health were not good, along with the number of days poor physical or mental health limited the respondent's usual activities. We will create dichotomous variables for fair or poor health (vs excellent, very good, or good) and for frequent physical distress, mental distress, and activity limitation, defined as distress or limitations experienced for ≥14 days in the past 30 days [55].

We will adapt a caregiver needs assessment developed by O'Malley and Qualls [56] that evaluates both current service use, current needs, and reasons that services are not being used. The assessment includes 10 caregiver support items (eg, counseling, respite care, and support group), 12 care recipient support items (eg, help with housekeeping, home adaptation, and financial assistance), and 9 types of information needed (eg, list of local caregiving resources and information about long-term care planning). We may limit these items in consultation with the Service Member, Veteran, and Caregiver Community Stakeholders Group to keep the survey at a manageable length.

In addition to the main outcome measures described above, we will collect a wealth of additional information about veterans and caregivers, including validated and commonly used measures of disability status, social support, stress, thriving, caregiver-care recipient relationship, challenging behaviors, personal and family information, and socioeconomic status (Table 2).

Table 2. Domains and constructs covered in baseline veteran and caregiver surveys, and items used to assess each domain.

Domain and construct	Measure or item source
Both veteran and caregiver survey	
Relationship between veteran and caregiver	• Behavioral Risk Factor Surveillance System caregiver module [43] • Dyadic Relationship Scale [57] • Family Resilience Scale for Veterans [58]
Length of care	• Modified Behavioral Risk Factor Surveillance System. caregiver module [43]
Caregiving tasks	• Modified NAC[a] Questionnaire [44]
Amount of care	• NAC Questionnaire [44]
Primary caregiver	• Modified NAC Questionnaire [44]
Social support	• Perceived social support from the Veterans Health Study [59]
Health status	• The Veterans RAND-12 item Health Survey [51]
Sleep	• Insomnia Severity Index [60]
Traumatic brain injury screener	• Ohio State University Traumatic Brain Injury Identification Method [40,61]
Service use	• Modified O'Malley Measure of Caregiver Service Use [56]
Stress	• Perceived Stress Scale-14 [62]
Thriving	• Brief Inventory of Thriving [63]
Loneliness	• Three-Item Loneliness Scale [64]
COVID-19	• Lived Experience of Epilepsy: Patient and Caregiver Perspectives Study [65] • Beach Questionnaire [66]
Anxiety	• Generalized Anxiety Disorder 2-item [67]
Depression	• Patient Health Questionnaire-2 [68]
Veteran survey only	
Posttraumatic epilepsy screen	• US National Institute of Neurological Disorders and Stroke common data element
Illness perception	• Brief Illness Perception Questionnaire [69]
Caregiver survey only	
Distance from Veteran	• NAC Questionnaire [44]
Challenging behaviors	• Care recipient impairment: problem behaviors subscale [70]
Positive aspects of caregiving	• Caregiving Uplifts Scale [71]
Resilience	• Response to Stressful Experiences Scale-4 [72]
Caregiver choice	• NAC Questionnaire
Incident health conditions since starting caregiver	• Delgado Survey [73]
Payment and financial support	• Delgado Survey [73]
Loss of self	• Loss of Self Scale [74]
Caregiver burden	• Zarit Burden Interview-12 [50]

ªNAC: National Alliance for Caregiving.

Ecological Momentary Assessment

EMA data collection will focus on primary outcome variables in this study (eg, health, quality of life), aspects of living with PTE, TBI, and other associated comorbidities, as well as aspects of providing care that are likely to change frequently, such as stress, burden, symptoms, unmet needs for support, and thriving. As most traditional surveys are worded retrospectively, the wording of the questions will be modified to reflect the in-the-moment nature of EMA studies. For example, rather than evaluating all unmet needs, we may ask respondents to report what they currently need. In addition, longer questionnaires lead to a higher perceived burden, lower compliance, and more careless responses [75]; therefore, we will avoid using long questionnaires in EMA. Before beginning the EMA data collection, selected items will be used to pilot the study. We will ask 10 people who are similar to the intended study sample to participate in pilot testing, including a brief interview thereafter. This step will provide reasons for missing or noncompliant reports to adapt reliable and valid measures accordingly. Cronbach α will be used to estimate the internal reliability of the questions and the consistency of respondents' answers.

Participants will be trained on how to use the software, what questions mean, when is the timing of prompts, what to do if a prompt is missed, and whom to contact for assistance. Previous studies on people with acquired brain injury have demonstrated that EMA is a feasible data collection option in this population. For example, Forster et al [76] reported that among a sample of hospitalized patients with TBI who completed an EMA study of 8 assessments per day for 7 consecutive days, 71.6% of prompts were fully completed. There was no difference in compliance based on age or functional impairment level [76].

Qualitative Data

We propose a descriptive design to capture information about the experiences of veterans and caregivers. We will consent ≤40 participants for individual interviews. Semistructured individual telephone interviews will be audio recorded and transcribed. The use of audio recording will facilitate the verbatim transcription of these interviews and, subsequently, content analysis. Each interview will be conducted using an interview guide that will include structured, open-ended questions and probes to stimulate a discussion between the participant and the interviewer. The interviewer will be one of the research team members, and this person will have training and experience in qualitative research. The interviews will be conducted by phone after the interviewer establishes a connection with the participant [77,78]. The first 2 interviews will be used as pilots to assess the content and flow of the conversation. Performing this pilot test will provide the opportunity to modify and add probes based on new information valuable for the aims of this study [79]. Using the secondary data for veterans and a web-based survey, we will incorporate probes and questions of interest associated with the effect of epilepsy, TBI, or other conditions in veterans and caregivers.

Transcripts will be the main source of information during the analysis [78]. Field notes are a secondary data collection method used in qualitative research [80]. After each interview, the interviewer will record observational and methodological field notes. Field notes recording the experience of the interviewer performing the interview are useful to maintain the rigor of the study and when conducting an audit trail of the study activities. Some guiding questions in developing field notes are, "What happened and what was involved?", "Who (nonidentifiable) was involved?". "Where did the activities occur?", and "Why did an incident take place and how did it actually happen?" [81]. Data will be digitally recorded and transcribed by the research assistant for analysis.

Study Duration

We plan to begin collecting baseline surveys and EMA data from January 2022. Baseline data collection will continue for approximately 9 months. EMA data collection will begin shortly after baseline surveys are launched and will continue for 2 years after baseline data collection is complete, or nearly 3 years in total. Depending on recruitment and saturation, qualitative interviews will begin approximately 6 months after EMA data collection begins and will continue for up to 2 years thereafter. The project will be complete by September 30, 2024.

Study Status

We have drafted the baseline surveys, EMA measures, and interview guides and have begun working to secure human subject approval. We have started recruiting the Service Member, Veteran, and Caregiver Community Stakeholders Group members.

Ethical Approval

The University of Utah, Salt Lake City VA, and the University of Texas Health Science Center, San Antonio, approved this study. The study is currently being reviewed by the Human Research Protection Office of the United States Army Medical Research and Development Command. All data with protected health information or personal identifiable information will remain on a server that has federally approved encryption at VA Salt Lake City. Analyses of the deidentified data may occur at other sites.

Data Analysis

Overview

We will conduct cross-sectional analyses using baseline survey data to address aim 1, and we will conduct longitudinal analyses incorporating baseline and follow-up EMA data to address aim 2 and aim 3. In all analyses that incorporate both the veteran and caregiver, we will treat the data as correlated. Below, we outline our analytical approaches for each aim.

Aim 1

Describe and compare the caregiver and veteran experiences of post-9/11 veterans with PTE to those of other post-9/11 veterans without PTE.

Using the baseline survey, we will calculate and report means and SDs for continuous measures (eg, hours of care and length of care), as well as percentages and 95% CIs for categorical variables (eg, relationship to veteran, choice in caregiving, and veteran comorbidities; Table 3).

When comparing the health and caregiving characteristics of veterans and their caregivers by PTE status, we will use *t* tests for continuous scores and chi-square tests for categorical variables. For all hypotheses, we will compare veterans with PTE and their caregivers to those with: (1) NTE; (2) TBI only; and (3) neither epilepsy nor TBI. We will also make comparisons adjusting for important covariate information using log-binomial regression models to estimate the prevalence ratio [82].

Table 3. Summary of statistical tests to be conducted for hypotheses within specific aim 1.

Hypotheses	Outcome measure	Statistical tests	
		Crude	Adjusted covariates
Veterans with PTE[a] will report poorer health than veterans with NTE[b], TBI[c] only, and neither epilepsy nor TBI.	VR-12[d] Veteran health	2-tailed *t* test: VR-12 score; χ^2 test: VR-12 ≤45; χ^2 test: presence of comorbidity	Veteran age, sex, SES[e], social support
Caregivers of veterans with PTE will report poorer health than caregivers of veterans with NTE, with TBI only, and neither epilepsy nor TBI.	VR-12 Caregiver health	2-tailed *t* test: VR-12 score; χ^2 test: VR-12 ≤45	CG[f] age, sex, SES, social support
Caregivers of veterans with PTE will higher burden than caregivers of veterans with NTE, with TBI only, and neither epilepsy nor TBI.	Zarit 12-item caregiver burden	2-tailed *t* test: Zarit score; χ^2 test: Zarit score ≥16	CG age, sex, SES, social support, health, relationship to Veteran
Caregivers of veterans with PTE will report higher caregiving intensity than caregivers of veterans with NTE, with TBI only, and neither epilepsy nor TBI.	NAC[g] caregiving intensity level	χ^2 test: intensity category; χ^2 test: intensity ≥4	CG age, sex, SES, social support, health, relationship to Veteran
Caregivers of veterans with PTE and associated comorbidities will report poorer health, higher burden, and higher caregiving intensity than caregivers of veterans with PTE without comorbidities and veterans with similar comorbidities (eg, depression and headache) but without epilepsy.	Modified O'Malley caregiver needs measure	2-tailed *t* test: number of unmet needs; χ^2 test: presence of each unmet need	CG social support and SES

[a]PTE: posttraumatic epilepsy.

[b]NTE: nontraumatic epilepsy.

[c]TBI: traumatic brain injury.

[d]VR-12: veterans RAND-12.

[e]SES: socioeconomic status.

[f]CG: caregiver.

[g]NAC: National Alliance for Caregiving.

Aim 2

Evaluate the change in available support and unmet needs for care among caregivers of post-9/11 veterans with PTE over a 2-year period.

To evaluate differences in the unmet needs among caregivers, we will use a 2-tailed *t* test to compare the number of unmet needs among caregivers of veterans with and without PTE at baseline. We will also compare the PTE group and each of the other 3 groups. At follow-up, we will calculate the proportion of caregivers who had the same unmet needs at both time points and determine whether specific needs remained constant over time. To account for potential confounding, we will use a generalized estimating equation model to estimate the likelihood of unmet needs being resolved over time, running models separately for all unmet needs being resolved and for each individual need that is evaluated [83]. We will adjust for changes in caregiver and veteran health (trajectories; described the *Aim 3* section), Veteran comorbidity, and the demographic characteristics of both veterans and their caregivers (age, sex, and socioeconomic position).

Qualitative data will contribute to both aim 1 and aim 2. We will use a descriptive phenomenological approach for qualitative data analysis [81,84]. The analysis will include the following steps:

1. Bracketing and phenomenological reduction: In-depth description of the researcher's experience with the phenomena. A detailed description of the interviews will be provided. The stories or narrative will exclude any information that may link the information with the identity of the participant (eg, names, specific units, and platoon) [85,86].

2. Development of units of meaning: The list of units of relevant meaning extracted from each interview will be carefully scrutinized and clearly redundant units will be eliminated [81].

3. Clustering of units of meaning to form themes: With the list of nonredundant units of meaning in hand, we will again bracket our presuppositions to remain true to the phenomenon. We will seek to elicit the essence of *meaning units* within a holistic context. Clusters of themes are typically formed by grouping units of meaning together [78,81]. The data will be examined to identify common themes, and extract significant statements

to compile a set of themes based on the research question, leading to the creation of *meaning units* and textual descriptions. To achieve this, the transcripts will be read several times, and significant statements will be extracted for closer evaluation. Statements that are similar in meaning will be grouped together, forming *meaning units*.

4. Summarize each interview, validate and modify: A summary that incorporates all the themes elicited from the data provides a holistic context. Reflecting on the transcripts, we will provide a textural description, which is a description of what the participant's experience is with the phenomenon. The description will include verbatim examples or quotes. In addition, we will use triangulation, which is a method that compares the information captured from interviews and paired with other sources of information [78]. Triangulation will incorporate information from interviews and surveys to identify commonalities and themes.

Aim 3

Identify veteran and caregiver characteristics associated with the 2-year health trajectories of caregivers and veterans with PTE compared with veterans without PTE.

To identify health trajectories among both veterans and caregivers, we will use group-based trajectory modeling, a finite mixture modeling approach that estimates the mean trajectories for a given number of groups and for each individual provides a probability of membership to each latent class (group) [87,88]. We will construct a model for veterans and a separate model for caregivers using the traj command in Stata, a user-created plugin available for download, and the associated trajplot command to plot the estimated trajectories. We will estimate these trajectories using only time since the onset of epilepsy as the independent variable and change in health status as the outcome, considering between 1 and 7 different trajectory groups and choosing the best model based on the Bayesian information criterion along with a qualitative assessment of whether each trajectory group identified by the model provides unique information [87]. Individuals will be assigned to the trajectory group for which they have the highest probability of membership (posterior probability). We will characterize trajectory groups based on their shape (eg, increasing, decreasing, and stable health). We will use the recommended approaches to test the assumptions [89] of our model and evaluate the goodness of fit [87].

We will calculate and compare the percentage of veterans in each health trajectory group based on their PTE and TBI status,

and repeat this for caregivers, using chi-square tests for comparisons. As in aim 1 and as the sample size allows, we will compare veterans or caregivers of veterans with PTE to those with: (1) NTE and (2) TBI only, and no epilepsy and no TBI.

We will evaluate how demographic characteristics, veteran symptoms, comorbidity, and caregiving characteristics (eg, burden and intensity) vary across groups by calculating the proportion of individuals assigned to each group with a given characteristic. In addition, we will use a generalized estimating equation model to estimate the likelihood of veteran trajectory membership based on caregiver burden and caregiver health trajectory. We will also run more fully adjusted versions of this model to account for veteran and caregiver age, sex, relationship, and socioeconomic status.

To examine the degree to which changes in caregiver burden and caregiver intensity are dynamically related to changes in the health trajectory of the care recipient over time, we will use the changes-on-changes extension of the bivariate dual latent change score model [90], a simplified version of which is presented in Figure 3. This specialized structural equation model is particularly useful in examining so-called *chicken and egg* questions about causality, as it allows the changes over time in 2-coupled variables to be modeled as a dynamic system in which each outcome in the model can simultaneously predict and be predicted by the other variable in the system. With this model, changes between assessments for each construct are explicitly modeled (labeled ΔCaregiver Burden and ΔPatient Functioning) at each time point, and changes in each of the 2 outcomes in the model can be predicted as a function of up to 5 predictors, 3 of which emanate *within-construct* and 2 of which emanate *across-constructs* [90]. The highlighted box in the figure represents the within-construct predictors of change and includes the following: (1) a constant change component (arrows designated as *C*), (2) the focal variables prior levels (*A*), and (3) the focal variables prior changes (*B*) [90]. The across-construct predictors, which are typically of most interest, allow a focal variable to be predicted by the following: (1) prior levels of a coupled variable (*D*), and (2) prior changes in a coupled variable (*E*) [90]. To the degree to which prior changes in one variable predict later changes in another, it is said to be a leading indicator of that variable, and it is possible that both variables in a dynamic system are reciprocally related such both are causes and effects of one another. This model can be used to predict complex web-based trajectories owing to the variety of combinations of possible predictors.

Figure 3. Simplified example of changes-on-changes extension of the bivariate dual latent change model. C: caregiver; CB: caregiver burden; P: patient; PF: patient functioning; T: time.
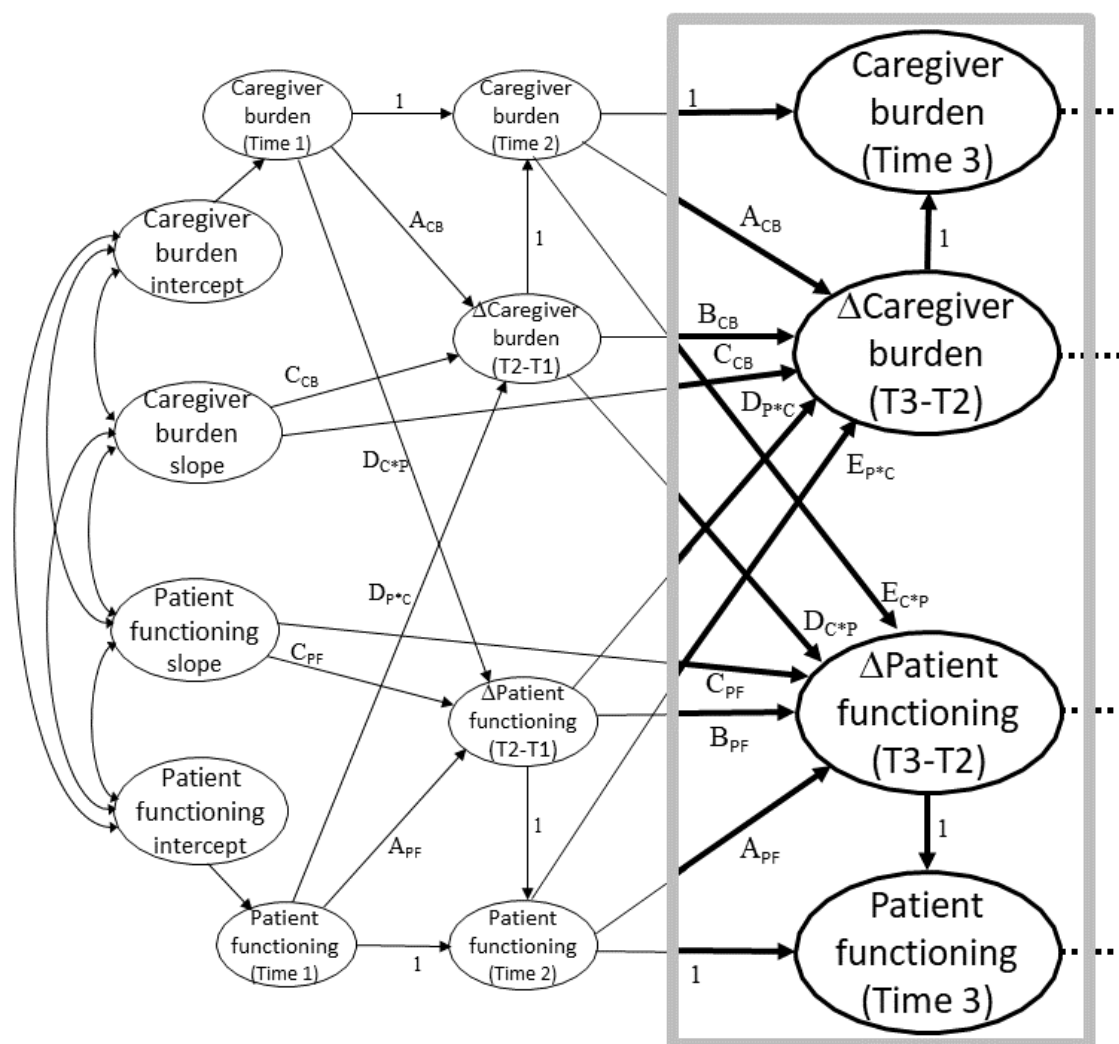
Missing Data

We will examine several pairs of theoretically related constructs using this approach for the entire sample. Models will be estimated using full information maximum likelihood estimation to account for missing data that may exist. Models will be evaluated using common indexes for structural equation models (eg, comparative fit index and root mean square error of approximation). After establishing the best-fitting dynamic model for a particular pair of grouped variables, we will examine multiple-group models to compare the model fit for PTE dyads versus non-PTE dyads. In addition to the specific full information maximum likelihood estimation strategy for the bivariate dual latent change score model, we will conduct both complete-case analyses, in which only respondents or dyads with complete information on all covariates assessed are included, and we will create imputed data sets using multiple imputation using chained equations [91,92] to retain all participants. We will descriptively compare the characteristics of people with no missing data and those with imputed data to evaluate whether the groups differ systematically or if data appear to be missing at random. We will report the results from both sets of analyses in manuscripts and presentations.

Sensitivity Analyses

Across aims, we will conduct sensitivity analyses in which we repeat our analyses using (1) only the primary caregiver (as identified by the veteran); (2) only definite or probable cases of PTE, and combine suspected cases with participants without PTE; and (3) excluding people with epilepsy before combat exposure or TBI.

Results

The University of Utah approved this study on December 14, 2020. Recruitment will begin once it is approved by the Human Research Protection Office of the United States Army Medical Research and Development Command.

Discussion

Principal Findings

The Institute of Medicine identified the evaluation of quality of life in epilepsy as a priority. Concern about the profound impact of epilepsy led to the Institute of Medicine (now the National Academy of Medicine) conducting an in-depth study of the public health dimensions of epilepsy. The study concluded

that "comprehensive, timely, and accurate epilepsy surveillance data are needed to provide a better understanding of the burden of epilepsy, its risk factors and *outcomes*, and *health service needs*" [93]. This study will address this priority and the existing gap in the literature related to the needs and health impacts of caregiving for veterans with epilepsy, including both PTE and NTE.

Our long-term goal is to implement the findings of the proposed study in practice to improve the health and well-being of veterans with PTE and epilepsy and their caregivers. We follow the RAND Corporation's blueprint for MVC research [94] as we develop our strategy. Specifically, of the 10 research objectives identified by their stakeholder panels, we will directly address the following 5 objectives: (1) describe caregivers (and

unique characteristics of caregivers of PTE or epilepsy); (2) assess how the needs of care recipients change over time; (3) document the effects of caregiving on care recipient outcomes; (4) document the effects of caregiving on caregiver outcomes; and (5) examine factors associated with caregiver and care recipient harm.

We also believe that it is critical to plan for implementation as we conduct the research. To this end, we have developed a pathway for clinical implementation and improved health outcomes to guide the work, which considers benefits to both veterans and caregivers. Figure 4 illustrates the process by which we plan to implement the findings of the proposed study into practice to improve the health and well-being of veterans with PTE or epilepsy and their caregivers.

Figure 4. Pathway for implementation.
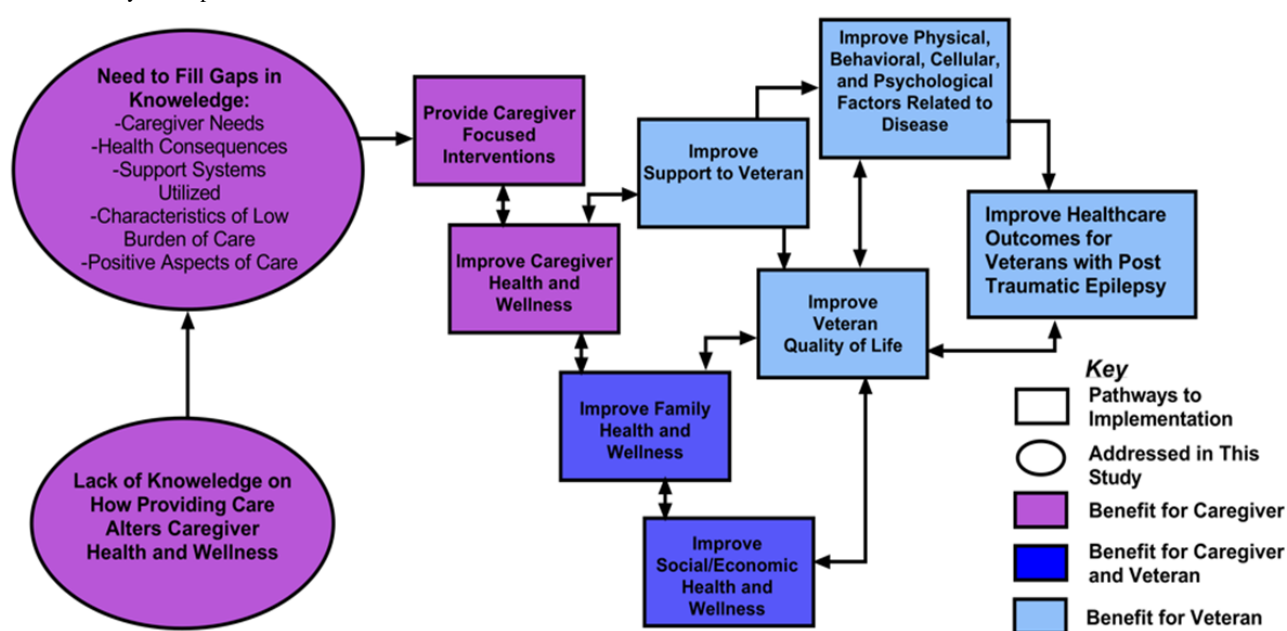
Strengths

Our baseline survey will include validated measures that have been used in many previous studies and therefore will enable comparisons to other veteran and caregiver populations. In addition, EMA data will enhance our ability to use real time experiences of veterans and their caregivers to identify health outcomes, quality of life, unmet needs, and supports that may inform programs and interventions. By collecting numerous random assessments over a period of time, the EMA provides a representation of how individuals' experiences and behaviors vary over time and across situations. For this study, the method focuses on symptoms, experiences with caregiving and adaptive behaviors, and aims to map the fluctuations of daily function within both caregivers and care recipients. This method is considered suitable for understanding daily changes in mood, stress, and medical symptomology [38,45,95]. EMA is a useful tool in research for collecting data which are often unobtainable by other methods and providing ecologic validity based on a reduction of recall bias and therefore assessment error. It has also been shown to provide clarity on individual pattern assessments that can otherwise be misunderstood. EMA will

allow unprecedented information on unmet needs among MVCs and veterans with PTE.

To our knowledge, our analyses will be novel, as no one has examined longitudinal dyadic data using the changes in the extension of the bivariate dual latent change score model. The partitioning of prior levels and prior changes as distinct predictors of later changes is invaluable in helping us understand the underlying mechanisms that can be targeted for intervention. In addition, the study includes a broad range of measures that represent physical, mental, and emotional health of dyads. These data will enable us to not only evaluate individual-level impact on key outcomes but also to better understand the bidirectional health-related influences between veterans and caregivers. We expect that interventions designed to leverage relational strengths or address interpersonal barriers will ultimately result in better outcomes for both care recipients and caregivers [96-98].

Limitations

Study limitations include the fact that the sample may not represent all geographic regions of the United States or all subgroups of veterans. In addition, whereas the study is

longitudinal, follow-up will occur over a 2-year period, and therefore, we will not be able to assess the veterans' and caregivers' experiences over a longer period of time. As noted in the methods, our sample size may be too small to compare all 4 study groups on some measures, including health trajectory groups, depending on the distribution of responses and experiences. To keep the survey length manageable, we used screening versions of validated questionnaires for anxiety and depressive symptoms and therefore do not have more detailed measures of these experiences.

Conclusions

This study will fill a critical gap in the literature related to the needs, activities, and positive aspects of veterans with PTE and their caregivers. It will also strengthen our understanding of the relationship and positive aspects of caregiving for veterans with TBI and other injuries. We have designed the study using integrative frameworks and are leveraging a multidisciplinary team to use this work as the foundation for future interventions that will strengthen caregiver resilience and improve the health and quality of life of post-9/11 veterans and their family members who support them.

Conflicts of Interest

None declared.

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Abbreviations

BRFSS: Behavioral Risk Factor Surveillance System
EMA: ecological momentary assessment
mTBI: mild traumatic brain injury
MVC: military and veteran caregiver
MVCHW: Military and Veteran Caregiver Health and Well-being
NTE: nontraumatic epilepsy
PTE: posttraumatic epilepsy
TBI: traumatic brain injury
VA: Department of Veterans Affairs
VPES: Veterans Posttraumatic Epilepsy Study

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Protocol

A Nationwide Evaluation of the Prevalence of Human Papillomavirus in Brazil (POP-Brazil Study): Protocol for Data Quality Assurance and Control

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Abstract

Background: The credibility of a study and its internal and external validity depend crucially on the quality of the data produced. An in-depth knowledge of quality control processes is essential as large and integrative epidemiological studies are increasingly prioritized.

Objective: This study aimed to describe the stages of quality control in the POP-Brazil study and to present an analysis of the quality indicators.

Methods: Quality assurance and control were initiated with the planning of this nationwide, multicentric study and continued through the development of the project. All quality control protocol strategies, such as training, protocol implementation, audits, and inspection, were discussed one by one. We highlight the importance of conducting a pilot study that provides the researcher the opportunity to refine or modify the research methodology and validating the results through double data entry, test-retest, and analysis of nonresponse rates.

Results: This cross-sectional, nationwide, multicentric study recruited 8628 sexually active young adults (16-25 years old) in 119 public health units between September 2016 and November 2017. The Human Research Ethics Committee of the Moinhos de Vento Hospital approved this project.

Conclusions: Quality control processes are a continuum, not restricted to a single event, and are fundamental to the success of data integrity and the minimization of bias in epidemiological studies. The quality control steps described can be used as a guide to implement evidence-based, valid, reliable, and useful procedures in most observational studies to ensure data integrity.

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KEYWORDS

quality control; quality assurance; evidence-based medicine; quality data

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Introduction

Data quality assurance is essential to maintain the credibility and internal validity of a study and to enable further generalization of the results [1]. Quality control must be the basis of any work process for guaranteeing process standardization, resource maximization, and loss reduction and costs [2].

Research protocols traditionally include some tools to control sampling and measurement errors during their execution [3]. High-quality data and effective data quality assessments are required to measure the real impact of interventions and outcomes. The process of quality control of epidemiological studies is usually briefly described or not described in detail despite being an important step to ensure the reliability of the results. Although many studies have used quality assurance and quality control procedures, few have described those procedures in enough detail to support other researchers' ability to improve research quality [4-8]. Therefore, detailed descriptions of the quality control process should be more widely discussed among researchers.

It is recommended that protocols follow at least 3 steps: planning and standardization, planned implementation, and process analysis [3]. Although all of these steps are critical, one of the most important factors is based on the planning and standardization of procedures [9-11]. Standardized procedures are reflected in bias reduction [9] and reliable data [12]. Data standardization is essential when large and integrative studies are increasingly prioritized [13]. In addition, standardized surveys are able to provide comparable data across populations or periods [14].

Thus, this paper aims to describe the stages of quality control of the POP-Brazil study [15] and to present an analysis of the quality indicators. The POP-Brazil study was designed to provide representative data on human papillomavirus (HPV) prevalence in young adults who use the public health system in all 26 Brazilian state capitals plus the Federal District of Brasilia. High-quality public health data are needed to facilitate decision making and planning at all levels of the health system, monitor program performance, justify financial support, and, especially, provide data to evaluate the HPV vaccine program in a continental country, such as Brazil. To ensure standardization in all centers and the quality of the data produced by the POP-Brazil study, a quality control plan was carried out, with control points and key quality indicators [16].

Methods

Overview

The POP-Brazil study is a cross-sectional, nationwide, multicentric study [15]. Large-scale population studies face difficulties in recruiting representative samples [17]; thus, the initial planning involved a series of agreements with all 26 Brazilian state capitals plus the Federal District of Brasilia to choose the primary care health centers (ie, those with appropriate infrastructure and serving a diverse local population).

All quality control protocol strategies are presented in Figure 1, and these points will be explored and discussed one by one.

Figure 1. Quality control protocol strategies of the POP-Brazil study. IATA: International Air Transport Association.
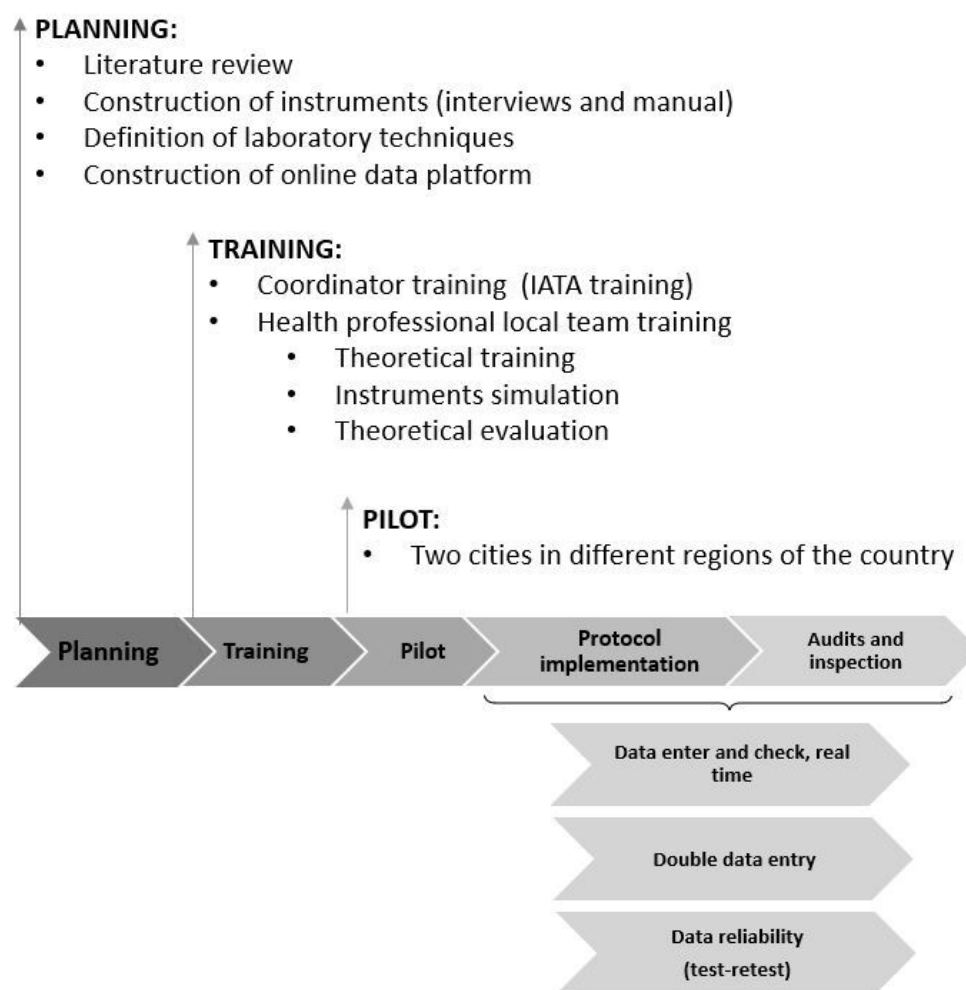
Planning

The planning phase included a comprehensive literature review [18] to obtain support for the development of the research protocol, construction of data collection instruments (structured interviews), and definition of laboratory techniques to be used. These actions are part of quality assurance, meaning they are activities planned and systematically implemented to provide confidence that the study will meet quality requirements.

The structured interview guide was developed through adaptations of previously validated questionnaires, followed by consultation with sexual behavior experts and pretests [19,20]. The questions accessed in the interview can be found in Multimedia Appendix 1. A part of the questionnaire was validated as the first instrument able to describe the knowledge, beliefs, and behaviors regarding HPV and related subjects [20].

In addition, an operation manual was constructed, consisting of specific instructions for conducting the interview, collecting biological samples, storing and transporting samples, and entering data on the online data platform (Sisepidemio—built exclusively for the project). Additionally, the manual contained guidance for the correct photographic recording of suspected oral or genital HPV lesions.

Training

Municipal health departments from each city invited a health professional to be the local study coordinator. Local study coordinators were responsible for packing and shipping the biological material, as well as organizing the study logistics at the local level. To ensure the safe transportation of biological samples and their quality [21-23], all coordinators were trained and certified by the International Air Transport Association since reliability and generalization of search results depend on data collection methods [24].

All 250 health professionals involved in data collection were trained, in loco, by the research group. This training was divided into theoretical and practical phases. Theoretical training, lasting 4 hours, presented the procedures to be performed and simulated the collection of biological material with anatomical models. For practical training, when the centers were visited by the researchers from the central team, the professionals responsible for data collection participated in an interview simulation (recorded for analysis) [9].

During the visit to the centers, their structural suitability for biological sample collection and storage was analyzed, and the logistics for transportation of these samples were defined. In all centers, the samples were kept at a temperature below 25 °C inside a refrigerator or portable coolers with reusable artificial

ice. To ensure that the collected biological samples were maintained at adequate temperature, a thermometer close to the samples automatically measured the temperature every 30 seconds. All professionals received a temperature control worksheet, where the thermometer temperature should be noted daily, for future audits.

A theoretical evaluation was performed at the end of training and served as the basis to verify the adequacy of the training. This evaluation was composed of 10 questions regarding training focal points. All professionals scored at least 82.7%. A minimum score of 70% was considered as a quality indicator.

At the end of the data collection, the professionals performed this evaluation again and scored at least 83.4% (*P*=.01). The second evaluation was used to verify the retention of knowledge and the maintenance of procedure adequacy throughout the data collection process. These evaluations helped to ensure standardization in all centers, since standardization must be treated as a priority for guaranteed quality [25].

When the differences between each question were analyzed, no significant differences were found among them, with the exception of one question regarding the handling of biological specimens, where an increase in the knowledge of the collectors was observed during the research period (51.0% to 72.5%; *P*=.02). For these analyses, a Cohen kappa coefficient was calculated using SAS software (SAS Institute Inc, Cary, NC), version 9.4.

Pilot Study

The pilot stage is crucial for the adequacy of any research protocol. The pilot can provide recommendations to avoid or minimize observed errors and optimize logistics and quality management [9]. The adequacy of the methodology for collecting data and biological material, the functioning of the online platform, and the logistics and security of the sample shipment were verified.

It was identified that the penile material collection methodology needed to be improved. The initial choice of technique was not retaining sufficient biological material for penile HPV detection. First, it was proposed that the collection be performed by health professionals through friction of the epithelium using a Digene "brush" (Qiagen, Hilden, Germany) moistened with saline. This technique was changed to self-collection under the guidance and supervision of a health care professional, with a moistened Dacron swab (Qiagen). Apparently, self-collected specimens produced a better [26] or equal [27] proportion of sufficient specimens than physician-collected specimens for penile samples. The data entry platform was enhanced to accommodate changes in the biological material logistics process.

Protocol Implementation

To standardize procedures and harmonize work conduct with the aim of increasing management efficiency and meeting the required demands, logistics systems for material transport, as well as for the inventory and systematic storage of samples, were created. All materials sent to public health units were cataloged and monitored by tracking codes. Participant data were collected on paper and typed on an online platform. The biological materials were sent to Porto Alegre through a logistics company by air weekly. All barcode-identified control worksheets, materials, and questionnaires were returned to the technical team in Porto Alegre.

The control of samples was performed through an online platform using barcode identification. Upon arrival at the laboratory in Porto Alegre, samples were recorded and visually inspected for volume, tube integrity, presence of blood, and particles, and any inadequacy was recorded in the online platform. The oral samples were stored without processing at –80 °C in 2 aliquots for future DNA extraction and analysis. The genital samples were centrifuged and aliquoted in 2 cryovials for storage at –80 °C. DNA extraction and analyses were gradually performed as previously described [15].

Audits and Inspection

All public health units received at least one monitoring visit (an audit) for quality control of the study. The audit aimed to identify any inadequacies in the collection, storage, or registration of data in the online platform. In case of delays in data collection or when inadequacies were found, new training was performed, and new centers or new professionals were included.

During the audit visits, researchers from the technical team supervised at least one data collection (interview and biological material) from a participant. All visits were documented through photographic records and report production.

Temperature controls were checked by auditing the thermometer graphics along with the temperature control worksheets. Each thermometer generated a temperature variation graph that was analyzed to ensure proper storage of biological materials. The database was also monitored, with a daily backup of the online platform. As a quality indicator, the temperature should always be below 25 °C.

In the POP-Brazil study, the nonresponse rates (when the respondent reported that they preferred not to answer or report that they did not know or remember) were monitored and are presented in Table 1. The only significant difference found between genders was regarding contraception. A response rate of 95% was considered good quality, based on a previous study [28], assuming that nonrespondents have similar characteristics as respondents.

Table 1. Nonresponse rates by question groups in the POP-Brazil study.

Variable	Total, n (%)	Women, n (%)	Men, n (%)	*P* value
Sociodemographic	1096 (15.29)	830 (15.32)	266 (5.26)	.97
Sexual behavior (symptoms and practices)	761 (8.17)	544 (3.75)	217 (4.43)	.12
Sexual health	656 (7.28)	501 (3.77)	155 (3.50)	.77
Women's sexual health	287 (3.23)	—a	—	—
Drugs	185 (2.82)	131 (2.36)	54 (3.30)	.19
Contraception	93 (1.26)	35 (0.25)	58 (2.30)	<.001

aThis variable applied to women only, so no comparison was conducted.

Double Data Entry

The reliability of a procedure can be defined as the ability to achieve the same results (with minimal variations) when the same procedure is performed by a different person or at a different time. To test the reliability of data entry, we opted for double-checking data validation: All questionnaires were typed on an online platform by health professionals and digitized using optical brand recognition by the technical team. In cases of disagreement in any answer, corrections were made using the answers written on the paper questionnaire as the gold standard.

We used Remark Office OMR 2014 v.9.5 software (Gravic Inc, Malvern, PA) for optical brand recognition. Questionnaires were scanned using ScanSnap Manager v.6.5 (Fujitsu Global, Tokyo, Japan) and processed in Remark. Additionally, manual validation was performed during the scan. Manual validation occurred when Remark did not recognize some answer in the scanned questionnaire. Under these circumstances, Remark highlights the variable for manual validation.

The error rate (inconsistencies) was calculated based on the total number of inadequacies by the total number of answers. Additionally, we analyzed survey responses to ensure nonduplication [29]. The first comparison between Sisepidemio and Remark was performed when 10% of the total sample was reached, to test the effectiveness of these systems. An error rate of 2.67% was observed. A second comparison between the databases was performed to verify the overall quality of the data produced by POP-Brazil. From 2100 questionnaires, an average inconsistency of 0.71% (range 0% to 4.37%) was found. Date of birth was the variable with the highest typing error rate.

Test-Retest

Additionally, data reliability was analyzed by comparing a first application of the interview, conducted by a health professional, to a second application of the interview, conducted by the technical team via telephone. The average time between test-retest was 166.17 (SD 69.5) days and ranged from 1 month to 14 months.

The calls were standardized. For this, a manual for telephone interviews was used. This manual outlined each step of the call (conducting the interview and how to present the questions), as well as highlighting confidentiality issues. The telephone interview was conducted to confirm the validity of previously obtained data and included part of the main questionnaire (29 of 65 questions). The questions chosen for this second interview were those with answers that are easy to remember or do not change over time (eg, date of birth). Calls were made on alternate weekdays and shifts, with at least 3 calls to each participant before classifying them as a "noncontact."

From the total sample, 20% of patients were randomized to be enrolled in this quality control step. The reliability of the test and retest questions was measured using kappa coefficients [30,31]. To classify the degree of concordance, the criteria by Landis and Koch [31] were used: excellent: >0.74; good: 0.59 to 0.74; moderate: 0.40 to 0.58; and poor: <0.40. A minimum sample size of 173 interviews was estimated based on the Cohen kappa coefficient value [32] of the variable "race" (κ = 0.63), with a power of 80% and a 2-tailed alpha of .05. Overall, the agreement between the test and retest was considered good (kappa range across questions = 0.59 to 0.74).

The rate of inconsistencies was also calculated, as previously mentioned. A total of 1311 individuals were contacted, and 448 interviews were completed. The effective percentage of contact with the participant through phone calls was, on average, 34.17% (448/1311), with most calls being classified as "noncontact" (843/1311, 64.30%). When we obtained contact for the interview, the confirmation rate of participation in the POP-Brazil study was high: 95.7% (448/468) confirmed participation and agreed to answer the survey again. Only 14 individuals confirmed participation in the survey but refused to answer again (14/468, 3.0%); 6 individuals reported not remembering being part of the POP-Brazil survey.

Results

The POP-Brazil study protocol was approved by the Moinhos de Vento Hospital research board (Approval Number 1607032) and was designed in accordance with the 1964 Helsinki declaration and its later amendments. The pilot study was conducted in 2 cities in different regions of the country (north: Rio Branco; south: Curitiba) between September 2016 and December 2016. A total of 8628 sexually active young adults (16-25 years old) were enrolled in 119 public health units between September 2016 and November 2017 [15].

Discussion

Inaccurate reporting of data hampers the generalizability and correct interpretation of results from scientific papers, so assessing research quality and susceptibility to bias is essential when interpreting and conducting studies. Large multicenter

epidemiological studies are the cornerstone of evidence-based medicine, so their design, logistics, and quality processes should always be disclosed to ensure data integrity. A broad discussion of quality processes among epidemiological studies, such as the POP-Brazil study, is important to ensure data reliability and to highlight the necessity of the process in observational studies.

Epidemiological data, as in other types of research, are susceptible to variations that can lead to inappropriate conclusions. For this reason, quality control is critical in conducting any study, and the integrity of the study results is determined by the quality of the collected data [33]. Although the importance of quality assurance and control in epidemiological studies is consistent among researchers and widely discussed, few studies have been written about the results of quality control [33,34] or described the tools applied. Moreover, although it is expected that studies, especially larger ones, perform quality control, there is no information about the process in smaller or observational studies.

In the present study, several steps were mentioned. Among these factors, we highlight the importance of conducting a pilot study that provides the researcher the opportunity to refine or modify the research methodology and to develop large-scale studies [35]. A well-conducted pilot will encourage methodological rigor and ensure that the work is scientifically valid and publishable [36,37]. Although pilots play an important role in any research, the reality is that they receive little or no attention in many studies. Few articles, epidemiology, or research textbooks cover the topic with the necessary detail [35]. The pilot study provided important information regarding penile HPV sample collection, allowing us to intervene appropriately to correct the process and ensure the quality of the collected samples.

Another fundamental factor is validating the results through double data entry, test-retest, and analysis of nonresponse rates. Double data entry is considered the criterion standard for minimizing data entry errors [38], and the rate was low in this study (2.67%). Automated form processing is a valid alternative to double manual data entry [39]. It is noteworthy that, in general, there are no differences in the use of computerized systems and manual systems regarding the quality of the final data obtained [38,39]. However, the efficiency of brand recognition systems has recently been evidenced, thereby providing more cost-effective and operationally efficient systems [38,39]. Test-retest findings should not be used as a single

quality control measure since contact attempts were mostly unsuccessful (64.30%). Lack of contact is a common finding in this type of data collection. Herath et al [40] reported that 78% of respondents did not respond to phone calls. Another study using a similar methodology reported a noncontact rate of approximately 60% [41,42]. The refusal to participate in the interview (2.99%) was similar to that presented by a large Brazilian epidemiology study (3.8%) [43]. This same survey observed that approximately 22.8 calls were needed to obtain a full interview [43]. Our effectiveness rate was higher, requiring 8.54 calls for a full interview. Although the test-retest estimate was considered generally good and similar to previous studies [44], some questions showed lower agreement, such as reporting sexually transmitted infections and drug use. The retest emphasized the relevant time frame (for example, "Did you smoke at the time you answered the POP-Brazil survey?" or "Did you start to smoke, after the survey?"), but it is possible that the participant would not remember the answer he or she had previously given due to the time gap between the tests. It is recognized that longer recall periods result in less accurately reported estimates [45,46]. However, there is no definition of the appropriate length of the recall period, and it also depends on the type of information, individual characteristics such as cognitive ability or socioeconomic variables, and the nature of the survey [45].

The nonresponse level is considered a central indicator of data quality, but little is known about the possible bias caused by nonresponse. Few studies check this parameter, and nonresponse rates vary between surveys [28,47], which may lead to bias in estimates [24,48,49] because it is dependent on the sample population [24]. Important differences between survey responders and those who do not answer some questions may lead to a bias associated with nonresponse that impacts the generalizability and validity of the study findings. In POP-Brazil, most of the nonresponses were about not knowing or remembering some answers, and these variables depended on participant memory rather than a refusal to answer such questions.

In conclusion, quality control processes are a continuum, not restricted to a single event, and are fundamental to the success of data integrity and to minimizing bias in epidemiological studies. A number of useful items has been discussed in this report. The quality control steps described can be used as a guide to implement evidence-based, valid, reliable, and useful procedures in most observational studies to ensure data integrity.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Topics accessed in the interview.

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Abbreviations

HPV: human papillomavirus

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Protocol

COCARDE Study–Cardiac Imaging Phenotype in Patients With COVID-19: Protocol for a Prospective Observational Study

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Abstract

Background: The effects of SARS-CoV-2 (COVID-19) on the myocardium and their role in the clinical course of infected patients are still unknown. The severity of SARS-CoV-2 is driven by hyperinflammation, and the effects of SARS-CoV-2 on the myocardium may be significant. This study proposes to use bedside observations and biomarkers to characterize the association of COVID-19 with myocardial injury.

Objective: The aim of the study is to describe the myocardial function and its evolution over time in patients infected with SARS-CoV-2 and to investigate the link between inflammation and cardiac injury.

Methods: This prospective, monocentric, observational study enrolled 150 patients with suspected or confirmed SARS-CoV-2 infection at Toulouse University Hospital, Toulouse, France. Patients admitted to the intensive care unit (ICU), regular cardiologic ward, and geriatric ward of our tertiary university hospital were included during the pandemic period. Blood sampling, electrocardiography, echocardiography, and morphometric and demographic data were prospectively collected.

Results: A total of 100 patients were included. The final enrolment day was March 31, 2020, with first report of results at the end of the first quarter of 2021. The first echocardiographic results at admission of 31 patients of the COCARDE-ICU substudy population show that biological myocardial injury in COVID-19 has low functional impact on left ventricular systolic function.

Conclusions: A better understanding of the effects of COVID-19 on myocardial function and its link with inflammation would improve patient follow-up and care.

Trial Registration: Clinicaltrials.gov NCT04358952; https://clinicaltrials.gov/ct2/show/NCT04358952

International Registered Report Identifier (IRRID): DERR1-10.2196/24931

Introduction

Background

SARS-CoV-2 infection, the pathogen which is responsible for COVID-19 and which can lead to acute respiratory distress syndrome, is not limited to the pulmonary sphere and has systemic effects that contribute to its significant mortality. The effects of SARS-COV-2 on the myocardium and their role in the clinical course of infected patients are still unknown. Cardiovascular risk factors such as diabetes and hypertension, as well as coronary or cerebral cardiovascular history, have been associated with severe forms of infection [1-3]. In addition, most of the cohort data currently available report biological myocardial injury with troponin increase in about 12% of patients [4-6] with a prevalence ranging from 4% to 31% according to the burden of the disease and the need for resuscitative management [4,7,8]. Myocardial injury is associated with excess mortality, which is particularly prevalent in older adults [7-9]. Individuals at greatest risk of severe disease and mortality are older patients, particularly those with underlying cardiovascular risk factors and chronic conditions.

The pathophysiology of the myocardial involvement of SARS-CoV-2 remains poorly understood despite research flourishing in the field [10]. Some observations suggest an association with the cytokine storm that accompanies the infection [5]. The more or less massive release of proinflammatory cytokines has been linked to the pathophysiology of organ failure that accompanies viral infection [11], further explaining the prognostic role of several biological parameters such as increased C-reactive protein, procalcitonin, D-dimers, creatine phosphokinase, lactate dehydrogenase, lymphopenia, and leukopenia [2,4,12,13]. The cytokine storm is thought to cause an imbalance between myocardial oxygen needs and supply, leading to a type 2 myocardial infarction [14]. However, given the importance of cardiovascular risk factors in severe forms of the disease, a type 1 myocardial infarction [14] via an atheromatous plaque rupture mechanism cannot be excluded [15,16] despite there being a trend of reduced admissions for acute coronary syndrome [17]. Finally, the possibility of a myocardial tropism of SARS-CoV-2 through the myocardial angiotensin-converting enzyme 2 receptors [18] could explain a direct viral infection of the myocardium, which may lead to fulminant myocarditis [19,20]. More generally, the inflammatory mechanisms involved could also affect skeletal muscle tissue and body composition resulting in cardiac cachexia [21].

However, despite there being substantial biological data on cardiac injury during SARS-CoV-2 infection, to date, no data on the functional impact of the infection on the myocardium have been collected.

Rationale

Based on the observation that cardiac injury—as evidenced by an increase in troponin—is associated with a poor prognosis and that the most severe forms affect older adult patients, the COCARDE study was designed in 2 arms: intensive care unit (COCARDE-ICU) and geriatrics (COCARDE-Geria) with the aim to describe the cardiac imaging phenotype of patients infected with SARS-CoV-2.

Objectives

The objective of this study is to describe the myocardial function and its evolution during infection in high-risk patients infected with SARS-CoV-2 and to establish the role of inflammation in the cardiac involvement.

Methods

Study Design

The COCARDE study is an investigator-initiated, prospective, monocentric, observational study with a planned enrolment of 150 patients at Toulouse University Hospital, Toulouse, France. The patient flowchart is presented in Figure 1.

Figure 1. Patient flowchart. CMR: cardiac magnetic resonance; COV–: without SARS-CoV-2 infection; COV+: with SARS-CoV-2 infection; CT: computed tomography; ECG: electrocardiography; hs-TnT: high-sensitivity troponin T; RT-PCR: real-time reverse transcription–polymerase chain reaction; TnT–: without biological cardiac injury; TnT+: with biological cardiac injury; TTE: transthoracic echocardiography.
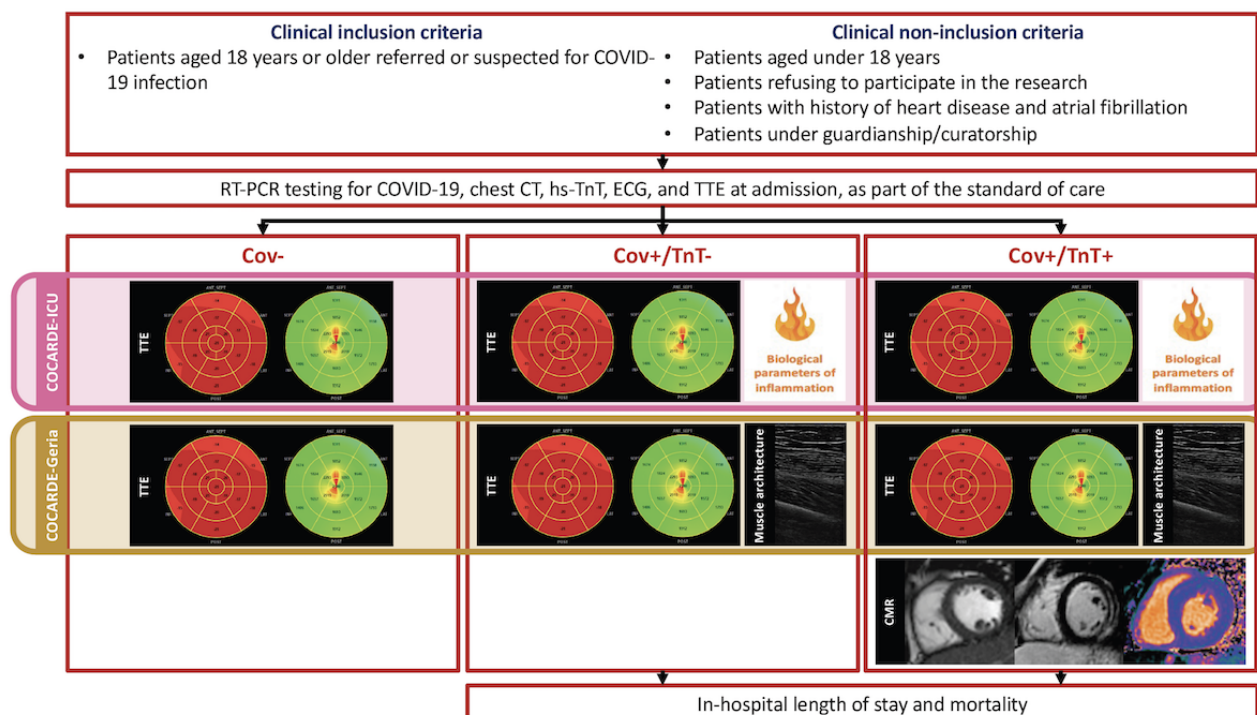
Notifications and Registration

The study was considered to as appropriate by the national ethics committees (protocol number ID-RCB: 2020-A00852-37; positive endorsement of the protection of persons committee West IV dated April 8, 2020) and the French Data Protection Agency. The study is registered with Clinicaltrials.gov (NCT04358952). The investigation conforms with the principles outlined in the Declaration of Helsinki. All patients or their dependents have been informed that the data collected can be used for research purposes, and the absence of opposition has been collected for each patient in accordance with French legislation.

Objectives

Primary and secondary objectives and definitions of the COCARDE study are listed in Textbox 1.

Textbox 1. Primary and secondary objectives and definitions of the COCARDE study.

Primary objective

- Prospectively describe the myocardial function at admission in a population of high-risk patients infected with SARS-CoV-2 compared to a matched population of uninfected patients.

Primary objective definition

- Myocardial function assessed by global longitudinal strain and myocardial work indices (global work index and global work efficiency) by speckle-tracking echocardiography.

Secondary objectives

- Describe the evolution of myocardial function over time (admission, day 3, day 7, and day 14) in high-risk patients infected with COVID-19.

- Describe the relationship between myocardial function and biological parameters of inflammation in high-risk patients infected with COVID-19.

- Describe the relationship between myocardial function and vastus lateralis muscle architecture in patients over 70 years old infected with COVID-19.

- Describe the myocardial lesion pattern by cardiac magnetic resonance imaging in patients infected with COVID-19 with biological cardiac injury.

- Describe the impact of myocardial function on prognosis in hospitalized patients infected with COVID-19.

Secondary objectives definitions

- Myocardial function assessed by global longitudinal strain and myocardial work indices (global work index and global work efficiency) by speckle-tracking echocardiography.

- Biological parameters of inflammation: proinflammatory cytokines, anti-inflammatory cytokines, alarmins, and resolvins.

- Morphometric parameters assessed by muscle architecture to determine muscle thickness, penetration angle, and muscle fiber length of the vastus lateralis using ultrasound [22].

- Myocardial lesion pattern assessed by T2-weighted, T2 mapping, and precontrast T1 mapping imaging. (edema); and early gadolinium enhancement (hyperemia), late gadolinium enhancement, and postcontrast T1 mapping (necrosis/edema) by cardiac magnetic resonance imaging.

- Prognosis assessed by hospital length of stay and in-hospital mortality.

Patient Population

Following the classification of the SARS-CoV-2 infection as a pandemic by the World Health Organization on March 11, 2020, and following an epidemiological alert issued by the French health authorities on March 14, 2020, the organization of patient reception at our university hospital has been reviewed to allow for the screening and isolation of infected patients. All patients with suspected SARS-CoV-2 infection have undergone collection of specimens from the upper respiratory tract for SARS-CoV-2 testing by real-time reverse transcription–polymerase chain reaction (RT-PCR), chest computed tomography (CT), cardiac biomarkers including values of high-sensitivity troponin T and N-terminal pro b-type natriuretic peptide, electrocardiography, and transthoracic echocardiography at admission as part of the standard of care.

A diagnosis of a SARS-CoV-2 infection should be retained in the presence of an evocative chest CT and a positive RT-PCR for SARS-CoV-2 or an evocative chest CT in the presence of a negative RT-PCR for SARS-CoV-2 after other common respiratory viral and bacterial infections have been ruled out [23]. Biological cardiac injury was defined as blood levels of high-sensitivity troponin T above the 99th percentile upper reference limit.

Patients have been categorized into 3 groups according to the presence of SARS-CoV-2 infection or biological cardiac injury, and the study population has been divided into 2 arms: patients requiring or not requiring the ICU (COCARDE-ICU) and patients over 70 years old not referred to the ICU (COCARDE-Geria).

The serum of patients from the COCARDE-ICU population was collected after centrifugation for a study of inflammatory parameters. Patients from the COCARDE-Geria population were assessed for the muscle architecture of the vastus lateralis.

Patients with biological cardiac injury were referred for cardiac magnetic resonance imaging when suitable.

Inclusion Criteria

The inclusion criteria for patients are an age 18 years or older and those referred for or suspected of SARS-COV-2 infection.

Exclusion Criteria

The exclusion criteria for patients are the following: patients aged under 18 years old; patients refusing to participate to the research; patients with a history of heart disease and atrial fibrillation; and patients under guardianship, curatorship, or safeguard of justice.

Data Collection

The demographic characteristics (age and sex), clinical data (weight, height, symptoms, delay between first symptom and admission, comorbidities, treatments), arterial blood pressure, and laboratory findings for patients during hospitalization were collected from electronic medical records and entered into the database by 2 investigators (VB and VH). Electrocardiography,

transthoracic echocardiography, cardiac magnetic resonance imaging, and muscle architecture assessment were performed and analyzed by independent investigators blinded to the clinical characteristics of the patients.

Biomarkers

Inflammatory pathway parameters were collected for plasma extracted from venous blood sampling into sodium citrate tubes. Blood samples were centrifuged at 3000 g for 5 minutes at room temperature. Superior two-thirds supernatant was recovered and again centrifuged for 5 minutes. The following analyses were then performed in the same laboratory: proinflammatory cytokines, including tumor necrosis factor alpha, interleukin 6 (IL-6), IL-1β, IL-1α, interferon gamma (IFN-γ), IFN-α2, monocyte chemoattractant protein-1 (CCL2), IL-12, IL-17, IL-23, IL-33, and IL-8 (CXCL8); the anti-inflammatory cytokine, IL-10; alarmins, including high-mobility group box protein 1, S100 protein, and DNA; and resolvins, including 18-HETE (18-hydroxyarachidonic acid), 15-HETE, 12-HETE, 17-HDOHE (17-hydroxydocosahexaenoic acid), 5-HETE, 14-HDOHE, eicosapentaenoic acid, docosahexaenoic acid, arachidonic acid, protectin DX, prostaglandin, and thromboxan B2.

Electrocardiography

Electrocardiography was analyzed for heart rate, rhythm, intraventricular conduction delay, QRS duration, and QT duration.

Transthoracic Echocardiography and Image Analysis

Transthoracic echocardiography was performed with either a Vivid E95 or Vivid S70 ultrasound system (GE Healthcare) using a 3.5 MHz transducer, which facilitated the archiving of acquisitions for a deferred analysis. Doppler, M-mode, and 2D gray scale echocardiography including the 3 standard apical views (4-, 3-, and 2-chamber) with high frame rates (>60 frames/s); pulsed Doppler transmitral inflow and left ventricular outflow; and the pulsed-Doppler tissue imaging lateral mitral and tricuspid annular velocities were performed for each patient with simultaneous arterial blood pressure recording.

Image analyses were performed offline using EchoPAC V202 software (GE Medical Systems). Two-dimensional and Doppler echocardiography measurements and quantification were performed according to the American Society of Echocardiography and the European Association of Cardiovascular Imaging guidelines [24,25]. The following measurements were collected: diastolic parameters, including peak early and late diastolic mitral inflow velocity, E/A ratio, deceleration time, lateral mitral annular diastolic velocity, peak systolic tricuspid annular velocity, and tricuspid annular plane systolic excursion. All Doppler measurements were made over 3 cardiac cycles and averaged. Left ventricular end-diastolic and -systolic volumes and ejection fraction were measured using the modified biplane Simpson's method from apical 2- and 4-chamber views. Global longitudinal strain (GLS) was calculated from the average of the segmental strain on a 17-segment model using 2D speckle tracking from grayscale images and the automated function imaging technique from the apical 4-chamber, 3-chamber, and 2-chamber views [26].

Myocardial work was calculated from left ventricular GLS and the estimated left ventricular pressure curve as proposed by Russell et al [27]. The wasted work is defined by the work performed by the myocardium during segmental elongation and the constructive work by the work performed during segmental shortening. During isovolumetric relaxation, this definition is reversed such that myocardial work during shortening is considered wasted work and work during lengthening is considered constructive work. Work efficiency is then calculated as the constructive work divided by the sum of the constructive and the wasted work.

Muscle Architecture Processing and Analysis

Skeletal muscle ultrasound assessment of the vastus lateralis was performed using a Vivid E95 ultrasound system (GE Healthcare) and a 15 MHz linear probe by acquisition at the lower third of the femur for exploration as described by Aubertin-Leheudre et al [22]. In this procedure, patients sit with hip and knee angled at 90° and with limb muscles relaxed. The probe is positioned perpendicular to the dermal surface of the vastus lateralis muscle and oriented along the median longitudinal plane of the muscle. For this study, 3 sagittal ultrasounds of the vastus lateralis were then digitized and images analyzed offline using EchoPAC V202 software (GE Medical Systems) to determine muscle thickness (distance from the superior and deepest aponeurosis at the greatest distance), penetration angle (angle of insertion of the bundle of muscle fibers into the deep aponeurosis), and muscle fiber length (length of the fascicle between the superior and deep aponeurosis).

Cardiac Magnetic Resonance Protocol and Imaging Analysis

Cardiac magnetic resonance was performed in breath-hold mode with the use of a 1.5-T Ingenia Ambition X magnetic resonance imaging system (Philips Medical Systems) using a 32-element phased-array cardiac coil with cardiac gating in accordance with the recommendations of the Society for Cardiovascular Magnetic Resonance endorsed by the European Association for Cardiovascular Imaging [28]. Following scout imaging, balanced steady-state free precession breath-hold images were acquired with a slice thickness of 6 mm (long-axis and 4-chamber views) or 8 mm (contiguous short-axis views with no gap between slices from the atrioventricular ring to the apex). Subsequently, standard sequences for T2-weighted, T2 mapping, and precontrast T1 mapping images were obtained in the short axis, through the basal, midcavity, and apical slices, and then early and late gadolinium enhancement images were obtained in the long-axis, 4-chamber, and short-axis orientations 10 minutes after the injection of 0.2 mmol/kg of gadolinium dimenglumine (Magnevist) using a phase-sensitive inversion recovery spoiled gradient echo sequence. Postcontrast T1 mapping was obtained in the short axis, through the basal, midcavity, and apical slices.

Image analysis was performed using the clinically available imaging software workstation ViewForum (Philips Medical Systems). The endocardial border was outlined on the short-axis cine images on the right and left ventricles, in systole and diastole, from the base to the apex to calculate volumes and ejection fractions. T2 and pre- and postcontrast T1 mapping measurements were performed on motion-corrected maps to

cover the entire myocardium in the short axis, and 6 separate segments where both mean and maximum values were noted. The extent and pattern of late gadolinium enhancement were assessed by a planimeter on the short-axis contrast images and confirmed on an orthogonal view (either long-axis or 4-chamber) with the use of an image intensity level ≥2 SDs above the mean of the remote myocardium to define late gadolinium enhancement. The 17-segment model was used to localize late gadolinium enhancement within the left ventricle.

Sample Size

This is a descriptive pilot study. As there is no data on the topic, to date, the number of patients included is 50 per group. The group allocation is as follows: 50 patients without SARS-CoV-2 infection (Cov–), 25 in the COCARDE-ICU substudy and 25 in the COCARDE-Geria substudy; 50 patients with SARS-COV-2 infection without biological cardiac injury (Cov+/TnT–), 25 in the COCARDE-ICU substudy and 25 in the COCARDE-Geria substudy; and 50 patients with SARS-COV-2 infection with biological cardiac injury (Cov+/TnT+), 25 in the COCARDE-ICU substudy and 25 in the COCARDE-Geria substudy.

Timeline for Myocardial Function Monitoring

The timeline for myocardial function monitoring is presented in Figure 2.

Figure 2. Timeline for myocardial function monitoring. ICU: intensive care unit; hs-TNT: high-sensitivity troponin T.
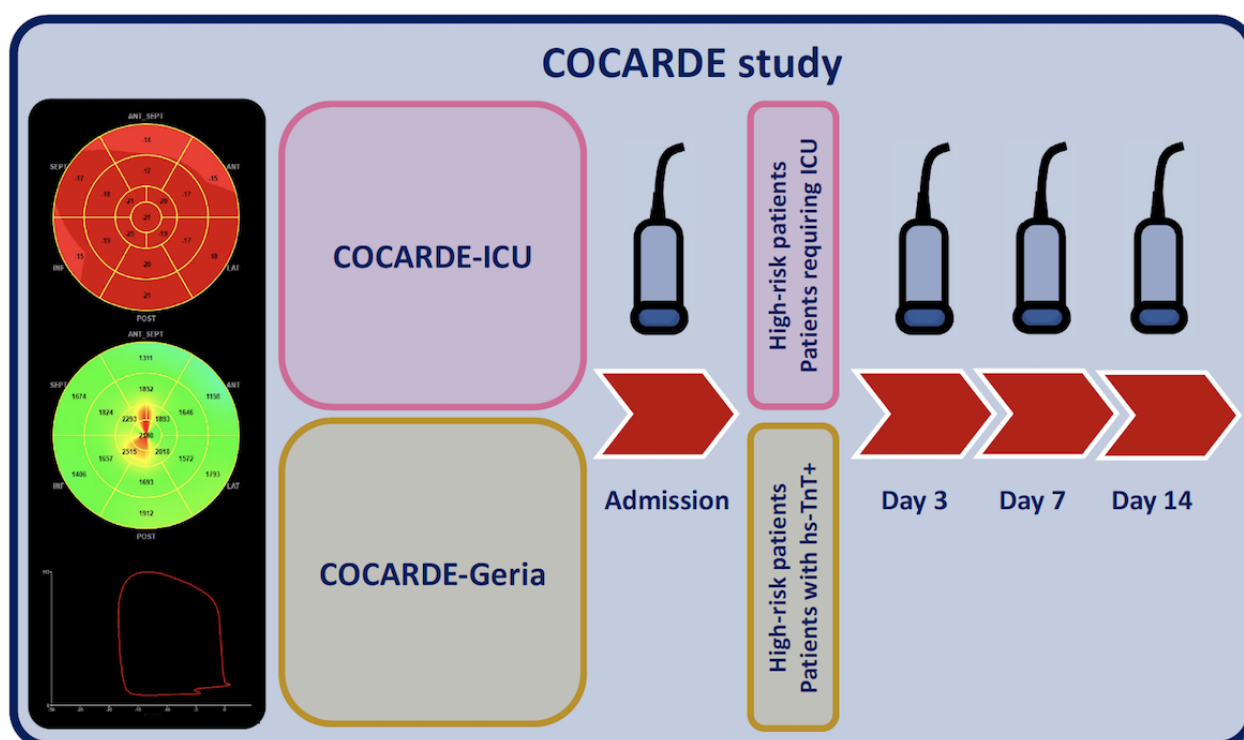
Statistical Analysis

Continuous variables have been tested for normal distribution using the Kolmogorov-Smirnov test and are expressed as mean and SD. Laboratory findings were not normally distributed, and the results will be, therefore, presented as medians with IQR. Nominal values will be expressed as numbers and percentages. The study population was categorized into 3 groups: Cov–, Cov+/TnT–, and Cov+/TnT+. Group comparisons have been made using nonparametric Kruskal-Wallis tests or analysis for variance for continuous variables and $\chi2$ test for categorical variables, with Bonferroni corrections being used for multiple comparisons. Logistic regression models and classification regression trees were used to identify predictors of myocardial dysfunction at admission. Differences are being considered statistically significant for P values <.05. All analyses were performed using SPSS version 20 software (IBM Corp).

Results

A total of 100 patients were included. The final enrolment day was March 31, 2021, with first report of results at the end of the first quarter of 2021.

The first results of the study presenting the echocardiographic phenotype at admission of 31 patients of the COCARDE-ICU substudy population have been published, showing that biological myocardial injury in COVID 19 has low functional impact on left ventricular systolic function [29]. Longitudinal data are being collected and the COCARDE-Geria substudy data are being analyzed.

Discussion

The COCARDE study is the first study to date to propose a cardiac imaging phenotyping of patients infected with SARS-CoV-2. Data on myocardial injury in these patients are scarce and limited to biological parameters of myocardial injury.

Although sensitive, these parameters do not prejudge the mechanism and functional impact on the myocardium. Troponin is a marker of myocardial injury, including, but not limited to, myocardial infarction or myocarditis, and the clinical relevance of this distinction has never been clear and is even less clear in the context of the SARS-COV-2 infection, which causes a plethora of ischemic and nonischemic origins of myocardial lesions [30]. However, to date, most of the data regarding SARS-CoV-2–associated cardiovascular complications are anecdotal and in the absence of systematic studies [31].

The COCARDE study will be able to describe myocardial function assessed by GLS and myocardial work indices in a population patients infected with SARS-COV-2. Furthermore, the study will be able to describe the evolution over the time of myocardial function among the high-risk patients in this population (ie, patients hospitalized in the intensive care unit and older patients with biological cardiac injury).

This study will help in understanding the impact of the kinetics of inflammatory parameters on myocardial function during infection. The magnetic resonance imaging data will allow for the differentiation between direct myocardial involvement by the inflammatory process and indirect vascular involvement, regardless of whether it is a type 1 or type 2 myocardial infarction.

The COCARDE study has the limitations associated with single-site and limited-sample studies. Therefore, our patients may not represent patients admitted to other facilities for SARS-CoV-2 management. However, the study is being carried out in a tertiary care teaching hospital to which the majority of patients of the suburban area are referred. Moreover, the selection of high-risk patients (ie, patients hospitalized in the intensive care unit and older patients) provides a choice sample to help better understand myocardial injury in the population of patients infected with SARS-CoV-2.

Given the severity of illness and the primary focus on urgently managing infection and respiratory failure, it is understandable that not all patients have complete cardiac data, such as electrocardiography, and that information from more sophisticated cardiac testing, such as echocardiography, coronary angiography, and magnetic resonance imaging, are not available [15]. To date, there are no data on the relationship between myocardial function and biological parameters of inflammatory activation pathways in patients infected with SARS-CoV-2. This study proposes to use bedside observations and biomarkers to characterize the association SARS-COV-2 with myocardial injury.

Acknowledgments

Conflicts of Interest

OL has received personal compensation for speaking with General Electric. The other authors have no conflicts of interest to declare.

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Abbreviations

Cov–: without SARS-CoV-2 infection
Cov+: with SARS-CoV-2 infection
CT: computed tomography
GLS: global longitudinal strain
HDOHE: hydroxydocosahexaenoic acid
HETE: hydroxyarachidonic acid
IFN: interferon
IL: interleukin
RT-PCR: real-time reverse transcription–polymerase chain reaction
TnT–: without biological cardiac injury
TnT+: with biological cardiac injury
TTE: transthoracic echocardiography

Protocol

Determining the Prevalence and Incidence of SARS-CoV-2 Infection in Prisons in England: Protocol for a Repeated Panel Survey and Enhanced Outbreak Study

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Abstract

Background: There are over 80,000 people imprisoned in England and Wales in 117 prisons. The management of the COVID-19 pandemic presents particular challenges in this setting where confined, crowded, and poorly ventilated conditions facilitate the rapid spread of infectious diseases.

Objective: The COVID-19 in Prison Study aims to examine the epidemiology of SARS-CoV-2 in prisons in England in order to inform public health policy and practice during the pandemic and recovery. The primary objective is to estimate the proportion of positive tests of SARS-CoV-2 infection among residents and staff within selected prisons. The secondary objectives include estimating the incidence rate of SARS-CoV-2 infection and examining how the proportion of positive tests and the incidence rate vary among individual, institutional, and system level factors.

Methods: Phase 1 comprises a repeated panel survey of prison residents and staff in a representative sample of 28 prisons across England. All residents and staff in the study prisons are eligible for inclusion. Participants will be tested for SARS-CoV-2 using a nasopharyngeal swab twice (6 weeks apart). Staff will also be tested for antibodies to SARS-CoV-2. Phase 2 focuses on SARS-CoV-2 infection in prisons with recognized COVID-19 outbreaks. Any prison in England will be eligible to participate if an outbreak is declared. In 3 outbreak prisons, all participating staff and residents will be tested for SARS-CoV-2 antigens at the following 3 timepoints: as soon as possible after the outbreak is declared (day 0), 7 days later (day 7), and at day 28. They will be swabbed twice (a nasal swab for lateral flow device testing and a nasopharyngeal swab for polymerase chain reaction testing). Testing will be done by external contractors. Data will also be collected on individual, prison level, and community factors. Data will be stored and handled at the University of Southampton and Public Health England. Summary statistics will summarize the prison and participant characteristics. For the primary objective, simple proportions of individuals testing positive for SARS-CoV-2 and incidence rates will be calculated. Linear regression will examine the individual, institutional, system, and community factors associated with SARS-CoV-2 infection within prisons.

Results: The UK Government's Department for Health and Social Care funds the study. Data collection started on July 20, 2020, and will end on May 31, 2021. As of May 2021, we had enrolled 4192 staff members and 6496 imprisoned people in the study. Data analysis has started, and we expect to publish the initial findings in summer/autumn 2021. The main ethical consideration is the inclusion of prisoners, who are vulnerable participants.

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Conclusions: This study will provide unique data to inform the public health management of SARS-CoV-2 in prisons. Its findings will be of relevance to health policy makers and practitioners working in prisons.

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Introduction

On March 11, 2020, the World Health Organization (WHO) declared a global pandemic of COVID-19, an illness caused by infection with SARS-CoV-2. By May 26, 2021, there were over 167 million confirmed infections and over 3.4 million deaths globally [1]. The pandemic has affected the United Kingdom, and over 1 million people have now tested positive for SARS-CoV-2 [2]. The pandemic has resulted in considerable adverse health, economic, and social consequences, with disproportionate impacts on Black, Asian, and minority ethnic groups and poorer communities [3].

The management of the COVID-19 pandemic presents particular challenges in the prison setting, and currently, over 80,000 people are imprisoned in England and Wales in 117 prisons [4]. Outbreaks of infectious diseases are not uncommon in prison settings where the confined, crowded, and poorly ventilated conditions facilitate the rapid spread of infectious diseases [5]. Given emerging evidence that SARS-CoV-2 is transmitted easily and is much more likely to spread in closed settings [6], the potential for rapid "explosive" COVID-19 outbreaks within prisons is considerable. The consequences for the imprisoned people (residents) are likely to be serious given the high proportion of individuals with risk factors for serious disease and death. The prevalence rates of chronic liver disease, lung disease, obesity, and other noncommunicable diseases are likely to be higher in prison populations [7,8]. Furthermore, the proportion of "older" people in prisons is rising rapidly, and imprisoned people are more likely to come from an ethnic minority [9]. Both these are important emerging risk factors for severe disease.

COVID-19 outbreaks are of importance to not only prison residents and staff, but also the wider community, as prisons are not sealed off from the rest of society. Staff and professional and social visitors (such as lawyers and families of residents) enter and leave daily. Residents leave to attend court hearings or hospital appointments, and they might return to a different prison. Moreover, newly imprisoned people and those transferred from other prisons enter many prisons daily. Thus, there is a high risk of the introduction of SARS-CoV-2 into prisons and its transmission among residents, staff, and visitors. There is potential for onward transmission to the community by staff and visitors, and by people who are released. The risks of "feeding and seeding" outbreaks in prisons through the in and out movements of staff, residents, and others are considerable [10], and the WHO has asserted that prisons should be an integral part of the public health response to COVID-19 [11].

In England, 3 key organizations (Her Majesty's Prison and Probation Service [HMPPS], National Health Service [NHS], and Public Health England [PHE]) work together to tackle COVID-19 in prisons, implementing measures across all prisons to save lives, protecting the NHS by reducing the number of people requiring specialist care in community-based hospitals, and enabling the continued operation of the prison estate. The implementation of a restricted prison regime and "compartmentalization" of residents have been key elements in preventing the spread of SARS-CoV-2 [10]. The restricted prison regime, instituted by HMPPS on March 24, 2020, resulted in the cessation of social visits, face-to-face education provision, training and employment activities (except for essential workers), access to gyms, and religious association. Time out of prison cells for residents was also limited to as little as the statutory minimum of an hour a day. There were restrictions on the number of people unlocked and number of people in exercise yards at any one time, thus enabling the enforcement of social distancing of 2 m for staff and residents. "Compartmentalization" has been implemented both between and within prisons. Between prison transfers have been minimized to reduce the risk of "seeding" infections into prisons. Within each prison, "cohorting" strategies have been developed to prevent the spread of infection among residents and to protect the most vulnerable. Shielding units have been established to isolate those who meet the criteria for extremely vulnerable or vulnerable [9]. These units have enhanced the levels of biosecurity, including dedicated staff. Protective isolation units accommodate known or probable COVID-19 cases in, primarily, single-cell accommodation. Reverse cohorting units enable the quarantining of newly imprisoned people for a period of up to 14 days (upper limit of the known incubation period for SARS-CoV-2) before they enter the general population.

Emerging data suggest that these strategies have been effective in the first wave of the pandemic [10], but outbreaks involving prisons occurred when community prevalence was low and prisons moved into the "recovery" period. In this period, the restricted regime was eased, with population flows into and out of prisons increasing as courts opened up [12]. Social and legal visits were reintroduced, and activities in the prison, such as exercise and education provision, increased. While the risk of incursion of infection into prisons (via infected staff in particular) is likely to be related to the community incidence, the risk of outbreaks will continue as long as the virus circulates. Closed settings, such as prisons, experience outbreaks even when the wider community prevalence is low. The opening up of the prison regime led to more interactions and therefore a greater transmission risk, creating a period of risk for the prison

system, where the potential for new and large COVID-19 outbreaks might increase considerably.

There is evidence of an increase in mental distress in the community attributable to COVID-19 [13]. Concerns have grown about the impact of prison regime restrictions, which were introduced to prevent the spread of COVID-19, on the mental well-being of imprisoned people. Staff have also faced considerable work pressures. Some staff have been ill with COVID-19, vulnerable staff have been shielding, and most staff have faced additional care responsibilities for imprisoned people, peers, families, and friends. As a result of high staff absence, the whole workforce is impacted, with the remaining staff struggling to ensure a decent and safe regime. This has consequences for the health of all those who live and work in prisons. There have been no studies examining the effects of COVID-19 on the mental health of these populations, although anecdotal reports include both positive impacts, such as an improved sense of safety, and many negative impacts, such as increased isolation, self-harm, and fear of the disease. Health care data from 31 prisons suggested an early reduction in self-harm [14], while a report on 3 women's prisons suggested an increase in self-harm [15]. Further information on resident and staff mental well-being will complement the data on the epidemiology of SARS-CoV-2 infection in prisons, providing an additional dimension to inform policy and practice in managing COVID in prisons during the pandemic.

The COVID-19 in Prison Study aims to examine the epidemiology of SARS-CoV-2 in prisons in England in order to inform public health policy and practice during the pandemic and the recovery period.

The primary objective is to estimate the proportion of positive tests of SARS-CoV-2 infection among residents and staff within selected prisons. The secondary objectives are to (1) estimate the incidence rate of SARS-CoV-2 infection separately in residents and staff within selected prisons; (2) examine how the proportion of positive tests and the incidence rate vary among individual, institutional, and system level factors; (3) estimate the proportion of positive tests of antibodies (immunoglobulin G) to SARS-CoV-2 in prison staff; (4) characterize viral strains by genomic analysis; (5) examine the mental well-being of residents and staff in prisons; and (6) examine the sensitivity and specificity of the Innova lateral flow test in prison outbreaks.

This new knowledge will be used to inform decisions regarding the effectiveness of existing strategies to mitigate the spread of SARS-CoV-2 between and within prisons and to help develop effective recovery strategies within the prison estate in England.

Methods

Study Design

Phase 1 is a repeated panel survey of prison residents and staff in a sample of 28 prisons across England. The survey will be repeated to enable the calculation of incidence rates of SARS-CoV-2 infection in the study prisons as well as the proportion of positive tests of SARS-CoV-2 infection among residents and staff within the selected prisons.

Phase 2 comprises an enhanced outbreak investigation in 3 prisons in which a SARS-CoV-2 outbreak is declared. An outbreak is defined as two or more cases of SARS-CoV-2 that are epidemiologically linked [16].

Setting and Site Selection

This study will be conducted in prisons across England. The sample of 28 prisons will be selected to be as representative of the closed prison estate as possible with regard to important features. These features are prison function and security category, geographical area, whether or not a COVID-19 outbreak was previously reported in that prison, staff numbers, resident population, and the proportion of the population classified as "older residents." Operational factors, including capacity to undertake whole prison testing, will also be given consideration. In phase 1, all prisons will be selected. In phase 2, 3 prisons from the sample of 28 will be included when an outbreak is declared.

When rounds 1 and 2 of antigen testing have finished, if an outbreak of COVID-19 is declared by the local health protection team in any prison in England, further antigen testing of all prisoners and staff will take place as soon as is feasible after the outbreak has been declared. Testing will be repeated 7 days later and again at 28 days after the first test. This periodicity will give detailed information on outbreak dynamics. Staff will also be tested for antibodies to SARS-CoV-2 12 weeks after the start of the outbreak.

In both phases, the governor of each study prison will appoint a member of custodial staff to be the single point of contact (SPOC) to support the research project within the prison. The SPOC will be there to support staff and residents, and answer any questions or concerns they may have about the process.

Sampling and Sample Size

For the primary objective of estimating the proportion of positive tests of SARS-CoV-2 infection within the selected prisons, the precision (margin of error) that various sample sizes (assuming 80% response) provide around various estimates of infection rates is illustrated in Figure 1.

Figure 1. Impact of sample size on precision for various estimates of the proportion of positive tests.
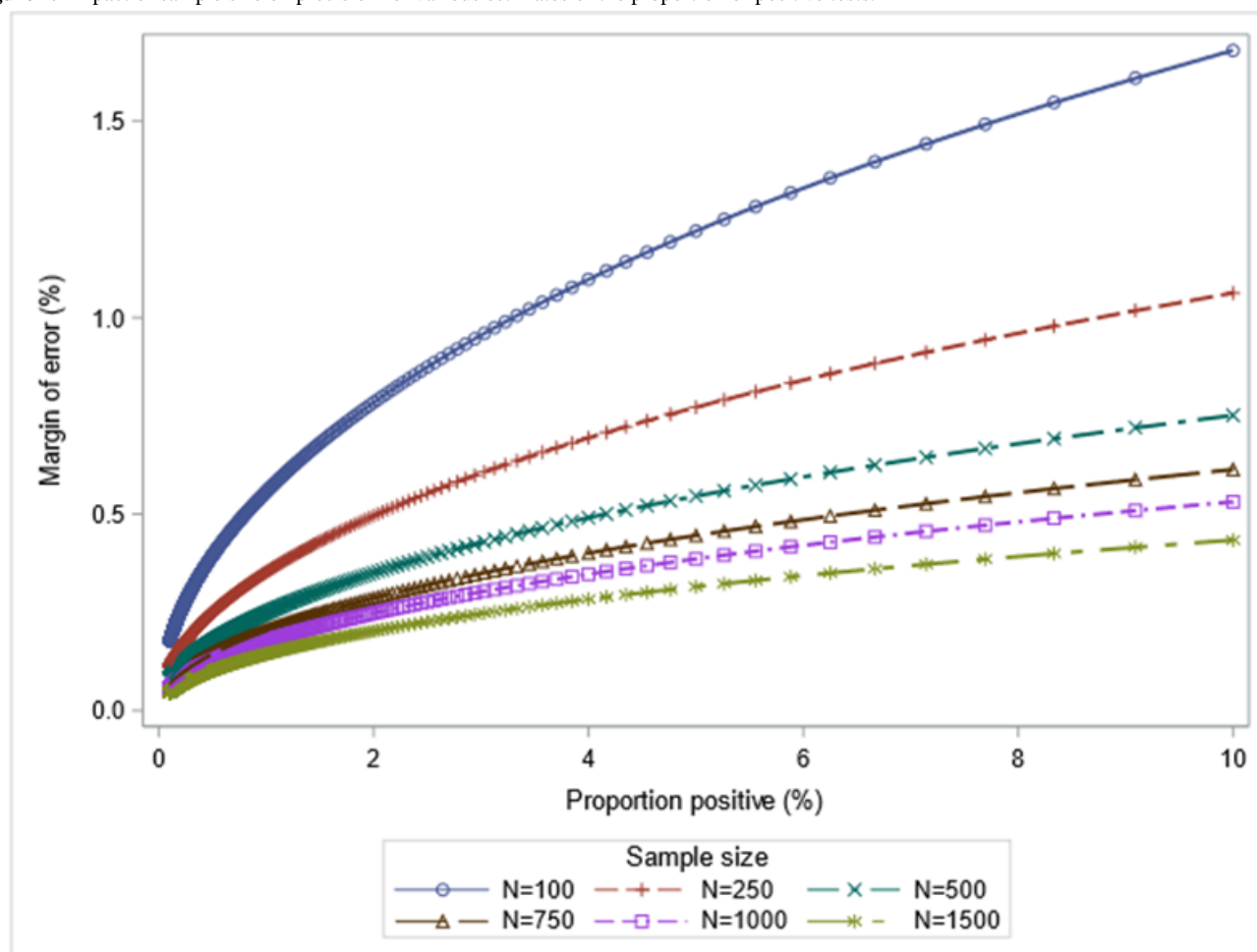
The sample sizes (N) represent a range of individual prison population sizes from the smallest participating prison (approximately 100 prisoners) to the largest (approximately 1500 prisoners). For a given proportion of positive tests and sample size (N), the expected margin of error corresponds to the expected half-width of the 95% CI associated with the point estimate of the proportion of positive tests obtained using an exact binomial test. As illustrated, the precision of the SARS-CoV-2 positivity estimates in participating prisons is expected to be smaller for larger prisons. The 2 rounds allow for the secondary objective, the incidence of SARS-CoV-2, to

be estimated; however, there will be limited power to detect small incidence rates.

Study Team

The team comprises individuals with expertise in epidemiology and statistics, infectious diseases, public health, the prison system, and the conduct of research in prisons.

Participant Eligibility and Recruitment

For all testing rounds in each participating prison (whether phase 1 or 2), all residents and staff present on the first day of data collection in that prison (the census date) are eligible to be included in the study (Textbox 1).

Textbox 1. Study inclusion and exclusion criteria for antigen testing.

Residents

Inclusion criteria

- Age 16 years or older; male or female

- Currently a resident in the study prison

- Is willing and able to give informed voluntary consent for participation in the study

- Does not pose a security risk to the research team (risk assessed by custodial staff)

Exclusion criteria

- Is unwilling or unable to give informed voluntary consent for participation in the study

- Poses a security risk to the research team (risk assessed by custodial staff)

Staff

Inclusion criteria

- Age 18 years or older; male or female

- Currently employed to work in one of the study prisons

- Is willing and able to give informed voluntary consent for participation in the study

Exclusion criteria

- Is unwilling to give informed voluntary consent for participation in the study

- Shielding or long-term absence for the duration of the pandemic

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Study Variables

Data Collected From Imprisoned People

Prisoners will be asked to complete a paper questionnaire, and other data will be extracted by prison administrators for each individual from a secure prison information system (prison-National Offender Management Information System [p-NOMIS]). A summary of the data collected is provided in Table 1.

Table 1. Data collected from imprisoned people.

Data item	Data source	Time captured		
		Round 1 of antigen testing	Round 2 of antigen testing	Round 3 of antigen testing
Age	p-NOMIS[a]	Yes[b]	No[c]	Yes
Sex	p-NOMIS	Yes	No	Yes
Ethnicity	p-NOMIS	Yes	No	Yes
Time in the current prison	p-NOMIS	Yes	No	Yes
Place or residence prior to prison entry	p-NOMIS	Yes	No	Yes
Prison movements in the last 14 days	p-NOMIS	Yes	Yes	Yes
Current location	p-NOMIS	Yes	Yes	Yes
Shielding	Q[d]/p-NOMIS	Yes	Yes	Yes
Comorbidities	Q	Yes	No	No
Obesity	Q	Yes	No	No
Smoking status	Q	Yes	No	No
Symptoms for COVID (on testing day)	Q	Yes	Yes	No
Contact with COVID	Q	Yes	Yes	No
Past history of COVID	Q	Yes	Yes	No
Mental well-being	Q	No	Yes	No

[a]p-NOMIS: prison-National Offender Management Information System.

[b]Yes: data collected.

[c]No: data not collected.

[d]Q: paper questionnaire.

Data Collected From Staff

All data will be obtained from a self-complete questionnaire with the exception of data in an outbreak and second round of antibody testing if all staff are invited. These will be provided by the prison linked to the staff member's number (not name). A summary of the data collected is provided in Table 2.

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Table 2. Data collected from prison staff.

Data item	Time captured		
	Round 1 of antigen testing	Round 2 of antigen testing	Round 3 of antigen testing and antibody testing
Age	Yes[a]	No[b]	Yes
Sex	Yes	No	Yes
Ethnicity	Yes	No	Yes
Professional role	Yes	No	Yes
Area of residence	Yes	No	No
Occupations of household	Yes	No	No
Symptoms	Yes	Yes	No
Contact with COVID	Yes	Yes	No
Past history of COVID	Yes	Yes	No
Test history for COVID	Yes	Yes	No
Comorbidities	Yes	No	No
Smoking	Yes	No	No
Mental well-being	No	Yes	No
Vaccination status (against SARS-CoV-2)	No	No	Yes

[a]Yes: data collected.

[b]No: data not collected.

Prison-Level Data

The operational SPOC will be asked to obtain data outlined in Table 3 and complete an electronic questionnaire provided by the research team. The research team will obtain further information from Her Majesty's Inspectorate for Prisons reports on information, such as concerns about the fabric of the building or sanitation issues. A summary of the data collected is provided in Table 3.

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Table 3. Data collected about each participating prison.

Data item	Data source	Time captured		
		R1	R2	R3
Name of prison	Q[a]	Yes[b]	No[c]	No
Security category (if appropriate)	Q	Yes	No	No
Functional designation	Q	Yes	No	No
HMPPS[d] region	Q	Yes	No	No
In-use certified normal accommodation	Q	Yes	No	No
Current population	Q	Yes	Yes	Yes
Percentage aged 50 years or more	Q	Yes	No	No
Percentage from Black, Asian, and minority ethnic groups (with breakdown)	Q	Yes	No	No
Number of staff directly employed	Q	Yes	No	No
Number of staff indirectly employed and by which contractor	Q	Yes	No	No
Year the prison was built (and additions)	Q	Yes	No	No
Geographical layout	Map/photo	Yes	No	No
Number of wings	Q	Yes	No	No
Number of landings on each wing	Q	Yes	No	No
Number of cells on each landing	Q	Yes	No	No
Number of single cells	Q	Yes	No	No
Number of multiple occupancy cells	Q	Yes	No	No
Number of cells currently occupied by two or more people	Q	Yes	Yes	Yes
Number of cells with the following types of in-cell sanitation: in-cell washbasin, in-cell toilet plus washbasin, in-cell toilet plus washbasin plus shower	Q	Yes	No	No
Sanitation problems reported in HMIPRs[e]	HMIPRs	Yes	No	No
Problems reported by HMIP[f] regarding the fabric of the building	HMIPRs	Yes	No	No
Ventilation system (air conditioning/natural air flow from windows/ceiling fans)	Q	Yes	No	No
Date created, capacity, and current occupancy of the following 3 units: protective isolation unit, reverse cohorting unit, and shielding unit	Q	Yes	Yes	Yes
Regime changes (eg, reinstatement of visits)	Q	No	Yes	Yes

[a]Q: electronic questionnaire.

[b]Yes: data collected.

[c]No: data not collected.

[d]HMPPS: Her Majesty's Prison and Probation Service.

[e]HMIPRs: Her Majesty's Inspectorate for Prisons reports.

[f]HMIP: Her Majesty's Inspectorate for Prisons.

Study Processes: Testing

All data collection will be done within the prison. Private contractors will undertake the testing. In each prison, there will be a team of 6 to 10 testing staff fully trained in testing procedures by their employer and trained in the study procedures and ethical practice by the University of Southampton. Each tester will be escorted around the prison by a member of the custodial staff, who will open the cell door to each participant. At the first contact, the tester will take written consent for the whole study from the participant and collect the completed paper questionnaire. At subsequent testing rounds, verbal consent will be obtained. In phase 1, participants will complete a self-swab of their nose and throat as instructed and observed at 2 m by the tester. In phase 2, participants will self-swab twice. They will provide a nasal swab for testing using a lateral flow device and a nasopharyngeal swab for polymerase chain reaction testing. A member of the health care team will swab any residents with a physical disability that makes it difficult for them to self-swab. For later rounds of testing in an outbreak situation, the testing process will be supervised as previously, by externally contracted staff, or by the prison health care team, dependent on local circumstances.

A private provider, commissioned by HMPPS to provide occupational health services to prison staff, will take a swab of

their nose and throat or, alternatively, staff will swab their own nose and throat if the occupational health provider is unable to do this. For later rounds of testing in an outbreak situation, staff will self-administer the test as part of HMPPS's ongoing weekly testing program. They will also self-administer a second nasal swab that will be used by the testing team to test using a lateral flow device. They will receive an information sheet and a consent form to enable their data to be shared with the study team.

The nose and throat swabs will be couriered to an accredited laboratory where swabs will be tested for the presence of SARS-CoV-2 using reverse transcription polymerase chain reaction (RT-PCR). Before residual material is discarded, if the virus is detected, the material will be couriered securely to a COVID-19 Genomics UK Consortium study laboratory for genomic sequencing of the virus in accordance with the COVID-19 Genomics UK Consortium study protocol [16]. The nasal swabs will be tested on site using Innova lateral flow devices; these provide a result within 30 minutes.

Staff who participate in round 1 or 2 of antigen testing will be invited to participate in antibody testing. Following the second round of testing, the SPOC will issue participating staff with a home testing kit for antibody testing.

Data Collection: Instruments and Sources

Participating residents will complete a brief paper questionnaire that asks about medical risk factors for severe COVID-19, current COVID-19 symptoms, and symptoms in the past 14 days in line with other COVID studies in England. In the second round, the short version of the Warwick Edinburgh Mental Well-Being Scale (WEMWBS), a well-validated measure of mental well-being [17], will be included in the questionnaire. Further information about residents' age, ethnicity, location, and movements within the prison will be obtained by the SPOC (or appointed administrator) from the secure p-NOMIS. In an outbreak situation, questionnaires will not be completed, but data will be obtained on residents' ethnicity, age, and sex.

Each time they are tested, each participating staff member will complete a short online questionnaire providing details of medical risk factors for severe COVID-19, current COVID-19 symptoms, and symptoms in the past 14 days. In the second round, the WEMWBS will be included in the staff questionnaire too. In an outbreak situation, questionnaires will not be completed, but data will be obtained on the staff members' ethnicity, age, and sex.

The SPOC will gather information about the prison for the study team, including geographical layout, age, ventilation systems, sanitation, numbers of residents and staff, and what infection control measures have been implemented. The study team will obtain data on the prevalence of SARS-CoV-2 in the community from the ongoing Office of National Statistics Community Survey [18].

Data Management and Analysis

Data will be stored and handled at the University of Southampton and PHE. A pseudonymized database will be created using unique participant IDs.

Summary statistics (N, proportion, mean, SD, and IQR) will be obtained to summarize the prison and participant characteristics. Tables will display the number of participants in each of the 2 surveys, the number of new participants (eg, new residents), and the number of individuals withdrawn/lost to follow-up from the previous survey (eg, withdrawn consent or left the prison).

For the primary objective, simple proportions of individuals testing positive for SARS-CoV-2 following RT-PCR of samples (based on nose and throat swabs) will be calculated for each prison population of staff and prisoners separately. The proportion of positive individuals with symptomatic infection, defined as "yes" to any of the listed symptoms in the questionnaire, will also be calculated for each prison.

Stratified proportions will be estimated to understand the variation in the prevalence of infection among different prison characteristics and different populations (eg, the strata of staff/resident population; prison type; participant age, gender, and ethnicity; current location in prison [prison population only]; and staff role [staff population only]).

Incidence rates within each prison will be calculated. Variation in incidence rates among different prison characteristics and different populations will be explored by estimating stratified incidence rates within the strata of staff/prisoner population; prison type; participant age, gender, and ethnicity; current location in prison (prisoner population only); and staff role (staff population only).

To examine the individual, institutional, system, and community factors associated with SARS-CoV-2 infection within prisons, generalized linear regression models will be fitted to adjust prevalence and incidence rates for relevant hypothesized risk factors. The list of individual-level risk factors includes participant age, gender, ethnicity, and existing comorbidities; and staff role and responsibilities (for staff analyses only). Institutional factors include in-cell sanitation (for resident analyses only), establishment age, ventilation type, use of compartmentalization measures, and regional location. All point estimates will be provided with 95% CIs.

The proportion of staff who test antibody positive at week 6 (overall and according to whether they are prisoner-facing or not) will be calculated for each prison.

The WEMWBS will be scored according to the user guide [19]. The mean scores from the short WEMWBS will be presented for residents and staff, and their associated demographic factors.

Imputation methods may be employed depending on the level of completeness for any specific analysis.

Ethical Considerations

This is a time-pressured study that has high-level UK Government support. All research within prisons has currently been stopped because of the COVID-19 pandemic, and researchers are not allowed into prisons. This study has been allowed to go ahead using professional testing staff who will be wearing appropriate personal protective equipment (PPE). The University of Southampton team will be training (remotely) these staff members to inform them about the study, with a particular emphasis on understanding the principles of ethical

research conduct and the specificities of this in a prison setting. The Southampton research team will act as an ongoing resource for advice about the conduct of the study for all testing staff.

The main study-specific ethical consideration is the inclusion of prisoners, a group regarded as vulnerable in international guidance on the ethical conduct of health research. In addition, some of these prisoners are 16 and 17 years old. There are a number of key considerations as presented below.

Informed Voluntary Consent

The participant information sheet (PIS) for residents gives a detailed account of the aims of the research and what it will involve, highlighting that participation is entirely voluntary and that nonparticipation will not have any adverse effects for participants (specifically, it will not affect care or parole). Participants will have the opportunity to discuss the research and ask questions with a number of people. There will be 2 SPOCs in each prison who will be available to discuss any issues with individuals. Each prison has also been asked to identify "peer mentors," prisoners who will familiarize themselves with the study and receive written materials prepared by the University of Southampton. They will be able to discuss issues with their fellow prisoners. Finally, the tester is an independent person who is not allied to the prison. It is important that consent to participate in the research is not undertaken by the prison officers or other members of the prison staff to ensure that the decision is not influenced by someone in a position of authority. This is important as prisons are widely perceived to be a coercive environment, and all prisoners must feel able to decline participation should they wish. For those who do want to participate, the consent form will be used to ensure that participants have understood the information provided and are aware what participation involves.

The level of literacy in the prison population is lower than that in the general population, and so, the consent form and PIS are suitable for people with limited literacy skills.

The prison health care team will be asked to draw up a list of prisoners who should be excluded as they are unable to give informed consent because of mental illness. These particularly vulnerable individuals will be excluded from the study.

Staff might also feel pressurized to participate because of the hierarchical nature of the prison service. The PIS will emphasize that participation is voluntary, and an occupational health professional, independent of the prison service, will discuss the study with them and ensure consent is provided voluntarily. Nonparticipation will not affect their work in any way.

Right to Withdraw

The PIS for each participant group provides details of how to withdraw from the study. Withdrawal from the study does not affect care or treatment in the prison for the prisoner or staff member.

Risk of Harm

The risk of harm has been assessed by the study team as low. The questionnaire does not require sensitive information, and the throat and nose swabs are unpleasant but not invasive. The blood test is a simple standardized procedure conducted by trained staff who will adopt the necessary precautions.

Confidentiality

Only the research team (named on the information sheet) and authorized personnel from the study team will have access to participant data. All information gathered will be stored in accordance with General Data Protection Regulation (GDPR) guidelines.

In this study, complete confidentiality of the antigen testing results is not possible. Prisoners who test positive will be isolated in accordance with government guidelines, and this will be apparent to staff and prisoners in their wing. Similarly, staff who test positive will have to isolate at home, and because they will be unable to come in to work, this will be apparent to colleagues. This will be made clear in the PIS.

Involvement of Young People Aged Under 18 Years

In the absence of law relating specifically to research, it is commonly assumed that the principle of "Gillick competence" can be applied to consent for research. This means that if a young person has sufficient understanding and intelligence to understand fully what is proposed and can use and weigh this information in reaching a decision, they can give consent. As their competence to understand is influenced by how the information is presented, we have ensured that the young person's chances of understanding what is involved in the study are maximized by developing an information sheet that uses straightforward language and has been formally assessed for ease of reading. In addition, the young people will have the opportunity to discuss the study with fully briefed staff members and SPOCs.

Infection Risk to Professionals Involved in Conducting the Study

There is a risk that if those participating in the study are infected with SARS-CoV-2 (either staff or prisoners), they might infect those testing them. Equally, participating prisoners and staff might be infected by the testing staff. This risk will be minimized by the use of PPE and observing social distancing rules.

All residents and staff who are willing to participate will provide informed consent. Approval for this study has been granted by the University of Southampton Research Integrity Group (number 57844) and by the Health Research Authority and Health and Care Research Wales (IRAS project ID: 285534; REC reference: 20/NW/0320). These are the bodies that provide ethical approval for this sort of study in England.

Study Timeline

The study timeline is as follows: antigen testing in round 1 from July 20 to August 22, 2020; antigen testing in round 2 from September 1 to October 2, 2020; antigen testing in round 3 from February 11 to March 31, 2021; antibody testing from October 5, 2020, to March 31, 2021; analysis of data from August 1, 2020, to December 31, 2021; and dissemination of findings from April 1, 2021, to April 1, 2022.

Results

We secured all relevant ethical approvals on July 7, 2020, and data collection was started on July 20, 2020. Data collection will end on May 31, 2021. As of May 2021, we have enrolled 4192 staff members and 6496 imprisoned people in the study. Data analysis has started, and we expect to publish the initial findings in autumn/winter 2021/2022.

Discussion

Study Strengths

There are approximately 12 million people imprisoned worldwide [20], and to the best of our knowledge, this is the first national study to examine the incidence and prevalence of SARS-CoV-2 in prisons in the world. COVID-19 in prisons is an important public health issue that has implications for not only those who live and work in prisons, but also the wider society. Prisons are high-risk settings for the transmission of infectious diseases, and this study will provide data important for practice, public health, and policy making across prisons in an entire country during the COVID-19 pandemic. There needs to be an in-depth understanding of the transmission of SARS-CoV-2 within prisons, from the community to prisons and from prisons to the community, in order to inform effective measures to tackle the virus within this unique setting.

With an increasing focus on the mental health implications of the pandemic, the findings from this study will quantify mental well-being in a sample of participants (both residents and staff) using a tool that has been widely validated in the community and in imprisoned people. This will provide important information to enable infection control measures to be appropriately targeted, balancing interventions to prevent infection with the needs of residents and staff to maintain physical and mental health. This unique combination of complimentary data on the epidemiology of SARS-CoV-2 within prisons and on mental well-being will be invaluable in helping adopt a more holistic approach to the implementation of infection control measures in prisons, ensuring that any measures adopted can, as far as is practicable, take into account the impact on the mental well-being of imprisoned people. This is particularly important because of the long-standing nature of this pandemic and can inform health security challenges in the future.

The findings from the study will be made widely available through open-access publications to enable the benefits of the knowledge gained to extend beyond national boundaries. Furthermore, the expertise gained by the research team from the conduct of this unique research in prisons will be shared with other countries using platforms such as the Worldwide Prison Health Research and Engagement Network.

Study Limitations

The study does however present huge logistical challenges. Testing up to 10,000 prison staff and 20,000 prison residents at 2 different time points is a considerable undertaking. Researchers are currently not allowed into prisons, and therefore, testing teams, trained in antigen testing for SARS-CoV-2 and the use of PPE, must be deployed. They will need security clearance to enable them to go into prisons. They must be trained remotely in ethical research conduct to enable them to receive informed voluntary consent from participants. This is particularly important as prison residents are classified as "vulnerable" participants according to international ethical guidelines [21] and many challenges in the ethical conduct of prison research have been identified prior to the pandemic, which adds complexity to the processes [22].

The use of information technology in the study is limited because of the prison environment. Questionnaires for residents will be on paper; the use of electronic devices by resident participants is not permitted. This creates delays in receiving data in a form that can be readily analyzed and the potential for data losses through lost questionnaires, transcription errors, etc. Staff will complete an online questionnaire in the prison at the time of testing, but ensuring all staff have access to a computer presents logistical challenges in an environment where the use of information technology, even by staff, is greatly restricted.

The study was developed at great speed and in a fraction of the time that a study of this nature would ordinarily require. This resulted in a level of patient and public involvement (PPI) that was significantly lower than usual for the research team. Furthermore, during the protocol development phase, the research team was not directly working with prison staff or residents. HMPPS liaised directly with the key staff union, the Prison Officers Association, and the governor of each prison was delegated the task of working with resident groups. PPI representation on the independent study steering group was, however, highly engaged and a source of valuable insights.

Potential Study Impact

The COVID-19 in Prison Study presents an important opportunity to gather data in a unique high-risk setting from the whole population (residents and staff alike). It will provide important epidemiological data to develop our understanding of the transmission dynamics of SARS-CoV-2 in prisons and provide preliminary data on the mental well-being of staff and residents. The study will thus provide broad and more holistic data to inform public health policy and practice in prisons during the COVID-19 pandemic.

the manuscript. Colleagues from the DHSC were instrumental in operationalizing the testing that was a key part of the study design.

Authors' Contributions

EP was involved in the design of the study and created the first draft of the paper. DB, MC, KG, FM, NMcG, OOM, EOM, and JP were involved in the design of the study and the critical revision of the first and subsequent drafts of the manuscript. All authors read and approved the version submitted for publication.

Conflicts of Interest

None declared.

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Abbreviations

HMPPS: Her Majesty's Prison and Probation Service
NHS: National Health Service
PHE: Public Health England
PIS: participant information sheet
p-NOMIS: prison-National Offender Management Information System
PPE: personal protective equipment
PPI: patient and public involvement
RT-PCR: reverse transcription polymerase chain reaction
SPOC: single point of contact
WEMWEBS: Warwick Edinburgh Mental Well-Being Scale
WHO: World Health Organization

Protocol

Regional Utilization of Preventive Services in the 55-Plus Age Group: Protocol for a Mixed Methods Study

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Abstract

Background: In Germany, the proportion of people with chronic diseases and multimorbidity is increasing. To counteract the emergence and worsening of age-related conditions, there is a need for preventive care structures and measures. The preventive services that are financed by statutory health insurance (SHI; eg, vaccinations, cancer screening) are only used by part of the German population. There are no current findings about the utilization of these services by older adults in the eastern German federal state of Saxony-Anhalt, which is particularly strongly affected by demographic change.

Objective: The aim of this study is to investigate the actual utilization and determinants of, reasons for, and barriers to utilization of preventive services financed by the SHI in Saxony-Anhalt in the 55-plus age group.

Methods: In this study, a convergent mixed methods design is used. The actual use of preventive services will be shown by means of (1) a claims data analysis looking at data on statutory outpatient medical care from both the Central Research Institute of Ambulatory Health Care in Germany (Zi) and the Association of Statutory Health Insurance Dentists in Saxony-Anhalt (KZV LSA). The determinants, attitudes, and behaviors associated with use will be analyzed through (2) a cross-sectional survey as well as (3) qualitative data from semistructured interviews with residents of Saxony-Anhalt and from focus group discussions with physicians. (4) A stock take and systematic evaluation of digitally available informational material on colorectal cancer screening, by way of example, provides an insight into the information available as well as its quality. The conceptual framework of the study is the behavioral model of health services use by Andersen et al (last modified in 2014).

Results: (1) The Zi and KZV LSA are currently preparing the requested claims data. (2) The survey was carried out from April 2021 to June 2021 in 2 urban and 2 rural municipalities (encompassing a small town and surrounding area) in Saxony-Anhalt. In total, 3665 people were contacted, with a response rate of 25.84% (n=954). (3) For the semistructured interviews, 18 participants from the 4 different study regions were recruited in the same period. A total of 4 general practitioners and 3 medical specialists participated in 2 focus group discussions. (4) For the systematic evaluation of existing informational material on colorectal cancer screening, 37 different informational materials were identified on the websites of 16 health care actors.

Conclusions: This study will provide current and reliable data on the use of preventive services in the 55-plus age group in Saxony-Anhalt. It will yield insights into the determinants, reasons, and barriers associated with their utilization. The results will reveal the potential for preventive measures and enable concrete recommendations for action for the target population of the study.

Trial Registration: German Clinical Trials Register DRKS00024059; https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00024059

International Registered Report Identifier (IRRID): DERR1-10.2196/33512

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KEYWORDS

prevention; utilization; determinants; barriers; Germany; cancer screening; medical check-ups; vaccinations; preventive dental care; older people

Introduction

Background

The eastern German federal state Saxony-Anhalt (part of the former German Democratic Republic) is strongly affected by demographic change. In 2019, the proportion of the population of Saxony-Anhalt aged 65 years and older was approximately 27% of the total population [1]. The aging of the population is accompanied by an increasing need for care, which is leading to growing structural challenges in medical care. For instance, the density of physicians in Saxony-Anhalt in 2020 was 197.9 physicians per 100,000 inhabitants. In comparison, the density of physicians in the western German federal state of Bavaria was 221.5 physicians per 100,000 inhabitants [2]. According to the German Index of Socioeconomic Deprivation, developed by the Robert Koch Institute, Saxony-Anhalt has a comparatively high level of socioeconomic deprivation. Empirical evidence has shown that this is associated with negative health impacts such as an accumulation of health risks. Moreover, the prevalence of individual risk factors (eg, smoking, obesity) is higher in Saxony-Anhalt than the national average [3].

As in many developed countries, in Germany, the proportion of people with chronic diseases and multimorbidity is rising due to increasing life expectancy and advances in medical technology [4]. Furthermore, from 1959 to 1968, there were very high birth rates in East Germany. The children born in this period, the so-called "baby boomers," currently constitute the largest age group in Germany [5]. The first baby boomers will leave the labor force in 2025 and pass the aforementioned threshold of 65 years of age. It is expected that there will be an increase in chronic diseases in this age group in the coming years [6]. Cardiovascular diseases and cancer, which can be influenced by preventive measures, mainly cause the burden of disease in Germany [4]. According to hospital diagnosis–related group statistics, cardiovascular diseases caused 8.8% of all full inpatient hospital cases in 2019. In Saxony-Anhalt, the full inpatient hospitalization rate is 17.4% higher than the national average [7].

Preventive care structures and measures are needed to counteract the development and deterioration of age-associated diseases and to maintain and strengthen health, independence, and participation in social life into old age. Therefore, in addition to the avoidance of disease risks, prevention in old age pursues the goal of strengthening physical, psychological, and social resources, also in the case of existing health-related and functional restrictions [8]. In this context, primary and secondary preventive measures are particularly relevant. In Germany, public health is the responsibility of the federal states and covers, for example, the surveillance of infectious diseases. Some public health services, such as medical and dental check-ups, vaccinations, and cancer screening are financed by statutory health insurance (SHI), which insures approximately 87% of the German population. In Germany, all citizens must have either statutory or private health insurance, whereby a number of criteria regulates who is insured in which system [9]. Further details about the German health system and its financing were published in [9,10]. Details on the scope, eligible populations, and examination intervals of SHI-financed preventive services can be found in [11,12]. In 2015, the "Act to Strengthen Health Promotion and Disease Prevention" ("Gesetz zur Stärkung der Gesundheitsförderung und der Prävention") was passed by the German legislature. It aims particularly to strengthen health promotion in living environments (settings). Moreover, it contains regulations to strengthen the vaccination system and to further develop health and early detection examinations.

The effectiveness of preventive services depends on the extent of their use. In Germany, preventive services have been underutilized. In 2018, only about 35% of the German population aged 65 years and older had been vaccinated against seasonal influenza. This is below the European Union average of 44% [4]. In comparison, in 2018/2019, the vaccination coverage rate for seasonal influenza in Saxony-Anhalt was 59% among people aged 60 years and older, which is above the national average [13]. The target vaccination coverage rate defined by the World Health Organization for older people is at least 75%. This is not nearly achieved, neither nationwide nor in Saxony-Anhalt. The cancer screening tests offered (eg, breast cancer screening) are only used by part of the eligible population, but there is a mixed picture in terms of utilization rates depending on the screening program [4]. It should be noted that cancer screening can also cause harm (eg, overdiagnosis, false-positive results). Therefore, since 2013, Germany's health policy aims to increase informed decision making for or against screening [14]. Several studies have shown that numerous determinants and barriers influence the utilization of preventive services in Germany. The level of utilization differs according to social status, sex, age, residential region (eastern and western Germany), health status, and health-related behavior, among other factors [15-18].

Based on the initial situation described in the previous paragraphs, it can be assumed that, in the federal state Saxony-Anhalt, there are comparatively pronounced determinants that are negatively associated with the utilization of preventive services. However, for Saxony-Anhalt's older population, there are no current, representative findings on the utilization of these services and the associated influencing factors.

Objectives of the Study

In the mixed methods study, "Prevention in old-age Saxony-Anhalt" ("Prävention im Alter Sachsen-Anhalt" [PrimA LSA]), we examine the actual utilization and the determinants, reasons, and barriers influencing the use of preventive services

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in Saxony-Anhalt in the 55-plus age group. The aim is to identify further potential for prevention in the aging population and to derive recommendations for measures leading to needs-driven improvement or further development of preventive services and their utilization. Our focus is on medical services for primary prevention (vaccinations) and secondary prevention (cancer screening, medical and dental check-ups).
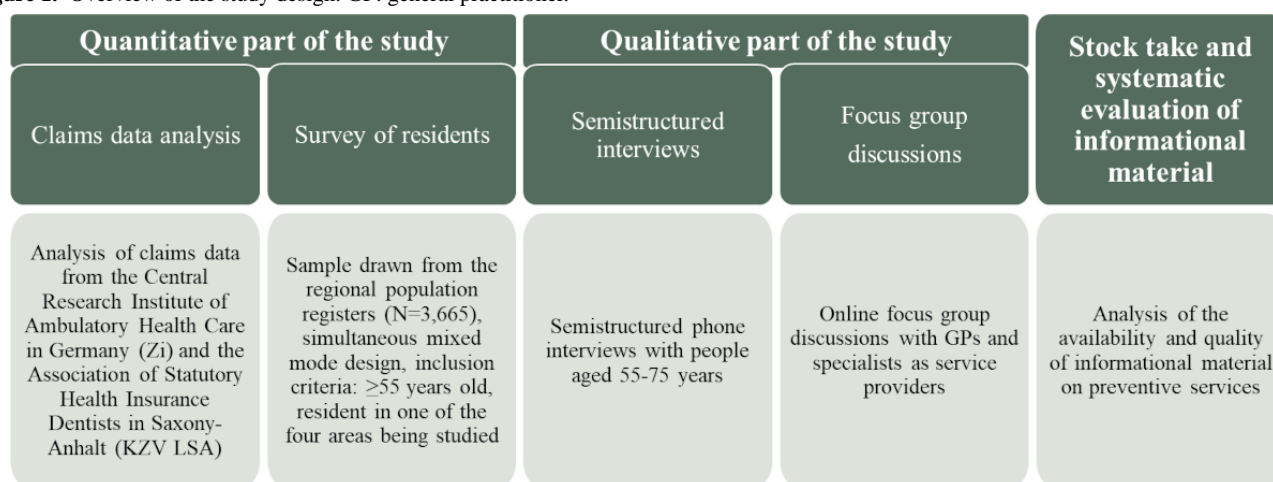
Methods

Overview of the Study Design

The target population of the study consists of residents aged 55 years and older living in the eastern German federal state of Saxony-Anhalt. By means of an analysis of claims data—the billing data from the SHI—the actual utilization of preventive services in the target population will be shown. The

determinants, attitudes, and behaviors associated with utilization will be analyzed using a survey as well as qualitative data from semistructured interviews with residents of Saxony-Anhalt and from focus group discussions with physicians. A search for and systematic evaluation of existing informational material on the applicable preventive services provide insight into the information available and its quality. In addition, it enables further development of existing informational material and an analysis of the relevant health care actors. Figure 1 provides an overview of the study design and its methodological strands.

In this study, a convergent mixed methods design is used (Figure 2). The qualitative and quantitative data are collected simultaneously with equal priority. First, the data will be analyzed separately and will then be merged and interpreted together. This ensures a comprehensive and complementary understanding of the investigated research topic [19].

Figure 1. Overview of the study design. GP: general practitioner.

Figure 2. Flowchart of the convergent mixed methods design of the study. Modified from [19].
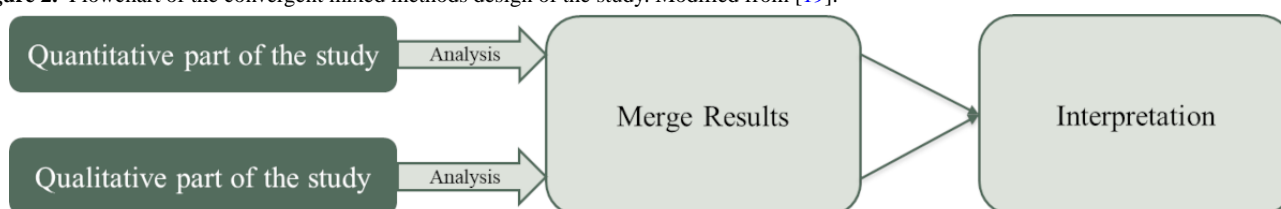
Our study is accompanied and supported by regional cooperation partners, like nonstatutory welfare institutions, the Association of Statutory Health Insurance Physicians in Saxony-Anhalt (Kassenärztliche Vereinigung Sachsen-Anhalt [KVSA]) and the Association of Statutory Health Insurance Dentists in Saxony-Anhalt (Kassenzahnärztliche Vereinigung Sachsen-Anhalt [KZV LSA]). In regular meetings, we discuss the current state of the study as well as further steps in order to ensure the transfer of research to practice. In addition, the study is part of the academic training of specialists in the field of prevention and health promotion.

The conceptual framework of the study is the behavioral model of health services use by Andersen et al (last modified in 2014) [20], which enables the identification of factors influencing the extent to which preventive services are utilized. It encompasses individual and contextual characteristics, the health behavior

of individuals, as well as the outcomes of the use of health services. At the level of individual and contextual characteristics, the model distinguishes predisposing (eg, sex, age), enabling (eg, health insurance status, accessibility of health care facilities), and need factors (eg, existing risk factors) [20]. In line with Andersen et al [20] and other previous studies that examined the determinants, reasons, and barriers to the use of preventive services [15-18], we assume that the utilization depends especially on the aforementioned 3 factors. The results of the qualitative and quantitative parts of the study will be analyzed and related to each other based on the dimensions of the model by Andersen et al [20].

Claims Data Analysis

Current and reliable data on the actual use of preventive services are indispensable for target group–specific communication about these services as well as for the evaluation and further

development of existing recommendations and programs (eg, organized cancer screening programs). For this reason, aggregated claims data from statutory outpatient health care from the Central Research Institute for Ambulatory Health Care in Germany (Zi) and the KVSA will be analyzed in the study. These data provide information about services billed to the SHI for all people aged 55 years and older who are insured under the SHI scheme in the federal state of Saxony-Anhalt. For legal or technical reasons, both institutions keep the data for different periods.

The Zi has national statutory health care billing and prescription data from outpatient care that are submitted by all 17 associations of SHI physicians in Germany [21]. Within the framework of our analysis, we will consider the following groups of services: consultations and examinations for early cancer detection, medical check-ups as well as the vaccinations recommended by the German Standing Committee on Vaccination (STIKO) for the relevant age group (eg, influenza, streptococcus pneumoniae, herpes zoster) [22]. The utilization rates will be calculated as the number of insured people who have made use of a certain service at least once within a defined reporting period, divided by the population eligible for the respective service among those with SHI. The key epidemiological figures will be shown for the entire target population and stratified according to age group (5-year age brackets up to age 95 years and older), sex, region, and reporting year as well as other characteristics, for example the existence of chronic diseases or diseases with a vaccination indication (eg, cardiovascular diseases, diabetes) [22]. The utilization will be presented chronologically from 2011 to 2020. Since the Zi has national claims data at its disposal, the utilization rate in Saxony-Anhalt will be compared with the rate for the entire German federal territory. Regional differences in Saxony-Anhalt will be examined at the district and urban district levels (German: *Landkreis* and *kreisfreie Stadt*, respectively).

In order to obtain additional empirical information about the preventive dental care of older residents in Saxony-Anhalt, data from the KZV LSA will be analyzed. Here, we will consider the utilization of dental check-ups, the costs of which are covered by the SHI once in every calendar half year, as well as visits to provide dentistry services to SHI-insured persons in need of inpatient long-term care. The calculation of the utilization rates will be carried out the same way as with the Zi data. The key figures will be calculated for the entire target population as well as stratified according to age group (5-year age brackets up to age 95 years and older), sex, and reporting year. The utilization from 2016 to 2020 will be presented chronologically. When implementing the described claims data analysis, we will follow the guidelines of Good Practice of Secondary Data Analysis [23].

Survey of Residents

The determinants, reasons, and barriers influencing the utilization of preventive services will be elicited using a cross-sectional survey. We selected 2 urban and 2 rural municipalities in Saxony-Anhalt as study areas: Magdeburg, Halle (each with around 240,000 inhabitants), Wanzleben-Börde (approximately 14,170 inhabitants), and Sangerhausen (about 26,200 inhabitants). The 4 municipalities differ in terms of their demographic and socioeconomic characteristics [1,24]. Thus, we were able to represent the heterogeneity of the eastern German federal state Saxony-Anhalt.

We developed the questionnaire based on a prior literature review of existing studies regarding our subjects of interest: determinants of, reasons for, and barriers to use of preventive services. The selection of relevant instruments was additionally guided by the behavioral model of health services use by Andersen et al [20]. For the design of the questionnaire, we mainly relied on already established or frequently used instruments. The questionnaire consisted of the Short Form-12 Health Survey Version 2 of the Socio-Economic Panel (SF-12v2 of the SOEP) [25] and the German-language short form of the European Health Literacy Survey Questionnaire (HLS-EU-Q47)—the HLS-EU-Q16 [26]. In addition, several items were adapted from the Robert Koch Institute's studies "German Health Update" (GEDA) 2014/15-EHIS [27], "The German Health Interview and Examination Survey for Adults" (DEGS) [28], the "Bertelsmann-Gesundheitsmonitor" (Bertelsmann Healthcare monitor) [29], "The National FINRISK Study" [30], "CaptureAccess" [31], and "Versichertenbefragung der Kassenärztlichen Bundesvereinigung 2020" (2020 survey of SHI insured people by The National Association of Statutory Health Insurance Physicians) [32]. Sociodemographic characteristics were recorded with items from the *Demographische Standards* (2016 edition) of the Federal Statistical Office [33]. In order to develop a questionnaire that is appropriate for the target group and did not exceed a certain length and complexity, we modified the wording or shortened some items from the original instruments.

We conducted pretesting of the questionnaire in the field with 16 participants (11 women, age range 55-84 years). In addition, we applied the method of respondent debriefing. This entailed the participants retrospectively answering open questions about the draft of the questionnaire such as regarding its comprehensibility and length [34]. The feedback was positive in general, and only minor changes were necessary (eg, verbalization of all the answer options when using Likert scales, linguistic modifications). The final questionnaire consisted of 56 questions and covered the following sections: general health status, health behavior, perceived spatial access to ambulatory health care, utilization of preventive services, health literacy and health-related information behavior, and personal characteristics. Further details about the survey sections and their operationalization are presented in Table 1.

Table 1. Survey sections and operationalization.

Survey section	Subtopics	Number of items
General health status	Subjective health [27], health-related quality of life [25]	5
Health behavior	Health awareness [29], physical activity [30], risk factors [28], medically diagnosed diseases[a], social support [28], need for long-term care [28]	8
Perceived spatial access to ambulatory health care	Satisfaction with the access to medical care, existence of a general practitioner (GP), self-estimated travel time to reach a physician and the mode of transport used, forgoing medically necessary outpatient care [31]	7
Utilization of preventive services	Utilization and related behavior regarding statutory health insurance (SHI) bonus programs, dental check-ups, medical check-ups, cancer screening and vaccinations, knowledge of SHI bonus programs [28,29,32]	20
Health literacy and health-related information behavior	Health literacy [26], information channels and behavior when seeking information, need for information [29]	4
Personal characteristics	Sex [33], year of birth, partnership [28] and household [33], highest general school qualification, highest vocational qualification, employment status [33], net household income, health insurance status [28], residential region[a], height, weight [28]	12

[a]Self-developed question.

The sex- and age-stratified random sample (women and men, each representing 50%; 20% each in the age groups 55-64, 65-74, 75-84, 85-94, and ≥95 years) was drawn from the general population via the regional population registers of the 4 municipalities. A further inclusion criterion was informed consent to participate in the study (implied consent). The targeted maximum sample size of 4000 participants could not be reached due to the demographic structure in 2 municipalities. Therefore, the gross sample consisted of 3665 people. Since long-term care home residents usually have their official residence at the nursing home in which they live, both persons from private households and residents of inpatient long-term care facilities were included in the study population.

The survey was announced in local daily newspapers and in various online media. We distributed the questionnaires in April 2021. With the questionnaire, the study participants also received a stamped, addressed return envelope allowing them to return the questionnaire directly to the Institute of Social Medicine and Health Systems Research (ISMHSR) of the Medical Faculty of the Otto von Guericke University of Magdeburg. A unique identifier (pseudonym) was assigned to all questionnaires before they were sent out. The participants were encouraged to promptly complete and return the questionnaires. As an incentive, they received a pen with the study logo. In a simultaneous mixed-mode design, participants could choose a self-administered online questionnaire as an alternative to the written postal version. LimeSurvey was used as the online survey system. The link for the online survey was provided in the accompanying information letter. The questionnaire was available in German. For the entire duration of the survey, an email contact and a telephone hotline were available for questions from the participants. The data will be analyzed using descriptive and inferential statistics (especially multivariate methods). Here, the existence of potential sociodemographic and regional differences in utilization of preventive services will be examined.

Semistructured Interviews and Focus Group Discussions

In the qualitative part of the study, semistructured interviews were conducted with residents of Saxony-Anhalt aged from 55 years to 75 years. The interview participants were recruited in the 4 study regions covered by the survey. For this purpose, a flyer was placed in the survey envelopes for the corresponding age group. Those who were interested could contact the study team by phone or via email. Additional recruitment occurred via personal and professional networks of the study team. The initial contact was made by phone and in writing. The aim of the interviews was an exploration of the subjective perspectives and attitudes that are relevant when making a decision for or against partaking in preventive services. The perspectives and experiences of physicians will complement these findings. One focus group discussion with general practitioners (GPs) and one with medical specialists who provide the relevant preventive services were conducted for this purpose. We contacted GPs and medical specialists (gynecologists, urologists, dermatologists, and internists/gastroenterologists) in Saxony-Anhalt via personal contacts and different media (email, telephone, professional networks, medical professional associations) between the beginning of July 2021 and mid-September 2021.

For the semistructured interviews, we developed an interview topic guide. It was designed based on the findings of the literature review conducted beforehand and includes the following aspects: attitudes toward medical check-ups, cancer screening, vaccinations, and dental check-ups, as well as reasons for (non-)participation in these services and strategies for the improvement of utilization behavior. In the focus group

discussions, the same topics were examined from a physician's perspective with the aid of a discussion guide.

The interviews and focus groups took place in German. Because of the coronavirus pandemic, phone interviews were conducted. The focus group discussions were conducted using a video conference system in compliance with data protection requirements. The interviews and focus group discussions were recorded digitally. Before the interview and focus group discussions were conducted, the participants were informed about the professional background of the interviewer, the aim of the study and interviews, and data protection. In order to contextualize the insights gained from the interviews and focus groups, sociodemographic characteristics and aspects of the interview situation (eg, situational aspects and the atmosphere) were collected. The audio recordings were transcribed verbatim. The data analysis is computer-assisted using the software MAXQDA and based on Kuckartz structuring qualitative content analysis. We developed coding schemes for the interviews and focus groups. Here, we first deductively created main and subcategories based on the interview and discussion guides and in the next step inductively developed categories and subcategories on the material. We use the final coding schemes to code and analyze the entire data [35]. Depending on the nature of the data, a further analysis method may also be used.

Stock Take and Systematic Evaluation of Informational Material

A systematic search was conducted to find digitally available informational material on preventive services on the websites of the SHIs with a dominant presence in Saxony-Anhalt and of other relevant health care actors. We chose to conduct this search with the example of colorectal cancer screening because there is obligatory informational material in the form of a brochure from the Federal Joint Committee (G-BA), which is compulsorily sent to insured people 50 years of age and older by their SHI with an invitation to participate in colorectal cancer screening [36].

We included both the SHIs with the greatest presence in Saxony-Anhalt (n=11) and other relevant health care actors (n=4) in the analysis. This also includes institutions that were explicitly referred to on the selected websites (eg, foundations). As a reference, we additionally considered the informational material from the Federal Joint Committee (G-BA). We selected the informational material from all relevant health care actors based on a defined search strategy and evaluated it systematically.

Between December 7, 2020 and July 15, 2021, we identified 37 materials on colorectal cancer screening on the websites of the aforementioned 16 health care actors. We screened various tabs and topic blocks on the websites as well as using the search field on the respective websites looking at the first hits (maximum of 100). Specific search terms were defined a priori: bowel cancer, colonoscopy, colon cancer, rectal cancer, FIT, and immunological stool test. Additionally, we also used the more general terms decision-making support, evidence-based information, early detection, early detection of cancer, cancer screening, prevention, and screening. Materials were included if they could be found on the websites of the health care actors or using the search field. We excluded materials that primarily described the clinical symptoms of colorectal cancer or the quality of prevention procedures (eg, colonoscopies and not early detection), which was primarily directed at people younger than 55 years of age, primarily directed at other groups of people or institutions (eg, health care providers, the press), or based first and foremost on a pictorial representation (eg, posters).

Information from a health care actor that was available in several formats (eg, the same text in the SHI members' magazine and on the website) was only included once in the analysis.

To evaluate the material, we developed a catalog of criteria following the Guideline evidence-based health information of the German Network for Evidence-based Medicine [37]. The catalog of criteria includes the categories of transparency, text layout, content, language, frequencies, and statistical information, visualization, and accessibility.

We conducted pretesting of the catalog of criteria. Four study team members evaluated the informational material about vaccination against the human papillomavirus from 4 SHIs. After minimal adjustments for optimal applicability of the catalog of criteria (eg, language concretization), the evaluation of the material on colorectal cancer screening commenced. Two study team members independently evaluated the informational material identified on the websites. The rating scheme (from "very good quality" to "very low quality" using a 5-point Likert-scale) from Wahl and Apfelbacher [38] was adapted and modified for the purposes of our systematic evaluation. Discrepancies in the evaluation between the reviewers were discussed and resolved with a third member of the study team.

The methodology of the systematic evaluation is also to be used for informational material on other preventive services in the future.

Ethics and Data Protection

On January 8, 2021, we received ethical approval for our study from the Ethics Committee of the University Medicine Magdeburg (200/20). Participation in the study is voluntary. The participants are informed about the aims and contents of the study as well as data protection. In the survey of residents, people consent to participation in the study by completing and returning the questionnaire (implied consent). For the semistructured interviews and focus group discussions, written, informed consent is a prerequisite for inclusion in the study. The study is conducted in strict compliance with the European Union's General Data Protection Regulation (GDPR) and the German Federal Data Protection Act (BDSG) and in accordance with the Declaration of Helsinki [39]. For the claims data analysis, the Zi and KZV LSA transmit the data to us as completely anonymized information. The data from the survey of residents, the interviews, and focus group discussions are collected and saved pseudonymized. An independent trusted third party at the Medical Faculty of the Otto von Guericke University of Magdeburg manages data containing personally identifiable information and stores those data separately from the study data. The questionnaires for the survey of residents were sent from the trusted third party.

Results

Claims Data Analysis

The Zi and KZV LSA are currently preparing the requested billing data and will make them available in January 2022 for further statistical evaluation and interpretation by the study team.

Survey of Residents

Data collection took place from April 21, 2021 to June 28, 2021. During this time period, a total of 954 people participated in the study out of the 3665 who were contacted. Of those respondents, a total of 16 people made use of the possibility to fill in the questionnaire online. The mean response proportion was 25.84%. ISMHSR staff entered the data from the questionnaires completed in written form using LimeSurvey. The data collected were checked for correctness by means of a cross-validation.

Semistructured Interviews and Focus Group Discussions

In May 2021, 2 pilot interviews were conducted. The semistructured interviews commenced in May 2021 and were completed in July 2021. In total, we were able to recruit 18 interview participants from the 4 study regions. Two focus group discussions with physicians were conducted in October 2021. We recruited 6 GPs and 5 medical specialists across Saxony-Anhalt. Between recruitment and the actual focus groups, 2 GPs and 2 medical specialists dropped out.

Stock Take and Systematic Evaluation of Informational Material

The systematic evaluation of digitally available informational material on colorectal cancer screening was completed in July 2021. Based on the catalog of criteria that had been developed, we identified and evaluated a total of 37 different informational materials from 16 health care actors. The results are currently being processed.

The results of the study will be published in peer-reviewed scientific journals after completion of the data collection and analysis. In addition, we are holding regular meetings with the regional cooperation partners while the study is being conducted, in order to discuss aspects of recruitment and data collection. In the final phase of the study, results shall be discussed with the purpose of a transfer from research to practice and in order to develop recommendations for improving the prevention utilization behavior in the aging population in Saxony-Anhalt.

Discussion

Principal Findings

This study will provide current and reliable data on the utilization of preventive services in the 55-plus age group in Saxony-Anhalt. It will provide knowledge about the determinants, reasons, and barriers associated with their use and thereby make it possible to derive prevention recommendations for the target population. Moreover, the search for information about this topic and the subsequent systematic

evaluation thereof sheds light on the information available and the quality of the material. The findings can be used by actors in the social and health sectors (eg, physicians, health insurances) for target group–specific evaluation and for further development of the existing range of information and preventive services offered.

With the differentiated methodical approaches, multifaceted knowledge about the use of preventive services in old age can be generated. The mixed methods design offers the potential to gain a comprehensive understanding of the utilization of preventive services. The strengths of the methods can synergistically complement each other and compensate for limitations. The regional focus in the analysis of the Zi data makes it possible to identify the extent of regional variations in the utilization of preventive services in Saxony-Anhalt. These empirical findings can serve as the basis for deriving strategies to reduce that variation. Furthermore, the study takes into account different perspectives and views of residents and relevant stakeholders, which is essential for the identification of further potential for prevention. In the semistructured interviews and in the survey of residents, we capture the perspectives of the target group. These insights are complemented by the experiences of physicians by means of the focus group discussions. There are continual discussions with the regional cooperation partners about, for example, the feasibility of the study and the development of prevention recommendations. The results of the study are primarily relevant for the federal state of Saxony-Anhalt. They are potentially transferable to other structurally weak regions in other federal states that are strongly affected by demographic change.

Limitations and Challenges

In 2019, the proportion of people with a migration background in Saxony-Anhalt was low, with 8% (173,100 people) compared with overall Germany (26%). Among migrants in Saxony-Anhalt, 39% had German citizenship. In the age groups of 45-65 years and ≥65 years, only 1.3% and 0.7%, respectively, had a migration background [40]. For the older population, it can be assumed that people with a migration background are mainly former contract workers from Vietnam or (late) repatriates from the former Soviet Union [41]. Therefore, migration background is not taken into account in this study. With regard to the survey of residents, there might be a social desirability bias in the respondents' answers. Since participation in the survey of the residents was voluntary, a selective nonresponse cannot be excluded. A potential nonresponse bias will be investigated within the analysis of the survey data, taking into account sociodemographic characteristics (age and sex). For the claims data analysis, the Zi and the KZV LSA provide aggregated regional-level data. Individual-level data are not provided. As this is an ecological study, it should be taken into account that the associations found on the regional level are valid for groups of people and not for individuals. In order to underline the findings of the claims data analysis and to obtain information about individual contexts, the self-reported utilization of the preventive services being investigated is recorded in the survey of residents. Since SHI-insured persons in Germany are usually also insured for long-term care through their health insurance, the Zi data also include people in need

of long-term care [9]. However, due to the aggregated nature of the data, this group cannot be shown and analyzed separately. As the interviews and focus group discussions were conducted by phone or using a video conference system, it was sometimes difficult to establish a trusting relationship with the interviewees due to the limited nonverbal communication. This challenge was addressed by conducting a phone call beforehand and thus providing the interviewees with detailed information about the study.

Authors' Contributions

CS, ES, and SM had the idea for the study, obtained funding for the study, and are the principal investigators of the study. AM, CS, ES, IH, and SM developed the research design and methods with input from SW. CS and IH developed the data protection concept with input from AM, ES, and SM. IH wrote the article with input from AM, CS, ES, SM, and SW. IH is responsible for study coordination. All authors reviewed the article for important intellectual content. All authors read and approved the final manuscript.

Conflicts of Interest

Until March 31, 2020, SM was financed within the framework of the EVA64 study, the nationwide uniform scientific evaluation of model projects according to §64b of the Social Security Code V (§64b SGB V). This study is funded by a consortium made up of 94 SHIs (statutory health insurance) and their associations.

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Abbreviations

AiA: Autonomy in Old Age
BDSG: German Federal Data Protection Act
ERDF: European Regional Development Fund
G-BA: Federal Joint Committee
GDPR: General Data Protection Regulation
GP: general practitioner
HLS-EU-Q16: German-language short form of the European Health Literacy Survey Questionnaire
ISMHSR: Institute of Social Medicine and Health Systems Research
KVSA: Association of Statutory Health Insurance Physicians in Saxony-Anhalt (Kassenärztliche Vereinigung Sachsen-Anhalt)
KZV LSA: Association of Statutory Health Insurance Dentists in Saxony-Anhalt (Kassenzahnärztliche Vereinigung Sachsen-Anhalt)
PrimA LSA: Prevention in old-age Saxony-Anhalt (Prävention im Alter Sachsen-Anhalt)
SF-12v2: Short Form-12 Health Survey Version 2
SHI: statutory health insurance
SOEP: Socio-Economic Panel
Zi: Central Research Institute of Ambulatory Health Care in Germany (Zentralinstitut für die kassenärztliche Versorgung)

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Protocol

School Attendance Registers for the Syndromic Surveillance of Infectious Intestinal Disease in UK Children: Protocol for a Retrospective Analysis

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Abstract

Background: Infectious intestinal disease (IID) is common, and children are more likely than adults both to have IID and to transmit infection onto others. Before the introduction of the vaccine, rotavirus was the leading cause of severe childhood diarrhea, with norovirus and *Campylobacter* predominate pathogens. Public health surveillance of IID is primarily based on health care data, and as such, illness that is managed within the community will often go undetected. School attendance registers offer a novel data set that has the potential to identify community cases and outbreaks of IID that would otherwise be missed by current health surveillance systems. Although studies have explored the role of school attendance registers in the monitoring of influenza among children, no studies have been identified that consider this approach in the surveillance of IID.

Objective: The aim of this study is to explore the role and utility of school attendance registers in the detection and surveillance of IID in children. The secondary aims are to estimate the burden of IID on school absenteeism and to assess the impact of the rotavirus vaccine on illness absence among school-aged children.

Methods: This study is a retrospective analysis of school attendance registers to investigate whether school absences due to illness can be used to capture seasonal trends and outbreaks of infectious intestinal disease among school-aged children. School absences in Merseyside, United Kingdom will be compared and combined with routine health surveillance data from primary care, laboratories, and telehealth services. These data will be used to model spatial and temporal variations in the incidence of IID and to apportion likely causes to changes in school absenteeism trends. This will be used to assess the potential utility of school attendance data in the surveillance of IID and to estimate the burden of IID absenteeism in schools. It will also inform an analysis of the impact of the rotavirus vaccine on disease within this age group.

Results: This study has received ethical approval from the University of Liverpool Research Ethics Committee (reference number 1819). Use of general practice data has been approved for the evaluation of rotavirus vaccination in Merseyside by NHS Research Ethics Committee, South Central-Berkshire REC Reference 14/SC/1140.

Conclusions: This study is unique in considering whether school attendance registers could be used to enhance the surveillance of IID. Such data have multiple potential applications and could improve the identification of outbreaks within schools, allowing early intervention to reduce transmission both within and outside of school settings. These data have the potential to act as an

early warning system, identifying infections circulating within the community before they enter health care settings. School attendance data could also inform the evaluation of vaccination programs, such as rotavirus and, in time, norovirus.

Introduction

Infectious intestinal diseases (IIDs) are common in both high- and low-income countries, causing an estimated 2 billion cases globally each year [1]. Norovirus is the leading cause of IID, with *Campylobacter* the most common bacterial cause [1-3]. In children, rotavirus has been a major cause of severe IID until the licensing of the vaccine in 2006 [4]. The high incidence of IID infection results in significant disease burden and economic costs due to work and school absenteeism, lost earnings, reduced workforce productivity, and increased health care use [5-7]. In the United Kingdom alone, IID has been estimated to result in one million additional general practice consultations each year [6], and norovirus, rotavirus, and *Campylobacter* combined cost the UK economy an estimated £150 million (US $200 million) per annum [5]. Over 80% of total costs are borne by patients, driven by lost income and out-of-pocket expenses [5].

Children are disproportionately affected by IID, with those younger than 5 years accounting for 38% of foodborne cases globally [1]. Children are thought to be important transmitters of IID infection and experience prolonged symptoms and viral shedding, reduced immunity, and higher levels of infectiousness [8-12]. The majority of a child's close contacts are based at school and home [13,14], and infections, especially viruses, can spread easily through these semienclosed environments [15]. This not only increases the risk of outbreaks within school settings but also provides a pathway through which infections can spread from schools into the wider community [13,16,17]. There is evidence that children may be the first affected by seasonal and pandemic disease [18-21], and hence, enhancing infectious disease surveillance in schools could not only improve the health of children but also provide advanced warning before infections start to circulate in the wider community.

Public health surveillance of IID is primarily based on health care data such as laboratory reports, statutory notifications, hospital admissions, primary care consultations, and calls to remote telehealth services [22,23]. The majority of IID cases, however, will be managed in the community, without involvement from health care services. As a result, current surveillance is likely to be substantially underestimating the impact of IID. Furthermore, there is an inherent bias in the surveillance of IID, as certain groups are more susceptible to complications and therefore more likely to present to health care, such as the very young, the comorbid, and older adults [2,3,24,25]. Laboratory testing policies can also be targeted toward detecting pathogens in these high-risk groups [26], further increasing the surveillance bias. Enhancing the surveillance of IID and improving detection of community cases

of disease would provide important information on the epidemiology of these infections. Such data would be of value to support the evaluation of public health interventions, such as rotavirus vaccination and, in time, norovirus vaccination. As vaccinations can alter the epidemiology of infection [27], it is crucial we are able to accurately monitor the long-term impact and effectiveness of these interventions, not only on health care services but also on prevalence in the community.

School attendance registers offer a novel data set that could be used to identify community cases of IID that might not otherwise be detected. School absenteeism data have shown potential in the surveillance of both seasonal and pandemic influenza [28-35], but no studies have been identified that consider their role in monitoring IID. Although mild cases of diarrhea and vomiting will not necessitate contact with health care services, they are likely to still result in an absence from school for the duration of the illness and, in line with public health guidance, an additional 48 hours after symptoms have resolved [36]. This provides a routine data set that has the potential to capture illness from the day of onset.

This study aims to explore the role and utility of school attendance registers in the detection and surveillance of IID in children. The secondary aims are to estimate the burden of IID on school absenteeism and to assess the impact of the rotavirus vaccine on illness absence among school-aged children.

Methods

Study Setting

This study will take place in local government areas within Merseyside in the North West of England. Merseyside is a predominately urban, metropolitan county with a population of 1.38 million, over 240,000 of whom are school-aged children [37]. It comprises five local government areas, which range in size from 145,000 residents to over 450,000 residents [37]. For this study, the population of interest is children aged 4-16 years who are registered at a school within Merseyside.

Study Design

The study will be a retrospective analysis of school absenteeism data to investigate whether school attendance registers can be used to capture seasonal trends and outbreaks of IID among school-aged children. Although these data are routinely collected by local government for school attendance management [38], this is a novel application of this data set. In the United Kingdom, all absences due to illness are given a single code, which distinguishes them from absences due to other causes, including those to attend medical appointments. However, the

nature of the illness is not reported. Routine health surveillance data from primary care, laboratories, and the NHS 111 telehealth service will be used to model spatial and temporal variations in the incidence of IID and to apportion likely cause to changes in school absenteeism trends. This will allow an assessment to be made of the potential value and lead time of school absenteeism data in the surveillance of IID and the overall burden of IID on illness absenteeism. The impact of the rotavirus vaccine, which was introduced in the United Kingdom in 2013, will also be explored. As none of the school-aged children included in this study will have received the rotavirus vaccine, this study will capture the impact of vaccinating infants on herd immunity and reducing illness absenteeism among older, unvaccinated children [27].

Data Sources

School absenteeism data is available at the individual school level. Attendance data for schools providing primary (4-11 years of age) and secondary (11-16 years of age) education, regardless of type of school, will be sought from the local government in Merseyside, with data broken down by school and year group. Total absences and absences due to illness will be requested. Details of the number of children in each school and year group will also be obtained to allow corresponding rates to be calculated.

Laboratory data reported to Public Health England (PHE) North West will be used to obtain organism-specific rates of IID within the different geographical areas. These data are routinely collected and reported to PHE from diagnostic and reference laboratories [39]. PHE also holds data from NHS 111, which is a telehealth service that operates across England [40]. Calls to NHS 111 (and its precursor, NHS Direct) for diarrhea or vomiting will be used to indicate probable cases of IID. NHS 111 and NHS Direct data are held securely by the PHE Real-time Syndromic Surveillance team and can be accessed with permission via PHE.

Primary care consultations for diarrhea or vomiting will be used as another measure of probable cases of IID. These data have recently been collected from clinical commissioning groups and general practices across Merseyside to inform an evaluation of the rotavirus vaccine [41]. Read codes were used to distinguish acute cases of IID from cases linked to chronic conditions or noninfective causes [41]. These data can be accessed from the University of Liverpool in an anonymized format as a secondary data set to further inform the evaluation of the rotavirus vaccine.

To facilitate the spatiotemporal modeling, numbers from each data set will be aggregated to weekly rates to enable a common timescale. The spatial measurement will depend upon the data source; for school absenteeism data, the postcode of the school will be used alongside the catchment area (where appropriate). Primary care consultation data has been mapped to lower super output areas (LSOAs), which represents a geographical area with between 1000 and 3000 residents [42]. Laboratory data contains full postcodes, but to protect the anonymity of patients, these will be reduced to LSOAs before the data is transferred to the research team for analysis. Telehealth data contains only the postcode district of patients [43], which is a larger geographical aggregation than LSOA, ensuring anonymity. Denominator populations will be derived from the Office of National Statistics midyear population estimates [42]. Comparison of derived population estimates will be made with the Health and Safety Laboratories National Population Database [44], and the most suitable denominator population will be used.

To allow the analysis to be conducted at the year-group level, the surveillance data will include details of the patient's age (year of birth) and their sex. All other personally identifiable information will be removed from the data before it is transferred to the research team. The outcomes of the analysis will be based on aggregated data.

Study Period

Data will be examined retrospectively from July 2007 to June 2016, capturing 9 IID seasons. Each season is considered to start in calendar week 27 and end in calendar week 26 of the following year.

Population Sample

This study will focus on three of the five local government areas within Merseyside to reflect the coverage of primary care data collected to inform an evaluation of the rotavirus vaccine [45]. The population sample was estimated using data from the Department for Education, which holds a record of all local government–registered schools [46]. Data were based on the 2017/2018 academic year, limited to schools providing primary and secondary education (ages 4-16 years).

The total number of schools across the three local government areas is 372, consisting of 299 primary schools and 103 secondary schools. Of these schools, 30 deliver both primary and secondary education. The total pupil population across all included schools is 140,164. Assuming that each year one in four pupils are affected by IID [47], in each academic year, we estimate there would be approximately 35,000 cases of IID in schools within the study area. As data will be requested over a 9-year period, the total number of cases across the study period is estimated to be 315,000.

Case Definitions

The case definitions used within each data set are outlined in Textbox 1.

Textbox 1. Case definitions.

School attendance registers

- Absence with registration code "I" (illness, not medical or dental appointments)

NHS 111 calls

- Calls for vomiting

- Calls for diarrhea

General practice consultations (read codes in parenthesis)

- Diarrhea and vomiting (19G)

- Diarrhea symptom not otherwise specified (19F6)

- Viral gastroenteritis (A07y0)

- Diarrhea (19F2)

- Gastroenteritis—presumed infectious origin (A0812)

- Diarrhea of presumed infectious origin (A083)

- Infantile viral gastroenteritis (A07y1)

- Infectious gastroenteritis (A0803)

- Enteritis due to rotavirus (A0762)

- Infectious diarrhea (A082)

Laboratory detections

- Detection of bacterial, viral, or protozoal infectious intestinal disease organisms in a fecal specimen

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Recruitment and Consent

Recruitment will be conducted at a local government level. Local government will be approached via their public health departments and invited to participate in this study. Consent for use of aggregated school attendance data will be sought from the local government, who carry the legal responsibility for the data and its use. As the data are aggregated and anonymized, consent will not be sought from individual schools or parents.

Data Analysis

A descriptive analysis will be undertaken of each data set to examine and describe the temporal trends and seasonality of illness absenteeism rates and of confirmed and probable cases of IID. The analysis will be stratified by age to capture varying rates of disease in different year groups. Rotavirus-specific incidence data will be obtained from laboratory reports. The mathematical and statistical analysis will include an organism-specific dynamic transmission model and a mixed effect regression analysis to apportion cause to the variations in absenteeism and to estimate organism-specific incidence rates. The complexity of dynamical models will be decided during the project based on the outputs of the descriptive analysis. Rotavirus modeling will include an interrupted time series analysis to explore changes in school absenteeism rates pre- and postintroduction of the vaccine. This will support an assessment of the impact of vaccination on disease transmission in the community. Other organisms that commonly cause IID in children will also be included in the analysis (eg, norovirus and *Campylobacter*) to test the ability of illness absenteeism data to accurately detect seasonal trends and outbreaks of

disease. This will inform an assessment of the suitability of school attendance registers as a potential form of disease surveillance in the community and its role in the long-term monitoring of vaccine-preventable diseases.

Results

This study received ethical approval from the University of Liverpool Research Ethics Committee (reference number 1819). Use of general practice data has been approved for the evaluation of rotavirus vaccination in Merseyside by the NHS Research Ethics Committee, South Central-Berkshire REC Reference 14/SC/1140. Study findings will be submitted to open access peer-reviewed journals and presented at scientific conferences and meetings, including meetings with stakeholders.

Discussion

Current surveillance of IID is predominantly based on health care data, and therefore, illness that is managed within the community will often go undetected. This study is unique in considering whether school absenteeism data could be used to enhance the surveillance of IID. The findings could have several important applications. These data could support the improved identification of outbreaks in schools, allowing early intervention to reduce transmission both within and outside of the school setting. As children may be the first affected by seasonal illness, these data have the potential to act as an early warning system, identifying infections circulating within the community before they enter health care settings. Absenteeism data could also be used to inform the evaluation of vaccination

programs, such as rotavirus and potentially, in time, norovirus. Similarly, these data could be used to monitor the impact of health improvement programs such as handwashing interventions.

However, there are some limitations that should be considered. The most pertinent is the low specificity of the case definition for illness absenteeism. As a single code is used for all causes of illness absenteeism, these data cannot distinguish between absences caused by IID and absences from other illnesses such as respiratory tract infections. Therefore, the burden of IID on absenteeism cannot be directly measured, and modeling of routine surveillance data is required to apportion likely cause to changes in absenteeism rates. A further consideration in this study is the spatial measure available within each data set; the NHS 111 telehealth service does not collect information below the level of postcode district and hence the statistical modeling, when including this data set, will be restricted to this geographical level. This limits the ability of this analysis to test whether school absenteeism data can detect localized outbreaks of IID within communities. However, this reflects a limitation within our current surveillance systems and one that school attendance data has the potential to rectify. Future work should consider the feasibility of collecting symptom-specific absence information from schools to enhance the specificity of the data and support the syndromic surveillance of a broader range of childhood infectious disease.

Authors' Contributions

ALD, JPH, RV, DH, and SJO all contributed to the study design. IH contributed to the statistical methods. ALD wrote the first draft of the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

DH report grants on the topic of rotavirus vaccines, outside of the submitted work, from GlaxoSmithKline Biologicals, Sanofi Pasteur, and Merck and Co (Kenilworth, NJ) after the closure of Sanofi Pasteur-MSD in December 2016. RV report grants on the topic of rotavirus vaccines, outside of the submitted work, from GlaxoSmithKline Biologicals. ALD, JPH, IH, and SJO have nothing to disclose.

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Abbreviations

HPRU: Health Protection Research Unit
IID: infectious intestinal disease
LSOA: lower super output area
NIHR: National Institute for Health Research
PHE: Public Health England

Protocol

Immune-Mediated Mechanisms in Patients Testing Positive for SARS-CoV-2: Protocol for a Multianalysis Study

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Abstract

Background: The novel coronavirus has a high mortality rate (over 1% for patients older than 50 years). This can only be partially ascribed to other comorbidities. A possible explanation is a factor that assures a prompt response to SARS-CoV-2 in younger people, independent from the novelty of the virus itself. A factor is believed to stimulate the immune system and provide immunity against more antigens. The only external stimulation received by healthy people is vaccination (eg, the diphtheria, tetanus, and pertussis [DTP] vaccine). One hypothesis is that vaccination helps develop specific immunity but generates sprouting immunity against antigens in transit. The underlying immunological phenomena are the "bystander effect" and "trained immunity." The developed immunity gives protection for years until it naturally fades out. After the fifth decade of life, the immune system is almost incompetent when a viral infection occurs, and thus, at this stage, the novel coronavirus can enter the body and cause acute respiratory distress syndrome.

Objective: The initial aim is to demonstrate that blood monocytes and natural killer cells show overpowering hyperactivity, while CD4+ and CD8+ T cells experience impediments to their defensive functions in patients with severe SARS-CoV-2 infection. The secondary objectives are to correlate clinical data and vaccination history with laboratory immune patterns in order to identify protective factors. Subsequently, we are also interested in characterizing the phenotypes and state of the degree of activation of peripheral blood mononuclear cells, including monocytes, natural killer cells, and CD4+ and CD8+ T cells, in healthy subjects vaccinated with the Pfizer vaccine.

Methods: Data will be collected using the following 3 approaches: (1) an experimental analysis to study the innate immune response and to identify genetic profiles; (2) an epidemiological analysis to identify the patients' vaccination history; and (3) a clinical analysis to detect the immunological profile.

Results: The protocol was approved by the Ethics Committee on April 16, 2020, and the study started on April 27, 2020. As of February 2021, enrollment has been completed. Immunological analysis is ongoing, and we expect to complete this analysis by December 2022.

Conclusions: We will recognize different populations of patients, each one with a specific immunological pattern in terms of cytokines, soluble factor serum levels, and immune cell activity. Anamnestic data, such as preceding vaccinations and comorbidities, biochemical findings like lymphocyte immunophenotyping, and pre-existing persistent cytomegalovirus infection, allow depicting the risk profile of severe COVID-19. Proof of the roles of these immunological phenomena in the development of COVID-19 can be the basis for the implementation of therapeutic immunomodulatory treatments.

Introduction

Background and Rationale

Coronaviruses are common human and animal pathogens. During epidemics, they cause up to one-third of community-acquired upper respiratory tract infections in adults and probably play a role in severe respiratory infections in both children and adults. However, coronaviruses are responsible for a limited amount of diagnosed pneumonia and acute severe illness, especially in the younger population, and a coinfection is frequently detected in hospitalized patients. Usually, the infection is responsible for mild-to-moderate symptoms that rapidly and spontaneously resolve [1].

The new strain of coronavirus, SARS-CoV-2, belongs to the beta-coronavirus family, and it shares all community-acquired coronavirus transmission routes and symptoms. However, the transmission rate is significantly higher, with a faster viral spread responsible for the worldwide outbreak.

In fact, it is a novel virus that was most likely recently passed from bats to humans, and consequently, it is almost unknown to the human immune system. Besides, SARS-CoV-2 seems to undergo modification rapidly during its spread, further avoiding immune defenses [2].

A higher mortality rate characterizes the novel coronavirus, and it has reached over 3% [3]. The death rate is over 1% only for patients aged over 50 years, and it is under 0.4% until 40 years of age. No fatalities have been declared among children under 10 years of age. Furthermore, the death rate is almost double for males when compared with females [4].

The mortality rate distribution of infected patients can be only partially explained by other comorbidities, in addition to older age. Patients with no pre-existing conditions have a fatality rate of 0.9% [4], due to the rapid spread of the virus among the population and within the infected patient, leading to quick and extensive lung injury. However, the near absence of severe illness in children and generally in patients younger than 40 years cannot be explained. Children represent the age group most exposed to all community-circulating viruses, including coronaviruses. Among younger patients, the behavior of the novel virus is similar to that of seasonal community-acquired coronaviruses that can cause severe (but rarely lethal) infections such as pneumonia and bronchiolitis. Indeed, an efficient immune response rapidly counteracts viral infection, even as this virus grows rapidly and changes continuously. In other words, infants, children, and young people could be infected by coronaviruses and by SARS-CoV-2 itself, but the infection is rapidly self-limited, and probably, most of them do not display symptoms. In contrast, older patients experience severe lung injury as a consequence of a slow immune response owing to the novelty of SARS-CoV-2. A possible explanation for these phenomena is a prompt response to SARS-CoV-2 in younger people compared with older people, independent of the novelty of the virus itself. The response might not be specific, but it can limit the infection in the infected host. This is similar to Bacillus Calmette-Guérin (BCG) vaccine immunization in mice that induced nonspecific protective effects against other pathogens such as *Staphylococcus aureus*, *Listeria monocytogenes*, *Salmonella typhimurium*, and *Schistosoma mansoni*. Monocytes and natural killer (NK) cells were believed to play key roles in triggering such trained immunity in murine studies [5]. In addition, the enhancement of monocyte and NK cell responses following BCG vaccination has been reported in humans, and this is due to epigenetic modification at the H3K4me3 (trimethylation of lysine 4 on histone H3) level [6].

However, several mechanisms of trained immunity remain unclear, because the trained immune memory–like phenomenon appears to be for a few months or at least a few years. This immunity is not persistent but progressively fades out. Decreased immune response in the elderly could be responsible for more severe acute respiratory disease from coronaviruses in general and higher mortality from COVID-19, since SARS-CoV-2 can cause an explosive attack against the respiratory system, which is similar to major trauma and allows the development of acute respiratory distress syndrome (ARDS). No evident differences were found in different age groups among healthy people, which could justify the drop in immunity against coronaviruses, except its natural fadeout. The trained immune response acts from the age of 2 years, when hypothetical stimulation occurs, to the fifth decade because of its slow decrease.

Vaccines provide external stimulations in healthy people that trigger immune system responses (eg, diphtheria, tetanus, and pertussis [DTP] vaccines stimulate the immune system). Specific vaccines trigger specific immune actions against specific infectious agents, but provide sprouting immunity against

antigens in transit, such as those of coronaviruses and other community-circulating viruses [6]. The underlying immunological phenomena are "bystander effect" and "trained immunity."

Children receive vaccines during the first year of life. Consequently, they become protected against not only specific pathogens but also multiple antigens from pathogens in transit. The developed immunity gives protection against multiple viral infections for years until naturally fading out. After the fifth decade, this immunity is slower to be recalled and reactivated. At this point, a viral infection will find the immune system almost incompetent, and the virus can enter the organism and cause extensive damage. Among elderly people, severe pneumonia and ARDS are frequently noted when they have a coronavirus infection, flu, etc. The history of pandemic viruses reveals an unexplained phenomenon, which could support this hypothesis. In fact, the "Spanish flu" showed a higher mortality rate among young people, especially those aged 20 to 45 years, which could be partly explained by their life conditions after the end of the First World War.

This epidemiological distribution of mortality rate remains unique, and it has not been noted in the successive pandemics of the 21st century [7]. A possible explanation for this is the advent of vaccines, with extensive vaccination after the 1930s. The population received vaccines 20 years before, and the Asiatic and Hong Kong pandemics showed the highest mortality rates after the fifth decade of life when the partially specific immunity had faded [7,8].

Additionally, transplant recipients and HIV-infected patients, characterized by a compromised immune system, unexpectedly do not seem to experience the worst complications of SARS-CoV-2 infection. An immune system imbalance could play a pivotal role during the viral infection, limiting destructive consequences of excessive inflammation.

Pathophysiological Considerations

The immune system monitors tissue homeostasis, eliminates damaged cells, prevents tumor cell development, and protects against pathogens or infectious agents. The first-line defense involves chemical-physical barriers, followed by the action of innate immune cells, such as cytolytic NK cells and phagocytic myeloid cells, including monocytes/macrophages, dendritic cells, and granulocytes. These cells are activated by the recognition of specific molecular profiles shared by different families of pathogens (Toll-like receptor [TLR], nucleotide oligomerization domain–like receptor, and caspase activation and recruitment domain), including bacteria and viruses, and the innate immune system acts quickly (within minutes/hours). On the other hand, the acquired immune system requires from 4 to 8 days to develop a primary response, and it is able to eliminate infectious agents more effectively due to the extremely specific recognition function of lymphocytes.

In addition, a characteristic of the acquired immune response is its ability to generate "immunological memory," the mechanism through which an organism develops a faster and more effective response against a subsequent exposure to the same infectious agent. The main actors and effector cells of acquired immunity are CD4$^+$ T helper (Th) and CD8$^+$ T cytotoxic lymphocytes, which are responsible for cellular immunity, and B lymphocytes, which are responsible for humoral immunity. For an effective response in the body, the innate and acquired immune systems cooperate, despite differences in specificity and activation times. However, more recently, it has been highlighted that cells of the innate immune system have a certain type of immunological memory [9-11].

Macrophages are innate immune cells that belong to the phagocyte cell type. They reside in all tissues and are the mature forms of monocytes, which circulate in the blood and continuously migrate to tissues where they differentiate. They live relatively long and perform several functions in the innate immune response and subsequent acquired immune response [9]. They have a defensive role against pathogens, and have roles in tissue homeostasis and the inflammatory process. Macrophages can be classified as classically activated M1 and alternatively activated M2 macrophages based on their distinct functional capacities in response to stimuli from the microenvironment. M1 macrophages are stimulated by bacterial infections and cytokines produced by Th1 lymphocytes (interferon [IFN]γ), and have roles in the defense against pathogens and killing of cancer cells. M2 macrophages are stimulated by cytokines produced by Th2 lymphocytes (interleukin [IL]-4 and IL-13), and promote physiological and tumor angiogenesis, wound repair, and suppression of immune responses [12-14]. The induction of specific macrophage functions is closely related to the surrounding microenvironment, which acts as an internal regulator. This phenomenon, called polarization, derives from cell-cell/cell-molecule interaction, which governs the functionality of macrophages within host tissues.

Moreover, enhanced responses of a type similar to memory responses (bystander effect or trained immunity) have been highlighted by various studies on monocytes and macrophages [9]. The mechanism involves epigenetic modification of these phagocytes, with enhanced responses in terms of increased responses through TLRs and the release of proinflammatory cytokines, particularly following BCG vaccination for up to 1 year postvaccination [15]. There is also epidemiological evidence indicating that other vaccines, such as the smallpox vaccine and DTP vaccine, could have beneficial contrasting effects on other microorganisms [16].

Interestingly, the release of delayed IFNα from inflammatory monocytes/macrophages has been shown to play a key role in a mouse model of SARS-CoV-2 infection with pulmonary hyperinflammation [17]. Only genetic depletion of the IFNα/β receptor protected mice from death. In addition, other cytokines released by inflammatory monocytes, such as IL1β, IL-6 (also confirmed in COVID-19 patients recently [18]), and inducible nitric oxide synthase, appeared important.

Therefore, the M2 phenotype (the type representing repairing or constructing macrophages) appears to be the one required to inhibit a strong M1 proinflammatory response associated with the late severe phase of ARDS. Multiple interactions between monocytes/macrophages and NK cells have been described both in vitro in humans [19] and in vivo in a mouse model [20]. In

the case of a melanoma metastasis mouse model, Sommariva et al showed that vaccine stimulation with TLR3 that recognizes viral double-stranded RNA (the agonist that mimics this response is polyinosinic polinosinic polycytidylic acid [poly I:C]) and TLR9 that recognizes bacterial DNA (CpG) was able to trigger bidirectional crosstalk between lung alveolar M1-type macrophages and NK cells [20].

NK cells are innate cells and represent 10% to 20% of circulating lymphocytes, a proportion that can vary with age. They are phenotypically characterized by the expression of the CD56 membrane molecule and the lack of expression of the CD3 molecule. They are a population of cells with cytotoxic activity toward cancer cells or virus-infected cells, in which they induce apoptosis owing to the release of perforins and granzymes contained within them. More recently, however, some trained immunity functions of these cells have been characterized, with memory-like responses [21,22] and regulatory functions toward monocytes [23]. The NK subtype with the $CD56^{dim}CD16^+$ phenotype, which represents about 90% to 95% of NK cells in peripheral blood, has perforin and granzyme release activity with cytotoxic action. The other subtype with the $CD56^{bright}CD16^-$ phenotype, which represents 5% to 20% of NK cells in peripheral blood, does not have cytotoxic action, but secretes high levels of cytokines such as IFNγ and tumor necrosis factor (TNF)α. However, it has been shown that this second subgroup when exposed in vitro to IL-2, IL-12, or IL-15 can assume a $CD56^{dim}CD16^+$ phenotype and therefore have cytotoxic activity. A third subpopulation has been identified in pregnancy at the deciduous level, where mechanisms of tolerance toward the fetus must be activated. During the first trimester of pregnancy, decidual NK (dNK) cells with the $CD56^{superbright}CD16^-$ phenotype show a high incidence up to 50% among immune cells. dNK cells are poorly cytolytic and exhibit proangiogenic functions by releasing vascular endothelial growth factor, placenta growth factor, and IL-8. In the tumor field, it has been shown that NK cells similar to dNK expand at the tumor site and are involved in the mechanism of tumor angiogenesis associated with the growth of solid tumors [24-28]. Furthermore, recent studies have suggested that peripheral blood $CD56^{bright}CD16^-$ NK cells may play a role in regulating the immune response as they produce adenosine, an immunosuppressive molecule, and are capable of inhibiting the proliferation of $CD4^+$ T cells, with a possible regulatory role in autoimmune diseases [29].

There will be an extension of the "Coronavirus Project" aim to study the cells involved in the immune response in order to understand the consequences of specific vaccine stimulation against SARS-CoV-2, parallel to the standard humoral response.

Approximately 60 subjects (aged ≥18 years) from the health care workforce, for whom the date of the first administration of the Pfizer vaccine is already defined, will be studied at the following 3 time points: T0, prior to or on the day of the first administration of the vaccine; T1, between the 14th day after the first administration and the day of the second administration; and T2, between the 32nd and 35th days after the first administration.

Objectives

Primary Objective

The primary objective of the study is to explore phenotypes and estimate the activity degrees of monocytes, NK cells, and $CD4^+$ and $CD8^+$ T cells (including the CD4/CD8 T ratio) in COVID-19 patients' peripheral blood. A dominant phenotype of these cell populations in patients affected by severe pneumonia could represent a possible therapeutic target. In fact, severe pneumonia and ARDS seems to follow excessive and disruptive inflammation sustained by monocytes in peripheral blood and macrophages in the lungs. NK cells play a pivotal role in antiviral responses and in regulating the activity of dendritic cells, monocytes, and macrophages, and this makes them extremely intriguing in this study. Simultaneously, cytokines and other soluble factors will be measured in plasma. Differences are expected among COVID-19 patients with varying disease severities and healthy people.

Secondary Objectives

The secondary objectives are to identify protective factors, using anamnestic data, such as preceding vaccinations, comorbidities, clinical presentation of COVID-19 in terms of clinical signs and symptoms, and biochemical findings. The recognition of a population of patients safe from excessive inflammation against SARS-CoV-2 could define a risk score for the severity of COVID-19, which could allow for the best clinical choice tailored to each patient. Moreover, favorable immunological pattern identification could be followed by implementation of prophylactic or therapeutic immunomodulatory treatments.

Additional Objective

We were also interested in characterizing the phenotypes and state of the degree of activation of peripheral blood mononuclear cells (PBMCs), including monocytes, NK cells, and $CD4^+$ and $CD8^+$ T cells, in healthy subjects vaccinated with the Pfizer vaccine.

Methods

Trial Design

This will be an investigator-initiated, institution-led, nonpharmacological intervention for patients with COVID-19.

Study Setting

The study will be conducted in "Ospedale di Circolo – ASST Sette Laghi," a teaching hospital affiliated to the University of Insubria in Varese, Italy.

Eligibility Criteria

The inclusion criteria will be checked before inclusion in the study. The inclusion criteria are as follows: age ≥18 years and documented SARS-CoV-2 infection, without sequencing to differentiate viral variants.

The exclusion criteria are as follows: refusal to the sign the agreement (informed consent); inability to sign the agreement; and HIV, hepatitis C virus, or hepatitis B virus (positive to hepatitis B surface antigen) infection.

Informed Consent

Inclusion will be feasible after patient approval, relative approval, or an emergency consent procedure (according to Italian law). The consent forms are available from the corresponding author on request. Day 0 will be considered the day of enrollment.

Additional Consent Provisions

Informed consent approval includes agreement for the collection of biological specimens in ancillary studies, which will be stored for a maximum duration of 15 years.

Outcomes

Primary Endpoint

The hypothesis is that monocytes, NK cells, and CD4^{+} and CD8^{+} T cells in patients with severe SARS-CoV-2 infection will show functional impairment. Moreover, innate cells will reveal overpowering hyperactivity, while adaptive T cells will show an impairment of activity that can provoke a pathologic inflammatory response with massive production of proinflammatory cytokines, edema, and pulmonary fibrosis.

Secondary Endpoints

The secondary endpoints are to correlate clinical data and vaccination history with laboratory immune patterns to identify protective factors for severe COVID-19 and break new ground for advanced therapeutic strategies.

Identifying differences between patients having mild infection with positive outcomes and patients having ARDS requiring ventilatory assistance could be useful to optimize the therapy and to come up with an immunostimulant therapy that can produce specific immunity and can decrease the hyperactivity of the innate response and thus the inflammatory condition.

Recruitment

The proposed study aims to analyze patients with confirmed SARS-CoV-2 infection by real-time reverse transcription polymerase chain reaction (RT-PCR) assays on throat swabs in order to identify differences in their immune responses. Patients will be recruited at the Emergency Department of "Ospedale di Circolo – ASST Sette Laghi," University of Insubria in Varese, Italy.

A control group of healthy people will be required for further comparison of the findings. We will consider healthy people (both males and females; aged ≥18 years) without infection (negative for SARS-CoV-2), without symptoms of infectious diseases (neither chronic nor acute), and without chronic pathologies (N=30).

After the informed consent procedure, the sample will be divided into 4 subgroups according to the severity of clinical impairment, with at least 30 people in each subgroup. The severity of pneumonia cases will be measured with SMART-COP (systolic blood pressure, multilobar chest radiography involvement, albumin level, respiratory rate, tachycardia, confusion, oxygenation, and arterial pH) [30-32]. The following 4 categories of patients positive for SARS-CoV-2 infection will be analyzed: (1) asymptomatic patients (AS19);

(2) mildly symptomatic patients with fever, tiredness, dry cough, diarrhea, etc and without full-blown pneumonia (PAU19); (3) patients with a diagnosis of pneumonia with a "low" risk score (SMART-COP) (POL19); and (4) patients with a diagnosis of pneumonia with a "moderate/high" risk score (SMART-COP) (ARD19).

Participant Timeline

The estimated study duration is 6 months from the first to last patient recruitment. Each patient will remain in the study until discharge or death.

Sample Size

The sample size has been determined to be 120, with 30 patients in each group (AS19, PAU19, POL19, and ARD19). In addition, a control group of 30 healthy individuals (negative for SARS-CoV-2) is required. From our experience, we presume that with this sample size, we would be able to identify a transparent variation in immune cell counts and serum cytokine levels. This conforms to most of the immunologic studies in the literature. Moreover, with this sampling, we can identify significant differences in the order of 20% to 30% in terms of the phenotype and function of immune cells.

Data Collection and Management

Data will be collected using the following 3 approaches: (1) an experimental analysis for clusters of patients to study the innate immune response and to identify genetic profiles; (2) an epidemiological analysis to identify patient vaccination history; and (3) a clinical analysis to detect the immunological profile.

Sample Description and Collection for the Experimental Analysis

For the specific analysis, to study the innate immune response and to identify the genetic profiles, we will analyze NK cells, monocytes, and CD4^{+} and CD8^{+} T cells from peripheral blood in both the healthy group (tested negative for SARS-CoV-2) and sick subgroups (AS19, PAU19, POL19, and ARD19). For each patient, a venous blood sample will be obtained (15 mL in EDTA solution).

Preparation of Plasma and Isolation of PBMCs From Blood

From different groups of patients, blood samples (10-15 mL) will be drawn in EDTA tubes and centrifuged at 360 g for 10 minutes to obtain plasma that will be stored at −80°C for subsequent analysis of cytokines and chemokines of interest by enzyme-linked immunosorbent assay (ELISA) (IL-1β, IL-6, TNFα, IFNα, IL-10, IL-12, CCL2, and CXCL10) at the end of enrollment.

The cell pellets will be brought back to the initial volume with phosphate-buffered saline (PBS) (Euroclone) and diluted 1:1 (v/v) with PBS. It will then be subjected to density gradient stratification with Lymphosep (Biowest) at 500 g for 30 minutes at room temperature with no brake. The PBMCs derived from the white ring will be collected, washed twice in PBS, and then used for subsequent experiments using a flow cytometer assay [25]. The in vitro culture using PBMCs can vary from ex vivo 1 day to a few days, and cells will be maintained in RPMI 1640

medium (Euroclone), supplemented with 10% fetal bovine serum (FBS) (Euroclone), 2 mM l-glutamine, and 100 U/mL penicillin and 100 μg/mL streptomycin (both Euroclone), at 37°C and 5% CO_2.

To perform ex vivo flow cytometry cell phenotype analysis, 2.5×10^5 fresh or frozen total PBMCs per tube will be stained for 30 minutes at 4°C with monoclonal antibodies (mAbs) (Becton Dickinson [BD]) as follows: CD3-BB700, CD56-APC, CD16-PE-Cy7, CD159a (NKG2A)-BV510, NKG2C-PE, NKGD2-PE, DNAM-1-PE, CD25-PerCP-Cy5.5, CD69-PE, CD279 (PD1)-BUV737, TIGIT-BV786, CD96-BB515, and CD366 (TIM3)-BV421. Samples will be acquired using BD LSR Fortessa. Following the forward/side scatter setting, NK cells will be divided into 2 cell subsets (ie, CD3$^-$ and CD56^{dim} CD16$^+$ cells [CD56^{dim} NK cells, the major subset, about 90%] and CD3$^-$ and CD56^{bright} CD16$^{-/low}$ cells [CD56^{bright} NK cells, the minor subset, about 10%]). Other marker expressions will be evaluated in both subsets of gated cells.

For ex vivo flow cytometry cell evaluation of monocyte phenotypes, 2.5×10^5 fresh or frozen total PBMCs per tube will be stained for 30 minutes at 4°C with mAbs (BD) as follows: CD45-APC, CD14-FITC, CD16-PE-Cy7, PE-CD209, and PE-CD80. Following the forward/side scatter setting, monocytes will be divided into 3 subsets (ie, CD14^{++} and CD16$^-$ cells [the classical subset, about 90%], CD14^{++} and CD16$^+$ cells [the intermediate subset, about 10%], and CD14$^{-/low}$ and CD16^{++} cells [the nonclassical subset]) [33].

We will also evaluate phenotypes for CD4$^+$ and CD8$^+$ T cells and the CD4/CD8 T ratio using 2×10^5 fresh or frozen total PBMCs, as previously described, with the following mAbs (BD): CD3-PerCP, CD4-APC, CD8-V450, and CD25-PE. We will also assess T regulatory (Treg) cells with CD3-PerCP, CD4-APC, and CD25-PE. Furthermore, we will analyze T-cell responses toward the spike protein using 15-mer peptides (6 nM each, final concentration; 11 amino acids overlapping) of the full-length spike protein (Milteny Biotec). The IFNγ response by spike-specific T cells will be studied by intracellular staining with a fluorescence-activated cell sorter. We will perform cytofluorimetric intracellular staining by using a Cytofix/Cytoperm fixation and permeabilization kit, according to the manufacturer's protocol (BD). Briefly, 5×10^5 PBMCs will be first stained with surface mAbs, such as CD3, CD4, and CD8, for 30 minutes at 4°C. Then, cells will be washed and treated with 200 μL of cytofix/cytoperm solution for 30 minutes at 4°C. Then, cells will be washed and incubated with anti-IFNγ mAbs (BD) for an additional 30 minutes. After a further washing step, cells will be analyzed using flow cytofluorimetric assay.

PBMCs will also be stimulated in vitro for 6 h with different types of stimuli, such as lipopolysaccharide (LPS) (Sigma Aldrich) (recognized by TLR4), poly (I:C) (Sigma Aldrich) (recognized by TLR3), poly (I:C) plus IL-2 plus IL-12, and phorbol myristate acetate (Sigma Aldrich) plus ionomycin (Sigma Aldrich) in the presence of monensin (Golgi Stop, BD) and brefeldin A (Golgi Plug, BD). This procedure will allow the detection of cytokine/chemokine production from NK cells,

monocytes, and T cells by using a flow cytometry intracellular assay, as described previously [34]. For NK cells, we will measure IFNγ-BV650, TNFα-PE, CCL2-PE, and CXCL10-PE by intracellular staining and CD107a-PE (surface degranulation marker) using flow cytofluorimetric assay (BD). For monocytes, we will investigate IL-6-PE, TNFα-PE, IL-12-PE, and CXCL10-PE (BD) (M1-type proinflammatory markers), and TGFβ-PE, IL-10-PE, and CCL18-PE (BD) (M2-type anti-inflammatory markers), and for CD4$^+$ and CD8$^+$ T cells, we will assess IFNγ-BV650 (BD) by intracellular staining as above.

Whenever the quantity of PBMCs is sufficient, other functional in vitro tests on NK cells and monocytes will be set up. In particular, NK cells within PBMCs will be studied in a 4-h coculture degranulation flow cytofluorimetric assay using NK cells and erytroleucemic K562 cells through assessment of CD107a-PE or CD107a-FITC NK cell surface staining [35]. Moreover, CD14$^+$ monocytes and CD3$^-$CD56$^+$ NK cells will be purified with specific mAbs linked to microbeads (Miltenyi Biotec) and a magnetic separator to obtain >90% purified cell populations.

Purified monocytes and purified NK cells will be cultured using RPMI 1640 medium with 10% FBS and supplementation with macrophage colony-stimulating factor and IL-2 (both Miltenyi Biotec), respectively. They will be stimulated with different stimuli (see above) and then checked for intracellular cytokines/chemokines of interest (see above). At the same time, monocytes and NK cells can be harvested at the end of the in vitro incubation culture. We will collect conditioned media for cytokine/chemokine detection using ELISA (IL-1β, IL-6, TNFα, IFNα, IL-10, IL-12, and CXCL10) according to the manufacturer's protocol (R&D Systems).

The 4- to 5-day monocyte culture will be further stimulated for 24 h with LPS (Sigma Aldrich) and IFNγ (Miltenyi Biotec) (M1 stimulus) or IL-4 (Miltenyi Biotec) (M2 stimulus) to investigate macrophage polarization, with assessment of surface M1 markers (TNFα and CXCL10 [BD]) or M2 markers (IL-10 and CCL18 [BD]) to check the prevalence of macrophage polarization in different groups of COVID-19 patients.

The epidemiological analysis will be carried out by integrating both vaccination history and the daily data collected after hospital admission. Azienda a tutela della salute Insubria archives will provide missing data.

Considering the immunological profile, patients with COVID-19 will undergo routine examinations and the following: lymphocyte immunophenotyping; determination of C3 and C4 complement fraction activity; determination of serum immunoglobulin (IgG, IgM, IgA, and IgE) levels; serum protein electrophoresis; determination of serum angiotensin converting enzyme levels [36,37]; cytomegalovirus serology tests; and determination of serum IL-6 levels.

A specific data collection form will store information quickly, and then, data will be collected in a database.

Data Management

Data will be collected in the Emergency and Trauma Research Centre, University of Insubria, Varese, Italy by clinical data technicians on an electronic case report form, using double password-protected computers. Prespecified lists, ranges of values, and drop-down menus in the electronic case report form will facilitate data entry and prevent writing errors. Study documents will be deidentified and stored in the Emergency and Trauma Research Centre, University of Insubria, Varese, Italy. All personnel involved in data analysis will be masked. Only the principal investigators and statisticians will have access to the final data set.

Confidentiality

People with direct access to the data will take all necessary precautions to maintain confidentiality. All data collected during the study will be rendered anonymous. Only initials and inclusion numbers will be registered.

Plans for the Collection, Laboratory Evaluation, and Storage of Biological Specimens

On day 0, blood samples (15 mL) will be drawn in EDTA tubes, centrifuged, and stored (−80°C) for subsequent analysis. After the first analysis, the remaining biological specimens will be kept for a maximum duration of 15 years.

Statistical Methods for the Primary and Secondary Outcomes

Associations between different variables will be examined using Pearson correlation coefficients. Paired comparisons will be made using the Wilcoxon matched pairs test. Nonpaired comparisons will be made using the 2-tailed Mann-Whitney test. Multiple comparisons will be made using appropriate one-way analysis of variance (ANOVA). A P value <.05 will be considered statistically significant. All statistical analyses will be performed using R version 3.4.3 (R Project for Statistical Computing) and SPSS 21 (SPSS Inc).

Plan for Access to the Full Protocol, Participant-Level Data, and Statistical Code

The protocol is available on the ClinicalTrials.gov website (NCT04375176). Study documents will be deidentified, stored by the Emergency and Trauma Research Centre, University of Insubria, and kept for at least 15 years in a locked secure office. All personnel involved in data analysis will be masked. Only the principal investigators and statisticians will have access to the final data set.

Oversight and Monitoring

Composition of the Coordinating Center and Trial Steering Committee

The coordinating center is the Emergency and Trauma Research Centre, University of Insubria, Varese, Italy. The steering committee includes GI, G Carcano, and LM. The data management team includes DI and DDG.

Dissemination Plans

The results of the study will be released to participating physicians, referring physicians, and the medical community no later than 1 year after the completion of the trial, through presentations at scientific conferences and publications in peer-reviewed journals. Eligible authors will meet all 4 requirements of the ICMJE guidelines: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; (2) Drafting the work or revising it critically for important intellectual content; (3) Final approval of the version to be published; (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval

Protocol version 1.0 was approved by the Ethics Committee on April 16, 2020. The clinical trial will adhere to the principles of the Declaration of Helsinki and to the Clinical Trials Directive 2001/20/EC of the European Parliament on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of Good Clinical Practices in the conduct of clinical trials on medicinal products for human use. All trial-related activities will be conducted with written informed consent and in accordance with relevant local and national guidelines.

Results

The study started on April 27, 2020. As of December 2020, we have enrolled 120 patients who have tested positive for SARS-CoV-2 and 30 healthy subjects. During January and February 2021, we enrolled 60 subjects from the health care workforce after they received the Pfizer vaccine.

The clinical data set is complete. Immunological analysis is ongoing, and we expect to complete this analysis by December 2022.

Discussion

According to the medical hypothesis on which the protocol is based, young people could benefit from functional adaptation of innate immune cells induced through epigenetic reprogramming and, especially, pre-existing "partially specific" immunity to community viruses associated with the "bystander effect" of preceding vaccinations [6]. In this study, we will explore the main differences among patients infected by SARS-CoV-2 who experience the illness at different degrees of severity. We will recognize different populations of patients, each one with a specific immunological pattern. There could be differences in terms of cytokines, soluble factor serum levels, and immune cell activity (both of the innate compartment and the acquired one). In this way, the contribution of trained immunity and the bystander effect to protection against SARS-CoV-2 could be explained. Anamnestic data, such as preceding vaccinations and comorbidities, biochemical findings like lymphocyte immunophenotyping, and pre-existing persistent cytomegalovirus infection, allow depicting the risk profile of severe COVID-19. Proof of the roles of these immunological phenomena in the pathogenesis of COVID-19 can be the basis for the implementation of therapeutic immunomodulatory

treatments. In addition, the definition of an immunological risk   profile could tailor established therapies to each type of patient.

Authors' Contributions

GI, LM, and DDG conceived the study, coordinated its design, and drafted and wrote the manuscript. All authors read and were involved in critical appraisal and revision of the manuscript. All authors approved the final manuscript prior to submission.

Conflicts of Interest

None declared.

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Abbreviations

ARDS: acute respiratory distress syndrome
BCG: Bacillus Calmette-Guérin
BD: Becton Dickinson
dNK: decidual natural killer
DTP: diphtheria, tetanus, and pertussis
ELISA: enzyme-linked immunosorbent assay

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FBS: fetal bovine serum
IFN: interferon
IL: interleukin
LPS: lipopolysaccharide
mAb: monoclonal antibody
NK: natural killer
PBMC: peripheral blood mononuclear cell
PBS: phosphate-buffered saline
RT-PCR: reverse transcription polymerase chain reaction
SMART-COP: systolic blood pressure, multilobar chest radiography involvement, albumin level, respiratory rate, tachycardia, confusion, oxygenation, and arterial pH
Th: T helper
TLR: Toll-like receptor
TNF: tumor necrosis factor

<u>Protocol</u>

Assessment of Personal Exposure to Particulate Air Pollution in Different Microenvironments and Traveling by Several Modes of Transportation in Bogotá, Colombia: Protocol for a Mixed Methods Study (ITHACA)

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Abstract

Background: Air pollution in most countries exceeds the levels recommended by the World Health Organization, causing up to one-third of deaths due to noncommunicable diseases. Fine particulate matter ($PM_{2.5}$) and black carbon (BC) from mobile sources are the main contaminants.

Objective: The aim of this study is to assess the relationship of exposure to air pollutants ($PM_{2.5}$ and BC) in microenvironments according to respiratory health and physical activity in users traveling by different types of transportation in Bogotá, Colombia.

Methods: A mixed methods study based on a convergent parallel design will be performed with workers and students. The sample will include 350 healthy transport users traveling by different urban transportation modes in three main routes in Bogotá. The study is broken down into two components: (1) a descriptive qualitative component focused on assessing the individual perception of air pollution using semistructured interviews; and (2) a cross-sectional study measuring the individual exposure to $PM_{2.5}$ and BC using portable instruments (DustTrak and microAeth, respectively), pulmonary function by spirometry, and physical activity with accelerometry. The analysis will include concurrent triangulation and logistic regression.

Results: The findings will be useful for the conception, design, and decision-making process in the sectors of health and mobility from public, academy, and private perspectives. This study includes personal measurements of $PM_{2.5}$ and BC during typical trips in the city to assess the exposure to these contaminants in the major roadways in real time. The study further compares the performance of two different lung tests to identify possible short-term respiratory effects. As a limitation, the protocol will include participants from different institutions in the city, which are not necessarily representative of all healthy populations in Bogotá. In this sense, it is not possible to draw causation conclusions. Moreover, a convergent parallel design could be especially problematic concerning integration because such a design often lacks a clear plan for making a connection between the two sets of results,

which may not be well connected. Nevertheless, this study adopts a procedure for how to integrate qualitative and quantitative data in the interpretation of the results and a multilevel regression. The time that participants must live in the city will be considered; this will be controlled in the stratified analysis. Another limitation is the wide age range and working status of the participants. Regional pollution levels and episodes ($PM_{2.5}$) will be handled as confounding variables. The study is currently in the enrollment phase of the participants. Measurements have been made on 300 participants. Pandemic conditions affected the study schedule; however, the results are likely to be obtained by late 2022.

Conclusions: This study investigates the exposure to air pollutants in microenvironments in Bogotá, Colombia. To our knowledge, this is the first mixed methods study focusing on $PM_{2.5}$, BC, and respiratory health effects in a city over 2 meters above sea level. This study will provide an integration of air pollution exposure variables and respiratory health effects in different microenvironments.

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KEYWORDS

air pollution; particulate matter; black carbon; mixed methods; toxic; air quality; respiratory; pollution; pollutants; microenvironments; Bogota; respiratory disease; exposure to air pollutants; air contamination

Introduction

Since the end of the 1950s, the world has experienced an exponential urban growth phenomenon [1]. The accelerated growth of cities has had a positive impact on the quality of life of citizens related to the supply of health, education, and work services, among other aspects. However, the growth of cities has also been accompanied by several emerging effects such as stress, mobility issues, and exposure to environmental pollutants [1,2]. To address these difficulties, a considerable number of cities worldwide have opted to promote citizens' use of active transport such as walking and cycling, either alone or in combination with public transit [3]. This strategy, in principle, seems to be extraordinarily successful insofar as it promotes decongestion of the roads, which leads to improved air quality while promoting physical activity with benefits to cardiovascular health [4-7].

Studies have suggested that the health benefits of active transport are substantially higher than the negative effects associated with exposure to air pollution [8,9]. By contrast, other studies have demonstrated that the effects of exposure to particulate matter (PM) are considerable, particularly in the generation of cardiovascular and respiratory pathologies in the healthy population [10-20], which are especially evident in children under 5 years and adults over 65 years of age [21-24]. Numerous studies have provided information on the effects of air pollution on users of multiple modes of transport, including walking, bicycle, vehicle, and public transportation [24-27]. These studies grouped information from a considerable number of users of different modes of transport in cities, mainly in the United States and Europe [24-27]. In contrast, some studies carried out in Latin American cities have combined factors such as high rates of urbanization [28,29], the quality of the fuel used in the region [30,31], and active transport strategies [22,32-36]. Although such strategies are framed within an assumption of benefits related to physical activity, the effects of these approaches on exposure to air pollutants are not known.

In the last decade, some studies performed in the city of Bogotá, Colombia, have provided important information regarding the distribution of air pollutants in the city and the effects on respiratory health in children and occupational exposure to PM [37-41]. Nevertheless, these studies suffer from some limitations in not considering the sample size, the major roadways involved, and the measurement of air pollutants, among others [42,43]. It is important to highlight that the Secretaria Distrital de Movilidad of Bogotá has implemented a 10-year plan to improve mobility in the city, including a strategy to promote nonmotorized trips [44] and increase the number of bicycle users in the medium term. In this sense, this study will constitute a baseline to understand the relationship between exposure to air pollutants in different microenvironments and the potential short-term respiratory health effects on users.

The proposed study seeks to relate the exposure to fine particulate matter (<2.5 microns; $PM_{2.5}$) and black carbon (BC) with the respiratory health and physical activity of healthy users who are mobilized in prioritized transportation microenvironments in Bogotá. The study has the following objectives: (1) to estimate the changes in lung volumes and respiratory symptoms of users according to the mode of transportation; (2) to determine the concentrations of $PM_{2.5}$ and BC in the evaluated microenvironments; (3) to identify relationships among the variables of exposure to environmental pollutants, perception of air quality, and respiratory health in study participants; (4) to assess participants' perceptions of air pollution in Bogotá; and (5) to measure physical activity in healthy volunteers.

Methods

Design

A mixed methods approach will be adopted using a convergent parallel design. The development of the study includes two phases: a phase of characterization of the population and a field phase (Figure 1). The objectives and methodologies to be used for the development of the study are summarized in Table 1.

Figure 1. Diagram depicting the proposed process for measurement of the concentration of environmental pollutants in the evaluated microenvironments.
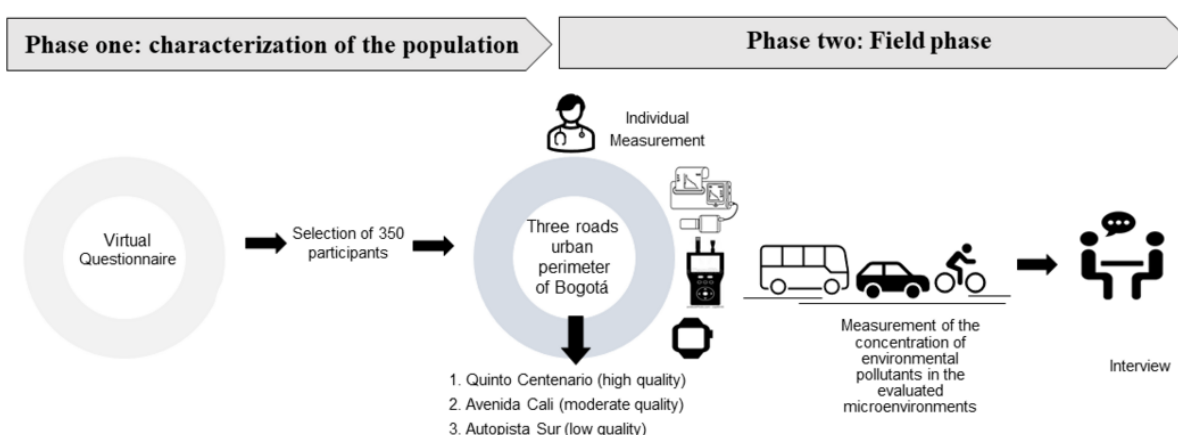
Table 1. Objectives and methodologies to be used for the mixed methods study.

Objective	Methods	Techniques	Analysis
Phase 1: Sample selection	Quantitative	Electronic questionnaire	Descriptive
Phase 2			
To describe the study participants' perceptions of air pollution in Bogotá	Qualitative (descriptive)	Semistructured interview	Categorization and coding
To measure physical activity in healthy volunteers	Quantitative (cross-sectional)	Measurement of vital signs, anthropometry, accelerometry (METs[a])	Descriptive and bivariate
To estimate the changes in lung volumes and respiratory symptoms of users according to the mode of transportation	Quantitative (cross-sectional)	Symptom questionnaire and spirometry	Descriptive and bivariate
To determine the concentrations of $PM_{2.5}$[b] and BC[c] in the evaluated microenvironments	Quantitative (cross-sectional)	$PM_{2.5}$ and BC levels in real time	Descriptive and bivariate
To identify relationships among the variables of exposure to environmental pollutants, perception of air quality, and respiratory health in study participants	Qualitative and quantitative	Triangulation	Triangulation

[a]MET: metabolic equivalent of task.

[b]$PM_{2.5}$: fine particulate matter.

[c]BC: black carbon.

Study Setting

Bogotá, the capital of Colombia, is located on the western slope of the eastern Cordillera of the Colombian Andes. The urban perimeter of Bogotá covers 37,945 hectares, which corresponds to 23.19% of the city. The average height of the urban perimeter is over 2600 meters above sea level. The average temperature is 14.4°C, with extreme values between –4°C and 25°C [45]. Bogotá has approximately 7,150,000 inhabitants, 52.2% of the population are women, with the majority aged between 16 and 50 years [46].

In 2006, Bogotá implemented a 10-year plan that focused on the promotion of active transport as part of the measures to improve mobility [44]. In this context, the use of nonmotorized transport, especially bicycles, has increased by 38%, from 611,000 trips in 2011 to 846,000 trips in 2015 [47].

Sample Size and Sampling

A nonprobabilistic sampling approach will be carried out for consecutive cases (comparing two means). A one-sided hypothesis (Ha: A>B, Ho: A=B) will be tested as follows:

Ha: People exposed to higher levels of contamination have worse spirometry values.

Ho: People exposed to higher levels of contamination have the same spirometry values.

For an α error of 5% and β error of 10%, power (1–β) of 90%, and the one-sided hypothesis, the calculated K value is 8.6. The minimum significant magnitude of the difference (μ1–μ2) in forced vital capacity (FVC) was set to 0.28 [48,49]. The standard deviation (σ) in each group was calculated to be 1.2 [49]. Considering an estimated loss of 10%, the calculated sample size was 350 participants.

Data Collection

This study will use questionnaires, semistructured interviews, medical evaluations, and personal air quality measurements to collect quantitative and qualitative data.

Phase One: Characterization Questionnaire

An invitation will be sent to all potential volunteers at participating institutions. Government and educational entities will be included in the study. A virtual questionnaire (Multimedia Appendix 1) will be sent by mail to the participants. The questionnaire will ask for individual informed consent and will collect information on the sociodemographic and transportation usage behavior of the study population, which will further help the researchers to select potential participants for the second phase. The target sample size for this phase was estimated at 1200, which corresponds to 10% of the total population (12,000) belonging to the study entities.

Phase Two: Field Measurements

A total of 350 participants will be selected from those participating in phase one of the study. The selection of the participants will be carried out by two researchers based on the inclusion/exclusion criteria. Subsequently, preselected participants will be contacted by phone. Participants will be picked up at their residence in vans that will take them to the initial point of the selected route. The mode of transport will be chosen by the participant.

Inclusion and Exclusion Criteria

The study will include healthy men and women between 18 and 55 years old with a BMI <30; who were residents of the urban area of Bogotá in the last 12 months; and are students or workers that use a bicycle, public transport, Transmilenio, or a private vehicle from 7 to 10 AM to get around the city. Users of public transport or Transmilenio will be considered to use a mixed mode of transport since walking or another mode of transport is needed to get to the bus station. This information will be considered in the analysis.

Three roads will be evaluated, which are representative of a gradient in contamination: Quinto Centenario (high air quality), Avenida Cali (moderate air quality), and Autopista Sur (poor air quality) (Figure 2). These roads were chosen according to the level of historical contamination based on the records of the Air Quality Monitoring Network of Bogotá (Red de Monitoreo de Calidad del Aire de Bogotá [RMCAB]).

Figure 2. Three roads to be evaluated with a gradient of air quality from low to high.

The study will exclude pregnant women; men and women with a chronic illness such as diabetes, asthma, chronic obstructive pulmonary disease, stroke, acute myocardial infarction, or deep vein thrombosis; and those with typical chest pain, fatigue, night sweats, or dyspnea on exertion in the last 6 months. Smokers

or exsmokers who quit the habit within the past 12 months will also not be considered for participation.

Participants' Perception of Air Quality

From preestablished categories, semistructured guidelines will be formulated, including 10 questions, following the recommendations of DeJonckheere and Vaughn [50]. The guideline will be probed in a pilot with 5 volunteers, one for each transport mode. After traveling the route, participants will undergo a semistructured interview with an approximate duration of 30 minutes. All interviews will be conducted by trained study investigators. The interviews will be transcribed in Microsoft Word by one of the researchers. Interview transcripts and observation narratives will be coded thematically by two researchers independently. An online platform for qualitative content analysis (QCAmap) will be used [51] to generate codes according to preestablished categories [52] extracted from a literature review, including air quality perception [53,54], health affectation related to air pollution [55], and reasons for the use of transport modes [56].

Spirometry-Based Estimation of Changes in Lung Volumes According to Mode of Transport

Spirometry tests will be performed and interpreted by a trained respiratory therapist following the recommendations of the Spanish Society of Pulmonology and Thoracic Surgery [57]. Spirometry will be performed before the start of the route and 2 hours after the end of the route [16]. The variables of the spirometry will be captured in a database. A survey (Multimedia Appendix 2) will also be used to evaluate the presence of respiratory symptoms after having completed the route [58].

Estimation of Physical Activity Level

Physical activity levels will be estimated with a three-axis accelerometer (ActiGraph wGT3X-BT) using 60-second epochs and a sampling rate of 30-100 Hz. The accelerometer will be placed on the participant's waist at the beginning of the travel route and will be removed at the end of the route. For participants traveling by bicycle, two accelerometers will be used with one placed on the waist and the other placed around the right ankle. Energy expenditure, measured as the metabolic equivalent of task (MET), will be estimated using ActiGraph software [59].

Anthropometric Measurements

Measurements of weight and height will be taken for each participant according to the National Nutrition Situation Survey in Colombia [60]. To guarantee the precision of weight and height measurements, the same scale will be used throughout the study.

Before starting the trip, heart rate and baseline blood pressure will be measured using a digital tensiometer, according to the recommendations from the European Society of Hypertension Practice Guidelines for home blood pressure monitoring [61].

Concentration of Environmental Pollutants in the Evaluated Microenvironments

Measurements of $PM_{2.5}$ and BC will be taken along the participants' routes. The duration of routes will consider the time reported in the Mobility Survey of Bogotá for 2019 [58]. To measure the $PM_{2.5}$ levels, a portable photometer (Dustrak AM520) will be used throughout the travel [62]. The photometer will be in a backpack and the tube will be secured with a clip next to the participant's neck. In this sense, the measurement of $PM_{2.5}$ will most closely reflect the actual exposure level. To ensure the quality of the measurements obtained by portable photometers, calibration will be performed according to the recommendations from Betancourt et al [62].

To determine the concentration of BC, a portable aethalometer (MicroAeth AE51) will be used [63]. This measurement will be performed in real time and in the same manner as described for $PM_{2.5}$ measurements. Before use, flow rate calibration of the aethalometer will be carried out following the manufacturer's instructions and the recommendations of Betancourt et al [62].

Determination of Potential Inhaled Dose

To estimate the potential inhaled dose of $PM_{2.5}$, the following variables will be considered: the concentration of $PM_{2.5}$ estimated for each mode of travel and roadway, the inhalation rate due to physical activity, and the exposure time to pollution, given in this case by the start and end time of each trip [62]. Three normalization factors will be used: dose per unit length, dose per unit time, and total dose [62].

Data Analysis

Quantitative Analysis

A descriptive analysis will be carried out in R version 4.0.2 for Windows. In the characterization of the sample, the qualitative variables will be presented using absolute and relative frequencies. For continuous variables with a normal distribution, the mean and SD will be calculated; variables that do not present a normal distribution will be described with the median and 25th to 75th percentiles.

The Student t test with two tails and a repeated-measures analysis of variance will be applied according to the assumptions of each test for comparing the means of transport, with statistical significance determined at $P<.05$.

In addition to measuring exposure to air pollutants, the doses of inhaled air pollutants will be estimated to consider the differences in ventilation during cycling compared to traveling by car or bus. The inhaled dose is calculated by multiplying the concentrations of pollutants, ventilation per minute, and duration of the trip, divided by the body surface area. Linear mixed models will be performed on these data to analyze the effects of the concentrations and the inhaled doses of contamination of the air-related traffic on changes in lung function before and after exposure. The model will adjust for potential confounders, including age, gender, BMI, day of the week, time of measurement, location, mode of transportation, and travel time.

Qualitative Analysis

A content analysis will initially be carried out, segmented by participants' characteristics (based on the mode of transport used). Next, categorization, and open, axial, and selective coding will be performed. From selective coding, attempts will be made

to identify metaphors to identify the perceptions of air pollution [53-56].

Quantitative and Qualitative Results Integration

Since the study will be based on concurrent triangulation, in which the qualitative and quantitative data will be collected and analyzed simultaneously, we expect to have two sets of results that will be integrated into the overall interpretation for comparisons, which can help to improve understanding of the study problem.

Emergent categories from qualitative results will be compared with quantitative results to identify the extent to which they converge, diverge, or are related. Subsequently, the most frequent emergent categories will be transformed into a set of a categorical variable. These variables will be integrated into a multilevel model.

Multilevel Model

Owing to the hierarchical nature of the associations estimated in this study, an analysis of combined effects will be performed at various levels to adjust for the effect of exposure to air pollution on other variables associated with health. The first-level results of the individual variables will be provided: age, gender, travel mode, socioeconomic status, occupation, physical activity, respiratory symptoms score, BMI, heart rate, blood pressure, inhalation rate, FVC before and after travel, coefficient of variation for forced expiratory volume in the first second (FEV_1) before and after travel, coefficient of variation for forced midexpiratory flow ($FEF_{25\%-75\%}$), coefficient of variation for small airway reactance (R5), and concentrations of $PM_{2.5}$ and BC [16]. The independent variables will be gender, age, occupation, place of study/work, socioeconomic status, air quality perception, average concentrations of $PM_{2.5}$ and BC, inhaled dose, MET, and Tiffeneau index. A reduction in the $FEF_{25\%-75\%}$ or an increase in the R5 coefficient of variation will be considered dependent variables. The microenvironment will be considered as a random variable and will be operationally defined by the combination of mode and route. Thus, there will be four possible modes and three routes, which provide 12 possible microenvironment combinations [64], resulting in the following level-1 model:

$$Yij = b0j + b1j\ X1ij + ... + bnj\ Xnij + eij,$$

where *Yij* is the dependent variable for participant *i* in unit *j*, b*nj* is the coefficient of level 1, *Xnij* is the explanatory variable *n* for participant *i* in unit *j*, *eij* is the random effect of level 1 (which is distributed normally with a mean of 0 and variance of σ^2).

The level-2 model is expressed as:

$$bnj = gn0 + gn1\ W1j + ... + gnp\ Wpj + unj,$$

where b*nj* is the dependent variable, g*n*0 and g*n*1 are the coefficients of level 1, g*np* is the coefficient of level 2, *Wpj* is the explanatory variable of level 2, and *unj* is the random effect of level 2; *u* is distributed in a normal multivalent manner with mean 0 and a matrix of variances.

Ethical Considerations

The study was approved by the technical and ethical committee of the National Institute of Health (Instituto Nacional de Salud), as evidenced by approval protocol number 7, issued on April 4, 2019.

To ensure that participation will be voluntary, the invitation to participate in the study will be made through employers or faculties of the institutions to which individuals are enrolled. Consent will be obtained for each aspect of data collection as described above.

Electronic data, including transcribed questionnaire and interview responses, and data collected using portable devices and medical testing will be stored on password-protected and encrypted laptops.

Along with the questionnaire, medical evaluations and interviews will include collection of demographic and personal data; this information will contain no participant identifiers. The results from medical tests and air quality measures will be stored in a secure database. The data set will be analyzed only after the data collection phase. No identifying data on patients or participants will be collected.

Patient and Public Involvement

This protocol was jointly developed between public and academic entities based on shared needs related to technical information for the promotion of policies that improve air quality in the city and reduce possible health effects. Some members of the Mesa Técnica Ciudadana por la Calidad del Aire de Bogotá were consulted as representatives of the citizenship, and their contributions were used to assign the participants to the road routes. Participants may voluntarily decide to participate in the study and may recommend participation in the study to others. Once data collection and analysis are complete, the results will be presented at academic events in addition to sharing with all participating entities.

Results

Enrollment of participants has begun with a sample of 300 enrolled to date. The measures of inhaled doses have been taken along with air pollution measures. Data cleaning and management are ongoing. Initial results based on primary outcomes are expected to be disseminated by the end of 2022. The results could provide information on the perceptions of users with respect to the air quality to which they believe they are exposed considering various modes of transportation. Likewise, it is expected that the participants' levels of physical activity and respiratory parameters may differ according to the different modes of transport, as well as with respect to variations in the amounts of $PM_{2.5}$ and BC inhaled when traveling on routes with different levels of contamination, as established by environmental monitoring. The bivariate and logistic regression models are expected to establish relationships between the selected roads for the study and their characteristics at the levels of physical activity, pollution, and health effects for each microenvironment. These results should further provide a

broader view of the problem of air quality in an active city such as Bogotá.

Discussion

The objective of this study is to relate exposure to $PM_{2.5}$ and BC with respiratory health and physical activity in a sample of healthy users mobilized in prioritized transportation microenvironments in Bogotá. The results of this study will allow us to establish a diagnosis of the effects of air pollution on the respiratory health of users of different modes of transport.

According to the report of the World Air Quality Index (IQAir AirVisual), among the 62 most polluted cities by $PM_{2.5}$, Bogotá ranks in 44th position based on the 10 μg/m^3 standard established by the World Health Organization [65]. Although the RMCAB reports data of contaminants as daily means, it is not possible to obtain a report of personal exposure in microenvironments [66,67]. Thus, the RMCAB network is inadequate for assessing personal exposure and cannot account for the measurement of BC [66].

This project will enable establishment of the pollution characteristics of $PM_{2.5}$ and BC for some of the most important roads in the city, complementing the data produced by the RMCAB at the microenvironmental level. Likewise, this project will provide guidance to the health sector to focus actions for the prevention of respiratory diseases in the areas surrounding these roads, and will further guide the mobility sector in the layout of cycling routes with consideration of possible health impacts. The information provided by the study will inform the decision-makers: this study was formulated with collaborations of public policymakers on health, environment, and mobility

in mind, in addition to considering the concerns of the Accidental Air Pollution Commission of the District Council. This ensures that the evidence generated is disseminated among public policymakers in the design of road infrastructure and active transport strategies to support evidence-based decision-making. Additionally, this study will allow participating work and study centers to learn about the health conditions and mobility of their population that could be used to implement plans for promoting physical activity in workers and students. Finally, this study will benefit the users of city transportation, who will be able to make autonomous decisions about the use of elements of personal protection, choice of routes, and means of transportation in the city using the information provided by the study.

This study has many limitations. The first limitation is related to the study design. Despite previous studies reporting changes in spirometry measures related to short-term exposure, such changes have not been reported in healthy populations living higher than 2000 meters above sea level. Second, to identify changes in spirometry parameters, the sample size is an important consideration. We have estimated a minimum sample size of 350 participants to guaranty the multilevel analysis requirements. Third, we will use the spirometric parameters to evaluate the health impacts of short-term exposure to air pollutants. However, the changes in the small airway may not be accurately measured by spirometry. We have considered alternative tests such as impulse oscillometry. Finally, in the qualitative analysis of the data, we will use a saturation criterion to define the number of semistructured interviews. This means that there will not be an interview for each participant, which can introduce bias in the multilevel model.

Authors' Contributions

JMR developed the main idea and designed the protocol. The manuscript for the protocol was drafted by JMR, DPS, EP, YT, and LL, and was reviewed by JMR, DPS, EP, YT, LHF, RM, SRM, DPS, ARC, and OS. All authors approved the publication of the protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Virtual questionnaire.
[PDF File (Adobe PDF File), 232 KB - resprot_v11i1e25690_app1.pdf]

Multimedia Appendix 2
Semistructured interview.

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Abbreviations

BC: black carbon
FEF25%-75%: forced midexpiratory flow
FEV1: forced expiratory volume in the first second
FVC: forced vital capacity
MET: metabolic equivalent of task
PM: particulate matter
PM$_{2.5}$: fine particulate matter <2.5 microns
R5: small airway reactance
RMCAB: Red de Monitoreo de Calidad del Aire de Bogotá (Air Quality Monitoring Network of Bogotá)

Protocol

The Future of Disability Research in Australia: Protocol for a Multiphase Research Agenda–Setting Study

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Abstract

Background: For people with disabilities to live a good life, it is essential that funded research in health and social care addresses their interests, meets their needs, and fills gaps in our understanding of the impact that services, systems, and policies may have on them. Decisions about research funding should be based on an understanding of the research priorities of people with disabilities, their supporters and allies, disability researchers, service providers, and policy makers working in the field.

Objective: The aim of this protocol is to describe the research design and methods of a large-scale, disability research agenda–setting exercise conducted in 2021 in Australia.

Methods: The research agenda–setting exercise involves 3 integrated phases of work. In the first phase, a previous audit of disability research in Australia is updated to understand previous research and continuing gaps in the research. Building on this, the second phase involves consultation with stakeholders—people with disabilities and their supporters and family members, the disability workforce, and people working within services and connected sectors (eg, aging, employment, education, and housing), academia, and public policy. Data for the second phase will be gathered as follows: a national web-based survey; a consultation process undertaken through the government and nongovernment sector; and targeted consultation with Aboriginal and Torres Strait Islander people, children with disabilities and their families, people with cognitive disability, and people with complex communication needs. The third phase involves a web-based survey to develop a research agenda based on the outcomes of all phases.

Results: We have started working on 2 parts of the research prioritization exercise. Through the research-mapping exercise we identified 1241 journal articles and book chapters (referred to as *research papers*) and 225 publicly available reports (referred to

as *research reports*) produced over the 2018-2020 period. Data collection for the national survey has also been completed. We received 973 fully completed responses to the survey. Analysis of these data is currently underway.

Conclusions: This multi-method research agenda–setting study will be the first to provide an indication of the areas of health and social research that people across the Australian disability community consider should be prioritized in disability research funding decisions. Project results from all phases will be made publicly available through reports, open-access journal publications, and Easy Read documents.

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Introduction

Background

Internationally, there is an increasing need for targeted disability research to align with the changing nature of disability practices, technologies, and policies [1]. In Australia, and internationally, research is needed to inform the implementation of new disability policies and changes to disability systems and services [2]. This is particularly salient now, as new disability-related policies, including the National Disability Insurance Scheme and the revised 10-year National Disability Strategy [3], are being implemented at federal, state, and territory levels. These new strategies and actions mean that disability services and the people they serve must rapidly and continually adapt to new funding, systems, and service structures [4]. Disability research should (1) create new knowledge; (2) encompass the situations of people with disability to address their needs and the issues that are of importance to them; (3) monitor the implementation of new policies; and (4) examine, inform, and affect policy change [5,6]. Furthermore, with finite funding available to support a growing number of active disability researchers in this sector, research resources need to be allocated and used strategically and effectively, by considering both current and emerging issues. Existing prioritization exercises undertaken internationally have been limited in scope and method or conducted only in relation to specific groups or without the participation of people with disability, or other interest groups, and therefore do not represent a broad range of voices [7-9].

In 2020, the project team successfully tendered to undertake the research agenda–setting study in a 2-stage expression of interest process judged by a selection panel within the National Disability Research Partnership, which included senior disability researchers, people with disability, supporters, and allies [10]. The project team is a consortium of 31 individuals comprising people with lived experience of disability, family members or other supporters, Aboriginal and Torres Strait Islander people, academic disability researchers, and representatives from nongovernmental organizations (NGOs). A full list of organizations named as part of the tender is shown in Table 1. The team is led by a core project group and administered by the University of Sydney. Members of the consortium work in teams to lead and implement different project phases (Figure 1). Working groups of interested partners were formed from broader consortium membership to develop and advise on each project phase.

Disability, and disability research, is a broad field encompassing a range of sectoral interests, different *diagnostic* or *impairment* groups (eg, spinal cord injury, cerebral palsy, intellectual disability, or autism), or situations (eg, housing, education, employment, health, justice, and citizenship). In addition, disability research has many intersections and overlapping boundaries (eg, in Australia, Aboriginal and Torres Strait Islander people; gender, ethnicity, and lesbian, gay, bisexual, transgender, queer, and intersex [LGBTQI+] communities). Similarly, disability policy is expansive and overlaps with areas of concern for the wider community, such as health, housing, education, employment, leisure, and technology. As such, any attempt at disability research–mapping and agenda-setting must be as broad and inclusive as possible. Audits of Disability Research (2014 and updated in 2017) have mapped the Australian disability research field over the 2000-2017 period [11,12]. These audit reports have been an important resource used by national and international researchers as well as the Australian government and NGOs as a resource for identifying what research exists and can be used in service and policy development [2,13,14]. However, there have been no previous system-wide attempts to set a disability research agenda in Australia.

Table 1. The complete list of organizations.

Consortium organizations	Organization category
University of Sydney—Centre for Disability Research and Policy and Centre for Disability Studies (project leads)	Academic research
Ability first	Nongovernment organization
Australian Association of Special Education	Broad-based association
Australian Federation of Disability Organisations	Peak body
Australian National University Lived Research Unit	Academic research
Autism Awareness Australia	Nongovernment organization
Centre for Social Impact National (including University of New South Wales, Swinburne University, University of Western Australia)	Academic research
Children and young people research group (including Murdoch Children's Research Institute, Monash University, Australian Catholic University)	Academic research
Community Resource Unit	Nongovernment organization
Council of Regional Disability Organisations	Peak body
Deaf Victoria Inc (and Expression Australia)	Nongovernment organization
Deakin University	Academic research
Disability Advocacy Network Australia	Peak body
Disability Research Network, The University of Technology Sydney	Academic research
Family advocacy	Nongovernment organization
Inclusion Australia	Nongovernment organization
Inclusion Melbourne	Nongovernment organization
Kindship	Nongovernment organization
Nossal Institute for Global Health, The University of Melbourne	Academic research
Mobility and Accessibility for Children in Australia Inc.	Nongovernment organization
MND Australia	Nongovernment organization
National Disability Services	Nongovernment organization
Neurodevelopment Australia	Nongovernment organization
Ninti One	Indigenous-owned research nonprofit
NSW Council for Intellectual Disability	Nongovernment organization
Onemda Research and Innovation Centre	Nongovernment organization
Queenslanders with Disability Network	Nongovernment organization
Settlement Services International	Nongovernment organization
University of Melbourne	Academia
University of Queensland	Academia
Vision Australia	Nongovernment organization
Women with Disabilities Australia	Nongovernment organization
Academic advisers: Elizabeth McEntyre, Priscilla Ferazzi, Gerard Goggin	Academic research

Figure 1. Organization of project phases, advisory panels, and teams.
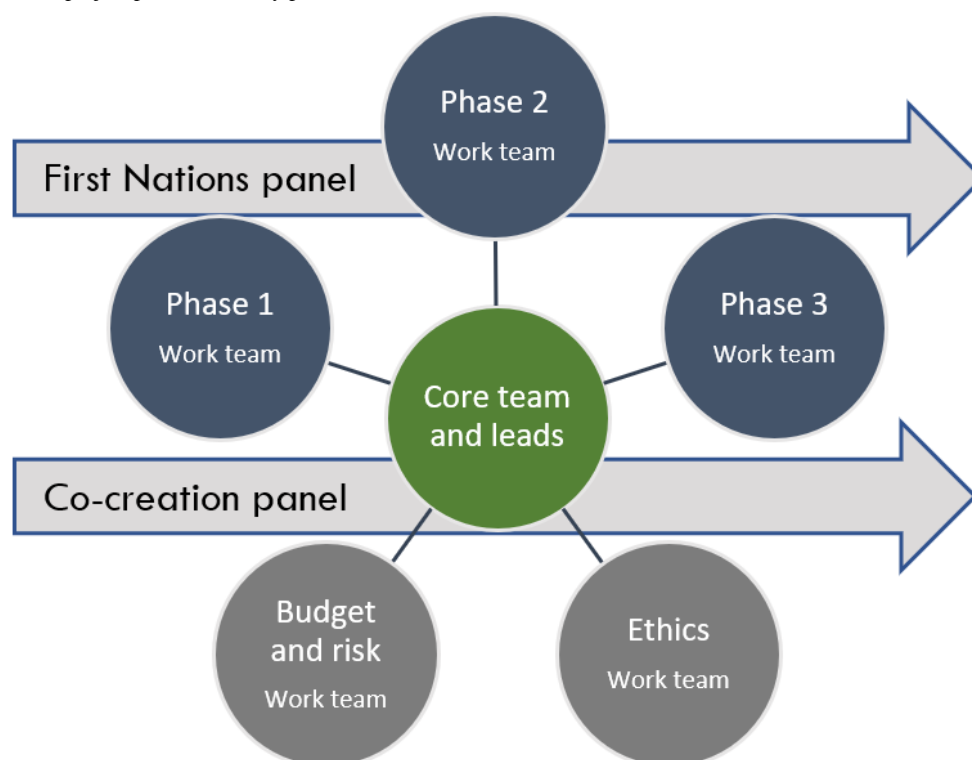

Objectives

In this context, the aim of this research agenda–setting exercise is to map Australian disability research to date, specifically focusing on progress since previous audits, and to identify gaps in the research and areas for further inquiry, to inform decisions regarding the design and funding of disability research programs in Australia [2]. The method and findings may inform the disability sector internationally as other countries move to identify agendas based on the priorities of people with disabilities, their families, and supporters. This research is novel and important as there have been no comparable consultation processes that span all states and territories across one nation, focusing on disability across the life course and encompassing the range of disability or impairment types, sectors, and disability-related issues [8].

Methods

Design

This multi-stage study involves research-mapping, community consultation, and agenda-setting exercises (Figure 2). Development of the research agenda will occur iteratively throughout the project, in consultation with the consortium partners, with multiple points of translation of research findings to stakeholders in accessible formats as the disability research agenda develops. In addition to consultation with the project consortium members, the project management structure includes a user-centered cocreation panel with people with disabilities and a First Nations–focused advisory panel, each comprising members of the consortium and others within the broader disability community. These panels are active throughout the project, meeting as needed to provide a focused critical voice to project design and analysis decisions, including development of the project outputs and the final research agenda.

Figure 2. Project design showing the 3 phases of the project. NGO: nongovernmental organization.
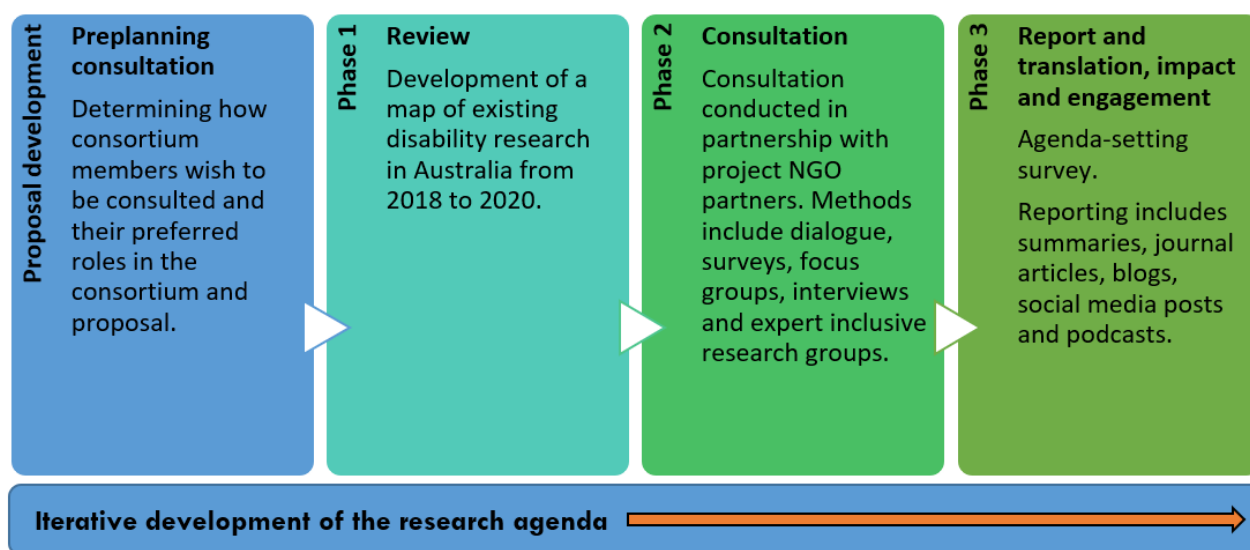
Preplanning and Project Design Phase

The preconsultation phase involved the consortium collectively and iteratively developing the proposal through a series of meetings. An initial consortium was developed from interested individuals and organizations who then invited other potential consortium members to participate, seeking their advice on ways to design a broader consultation to be attentive and responsive to the needs of people with disabilities and the disability community (completed in September 2020).

Phase 1: Mapping Existing Research

Overview

The research-mapping was designed to (1) determine existing published research and gaps in current research and (2) identify emerging research priorities based on these gaps (data collection completed in May 2021). The consortium members who were leading this phase (Figure 1) applied diverse knowledge and interdisciplinary understanding to question the group's situated knowledge of disability. These multiple perspectives were important for the relevance of the review approach and to be inclusive of all forms of knowledge to ensure that all views, including nondominant and traditionally excluded views, were heard.

A specified aim of the research agenda was to update the previous audits of disability research with research conducted between 2018 and 2020. The original audits used a conceptual framework based on 8 *domains of everyday life* for people with disability: (1) community and civic participation; (2) economic participation; (3) education; (4) health and well-being; (5) housing and the built environment; (6) safety and security; (7) social relationships; and (8) transport and communication [3,4]. These domains were used to restrict the search into these 8 categories and then as a structure for narrative analysis. In the current mapping process, we did away with these domains as limiters in the search terms, as we felt it would restrict the breadth of disability research, we were able to include in our reporting.

To locate research in peer-reviewed journal articles and books, we systematically searched multiple scientific databases: AMED, Avery, CINAHL, Compendex, Embase, ERIC, Global Health, MEDLINE, PsycINFO, Scopus, Sociological Abstracts, Web of Science Core Collection, and Informit (which includes the following databases: A+Education, Ausport, Families & Society Collection, Humanities & Social Sciences Collection, Literature & Culture Collection, Indigenous Australia, AGIS, FAMILY, APAIS, AMI, AusSportMed, Health & Society Collection, Health Collection, RURAL, Transport Index, ALISA, BUILD, ENGINE, and ARCH). This approach was developed with the assistance of a university librarian with experience in systematic reviews. An example of the search strategy adapted to multiple databases is presented in Textbox 1.

Textbox 1. An example of the search strategy adapted to multiple databases.

An example of the search strategy

(disab* OR handicap* OR *mental* retard* OR development* disabilit* OR intellectual disabilit* OR learning disabilit* OR learning disorder* OR hearing impair* OR vision disorder* OR hearing disorder* OR special needs*) OR (cognitive* disability* OR communication disorder* OR communication disability* OR neurological disorder* OR brain injury OR congenital disorder* OR autis* OR fragile x OR genetic disorder*) OR (Cerebral palsy OR Spina bifida OR neurodivers* OR down syndrome OR Fragile X syndrome OR F*tal Alcohol OR prenatal alcohol exposure OR Rett Syndrome) OR (psych* disorder* OR psych* disab* OR blind OR vis* impair* OR low vision OR hearing loss OR *mute OR deaf* OR sign language OR Auslan OR special education* OR hard of hearing OR attention deficit OR Tourette*)) AND (austral* OR new south wales OR south austral* OR west* austral* OR northern territory OR australian capital territory OR queensland* OR Tasmania OR Victoria))*

To identify research from public reports (sometimes called gray literature), web-based searches using the Google Australia internet search engine were systematically made. A base search string was used, and *Australia* disability research filetype:pdf* was adapted to the relevant search terms. We undertook a search for partner organizations and other key websites. Any reports that did not contain original data (eg, *how to* guidelines and policy submissions) were excluded from the mapping.

Eligibility Criteria for Study Inclusion

The integrative review identified qualitative, quantitative, and mixed methods studies with no limit on study design, data collection methods used, or study quality using the following criteria.

Inclusion Criteria

The following were the inclusion criteria:

- Studies published between 2011 and 2020
- Studies published in English in a peer-reviewed journal or published book chapter or as a publicly available report
- A full paper that documented the results of an investigation and secondary analysis of existing data reporting the aim of the investigation, method, findings, and conclusions and recommendations
- At least one aim of the study should be related to people with disability
- Disability research including Australian participants or topics and reporting results on those participants or topics. This included international comparative studies. *Topics* included to capture studies, such as those about Australian disability policy, social context, and services, where there were no participants
- The conclusions derived from results related to people with disability

Exclusion Criteria

The following were the exclusion criteria:

- The aims of the paper did not relate to people with disability or disability were mentioned only in passing
- Studies which did not contain original data (eg, commentaries, viewpoints, editorials, or policy documents)
- Studies only discussed disability was acute and transient (eg, rehabilitation from an acute injury, such as short-term limb dysfunction after a fracture)
- Studies included research that was primarily laboratory-based and related to genetics, treatment, diagnosis or cure (eg, medical prevention and cure, surgical or clinical), which did not also consider the broader functioning, disability, health, and well-being of people with disability
- Not a full paper (eg, conference abstracts) or unavailable as full text
- Paper was not written in English

Identification and Selection of Studies

The titles and abstracts of all studies generated through the combined database searches were uploaded to the systematic review software Covidence, and duplicates were removed. We used Microsoft Excel to manage research reports. Two team members independently screened all search results against the eligibility criteria in both the abstract and full-text screening phases. Conflicts were resolved by a third reviewer.

The initial list of all relevant papers and reports identified were sent to a large range of disability researchers, NGO partners, and government agencies to identify any papers missed from the search. The list of papers was sent out via the existing networks of consortium members and project advisory groups. Those who received the list were encouraged to send it through their own networks. Any additional papers that were identified were screened according to the method described earlier.

Data Analysis

The data extraction task has been shared by multiple members of the research-mapping team based on a standardized data extraction form. The extracted information included the title, year of publication, abstract, study population, focal group of participants, main type of disability being discussed, age group, aim of the paper, topic, primary focus, secondary focus, study design, further details, and study funding sources (Multimedia Appendix 1). These areas were developed collaboratively by the project team to ensure the mapping of key dimensions of disability research in Australia.

The extracted data were then analyzed, integrated, synthesized, and presented both quantitatively (number of papers, domain, age, disability group focus, and study design or type of research) and qualitatively. Narrative synthesis involved identifying (1) main topics within individual studies and synthesizing these across studies, (2) collective limitations of the research scope and methods used (eg, an absence of lived experience-led studies) and knowledge gaps across the studies, and (3) directions for future research across the studies.

Phase 2: Stakeholder Consultation

In this phase, stakeholders will be consulted using a range of quantitative and qualitative methods to determine their priorities for research, how they use research, and how future research should be shaped so that it is more useful for potential users.

Methods of Consultation

The 3 main principles underpinning consultation are *inclusion*, *flexibility*, and *self-determination*. These interlinked principles underpin choices made concerning research methods and their application. It is important to ensure that there are no barriers to participation in the consultation, and this demands flexibility in the approaches used. This includes seeking broad feedback and providing methods and resources that enable people to participate by accommodating their communication and information access needs. Thus, a multi-pronged, multi-stage, multi-platform consultation process has been designed. Nongovernment disabled people's organizations and advocacy organizations have the best knowledge about their members and, therefore, how to consult with them. Therefore, a consultation toolkit has been designed for use by organizations conducting their own tailored consultations, with resourcing or research support from the consortium as needed. The final approach to consultation by organizations is determined by the

communication preferences and styles of their members, using the consultation toolkit.

Data Collection

Three main routes of consultation will be used and adapted as needed in different situations.

1. Data collection will be administered by advocacy organizations, disabled people's organizations, and inclusive research groups. These groups will consult members and stakeholders across Australia, with peak bodies cascading consultations to member organizations. They will use the parts of the consultation toolkit most useful for collecting information from their constituents. Where requested, consortium members can lead consultations on behalf of or with organizations. This is particularly important for small advocacy organizations, who may be restricted in terms of resources to support a consultation.

2. Data collection via a web-based national survey: a national survey has been designed by a subgroup of the consortium, including people with disabilities and advocacy organization partners. It has been designed to be as open as possible in scope and to collect broad perspectives on how research should be designed and conducted and the main topics of interest for the following groups:

   a. People with disability, their supporters, and allies
   b. Researchers involved in disability research
   c. Service providers, disability workforce (eg, disability support workers, health professionals, and educators), policy makers, and others working with people with disabilities (eg, in housing, transport, employment, the arts, health, or education)
   d. Anyone who is not otherwise participating in the NGO-focused consultation

   - Data collection for the national survey has been completed.

3. Data collection with First Nations people in regional and metropolitan Aboriginal communities coordinated by the Aboriginal-owned research organization Ninti One. This part of the project is led by JG, who is a leader of the Aboriginal disability scholarship and is a descendant of the Yuin Nation of the New South Wales South Coast. Consultation involves a web-based survey adapted from the national survey. The project has embedded Indigenous Standpoint Theory developed specifically for disability research [15-17].

The consultation has been designed to be adapted to the COVID-19 pandemic restrictions as it can be conducted on the web and face-to-face following safety protocols. Furthermore, the partnership is geographically spread so that local consultations can proceed without the need to travel interstate.

Sample and Recruitment

Overview

Stakeholders include people with disability and their supporters and family members, the disability workforce, and people working within disability services and connected sectors (eg, aging, employment, education, and housing), academia, and

public policy. The proposed sampling strategy is not designed to be representative but rather to reach as many interested people as possible and enable in-depth consultation in relation to their views. The consultation aims to capture the interests of anyone who relates to the concept of disability, rather than using any set definition of inclusion. All partners to the consortium act as a gateway to their respective networks and share the consultation resources throughout these networks by distributing consultation resources and opportunities. Twitter is also used throughout the project to advertise the survey and consultation processes.

Developing the Consultation Toolkit

A subgroup of the consortium convened to develop and design the consultation toolkit. On the basis of the discussions across the consortium, data collection templates have been prepared, reviewed, and finalized. The aim was to provide a standardized template for the return of aggregated data to the consortium, while enabling the consultation to be flexible and responsive to the communication and information needs of the participating organizations and their members or stakeholders. Organizations were encouraged to use consultation approaches typically used with their stakeholder groups, with interview and focus group templates provided as guiding documents. Organizations were also responsible for obtaining informed voluntary consent following their usual processes. Templates for participant information sheets and consent forms were developed by the research team, approved by ethics, used in consultations led by consortium and inclusive researchers, and available for organizations if required. Where possible, the resources in the consultation toolkit were adapted from existing codeveloped resources [18,19]. Beyond the working group, draft resources were reviewed internally within 4 organizations (Council for Intellectual disability, Inclusion Melbourne, Deaf Victoria, and People with Disability Australia) in addition to the consortium's cocreation panel.

Elements of the Consultation Toolkit

The final consultation toolkit includes the following resources:

- Easy Read information leaflet
- Guidance on how to complete an interview and a focus group, including preparation and facilitation and example questions that could be asked
- Resource tip sheet for organizations with which to find additional information to support consultations (eg, information on consent and supported decision-making)
- Accessible surveys for different audiences, including video supplementation using Australian Sign Language, to provide context for the consultation and content and purpose of the survey
- A *how* template to be completed and returned by organizations or individuals detailing how the consultation took place, what method was used, and who was included, so the depth and breadth of the consultation could be characterized
- A *what* template to be completed and returned by organizations or individuals collating the findings from the consultation that could inform the agenda-setting task

The information reported in these standardized templates (the *How* and *What* templates) facilitates the process of synthesis

by the consortium who go on to bring together the consultation results collected through the different methodologies chosen for individual consultations. The *how* template will act as a quality indicator by reporting the extent to which people with disabilities participate in and facilitate the consultations nationally.

Data Analysis Plan

Survey data will be analyzed both quantitative and qualitatively. Quantitative data will be analyzed using Stata for Windows (version 11.0; StataCorp LP). Descriptive statistics will be used to summarize the data. Frequencies and proportions will be calculated. Qualitative data from open-ended text-based responses will be analyzed using a modified thematic analysis that involves an open coding technique [20].

For analysis of the qualitative data, an interpretive approach will be used in analyzing the feedback from each subsection of participants and strands (consultation, survey, and focused data collection). Analysis of the consultation *what* and *how* templates will take a combined deductive and inductive approach of thematic analysis with themes and research priorities contextualized by descriptive data with regard to involvement of people with disabilities and the nature of impairment groupings as recorded in the *how* template [21,22].

The analysis seeks not only to document people's views but also to develop a deep understanding of the context in which these views have been formulated and the meanings underpinning their perspectives. A report of core findings from each strand will be prepared and shared across the consortium to verify the team's interpretations. Thematic analysis and triangulation of findings across participant groups will be prepared, and this will form the basis of the phase 3 agenda-setting.

The main output of the consultation phase will be a consultation report that describes in detail the methodology, number of people engaged with through the process, and thematic results of the consultation. Consultation results will be produced in accessible formats, including Australian Sign Language and easy English, as well as ensuring screen reader accessibility. Additional accessibility needs will be met as requested.

Phase 3: Synthesis of Findings

Synthesis and Development of the Research Agenda

This phase will present to the National Disability Research Partnership, a policy- and practice-relevant research agenda. The agenda will bring together the priorities identified from each phase of the project. It will provide commentary on the evidence supporting the inclusion of each identified research priority, its utility for progressing policy and practice, advancing rights and enabling the flourishing of people with disability.

The third phase is informed by the James Lind Alliance Priority Setting Partnership methodology [23,24]. This is a detailed cocreation methodology used internationally since 2004 to set research agendas in an equal partnership between lay people, people affected by health conditions, and support people and professionals.

Phase 3 will involve consolidating the evidence from phases 1 and 2 using thematic consolidation and a comparison of findings to create overarching research themes that have been disproportionately underresearched or not researched at all in the Australian context in the past 10 years; of where publications do exist, but where findings have not been communicated or translated for use at the system, community, or individual level (evidence-practice gap); that are considered priorities for future research by nonresearchers including people with disability.

The themes, which are yet to be identified, will be presented in a web-based survey to stakeholders, including representatives of those groups and individuals who took part in phase 2 consultations and those who indicated their interest in participating in phase 3. Purposive sampling for participants not represented through this opt-in process will be conducted through the consortium, NGOs, governments, and research networks. We aim for 500-1000 responses, which is feasible given the response rate for the phase 2 survey that was completed by almost 1000 respondents. The survey will focus on high-level research themes and ask respondents to rank and comment on the importance and applicability of these themes from the following perspectives:

- Effectiveness of research into policy and practice related to each of the themes
- Enabling factors identified by research related to each of the themes
- Experiences explored in research about everyday life and outcomes for people with disability

Data Analysis Plan

Survey responses will be analyzed using the same quantitative and qualitative data analysis processes used for the phase 2 survey to produce the disability research agenda.

The main output of this final phase will be a report on identifying the research agenda themes.

Public and Patient Involvement

People with lived experience of disability and their supporters and allies will be involved in all phases of the project, from the beginning of the development of the tender documents and research plan. The research question underpinning this project concerns what should be prioritized in disability research in Australia. This question was developed by the National Disability Research Partnership, which includes people with disabilities. Within this project consortium, the strategies for data collection, analysis, and dissemination have all been developed in partnership with people with disabilities, including core project team members with disabilities, family members, and supporters.

Ethics

This project necessitates an enhanced ethical review because of the potential vulnerability of the participants. The coproduction of all aspects of data collection is an important part of the ethical approach. Ethics approval was obtained for the phase 2 survey and other consultation processes from the University of Sydney Human Research Ethics Committee (2021/175, 2021/318, 2021/443). The phase 3 survey is currently

under ethical consideration. All participants in the research will be requested to provide written consent to participate in the interviews and focus groups. For surveys, consent will be obtained by acknowledgment of reading the participant information sheet and submission of the survey. Only full survey data (where the participant has fully completed and submitted the survey) will be used. For individuals (eg, children and people with very complex intellectual disability) who do not have the legal ability to fully consent for themselves, their guardians will be requested to provide consent, but we will also ask for consent from the participants themselves.

Results

The project was launched in October 2020, and data collection has begun in phases 1 and 2. This project is currently in progress. We have completed the research-mapping phase and co-designed the consultation documents for dissemination across participating organizations. The national survey has been completed.

The main project outputs will be (1) full, accessible reports of all stages and (2) summary documents that explain the research agenda in a briefer format. These will be created in several accessible formats. Summary reports will be distributed to the disability community using email and team websites. Social media (eg, Twitter, Facebook, and LinkedIn) will be used to disseminate project outcomes and gather feedback progressively throughout the project, using the hashtag #AusDisAbilityResearch. Specific research articles will report all phases of the project, including the mapping and consultation phases.

Discussion

Disability research has the potential to radically improve the lives of people with disability if it is targeted to those areas that are priorities for people with disability, service providers, policy makers, and others across the disability sector [10,25]. Currently, there is no way of knowing what the nation's disability research priorities are, leading to a reliance on what researchers, government agencies, and funding bodies consider important based on their own domains, or areas of expertise or responsibility. This multi-method, research agenda–setting study will provide an indication of what people across the Australian disability community, including people with disability, consider should be prioritized in disability research [26].

Given that research outputs and impacts will ultimately inform structures for research funding priorities (and in turn policy), it is imperative that these outputs and outcomes have validity, confirmability, transferability, and verifiability across the disability community [6,9]. Communication with the disability community and the inclusion of as many voices as possible are essential to the project process. This need has underpinned decisions about the cross-sector consortium and project organization. It has also underpinned the decision to conduct consultations primarily through NGO partners. Key elements of the research findings will be released throughout the project to engage the disability sector, including people with disability, in the project as it develops and encourages participation in the consultation.

Authors' Contributions

JSM wrote the first draft of the protocol. MAO drafted phase 2 methodology and AD drafted phase 3. BH, CI, GC, SD, KE, GG, JG, AG, MM, KM, and JP contributed to the protocol design and edited and shaped the paper further. All the authors approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Data extraction template from Covidence.
[DOCX File , 32 KB - resprot_v11i1e31126_app1.docx]

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Abbreviations

LGBTQI+: lesbian, gay, bisexual, transgender, queer, and intersex
NGO: nongovernmental organization

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Protocol

Single-Group Trial of an Internet-Delivered Insomnia Intervention Among Higher-Intensity Family Caregivers: Rationale and Protocol for a Mixed Methods Study

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Abstract

Background: Family caregivers are more likely to experience insomnia relative to noncaregivers but have significant barriers to accessing gold standard cognitive behavioral therapy for insomnia treatment. Delivering interventions to caregivers through the internet may help increase access to care, particularly among higher-intensity caregivers who provide assistance with multiple care tasks over many hours per week. Although there are existing internet interventions that have been thoroughly studied and demonstrated as effective in the general population, the extent to which these interventions may be effective for caregivers without tailoring to address this population's unique psychosocial needs has not been studied.

Objective: The goal of this trial is to determine what tailoring may be necessary for which caregivers to ensure they receive optimal benefit from an existing evidence-based, internet-delivered cognitive behavioral therapy for insomnia program named Sleep Healthy Using the Internet (SHUTi). Specifically, we will test the association between caregivers' engagement with SHUTi and their caregiving context characteristics (ie, caregiving strain, self-efficacy, and guilt) and environment (ie, proximity to care recipient; functional status, cognitive status, and problem behavior of care recipient; and type of care provided). Among caregivers using the program, we will also test the associations between change in known treatment mechanisms (sleep beliefs and sleep locus of control) and caregiving context factors.

Methods: A total of 100 higher-intensity caregivers with significant insomnia symptoms will be recruited from across the United States to receive access to SHUTi in an open-label trial with mixed methods preassessments and postassessments. At postassessment (9 weeks following preassessment completion), participants will be categorized according to their engagement with the program (nonusers, incomplete users, or complete users). Study analyses will address 3 specific aims: to examine the association between caregivers' engagement with SHUTi and their caregiving context (aim 1a); to describe caregivers' barriers to and motivations for SHUTi engagement from open-ended survey responses (aim 1b); and among caregivers using SHUTi, to determine whether cognitive mechanisms of change targeted by SHUTi are associated with differences in caregiving context (aim 2).

Results: Institutional review board approvals have been received. Data collection is anticipated to begin in December 2021 and is expected to be completed in 2023.

Conclusions: Findings will inform the next research steps for tailoring and testing SHUTi for optimal impact and reach among caregivers. Beyond implication to the SHUTi program, the findings will be translatable across intervention programs and will

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hold significant promise to reduce inefficiencies in developing digital health interventions for caregivers while also increasing their impact and reach for this underserved population.

Introduction

Background

An estimated 47.9 million Americans provide unpaid care to ≥1 family members or close individuals with serious health conditions [1]. Support from family members to individuals who are seriously ill is critical to the sustainability of the US health care system [2]; however, it places a significant strain on these caregivers. Insomnia is among the most common, distressing, and impairing psychophysiological issues for caregivers [3,4]. As the responsibilities and stressors of the caregiving role can both precipitate and perpetuate insomnia [5], caregivers are up to 3 times more likely to report sleep disturbances than the general population (up to 90% vs approximately 33%-50%, respectively) [6,7]. Cognitive behavioral therapy for insomnia (CBT-I), the gold standard treatment for insomnia [6], has shown promise among caregivers; however, their uptake and completion of this therapy has been limited [8-10]. As such, directly assessing how the caregiving context affects CBT-I engagement and efficacy could help to ensure that caregivers have equitable access to and benefit from this evidence-based intervention.

Among caregivers, those who spend many hours per week supporting multiple care tasks for a loved one—or *higher-intensity caregivers*—have more difficulty in accessing affordable support services, although they are also more interested in receiving support to manage their own emotional and physical well-being [1,11]. Existing psychosocial services for caregivers are primarily delivered in person. Although these interventions have generally been effective, they have low enrollment, high dropout, and limited reach to caregivers who already have inadequate health care access [12-15].

Digital health interventions can lower the barriers to entry to supportive care for higher-intensity caregivers, as they are conveniently accessible anywhere and anytime through an internet-enabled device. These interventions are also more scalable and sustainable than standard in-person practices [16]. For these reasons, caregivers themselves express strong interest in digital health interventions [17-19], and leaders in caregiving research have deemed the development and distribution of technology-based solutions to support caregivers as a high priority [20-23].

Most digital health interventions tested among caregivers have been developed de novo for specific caregiving contexts [24-29] in recognition of the unique deficits, risk factors, and needs that caregivers experience. Compared with noncaregivers, caregivers report unique barriers to broadly accessing psychosocial support, including guilt [30-32] and chaotic schedules [31,32]. More specifically, with regards to behavioral treatment for sleep, caregivers report unique worry about the impact of sleep loss on their ability to provide care [33-35] and challenges with nighttime symptom management [34,35]. Tailoring interventions to specific user groups such as caregivers increases information salience, which increases users' attention to information and, therefore, the likelihood that the information will motivate behavior change [36]. When tested empirically, tailoring typically adds only small gains in outcomes relative to generic materials, although gains are typically maintained over time [37,38]. Although potentially appealing, tailoring reduces intervention reach as it narrows the user base and also increases the time for dissemination and costs for intervention development. Ultimately, the decision to tailor, and how to tailor, must balance any expected gains in treatment outcomes against the drawbacks of reduced reach and increased costs to maximize intervention impact.

Sleep Healthy Using the Internet (SHUTi [39,40]) is a fully automated, internet-delivered CBT-I program developed for the general population that holds significant promise for addressing insomnia among caregivers. In a recent trial of SHUTi among older adults, participants who self-identified as family caregivers (n=18) reported less improvement in their insomnia after using SHUTi (insomnia severity index [ISI] score difference=2.37, 95% CI 0.17-4.57; P=.03) and were less likely to rate their sleep quality as improved (χ^2_1 [N=190]=4.8; P=.03) compared with noncaregivers (n=189) [41]. However, significant differences (P>.10) between caregivers and noncaregivers were not observed for changes in cognitive mechanisms—more adaptive sleep beliefs and internalized sleep locus of control—or for ratings of program satisfaction, fit, or usability. Building on these preliminary observations, the goal of this trial is to determine what tailoring may be necessary for caregivers to receive optimal benefit from SHUTi.

To address this question, higher-intensity caregivers with significant insomnia symptoms will be recruited to receive access to SHUTi in a single-group, open-label trial with mixed methods preassessments and postassessments. This study design is recommended for establishing the plausibility of supporting subsequent fully powered efficacy testing [42]. At the end of the intervention period, caregivers will be categorized according to their level of engagement with the 6 SHUTi intervention lessons (or weekly *Cores*): nonusers (ie, completed 0 Cores),

incomplete users (ie, completed ≤3 Cores), and complete users (ie, completed ≥4 Cores).

Primary Trial Aims

Test the Association of SHUTi Engagement With Caregiving Context

Specifically, we will test how caregivers' engagement with SHUTi is associated with their user characteristics and environmental characteristics (aim 1a). We will also describe caregivers' barriers to and motivations for SHUTi engagement from open-ended survey responses (aim 1b).

Test the Association Between SHUTi Efficacy on Known Cognitive Mechanisms With Caregiving Context

Among caregivers using SHUTi, we will test whether cognitive mechanisms of change targeted by SHUTi are associated with differences in caregiving-related user or environmental characteristics.

Methods

Participants

This protocol manuscript has been developed in accordance with reporting recommended by the 2013 SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement [43,44]; see Textbox 1 for key study information. The protocol was revised following peer review through the National Institutes of Health; see Multimedia Appendix 1 for reviews and Multimedia Appendix 2 [1,6,40,45-54] for our team's response to reviews during the *just in time* period for our responsive protocol changes. Participants will be higher-intensity family caregivers reporting significant insomnia symptoms. Family caregiving is defined according to the National Alliance for Caregiving 2020 Caregiving in the United States survey methods [1]. Specifically, a family caregiver will be someone who is currently providing unpaid care to a relative or friend, aged ≥18 years, to help them take care of themselves and/or providing more than the normal amount of unpaid care for a child aged <18 years because of a medical, behavioral, or other condition or disability.

Higher-intensity caregiving will be defined by scoring ≥5 points on a scale modified from the National Alliance for Caregiving

Level of Care Index. Scoring is the function of the given number of hours of care and types of care tasks provided for activities of daily living (ADL; including medical and nursing tasks), instrumental ADL, and for child care recipients, selected caregiver support activities. If a caregiver provides care to >1 care recipient, the total amount of time and all care tasks across all care recipients are considered together to compute the care intensity score. See Table 1 for point assignments, which are summed to a total index score.

Although we considered reducing sample heterogeneity in the caregiving context, we chose to keep the caregiving inclusion criteria broad as it increases the generalizability of our findings. A broad sample will also facilitate our aim of understanding how broad or specific a caregiving audience can be addressed by a particular digital health intervention. Higher-intensity caregivers, regardless of disease context, share significant psychological (eg, guilt) and practical (eg, limited time) barriers that make them less likely than lower-intensity caregivers to be able to access care while also at risk for worse health outcomes. Therefore, our sample of higher-intensity caregivers will provide actionable insights into how to increase digital health intervention access to caregivers with the most barriers to care.

Potentially eligible caregivers must also have regular access to the internet (whether by computer, tablet, or smartphone) and be willing to receive study-related emails. Internet access is required to complete the SHUTi intervention. Although this requirement may introduce some bias to the sample, there is a strong rationale for it. Using 2017 nationally representative survey data [55], we found that 88% of caregivers reported accessing the internet (vs 89% of the general population [56]), and there was no difference in internet access by caregivers' level of distress, burden, or rurality [57]. Limitations in reach imposed by requiring internet access for this study will be offset by the increased convenience of a fully automated internet intervention (relative to the care delivered in person or scheduled with a provider).

Eligible caregivers will also be required to score ≥10 on the 7-item ISI [58]. This score corresponds to the cutoff suggestive of clinically significant insomnia symptoms among community samples [58]. All inclusion and exclusion criteria are listed in Textbox 1.

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Textbox 1. World Health Organization trial registration data set.

Primary registry and trial identifying number

- ClinicalTrials.gov NCT04986904

Date of registration in primary registry

- August 3, 2021

Secondary identifying numbers

- R21TR003522

- University of Virginia Health Sciences Research Institutional Review Board protocol HSR210255

- University of Pittsburgh Office of Research Protections Institutional Review Board protocol STUDY21080076

Source of monetary or material support

- National Institutes of Health–National Center for Advancing Translational Sciences (*this funding source has no significant role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit the results*)

Primary sponsor

- University of Virginia

Secondary sponsor

- University of Pittsburgh

Contact for public queries and scientific queries

- Kelly M Shaffer, PhD—Center for Behavioral Health and Technology, University of Virginia, Charlottesville, United States of America; (434) 982-1022; kshaffer (at) virginia.edu

Public title

- SHUTi CARE (Sleep Healthy Using the Internet–caregiver acceptability research)

Scientific title

- Optimizing efficiency and impact of digital health interventions for caregivers: A mixed methods approach

Country of recruitment

- United States

Health conditions or problems studied

- Family caregivers

- Insomnia

- Sleep initiation and maintenance disorders

Intervention

- SHUTi—internet-delivered cognitive behavioral therapy for insomnia program

Ages eligible for study

- ≥18 years

Sexes eligible for study

- All

Accepts healthy volunteers

- No

Inclusion criteria

- Caregiving

- Current higher-intensity caregiving (ie, level ≥3 on National Alliance for Caregiving Level of Care index)

- Expect to provide high-intensity caregiving for at least another 3 months (study duration)

- Sleep

  - Insomnia severity index score ≥10

- Internet access

  - Have access to any internet-enabled device (computer, tablet, or smartphone)

  - Willing to be emailed about the study

- Miscellaneous

  - Able to speak and read English

  - Residing in the United States or US territory

Exclusion criteria

- Sleep

  - Irregular schedule that would prevent adoption of intervention strategies (ie, shift work and typical bedtime earlier than 8 PM or later than 2 AM or arising time earlier than 4 AM or later than 10 AM)

  - Current behavioral or psychological treatment for insomnia

- Medical and psychiatric contraindications

  - Presence of another unmanaged sleep disorder (restless leg syndrome or periodic limb movement disorder, obstructive sleep apnea, narcolepsy, or parasomnia)

  - Diagnosis of dementia, Alzheimer disease, Parkinson disease, Huntington disease, schizophrenia, or psychosis

  - History of the following without recovery: stroke, traumatic brain injury, brain infection, or brain tumor

  - Current pregnancy or breastfeeding, chemotherapy for cancer, alcohol dependence or abuse, or substance dependence or abuse

  - Current unmanaged hyperthyroidism, severe respiratory disease, or epilepsy

  - Change in medication regimen for steroids, amphetamines stimulants, or prescribed sleep medications within the past 3 months

  - History of manic or hypomanic episode

- Miscellaneous

  - Severe computer literacy challenges

Study type

- Interventional

Allocation

- Not applicable

Intervention model

- Single-group assignment

Masking

- None (open label)

Primary purpose

- Treatment

Date of first enrollment

- December 2021 (anticipated)

Target sample size

- 100

Recruitment status

- Recruiting

Primary outcome

- SHUTi engagement (time frame: 9-week postassessment)

Key secondary outcomes

- Open-ended feedback about SHUTi (time frame: 9-week postassessment)

- SHUTi evaluation (time frame: 9-week postassessment)

- Change in sleep-related cognitions (time frame: preassessment and 9-week postassessment)

- Change in sleep locus of control (time frame: preassessment and 9-week postassessment)

Table 1. Level of care index for higher-intensity caregiving[a].

Points	Hours of care (average week)	Type of care provided	
		Adult care recipient	Child care recipient[b]
1	0-8	0 ADL[c,d], 1 IADL[e]	0 ADL, 1 IADL or CSA[f]
2	9-20	0 ADL, ≥2 IADLs	0 ADL, ≥2 IADL or CSAs (eg, 1 IADL plus 1 CSA)
3	21-40	1 ADL, any number IADLs	1 ADL, any number IADL or CSAs
4	≥41	≥2 ADLs, any number IADLs	≥2 ADLs, any number IADL or CSAs

[a]On the basis of the National Association for Caregiving (2020) Level of Care Index.

[b]Caregivers for child care recipients are only asked about developmentally appropriate ADLs and 3 IADLs: assisting with medical or nursing tasks, managing finances, and arranging outside services.

[c]ADL: activity of daily living.

[d]Includes medical and nursing tasks.

[e]IADL: instrumental activity of daily living.

[f]CSA: caregiver support activities—advocating with health care providers, community services, schools, or government agencies; monitoring the severity of their condition; communicating with health care professionals.

Procedures

Potential participants will learn about our trial from any of the three primary recruitment pathways (Figure 1 step 1): (1) University of Pittsburgh research registries, either receiving a letter through the Center for Social and Urban Research Caregiver Research Registry or matching with the study through the Clinical and Translational Science Institute Pitt+Me Research Registry; (2) web-based advertisement, including national social media advertisement campaigns by the University of Virginia Health System, social media postings, and website and newsletter postings through pertinent community organizations; or (3) in-clinic advertisements and informational flyers and handouts provided through partnering clinics at the University of Virginia and University of Pittsburgh.

Potentially interested individuals will contact the research staff and visit the study website for more information about the study. Interested individuals will complete a brief web-based interest and prescreening form (step 2). Where indicated, individuals' identities will be verified using TLOxp (TransUnion), a web-based people search tool [59]. Potentially eligible individuals will be contacted by research staff by phone to

complete eligibility screening, answer any remaining questions about the trial, and obtain informed consent to participate (step 3). Informed consent to participate will be collected electronically via DocuSign, and participants will have the opportunity to download a digitally signed copy of the form.

Enrolled participants will then be emailed log-in information for the SHUTi intervention website to complete preassessment (step 4). They will first complete a web-based questionnaire battery; then, participants will complete daily web-based sleep diaries through the SHUTi system. Participants must enter 10 daily sleep diaries in 14 days to advance through this stage. Upon completing these preassessment sleep diaries, participants will be compensated US $40.

Following completion of the preassessment, all participants will be advanced to the SHUTi intervention in this single-group, open-label trial (step 5; see *Intervention* section for more details). At the end of the 9-week intervention period, regardless of intervention progress, participants will complete postassessment (step 6). If a participant completes ≥1 Core, they will complete the full battery of questionnaires and 10 web-based sleep diaries. If a participant completes no Cores, they will complete a brief postassessment questionnaire battery.

These nonusers will not be asked to complete the full battery of questionnaires or sleep diaries to encourage retention.

Participants will be compensated US $40 upon completion of the postassessment.

Figure 1. Trial procedures. SHUTi: Sleep Healthy Using the Internet.
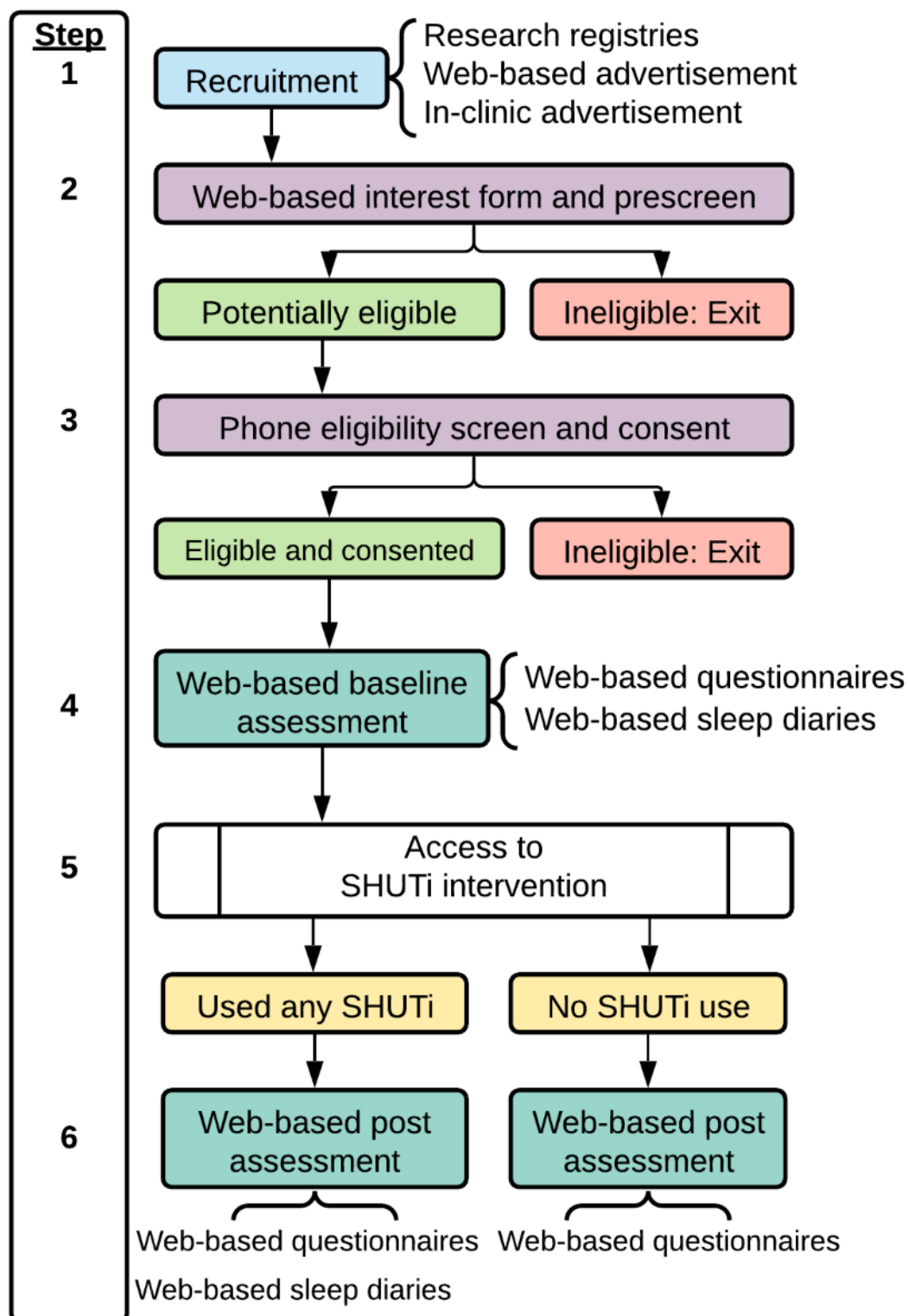
Intervention

Our team has established SHUTi as an effective treatment for insomnia over the past 15 years [39,40,45,60-65]. A complete description of the intervention has been published previously [40]; key intervention details are included here. SHUTi is a fully automated internet-delivered insomnia intervention that

is tailored from user-inputted data. The intervention is based on CBT-I, covering the primary tenets of sleep restriction, stimulus control, cognitive restructuring, sleep hygiene, and relapse prevention [40,66]. Study staff will be available to provide technical support; however, no clinical support will be provided to users. In this trial, participants will receive access

to the standard SHUTi program—meaning that the program has no tailoring to any specific user population. There is no content in the program that specifically addresses caregiving or caregiving-related impacts on sleep or treatment.

SHUTi content will be metered out over time through 6 *Cores*, or lessons, each of which will take approximately 45 minutes to 1 hour to complete. Core content (Textbox 2) will be delivered in a way that is designed to be engaging based on learning theory and instructional design [67], with interactive features such as graphical feedback of entered data, animations, quizzes, and videos. Cores will be delivered to users on a time-

and activity-based schedule. Specifically, the next Core will be made available to the user 1 week following their completion of the prior Core, which will allow participants time to practice skills. Users can track their sleep using daily web-based sleep diaries, each of which will take approximately ≤3 minutes to complete. The intervention will provide tailored content to users based on these diaries (eg, tailored *sleep prescriptions* as part of the sleep restriction technique) and other user-entered data. Participants will receive regular automated emails from the SHUTi program to support user engagement (eg, reminders to complete sleep diaries and notifications that a new Core is available).

Textbox 2. Sleep Healthy Using the Internet intervention content by Core.

Core 1: Overview

Insomnia defined, types, prevalence, risk factors, and impact (ie, daytime fatigue, psychological well-being, physical health, and economic cost); setting treatment goals; and treatment overview, appropriateness, and effectiveness

Core 2: Sleep Behavior 1

Explanation of poor sleep habits; situational or chronic sleep difficulties; cycle of chronic insomnia; introduction of sleep restriction; explanation of sleep efficiency; and instruction on adjustments of sleep window based on sleep efficiency

Core 3: Sleep Behavior 2

Introduction of stimulus control (ie, going to bed when sleepy, leaving bed if unable to sleep, regular sleep schedule, using bed for sleep only, and no napping)

Core 4: Sleep Thoughts

Relationship between thinking patterns and emotions; contributions of thought patterns to sleeplessness; cognitive restructuring; keeping realistic expectations; revising misconceptions about insomnia; eliminating catastrophizing; reducing sleep emphasis; developing tolerance for sleep loss effects; and dealing with setbacks

Core 5: Sleep Education

Sleep hygiene guidelines; avoiding stimulants; and effects of diet, environment, and exercise

Core 6: Problem Prevention

Relapse prevention techniques; considering therapeutic gains; review of sleep behavior techniques; sleep medication information; and maintaining program techniques

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Measures

Overview

Study measures are summarized in Table 2. Web-based questionnaires will be completed through a Health Insurance

Portability and Accountability Act–compliant web-based survey manager (Qualtrics Highly Sensitive Data). All items will include validation to notify participants if they skip an item to reduce accidentally missing data; however, responses will not be required, as participants may skip any question they would like.

Table 2. Measures.

Variable and measure	Outcome measured	Time	
		Pre	Post
Sample characteristics			
Sociodemographics	Age, gender, race or ethnicity, household income, health literacy, and relationship to care recipient	✓	
Predictors: caregiving-related user characteristics			
Caregiving strain	Pearlin Stress Scale–caregiving overload subscale	✓	✓
Caregiving self-efficacy	Pearlin Stress Scale–caregiving competence subscale	✓	
Caregiving guilt	Caregiver Guilt Questionnaire–guilt about doing wrong by the CR[a], not rising to the occasion as a caregiver, and self-care subscales	✓	
Predictors: caregiving-related environmental characteristics			
Proximity to CR[a]	Whether bedpartner, live together but not bedpartner, or other situations	✓	
CR functional status	Modified Barthel Activities of Daily Living Index	✓	
CR cognitive status	Pearlin Stress Scale–cognitive status subscale	✓	
CR problem behavior	Pearlin Stress Scale–problematic behavior subscale (includes nighttime problems)	✓	
Caregiving tasks	Involvement in supporting activities of daily living, instrumental activities of daily living, and caregiver support activities	✓	
Changes in caregiving	Single item question (with follow-up open-ended response) to assess if caregiving situation has significantly changed during study		✓
Aim 1 outcomes: SHUTi[b] engagement			
Core completion	Nonuser (no Cores completed); incompleter (1-3 Cores); completer (4-6 Cores)	Throughout SHUTi	
Open-ended feedback	Free-response survey items—separate surveys for nonusers and users		✓
SHUTi utility and barriers	Internet Intervention Utility, Evaluation, and Adherence Questionnaires—selected items		✓[c]
Aim 2 outcomes: SHUTi efficacy on known cognitive mechanisms			
Sleep beliefs	Dysfunctional Beliefs and Attitudes About Sleep	✓	✓[c]
Sleep control	Sleep Locus of Control Scale	✓	✓[c]
Exploratory: preliminary efficacy			
Insomnia severity	Insomnia severity index-2 item	✓	✓
Sleep diary metrics	10 days of sleep diaries in 14-day period	✓	✓[c]
Health-related quality of life	PROMIS[d]: 2-item Global Physical Health	✓	✓
General distress	Patient Health Questionnaire-4	✓	✓

[a]CR: care recipient.

[b]SHUTi: Sleep Healthy Using the Internet.

[c]Assessed among SHUTi users (ie, incompleters and completers) only.

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

Outcomes: Aim 1

The primary trial outcome will be the level of participants' engagement with SHUTi, operationalized by intervention Core completion. Participants will be categorized according to their Core completion: (1) nonusers, who complete no Cores; (2) incompleters, who complete 1 to 3 Cores; and (3) completers, who complete 4 to 6 Cores. Those completing ≥4 Cores are considered to have completed the program as they have completed content related to primary treatment change

mechanisms; also, approximately all (>90%) participants continue on to complete all 6 Cores based on multiple past SHUTi trials. Participants' Core completion will be automatically tracked by the SHUTi intervention platform.

Following the intervention period, we will also assess caregivers' barriers to the uptake and use of SHUTi (nonusers); their perceived satisfaction, utility, and efficacy of SHUTi (users—both incompleters and completers); and ways in which we may tailor the SHUTi program to better fit family caregivers' needs related to sleep. Depending on whether the participant is

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a nonuser or user, they will complete open-ended free-response items, 4 items from the Client Satisfaction Questionnaire [68], and selected items from the Internet Intervention Utility, Evaluation, and Adherence Questionnaires [40].

Outcomes: Aim 2

We will assess SHUTi users' change in key cognitive mechanisms of sleep beliefs (Dysfunctional Beliefs and Attitudes about Sleep [69]) and sleep locus of control (Sleep Locus of Control Scale [70]). These variables have been previously demonstrated to mediate SHUTi benefits on insomnia symptom severity [45].

Predictors: Caregiving Context

We will test the association of SHUTi engagement and change in cognitive mechanisms with caregiving-related user characteristics and environmental characteristics.

Caregiving-Related User Characteristics

We will assess 3 potentially modifiable, subjective aspects of caregiving: (1) caregiving strain (Pearlin Stress Scale [PSS]–caregiving overload subscale [71]), (2) caregiving self-efficacy (PSS–caregiving competence subscale [71]), and (3) caregiving guilt (Caregiver Guilt Questionnaire—guilt about doing wrong by the care recipient, not rising to the occasion as a caregiver, and self-care subscales [72]).

Caregiving-Related Environmental Characteristics

We will also assess 5 structural factors in the caregiving situation. In the event that the caregiver provides care to >1 care recipient, they will respond to the following about their main care recipient (ie, care recipient to whom they provide the most care), as has been done previously [1]: (1) proximity to the care recipient—whether bedpartner, living together but not bedpartner, or other living situation—(2) care recipient's functional status (Modified Barthel ADL Index [73]), (3) care recipient's cognitive status (PSS–cognitive status subscale [71]), (4) care recipient's problem behavior (PSS–problematic behavior subscale [71]), and (5) care provided—involvement in supporting ADL, instrumental ADL, and caregiver support activities.

Preliminary Efficacy Outcomes

As an exploratory analysis of SHUTi efficacy, we will also examine changes in caregivers' self-reported insomnia severity (ISI-2 item [74]), metrics from sleep diaries (eg, sleep onset latency, wake after sleep onset, and sleep quality; SHUTi users only), health-related quality of life (Patient-Reported Outcomes Measurement Information System Global Physical Health-2 item [75]), general distress (Patient Health Questionnaire-4 [76]), and caregiving strain (PSS–caregiving overload subscale [71]).

Sample Size and Power Analysis

A total of 100 caregivers will be enrolled in this trial. This sample size was identified based on a power analysis to detect moderate effects of the caregiving context variables on the primary outcome of engagement with SHUTi. We estimated the expected caregiver engagement with SHUTi based on our team's prior research. On the basis of engagement rates from a recently completed trial of an untailored internet depression management program among family caregivers [77] (nonusers=35%; incompleters=40%; completers=25%) and average completion rates across multiple SHUTi trials [61-63] (nonusers=10%; incompleters=25%; completers=65%), we estimate that the sample in the proposed trial will be categorized as follows: 22% (22/100) nonusers, 33% (33/100) incompleters, and 45% (45/100) completers. Assuming these engagement rates, the minimally detectable proportional odds for aim 1a analyses at power=80% with α=.05 would be a moderate effect size [78] (minimally detectable proportional odds=2.9) for a sample size of N=100 based on the rate of dichotomized predictor exposures (computed using the Whitehead formula [79] in R Hmisc [80]). An example of a detectable scenario (user status associated with caregiving strain) under these conditions is presented in Table 3. In this hypothetical situation, caregivers who did not complete any SHUTi Cores (nonusers) were more likely to report high caregiving strain relative to caregivers who completed any SHUTi Cores (users). As this primary analysis uses preassessment questionnaire data, and engagement is automatically assessed in the SHUTi intervention platform, the final sample size determination does not need to account for attrition.

Table 3. Example of a detectable scenario for aim 1a (odds ratio 3.4; N=100).

Engagement status	Caregiving strain		Sample (%)
	Above median	Below median	
Nonuser, n (%)	16 (72.7)	6 (27.3)	22
User, n (%)	34 (43.6)	44 (56.4)	78
Sample (%)	50	50	100

Data Analysis Plan

Aim 1a: Test the Association of SHUTi Engagement With Caregiver User and Environmental Characteristics

To test the effect of caregiver context on SHUTi engagement, ordered logistic regressions assuming proportional odds will be fit for each caregiving-related user and environmental characteristics on SHUTi Core completion, which is a 3-level ordinal-dependent variable (ie, nonusers vs incompleters vs completers). Where the proportional odds assumption is violated (P<.05), follow-up sensitivity analyses will be conducted: 2 logistic regressions will compare proportional odds between nonusers and users (incompleters and completers) and between noncompleters (nonusers and incompleters) and completers. For users, we will also examine the associations between user and environmental characteristics with SHUTi evaluations on

the Internet Intervention Utility, Evaluation, and Adherence Questionnaires.

Aim 1b: Describe Caregivers' Barriers to and Motivations for SHUTi Engagement

Users' open-ended survey responses from the postassessment will be qualitatively coded using 2 methods. First, an a priori codebook will be used to tag data according to whether it is (1) specific to SHUTi, (2) specific to CBT-I but not exclusively SHUTi, or (3) specific to digital health interventions but not exclusively SHUTi. This will facilitate the examination of the extent to which caregiver-specific tailoring recommendations are specific to SHUTi versus generalizable to other evidence-based psychosocial digital health interventions. Next, responses will be coded inductively using thematic text analysis [81] to identify themes related to caregivers' barriers to and motivations for SHUTi uptake and use as well as how caregiver-specific tailoring may affect each of those constructs. The coding team will iteratively determine a set of codes; identify, review, and name themes; and synthesize data into final actionable recommendations for tailoring SHUTi and other digital health interventions for caregivers.

Findings and resulting recommendations will be returned to caregivers who indicate that they are willing to be recontacted for synthesized member checking [82]. A concise report of the results will be sent to the caregivers. Then, the caregivers will review the report and comment on how the results compare and contrast with their experiences and needs, and their returned responses will be coded to ascertain the level of resonance with the researchers' results. The findings and recommendations will be revised according to the synthesized member checking results.

Aim 2: Test the Association of SHUTi Efficacy on Known Cognitive Mechanisms With Caregiving Context

Among SHUTi users, continuous regression modeling will test the association of each caregiving context predictor with cognitive mechanisms assessed at postassessment, controlling for preassessment [83]. Models will control for the level of SHUTi engagement, with significance set at α=.05.

Preliminary Efficacy

The preliminary efficacy of SHUTi for caregivers will be explored by computing within-group effect size on the change from preassessment to postassessment on insomnia symptoms (ie, self-reported severity), sleep outcomes (ie, sleep diary metrics), and related constructs of general distress and caregiving strain.

Results

Discussion

Principal Findings

This study will provide the data necessary to ensure the highest impact and efficiency from existing evidence-based digital health interventions to meet pressing psychosocial needs among caregivers. Specifically, this study will inform the next research steps for tailoring and testing SHUTi for optimal impact and reach among caregivers. More broadly, our results will address a key translational science research question for the caregiving field, namely, how existing evidence-based digital health interventions can be most effectively translated to meet psychosocial needs among caregivers

This is the first study to address this broad translational question by systematically studying what tailoring may be necessary to increase the impact of an existing evidence-based digital health intervention program among higher-intensity caregivers. Much of the available psychosocial care for caregivers is delivered face to face, a modality that has significant practical and financial barriers limiting accessibility for caregivers [31,32]. The findings will help address how to serve caregivers more quickly and effectively by addressing prevalent and high-burden psychosocial concerns with existing evidence-based digital health interventions. As the effects of SHUTi have been robustly established across multiple clinical trials, the present trial among family caregivers will be able to isolate the effects of caregiving context on the use and impact of SHUTi for this specific population.

Relatedly, this trial takes a fundamentally different approach to caregiving intervention development by directly studying the ways in which key intervention targets should differ—or not—according to the caregiving context. Caregiver interventions have primarily been developed for specific caregivers defined by the care recipient's disease [22,26,29]. This is appropriate for certain psychoeducational or caregiver training interventions. However, for interventions targeting specific problems such as insomnia, which is caused and exacerbated by multiple behavioral and psychological factors, it is not clear whether needs differ across caregiving contexts to justify increased specificity in the intervention. This trial will specifically assess how the caregiving context may relate to intervention engagement and efficacy among higher-intensity caregivers who are known to be at the highest risk for poor outcomes but have the most difficulty accessing interventions [1,11]. By examining what tailoring may be necessary for which caregivers, we can better balance intervention efficacy against reach by ensuring that interventions are applicable to the broadest possible population of family caregivers.

We expect that findings from this mixed methods proposal will direct the next research steps toward 1 of 2 primary paths. If the findings suggest that caregiving-related user and environmental characteristics are not related to SHUTi engagement or efficacy, with no significant intervention tailoring requirements identified by caregivers, then a trial designed to understand the efficacy of and dissemination strategies for the existing SHUTi program (without tailoring) among caregivers will be warranted. On the other hand, if findings suggest meaningful differences in SHUTi engagement or efficacy by caregiving context or if key themes arise regarding intervention tailoring that may better engage and support caregivers, then tailoring and testing SHUTi for caregivers will be warranted. Potential changes may include modifying content to be more caregiver salient, addressing specific caregiving-related barriers to sleep recommendations, or wrapping the intervention in an implementation intervention to promote engagement.

Findings from the proposed work will not only be necessary to direct the next research on SHUTi specifically but will also deliver key insights on tailoring other evidence-based digital health interventions for caregivers. By doing so, findings will advance the science toward our long-term goal of improving the quality and impact of digital health interventions for caregivers while reducing intervention development inefficiency—a goal identified as a high priority for current caregiving research. As such, findings will be translatable across intervention programs and hold significant promise for reducing inefficiencies in developing digital health interventions for caregivers while also increasing their impact and reach for this underserved population.

Acknowledgments

Authors' Contributions

KMS conceived the study. KMS, LMR, DB, MM, FC, and HD designed the study and obtained grant funding. JVG and JK will help with study implementation. WY will provide statistical expertise in clinical trial design and conduct primary statistical analyses. All authors contributed to the refinement of the study protocol and have approved the final manuscript.

Conflicts of Interest

Over the past 3 years, DJB has served as a paid consultant to the National Cancer Institute, Pear Therapeutics, Sleep Number, Idorsia, and Weight Watchers International. DJB is an author of the Pittsburgh Sleep Quality Index, Pittsburgh Sleep Quality Index Addendum for posttraumatic stress disorder, Brief Pittsburgh Sleep Quality Index, Daytime Insomnia Symptoms Scale, Pittsburgh Sleep Diary, Insomnia Symptom Questionnaire, and RU_SATED (copyrights held by the University of Pittsburgh). These instruments have been licensed to commercial entities for fees. He is also a coauthor of the Consensus Sleep Diary (copyright held by Ryerson University), which is licensed to commercial entities for a fee. LMR reports relationships with BeHealth Solutions (equity ownership and member of the board of directors) and Pear Therapeutics (consultant), which are 2 companies that develop and disseminate digital therapeutics, including licensing the therapeutic developed, based, in part, on early versions of the software used in the research reported in this paper. These companies had no role in the preparation of this manuscript. LMR is also a consultant to Mahana Therapeutics, a separate digital therapeutic company not affiliated with this research. The terms of these arrangements have been reviewed and approved by the University of Virginia in accordance with its policies.

Multimedia Appendix 1
Peer-review report by the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH, USA).
[PDF File (Adobe PDF File), 115 KB - resprot_v11i1e34792_app1.pdf]

Multimedia Appendix 2
Response to National Institute of Health reviewer feedback submitted at just-in-time phase.
[PDF File (Adobe PDF File), 141 KB - resprot_v11i1e34792_app2.pdf]

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Abbreviations

ADL: activities of daily living
CBT-I: cognitive behavioral therapy for insomnia
IRB: institutional review board
ISI: insomnia severity index
NIH: National Institutes of Health
PSS: Pearlin Stress Scale
SHUTi: Sleep Healthy Using the Internet
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
UVA: University of Virginia

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Corrigenda and Addenda

Correction: Effect of Door-to-Door Screening and Awareness Generation Activities in the Catchment Areas of Vision Centers on Service Use: Protocol for a Randomized Experimental Study

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Related Article:

Correction of: https://www.researchprotocols.org/2021/11/e31951/

In "Effect of Door-to-Door Screening and Awareness Generation Activities in the Catchment Areas of Vision Centers on Service Use: Protocol for a Randomized Experimental Study" (JMIR Res Protoc 2021;10(11):e31951) one error was noted.

The following text was originally published in the Acknowledgments section of the paper. This text has now been moved instead to the Authors' Contributions section:

> *The Operational Research Capacity Building Group consists of the following authors, who contributed equally to the paper: Gudlavalleti VS Murthy, Rajan Shukla, Samiksha Singh, Shailaja Tetali, Suresh K Rathi, Hemant Mahajan, Melissa G Lewis, Hira Pant, Tripura Batchu, Anirudh G Gaurang, Suzanne Gilbert, Ken Bassett, Priya A Reddy, Parami*

> *Dhakhwa, Ram P Kandel, Kuldeep Singh, and Prasanna Sharma.*

Accordingly, the affiliation for the group author Operational Research Capacity Building Group has been changed from:

> *See Acknowledgments*

to:

> *See Authors' Contributions*

The corrections will appear in the online version of the paper on the JMIR Publications website on January 18, 2022, with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Using Biological Feedback to Promote Health Behavior Change in Adults: Protocol for a Scoping Review

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Abstract

Background: Many health conditions can be prevented, managed, or improved through behavioral interventions. As a component of health behavior change interventions, biological feedback is of particular interest given recent advances in wearable biosensing technology, digital health apps, and personalized health and wellness. Nevertheless, there is a paucity of literature to guide the design and implementation of interventions that incorporate biological feedback to motivate health behavior change.

Objective: The goal of this scoping review is to deeply explore the use of biological feedback as a component of health behavior change interventions that target adults. The objectives of the review include (1) mapping the domains of research that incorporate biological feedback and (2) describing the operational characteristics of using biological feedback in the context of health behavior change.

Methods: A comprehensive list of search terms was developed to capture studies from a wide range of domains. The studies to be included are randomized controlled trials published as primary research articles, theses, or dissertations targeting adults 18 years and older, who use biological feedback to change a health-related behavior. The following electronic databases were searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, EBSCOhost, PsycINFO, and ProQuest Dissertations & Theses Global. The screening and data extraction process will be guided by the Joanna Briggs Institute Manual for Evidence Synthesis and conducted by trained reviewers.

Results: Database searches were completed in June 2021. A total of 50,459 unique records were returned after the removal of 48,634 duplicate records. The scoping review is planned for completion in 2022.

Conclusions: To our knowledge, this will be the first scoping review to map the literature that uses biological feedback as a component of health behavior change interventions targeting adults. The findings will be used to develop a framework to guide the design and implementation of future health behavior change interventions that incorporate biological feedback.

Trial Registration: OSF Registries OSF.IO/YP5WA; https://osf.io/yp5wa

International Registered Report Identifier (IRRID): DERR1-10.2196/32579

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Introduction

Historically, infectious diseases were the leading causes of death worldwide [1]. Medical advances were made to target infectious agents and successfully eradicate disease. Aside from COVID-19, health conditions including cardiovascular disease, cancer, and respiratory disease, all of which are affected by modifiable personal health behaviors, are the leading causes of death in developed countries [1,2]. Substance use, physical inactivity, and poor diet are examples of modifiable health behaviors that are causally associated with poor health outcomes [3,4]. Many health conditions can be prevented, managed, or even treated through interventions targeting these and other health-related behaviors [5,6]. However, the development of public health interventions aimed to improve health outcomes is complex, particularly in the context of advancing technology and science that serve to complement standard medical care [7,8]. For decades, health behavior change research has relied on behavioral theories, most commonly the transtheoretical model of change, theory of planned behavior, and social cognitive theory, to guide the development of effective health promotion interventions [9,10]. Although transformational, work in this field has mostly led to the development of comprehensive one-size-fits-all interventions to which not everyone responds favorably [11]. More recently, innovations in wearable biosensing technology as well as mobile and digital health have laid the foundation for moving from one-size-fits-all interventions toward personalized approaches to health and wellness [12-14]. Personalized interventions are tailored to an individual's traits (eg, via genotyping) or state (eg, via metabotyping) with the goal of improving personal health–related outcomes. Despite the promise of such interventions, their design and implementation are complex, and they are yet to be optimized [15]. Research examining best practices for using and sharing biological data to optimize personal health–related outcomes, particularly in the context of motivating health behavior change (ie, biological feedback), represents a fundamental step toward developing effective personalized health and wellness interventions for health promotion.

Using a person's biological data to choose an intervention that could have the greatest likelihood of success is not new. In fact, it is a relatively common practice in some fields of medicine, including genetic counseling, medical decision-making, and cancer treatment. However, we herein operationally define biological feedback as providing individuals with their biological data through direct communication (via an unblinded body-worn assessment device such as a heart rate monitor or a continuous glucose monitor) or indirect communication (via health coaches, patient educators, or messaging systems) to motivate health behavior change explicitly or implicitly for improving health-related outcomes. One type of biological feedback used in health behavior change interventions is biofeedback. Michie and colleagues define "biofeedback" as a behavior change technique (BCT) that "informs the person about their physiological or biochemical state using an external monitoring device to improve the adoption of health behaviors" [16]. An example of biofeedback as a BCT is the use of a heart rate monitor to achieve the prescribed exercise intensity as part of a physical activity intervention. It is important to note that biological feedback, as defined herein, and biofeedback as a BCT vary conceptually from the traditional mind-body therapy referred to as biofeedback. As a mind-body therapy, biofeedback is a technique that involves the use of electrical sensors to provide information about the body (eg, muscle contractions) to help people learn how to control bodily functions (eg, urinary incontinence) [17]. This form of biofeedback is most often used to treat or manage a range of clinical conditions often involving the autonomic nervous system, and it is not the focus here [18]. Instead, the goal of the planned scoping review is to deeply explore the use of biological feedback as a technique to motivate health behavior change. The findings will be used to guide the development of future health behavior change interventions that incorporate biological feedback.

The potential value of this work is exemplified by the highly novel but limitedly effective Food4Me trial. Food4Me was a 6-month randomized controlled trial (RCT) conducted across 7 European countries that emulated a real-life web-based personalized nutrition service where participants received 1 of 4 levels of personalized dietary advice (generalized, L0; based on dietary intake, L1; based on dietary intake + phenotype, L2; and based on dietary intake + phenotype + gene, L3) [19]. Additionally, those in the personalized feedback arms of the Food4Me trial were further randomized to receive low-intensity nutritional feedback (delivered at baseline, month 3, and month 6) or high-intensity feedback (delivered at baseline and months 1, 2, 3, and 6). The primary aim of the Food4Me trial was to determine if personalization of dietary advice helped people improve their diet quality (healthy eating index scores) in comparison with nonpersonalized conventional healthy eating guidelines [19]. A secondary aim was to compare high-intensity and low-intensity feedback to determine if they resulted in improved outcomes. Results showed no evidence that the addition of biological feedback on phenotypic and phenotypic plus genotypic information enhanced the effectiveness of the personalized nutrition advice [20]. Findings specific to feedback intensity showed that improvements in diet quality were greater in the high-intensity vs low-intensity feedback group at 3 months or when nutritional feedback was provided monthly (vs quarterly) [21]. Despite these findings, the Food4Me trial was among the first to show the positive outcomes of personalized dietary advice compared to conventional dietary advice. Since the completion of the Food4Me trial, there has been a substantial increase in related research initiatives worldwide, including the National Institutes for Health's precision medicine and precision nutrition initiatives in the Unites States. Given the substantial financial investment into precision health that is being made in the United States and elsewhere, it is imperative that research aimed at optimizing the health-related outcomes of precision health interventions be conducted.

As a first step to harnessing the potential of biological feedback as a health behavior change intervention, we are conducting a scoping review to explore the historical and current use of biological feedback in health behavior change interventions that target adults. This type of review is necessary because to our knowledge, the only known review on this topic was published

in 2002 [22]. It was an empirical review of 8 published RCTs that used biomarkers to educate individuals about their health status and disease risk to promote health behavior change. Findings were generally supportive and suggested that biological information related to harm exposure, disease risk, or impaired physical functioning increases the motivation to change behavior, particularly when there is evidence of physical damage or significant personal risk related to the behavior. However, significant effects on behavior change depended on the intensity of the concomitant treatment, similar to the Food4Me trial, and were only observed when a single biomarker was assessed on multiple occasions or when multiple biomarkers were assessed on a single occasion. Although the previous review provided evidence regarding the efficacy of using biological feedback to motivate health behavior change, a more comprehensive review is needed to learn how variable the use of biological feedback is as a first step toward determining the best method to implement future interventions. As such, the objectives of this scoping review are to (1) map the domains of research that incorporate biological feedback as a health behavior change intervention and (2) describe the operational characteristics for implementing biological feedback as a health behavior change intervention. Findings will be used to develop a framework to guide future health behavior change interventions that incorporate biological feedback. Further work will be done to examine the efficacy of using biological feedback to motivate health behavior change and improve health-related outcomes. The following questions will be answered as part of the scoping review:

1. Which public health domains are using biological feedback as a component of health behavior change interventions targeting adults (eg, diabetes, substance abuse)?
2. What are the targeted health behaviors (eg, diet, exercise, smoking) and outcomes (eg, weight loss, glucose stability) applicable to using biological feedback as a component of health behavior change interventions?
3. Which biological measures are being used for providing feedback (eg, body weight, carbon monoxide levels), and how are biological measurements obtained (eg, self-measurement, clinical)?
4. How is the feedback communicated (ie, on which platform and in which format)?
5. Which behavior change theories are cited, if any, as the foundation for using biological feedback to promote health behavior change?

Methods

The proposed scoping review (OSF Registries OSF.IO/YP5WA; http://doi.org/10.17605/OSF.IO/YP5WA) will be guided by the Joanna Briggs Institute Manual for Evidence Synthesis [23]. The review process is being managed using DistillerSR (Evidence Partners), a software package used for systematic reviews and literature reviews.

Types of Participants

Eligible studies will be those that target adults (18 years or older). Studies will be included regardless of the disease conditions of the participants. Studies targeting health behavior

change only in infants, children, and adolescents will be excluded.

Concept

This scoping review will consider RCTs that include biological feedback as a component of health behavior change interventions. RCTs meeting the following criteria will be selected: (1) Biological data reflecting a study participant's physiological state or traits are collected. (2) The study participants are provided with their biological data through direct or indirect feedback. (3) The intent of providing feedback is to motivate health behavior change explicitly or implicitly. The core concept of the scoping review is to describe the historical and current landscape and methodology for using biological feedback in health behavior change interventions. We aim to include any measurable biological states and traits for which feedback can be provided.

Context

All included studies must aim to change a health behavior. Here, health behavior is defined as "...behavior patterns, actions, and habits that relate to health maintenance, to health restoration, and to health improvement" [24]. The proposed scoping review will include all behaviors that are modifiable and can improve (or decline) health. Examples of health behaviors include diet, exercise, smoking cessation, medication adherence, and use of medical services [25]. In the context of the proposed scoping review, health behavior change must be the intended purpose for providing biological feedback (vs diagnostics). Studies using traditional forms of biofeedback as a mind-body therapy will be excluded, as this therapeutic technique most typically aims to directly modulate the disease or health condition as opposed to motivating health behavior change, though there may be some exceptions. Studies will be included regardless of the setting (ie, acute care, primary care, community).

Types of Evidence Sources

Evidence sources will include published primary research articles, theses, and dissertations in any language. There will be no limits set on the year of publication unless deemed evident by a sudden increase in eligible literature by year. If no trend is observed, the time frame will remain open.

The search will be limited to RCTs. Though cohort studies, case-control studies, cross-sectional studies, case reports, conference abstracts, and papers could incorporate biological feedback, these studies will be excluded for reasons of feasibility. Evidence syntheses including scoping reviews, systematic reviews, and meta-analyses will also be excluded. Websites, blogs, and published letters will be excluded as well as incomplete works such as clinical trial protocols and other gray literature such as government reports and policy or issue papers. Retracted articles will also be excluded.

Search Strategy

With the aid of a research librarian, terminology was identified to reflect 3 key components of the review, namely the biological measure, feedback modality, and intervention context. A search strategy was devised using controlled vocabulary and text words in MEDLINE and then adapted to the other databases. The

electronic databases that were searched included Ovid MEDLINE and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions, Embase, Cochrane Central Register of Controlled Trials, EBSCOhost, PsycINFO, and ProQuest Dissertations & Theses Global. The Ovid MEDLINE database search strategy is provided in Multimedia Appendix 1. After drafting an initial Ovid MEDLINE search strategy, the identified records from the databases were searched to examine if self-identified records that were known to meet the eligibility criteria were captured using this search strategy. If they were not, we modified the search to include the newly identified terms from known eligible records. Additional search methods included examining the reference lists of relevant scoping and systematic reviews and meta-analyses to find any additional eligible primary research articles.

Source of Evidence Selection

Prior to initiating the screening process, reviewers were trained via pilot tests using the screening form(s). Modifications to the screening questions were made during this time to ensure clarity for all reviewers.

The review of records is being conducted using 2 levels of screening. In the first level of screening, the trained reviewers independently screen the titles and abstracts for initial eligibility. Records that do not describe primary findings from RCTs targeting human adults will be excluded at this level. Quality control measures that include an additional reviewer and the DistillerSR artificial intelligence feature are being used to review excluded records for erroneous exclusion. Records confirmed to have been erroneously excluded will be included and subjected to the next level of review. In the second level of screening, trained reviewers will (1) confirm inclusion based on the first level of screening and (2) review abstracts for information regarding the use of biological feedback to motivate health behavior change. The decision to conduct this level of review via abstract screening only was informed by a pilot test where the accuracy of excluding articles via abstract screening vs full text screening was examined. A total of 34 of 100 records that passed the first level of screening were reviewed by both methods. Results indicated that 22 of the 23 articles (96%) were accurately excluded by abstract screening only. Therefore, we deemed this method acceptable. An exception to this approach was made for studies that implemented "self-monitoring" or "self-management" strategies or when feedback on health risk was provided to the study participants. For these articles, the full text was screened to determine whether a biological measure was used. Second-level screening will be conducted using double data entry. Data entry conflicts will be reviewed and resolved by an independent reviewer. Records passing second-level screening will be subjected to data extraction.

Data Extraction

Data extraction forms will be designed to collect data relevant to the aims of the scoping review. Key information to be extracted will aim to describe the implementation of biological feedback as a component of a health behavior change intervention targeting adults. This will include, but may not be limited to, the following:

1. Author(s)
2. Title
3. Year
4. Biological measure (eg, blood pressure, carbon monoxide, genetics)
5. Targeted behavior (eg, alcohol use cessation, diet, physical activity)
6. Targeted health-related outcome or intent of intervention (eg, glycemic control, weight management, mental health improvement)
7. Domain (eg, cancer, diabetes, substance abuse)
8. Method of obtaining biological measures (eg, self-measurement, clinic)
9. Feedback platform (eg, in person, monitoring device, telephone call)
10. Format of feedback (eg, number, graph, image)
11. Behavior change theory (eg, health belief model, theory of planned behavior)

A draft of the data extraction form is presented in Multimedia Appendix 2. If useful data that we did not plan to extract are available in the records, the data extraction form will be revised, and these additional data will be extracted from previously reviewed records. Additionally, ineligible articles may be identified during the data extraction process for reasons described in the first and second levels of screening. In such cases, the reason for exclusion will be noted and data from those records will not be included in the analysis of the evidence.

Analysis of the Evidence

As the aim of this scoping review is to map the domains of research that incorporate biological feedback, study results presented in the records will not be analyzed. Instead, summary data related to the aim will be synthesized descriptively.

Presentation of the Results

The PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) 2020 flow diagram will be used to present the selection process [26]. This includes the number of records identified, number of records after duplicates are removed, number of records after eligibility screening, and final included number of records. Findings of the included records will be presented through evidence mapping and descriptive summaries.

Results

The database search was completed in June 2021. The search yielded 99,093 records. All results were originally exported into EndNote X9 (Clarivate Analytics) and deduplicated by the research librarian. There were 48,510 duplicate records identified in EndNote. The resulting 50,583 records were imported into DistillerSR for review. An additional 124 duplicate records were identified in DistillerSR and removed. As a result, the search produced 50,459 unique records. The scoping review is planned for completion in 2022.

Discussion

A sizable but uncharacterized body of literature has shown the potential for the use of biological feedback as a component of

health behavior change interventions. The proposed scoping review aims to explore the breadth of domains using biological feedback as a health BCT in interventions targeting adults. More than 200 search terms characterizing a wide variety of biological measures and modes of delivering feedback in various health-promoting contexts were derived to fulfill this goal. To our knowledge, this will be the first scoping review to map the literature in this area with the intent of informing future health behavior change interventions that incorporate biological feedback.

The proposed review has some limitations. One of them is that there is no consistent terminology for the use of biological feedback in health behavior change interventions. For instance, "blood glucose self-monitoring" is a type of biological feedback but the term "biological feedback" is not explicitly stated in the bibliographic and abstracting information. Due to inconsistencies in terminology, a compilation of over 200 terms reflecting the collection of biological data, the provision of feedback either directly via body-worn sensors or indirectly by an external agent or software, and the contexts in which behavioral interventions can be delivered were used in the search strategy to capture a majority of the biological feedback studies. It is possible that the resulting list of search terms did not return all relevant records. In cases where additional search terms are identified through reviewing the returned records or relevant scoping or systematic reviews, these terms will be added to the search strategy to identify additional records. Another limitation is that for feasibility reasons, this scoping review will include only RCTs. However, with the breadth of our search strategy, we will still capture a considerable number of studies spanning many domains of research. Therefore, this limitation should not

negatively impact our ability to describe the use of biological feedback as a component of behavior change interventions. Moreover, we will not be including intervention studies targeting infants, children, or adolescents. As such, our findings will be generalizable to only adult populations. Lastly, due to feasibility issues, in our primary screening, only the titles and abstracts of the returned records will be reviewed (vs full text screening). Consequently, studies may be erroneously excluded. However, the decision to screen only the titles and abstracts was informed by a pilot test that confirmed an accuracy level exceeding 95% for this approach. Therefore, it is unlikely that this approach will negatively affect the objectives of our review. Despite these limitations, this scoping review represents a fundamental first step toward developing effective precision health interventions.

The methods outlined above were developed specifically to capture a wide range of health-promoting interventions that incorporate the use of biological feedback to motivate behavior change. The results will summarize the characteristics of this research, including the domains, targeted health behaviors and health-related outcomes, biological measures and forms of measurement, platforms and content on which feedback was provided, and behavior change theories used in interventions incorporating biological feedback. Future research will use the findings from this scoping review to generate ideas for primary research aimed to optimize the implementation of biological feedback to produce meaningful health behavior changes in public health interventions. Additionally, results from this scoping review and subsequently planned systematic reviews will be used to develop a framework to guide the use of biological feedback in future health behavior change interventions.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 25 KB - resprot_v11i1e32579_app1.docx]

Multimedia Appendix 2
Preliminary data extraction form.
[DOCX File , 14 KB - resprot_v11i1e32579_app2.docx]

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Abbreviations

BCT: behavior change technique
RCT: randomized controlled trial