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Evaluating the Efficacy of a Mobile App (Drinks:Ration) and Personalized Text and Push Messaging to Reduce Alcohol Consumption in a Veteran Population: Protocol for a Randomized Controlled Trial

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Abstract

Background: Alcohol misuse is higher in the UK Armed Forces than in the general population. Previous research has shown that interventions delivered via smartphones are efficacious in promoting self-monitoring of alcohol use, have utility in reducing alcohol consumption, and have a broad reach.

Objective: This single-blinded randomized controlled trial (RCT) aims to assess the efficacy of a 28-day brief alcohol intervention delivered via a smartphone app (*Drinks*:Ration) in reducing weekly self-reported alcohol consumption between baseline and 3-month follow-up among veterans who drink at a hazardous or harmful level and receive or have received support for mental health symptoms in a clinical setting.

Methods: In this two-arm, single-blinded RCT, a smartphone app that includes interactive features designed to enhance participants' motivation and personalized messaging is compared with a smartphone app that provides only government guidance on alcohol consumption. The trial will be conducted in a veteran population that has sought help through Combat Stress, a UK veteran's mental health charity. Recruitment, consent, and data collection will be carried out automatically through the *Drinks*:Ration platform. The primary outcome is the change in self-reported weekly alcohol consumption between baseline (day 0) and 3-month follow-up (day 84) as measured using the Time-Line Follow back for Alcohol Consumption. Secondary outcome measures include (1) change in the baseline to 3-month follow-up (day 84) Alcohol Use Disorder Identification Test score and (2) change in the baseline to 3-month follow-up (day 84) World Health Organization Quality of Life-BREF score to assess the quality of adjusted life years. Process evaluation measures include (1) app use and (2) usability ratings as measured by the mHealth App Usability Questionnaire. The primary and secondary outcomes will also be reassessed at the 6-month follow-up (day 168) to assess the longer-term benefits of the intervention, which will be reported as a secondary outcome.

Results: The study will begin recruitment in October 2020 and is expected to require 12 months to complete. The study results will be published in 2022.

Conclusions: This study assesses whether a smartphone app is efficacious in reducing self-reported alcohol consumption in a veteran population that has sought help through Combat Stress using personalized messaging and interactive features. This innovative approach, if successful, may provide a means to deliver a low-cost health promotion program that has the potential to reach large groups, in particular those who are geographically dispersed, such as military personnel.

Trial Registration: ClinicalTrials.gov NCT04494594; https://clinicaltrials.gov/ct2/show/NCT04494594

International Registered Report Identifier (IRRID): PRR1-10.2196/19720

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KEYWORDS

alcohol misuse; smartphone; intervention; SMS text messaging; push notifications

Introduction

Alcohol Misuse Burden

Alcohol misuse is common in the UK Armed Forces (AF), with the prevalence higher in the AF than in the general population [1-4]. Research indicates that this trend continues after personnel leave service (*veteran* or *ex-serving* is used interchangeably in the UK) [1,5]. It has been estimated that more than 50% of those who have left the AF meet the criteria for hazardous alcohol use, a score of 8 or above on the Alcohol Use Disorders Identification Test (AUDIT) [3,6].

Research has shown that individuals in the general population underestimate their drinking and do not perceive it as problematic, even at potentially harmful levels [7]. Young males are at particular risk of underestimating their drinking [7]. This pattern is similar among the UK AF, with less than half of UK AF hazardous drinkers recognizing that they have an alcohol problem [8]. There is also a culture of heavy alcohol use in the UK AF, which is encouraged by the social environment and carries on after personnel leave service [4,9,10]. Therefore, leaving service could provide an opportunity to initiate behavior change in settings with less peer pressure to conform to social norms and promote alcohol awareness.

Focusing on personnel who have left service, a similar pattern has emerged for those who are seeking support for mental health problems and consume alcohol to cope. A recent study of treatment-seeking UK service leavers identified that 43% of respondents reported misusing alcohol and that alcohol misuse was commonly comorbid with posttraumatic stress disorder (PTSD) and common mental health difficulties such as anxiety and depression [11]. Alcohol misuse can also have an impact on treatment adherence. Treatment-seeking veterans with alcohol misuse attended fewer mental health appointments and were more likely to have a negative perception of mental health treatment when alcohol misuse is comorbid with depression or PTSD [12]. It is, therefore, important to develop interventions that may target drinking to cope with motivations, which may subsequently enhance engagement with mental health services and improve mental health outcomes.

The impact of alcohol misuse by AF personnel on the wider society (eg, health care utilization, productivity, and welfare) is unknown; however, it is likely to be increased compared with the general population. Research has indicated that heavy drinking in England, which is frequently comorbid with mental health difficulties [13], is estimated to cost the National Health Service (NHS) of the UK £3.5 billion (US $4.4 billion) per year (3.6% of its annual budget) [14].

Brief Interventions

There is a range of effective intervention options for management and treatment of alcohol misuse categorized as brief interventions, specialist treatment, and less intensive treatments that span the two [15]. Personnel of the UK AF who have left service typically access the same health care system as the general public, and the same interventions are offered to both groups.

Brief interventions for alcohol misuse are a popular management and treatment option used in the UK general population, often provided to individuals scoring 15 or below on the AUDIT [16]. A common theme among these interventions is the goal of improving recognition, targeting the individual's motivations to reduce their alcohol consumption, and developing coping strategies to control and reduce intake [15-17]. This includes motivational interviewing, cognitive behavioral therapy, behavior self-control training, behavior change, and coping development, all of which are often tailored to the individual by a clinician [15].

Brief interventions aim to raise awareness of the risks associated with alcohol misuse and help individuals reduce their hazardous drinking. Often brief interventions are delivered to individuals who are not seeking help for alcohol misuse from a specialist alcohol service and are delivered in the general community setting (eg, general practitioners, hospital doctors, and nurses). There is a body of research that confirms the efficacy of brief interventions in reducing alcohol consumption and alcohol-related harm for those drinking at a hazardous level in the general population [18-20]. However, little is known about their efficacy in the AF context [19]. Given the shared culture in the military in which alcohol plays a meaningful role, it is important to evaluate the efficacy of brief interventions in this type of population.

Smartphone-Based Brief Interventions for Alcohol Misuse

The last two decades have seen a proliferation in the use of digital technologies to support brief intervention management

and treatment of alcohol misuse in the general public; however, little attention has been paid to the AF community [21-24]. In the late 1990s, interventions were commonly delivered via a computer using CD-ROM–based programs. However, with the advent of the World Wide Web, many new opportunities arose to harness increased reach, provide real-time monitoring, and offer personalized treatment [25-31]. This includes the use of SMS, which has been shown to be effective in encouraging people to change their behavior [32-34].

Over the last 5 years, the mode of intervention delivery has shifted from web- to smartphone-based [35]. Smartphone interventions for alcohol misuse, such as *Drink Less* [24] and *Drink Aware* [36], have several advantages over web-based interventions. These include having a low cost per use, allowing for rapid changes and iterative development, avoiding the stigma associated with receiving help in person, and are highly convenient because they can be used as and when the individual wants (discreetly or openly). However, these smartphone interventions are focused on the general population and do not target individual beliefs, prevailing social contexts, and perceptions of consumption experienced by the AF community [9,37]. Smartphone-based interventions allow users to revisit information about their drinking habits as often as they need to and, thus, have the potential to promote positive behavioral changes [18,38]. Furthermore, there are indications of the potential of smartphone-based interventions being cost effective if found to be efficacious [25,28,29].

Most existing alcohol apps targeted at the general public include self-monitoring (eg, *Drink Less* [24], *Drink Aware* [36], and One You Drinks Tracker [39]), whereby users are encouraged to regularly record and monitor (via visual graphics) their alcohol consumption within an app [24,40]. Self-monitoring (or self-recording) has been found to be associated with improved outcomes and an effective behavior change technique (BCT) for reducing alcohol use. A BCT is defined as a specific component of an intervention designed to change behavior and a putative active ingredient in an intervention [21]. A review of personalized digital interventions for reducing hazardous and harmful alcohol consumption found that providing behavior substitution, problem solving, and providing a credible source were associated with better outcomes, including reductions in alcohol consumption [41]. There are benefits to the use of digital technology for the UK AF community. However, to date, there is no published work that seeks to test a brief intervention alcohol reduction app that is personalized to individual users or targeted to support military veterans.

Study Aim

The aim of this randomized controlled trial (RCT) is to assess the efficacy of a 28-day brief alcohol intervention delivered via a smartphone app (*Drinks*:Ration) in reducing self-reported weekly alcohol consumption between baseline and 3-month follow-up (day 84) among veterans who drink at a hazardous or harmful level and receive or have received support for mental health symptoms in a clinical setting.

Methods

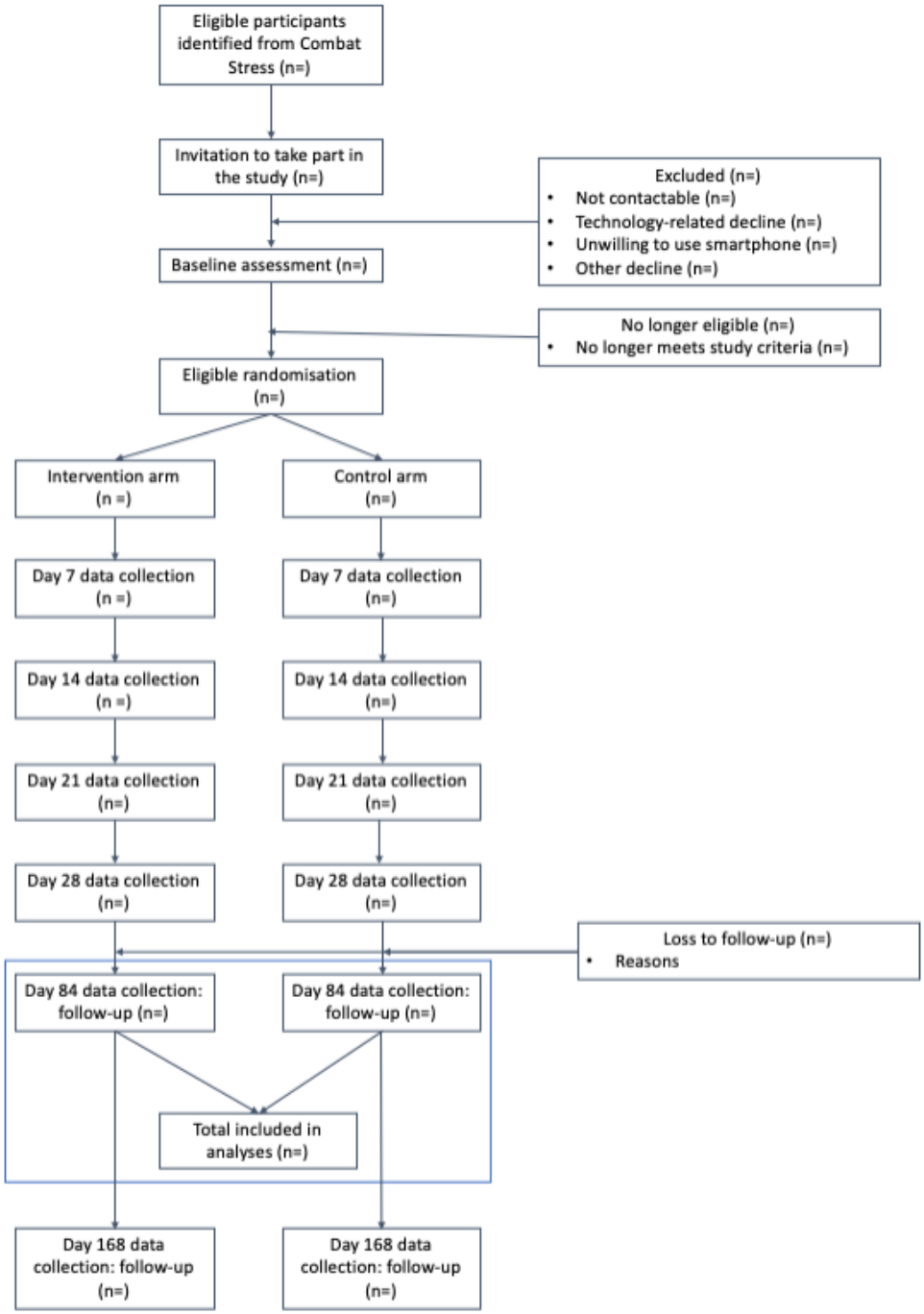
Ethical Approval

This study was approved by the local ethics committee of King's College London (registration number: HR-19/20-17438) and registered as a clinical trial (registration number: NCT04494594).

Study Design

This is a two-arm participant-blinded (single-blinded) RCT, which compares a smartphone app (control arm) that includes feedback on baseline self-reported alcohol consumption with a smartphone app (intervention arm) that includes individualized normative feedback, in addition to features designed to enhance participants' motivation, app interactive feedback, and self-efficacy in modifying their alcohol consumption. We hypothesize that the intervention arm app will be efficacious in reducing alcohol consumption compared with the control arm app. In this study, both the control and intervention arms will be delivered via one smartphone app known as *Drinks*:Ration. Participants in the control arm are given access only to the alcohol consumption feedback on the basis of publicly available health guidance [42] and reminder messaging to consult the feedback. Those in the intervention arm are given full access to the app, which includes all theoretically driven components and messaging (discussed further in the Intervention section). Both arms will be asked to use the app for 28 days. This study is designed such that the control arm structurally resembles the intervention arm but lacks the active ingredients (eg, drinks diary, interactive drinking feedback, and goal setting). This approach was selected to ensure (1) that both groups receive a digital intervention, (2) uniformity and provide relevance to real-world interventions, and (3) that participants are blinded from the study arm they are assigned to. The trial is conducted via the *Drinks*:Ration platform without any need for involvement of the research team, including the collection of informed consent and data collection. The study flow and data collection points are shown in Figure 1.

Figure 1. Study flow diagram. Data collected on day 7/14/21 are required to tailor and personalize the messaging of the Drinks:Ration app for the intervention arm. Primary and secondary outcomes are assessed at day 84, with the outcomes reassessed at day 168 to assess the longer-term benefits of the intervention.



Study Sample

Participants may have been, or are presently, receiving treatment through Combat Stress. Treatment offered via Combat Stress is for depression, anxiety, and PTSD. However, Combat Stress does not offer alcohol treatment services. The eligibility criteria are as follows:

Inclusion Criteria

Participants will be included in the study if they have downloaded the app onto an iOS or an Android device, are aged 18 years or older, live in the United Kingdom, consume 14 UK units (approximately 140 g) of alcohol or more per week as measured using Timeline Follow-back for alcohol consumption (TLFB) [43] at baseline (day 0), provide a mobile phone number, and are veterans of the UK AF. A minimum threshold of 14 UK units of alcohol per week is used in this study to reflect scientific research and UK national guidelines that indicate that regular drinking of more than this threshold risks damage to health [44,45]. It is important to note that in the United Kingdom, individuals are defined as veterans if they have completed a minimum of 1 day paid employment in the UK AF.

Exclusion Criteria

Participants will be excluded if they are listed as being *red* risk by Combat Stress, which is determined by the clinical team following an initial assessment and is based on a traffic light system to assess risk, where red indicates an immediate high risk to the individual and/or others. *Red* risk is applied independently of the research team and is used only where participation in the study could impact clinical treatment. The exclusion applies only during the contact list data extraction. Participants will be excluded if they do not have a mobile phone or have not given the Combat Stress consent for contact for research purposes.

A power calculation was performed based on previously reported data from Combat Stress [11,46]. This study requires a sample of 37 participants in each arm, with an 80% power to detect with a probability of 5% mean change in alcohol consumption of 4 UK units (approximately 40 g of alcohol per week, 10 g per unit) between control and intervention arms, at 3-month follow-up (day 84). Four units have been selected based on these 2 criteria: (1) reductions observed in similar studies [4,8,22,24,47] and (2) reductions observed in the feasibility trial of *Drinks*:Ration, which found a 7 UK-unit decrease at week 4. We aim to invite a minimum of 620 veterans to participate in the study to account for a 30% acceptance of invitation and 40% attrition rate.

Recruitment

This study will recruit participants through Combat Stress (established in 1919), a third-sector charitable organization that provides mental health services, including substance misuse to UK veterans. It is the largest military charity in the United Kingdom in terms of the number of individuals treated, providing both inpatient and outpatient secondary mental health services to veterans and specializing in PTSD. Since 2011, Combat Stress has been funded by the NHS in the United Kingdom to provide a national specialist PTSD clinical service for veterans [48]. Combat Stress facilitates access to eligible participants and jointly with King's College London oversees any risks that arise as a result of participation in the study. It is important to note that although this study uses a sample of veterans from Combat Stress, it is hoped that *Drinks*:Ration will be useful for the wider veteran community.

Potential participant contact details (postal address and/or email if available) will be extracted from the Combat Stress Patient Management System for those who meet the study eligibility criteria and who have provided consent to be contacted for research purposes. Only those who have had contact with Combat Stress over a 2-year period between January 1, 2018, and December 31, 2019, will be contacted. It is estimated that about 3000 patients with Combat Stress are eligible to be contacted by the research team.

Where contact details are available, eligible participants will be invited to take part via email in the first instance. The first contact will include an explanation of the study, link to the participant information sheet, and instructions on how to download *Drinks*:Ration using a unique quick response (QR) code. Once participants have downloaded the app, they will be invited to report alcohol consumption using TLFB for alcohol consumption [43] for the last 7 days and confirm the military serving status (to validate eligibility). Those meeting the study eligibility criteria will be invited to register an account and complete the baseline questionnaire (day 0).

Randomization and Blinding

Randomization occurs when a QR code is generated and a unique proxy identifier and participant gender are assigned. At this point, participants are automatically randomized to receive the control or intervention arm (see the Intervention section) and are blinded. Block randomization of size 2 will be used to ensure equal gender distribution across both conditions. The randomization procedure is carried out automatically by the *Drinks*:Ration platform with no human involvement, except to provide a proxy identifier and gender. The research team will be blinded to the randomization of the participant, except for DL, who led the development and will manage the *Drinks*:Ration app throughout the study.

Intervention

The *Drinks*:Ration app, formerly called *InDEx* [49-51], has been developed following the Medical Research Council Complex Intervention Guidelines and using co-design methodology. It has been developed by the King's Centre for Military Health Research (at King's College London) and the University of Liverpool, supported by experts in smartphone app development, epidemiology, addiction psychiatry, and military mental health. The app is designed to support veterans drinking at a hazardous or harmful level by providing bespoke advice and support over a 28-day period. The app is designed to enhance participants' motivation and self-efficacy in modifying their alcohol consumption by means of BCT in the content displayed (Multimedia Appendix 1) and the messaging sent to participants. The iterative development process, theoretical framework, and feasibility trial have already been reported [49-51]. Briefly, *Drinks*:Ration has been developed and tested with the following 5 core modules:

1. Account management: participants can modify personal information (eg, first name and mobile number) and app parameters (eg, automatic logout, clear local storage, data-sharing permission, and exiting the study).
2. Questionnaire and individualized normative feedback: it captures the participant's responses to a set of questions and aggregates responses to produce an individualized infographic that represent the participant's alcohol consumption compared with the general population, the AF Community, and other participants of *Drinks*:Ration.
3. Self-monitoring and feedback: it records alcohol consumption by participants and provides a range of visual illustrations (eg, charts, figures, and texts) to allow for monitoring of alcohol consumption. Moreover, the participants can select visual metrics relevant to their interest (eg, calories, cost, and exercise required).
4. Goals (setting and review): participants can set goal(s) based on the implementation intentions (if and then) [52] methodology; visual feedback provides feedback on progress toward achieving set goal(s).

5. Personalized messaging: participants are sent tailored messages via push notification or SMS text messaging that provides prompts to use the drinks diary, suggests alternative behaviors, and provides feedback on set goals.

The app is compatible with all modern iOS- and Android-supported devices, and no involvement of the research team is required for participant enrolment. Data is collected, managed, and processed using the Google Firebase server infrastructure in London, United Kingdom.

In this study, the intervention arm will receive the app with all functionalities, including push notifications and SMS text messaging. The control arm participants will have access to only the *questionnaire and feedback* module and will not receive any form of personalized messaging, except prompts to complete questionnaires and reminders to review alcohol consumption feedback (see the Message section for more information). Participants in both arms will complete additional questionnaires on their mood and general mental health when responding to the weekly questionnaires. These responses will be used to personalize the content of the app and push notifications and SMS text messaging delivered to the intervention arm only.

Participants in both arms will be asked to use the app for 28 days. After which, they can continue to use the app; however, they will not receive personalized messaging, and the data collected after this point will not be used in the analyses. However, participants will receive a reminder message on day 84 and day 168 to complete questionnaires.

Messaging: Push Notifications and SMS Text Messaging

In addition to the *Drinks*:Ration app, participants will receive personalized push notifications and SMS text messaging that provide prompts to use the drinks diary, complete questionnaires, suggest alternative behaviors, provide feedback on goals, and promote a healthy lifestyle. A bank of personalized messages (both for SMS text messages and push notifications) informed by 180 tailored messages developed previously (which are informed by the Health Action Process Approach framework and targeted toward specific BCTs) [49] will be used.

Drinks:Ration uses baseline and contiguous measurements (day 7/14/21) to inform the type of message a participant receives to provide an individual participant-centric approach. Baseline measurements are used to identify suitable messages, *and as a participant engages with Drinks*:Ration, continuous measurements, including questionnaires (baseline and weekly questionnaires) and the drinks diary, are used to reflect current behavior and attitude. The messages cover a wide range of topics to target beliefs and motivations, with the primary aim of increasing the participant's awareness of their drinking habits and behaviors. The messages are divided into 3 categories:

1. Tailored: personalized to drinking habits, baseline, and weekly questionnaires;
2. Tailored and triggered: tailored to baseline and contiguous measurements and a specific event occurring; and
3. Targeted (generic): sent on specific days to highlight inactivity, as a reminder to complete a questionnaire, or to alter participants to a new feature.

A participant can receive a maximum of 20 messages over the 28-day period, with a maximum of 2 messages in a single day. The system automatically decides when a message should be sent and the mode of delivery (push notification or SMS text messaging). A list of targeted (generic) messages to be sent to participants is defined in Table 1; except the messages listed in this table, participants in the control arm will receive no other messages. Participants in both arms will receive a generic message designed to promote retention of the *Drinks*:Ration app to allow for follow-up data collection. This will be sent monthly.

Table 1. A list of targeted (generic) messages and the day on which they are sent.

Day	Message content	Study arm
0	• Title: Welcome to *Drinks*:Ration • Message: Your signup is complete. Remember to log last week's alcohol consumption	Intervention
0	• Title: Welcome to *Drinks*:Ration • Message: Your signup is now complete	Control
2	• Title: Time to set a goal? • Message: Why not set a goal to reduce the amount you drink? You can start now by clicking on the *goals* tab in the app…	Intervention
7	• Title: Drinking Advice • Message: Remember to open *Drinks*:Ration for advice on how to make your alcohol consumption	Control
13	• Title: Remember the diary • Message: Completing the drinks diary each day allows you to see how well you are doing!	Intervention
14	• Title: Let us know… • Message: Remember to open the app to tell us how you're doing	Intervention and control
18	• Title: Remember to monitor • Message: Monitoring what you drink is proven to help you cut down—why not start fresh this week?	Intervention
21	• Title: Be aware! • Message: It is good to be aware of what you drink. Monitoring your alcohol consumption really can help your health!	Intervention and control
23	• Title: Think… • Message: Using Drinks:Ration may have changed some of the drinks you usually have. Try and think how you can keep it up!	Intervention
28	• Title: Let us know… • Message: Please let us know how you're getting on!	Intervention and control
56	• Title: Keep checking in… • Message: Please remember to open the Drinks:Ration app	Intervention and control
84	• Title: Let us know… • Message: Please let us know how you're getting on!	Intervention and control
112/140	• Title: Keep checking in… • Message: Please remember to open the Drinks:Ration app	Intervention and control
168	• Title: Let us know… • Message: Please let us know how you're getting on!	Intervention and control

Measures

A summary of the measures and data collection timepoints in this study are detailed in Table 2.

Baseline Measures

Upon successful registration, participants will complete a baseline questionnaire to assess physical and mental health, health status, resource utilization (eg, visits to hospital because of alcohol, and days in hospital because of alcohol), and sociodemographics (eg, age, gender, ethnicity, employment status, and occupation).

Table 2. Summary of measures and data collection timepoints.

Day or measure	0	7	14	21	28	84	168
Questionnaires (Multimedia Appendix 2)							
Informed consents	I[a]/C[b]	—[c]	—	—	—	—	—
Sociodemographic	I/C	—	—	—	—	—	—
Resource utilization	I/C	—	—	—	I/C	I/C	I/C
Depression (PHQ2[d]) [53]	I/C	I/C	I/C	I/C	I/C	I/C	I/C
Anxiety (GAD2[e]) [54]	I/C	I/C	I/C	I/C	I/C	I/C	I/C
International Trauma Questionnaire for PTSD[f] [55]	I/C	—	—	—	I/C	I/C	I/C
Readiness to Change Ruler [56]	I/C	—	—	—	I/C	I/C	I/C
Self-Efficacy Ruler [56]	I/C	—	—	—	I/C	I/C	I/C
Alcohol Use Disorder Identification Test [57]	I/C	—	—	—	I/C	I/C	I/C
World Health Organization Quality of Life-BREF [58]	I/C	—	—	—	I/C	I/C	I/C
7-day Timeline Follow-Back for alcohol consumption [43]	I/C	—	—	—	I/C	I/C	I/C
Usability evaluation							
Qualitative interviews[g]	—	—	—	—	I/C	—	—
mHealth App Usability Questionnaire [59]	—	—	—	—	I/C	—	—
Remote data collection							
Wearable sensors[h]	I/C	I/C	I/C	I/C	I/C	I/C	I/C
Smartphone sensors[h]	I/C	I/C	I/C	I/C	I/C	I/C	I/C

[a]I: Intervention arm.

[b]C: Control arm.

[c]—: no data is collected during this period.

[d]PHQ2: Patient Health Questionnaire 2-item.

[e]GAD2: Generalized Anxiety Questionnaire 2-item.

[f]PTSD: posttraumatic stress disorder.

[g]20 participants will be invited to participate in a qualitative interview.

[h]Additional participant consent required.

Outcome Measures

The primary outcome measure is the change between self-reported alcohol consumption as measured by the 7-day TLFB [43] over the previous 7 days between baseline (day 0) and 3-month follow-up (day 84). Participants will be asked to report how many drinks they consumed over the last 7 days as well as the type of drink they consumed on each day. Using the standard unit of measurements (Multimedia Appendix 3), weekly alcohol consumption will be determined by summing the number of units assigned to each drink. The TLFB has been extensively used to assess alcohol consumption and has demonstrated good test-retest reliability [43,60]. Secondary outcome measures will be (1) change in the baseline to follow-up AUDIT score and (2) change in the baseline to follow-up World Health Organization Quality of Life-BREF (WHOQOL-BREF) score to assess quality of adjusted life years. Process evaluation measures, following the model by Donabedian for evaluating quality of care [61], will be (1) app use (number of app engagement, screen views, and user retention) and (2) usability ratings as measured by the mHealth App Usability Questionnaire (MAUQ) [59]. A 3-month follow-up period was selected to assess the short-term benefits of the intervention on participants. The primary and secondary outcomes will also be reassessed at 6-month follow-up (day 168) to assess the longer term benefits of the intervention and will be reported as a secondary outcome.

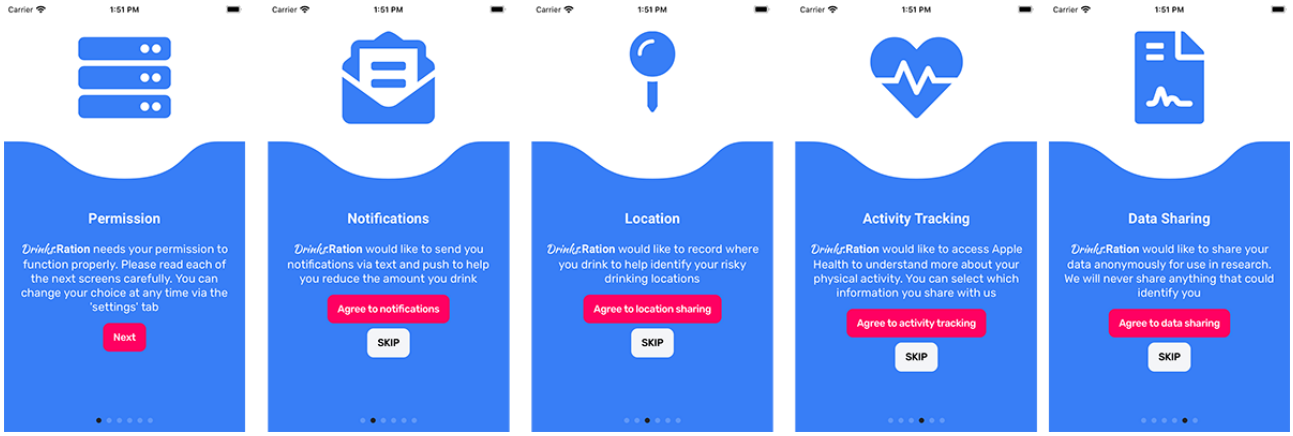
Study Debrief

At the end of the follow-up period, a random selection of 20 participants (10 from each study arm) will be invited to take part in a 60-min *debrief* session. The aim of this is to understand more about their use and experience of the *Drinks*:Ration app. During the session, participants will be asked to share their views on acceptability and usability and what can be done to improve their experiences. This will be done via telephone and transcript generated and used for analysis. Participants taking part in the debrief session will have the opportunity to view and discuss their own data.

Study Withdrawal and Consent

Informed consent will be sought from all participants via the *Drinks*:Ration app before the collection of any personal data, and they will be informed from the outset that they can withdraw from the study at any time. Individual optional consent (screenshots presented in Figure 2) will be sought for access to the GPS location, sending of push notifications, or SMS text messaging. In addition, to promote open science, consent will be sought from participants to share their data anonymously for research purposes. These data will be released upon completion of the study. Only the questionnaire response, remote measurement technology data, and alcohol consumption statistics will be shared. All data will be deidentified, and no personal data will be released. Participants can change optional consents at any time via the *settings* page of the app until analyses are performed at which point data will be extracted and analyzed.

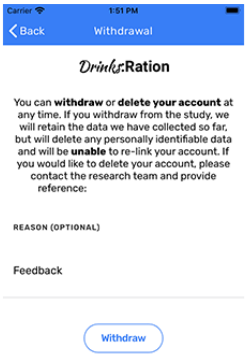
Figure 2. Consent flow screenshot examples presented to all participants of the study.



Participants can withdraw from the study at any time within the *Drinks*:Ration app (Figure 3). Participants can choose to withdraw from the study but allow the research team to use the data or delete their account by contacting the research team. We anticipate several reasons for withdrawal from the study, such as:

- Participant choosing to no longer take part in the study: participants will be informed via the *Drinks*:Ration app that participation is voluntary and that they can withdraw from the study at any point without providing a reason.
- Adverse event: participants may be withdrawn by the research team in the event of an adverse event, protocol violation, technical, administrative, or other reason(s).

Figure 3. Participant withdrawal screen with includes the ability to delete account or withdraw from the study.



In the event that participants choose to withdraw from the study, we will provide prompt for a reason as to why they are withdrawing; however, providing a reason will be optional. Participants will be asked to uninstall the *Drinks*:Ration app. All data, including those from withdrawn participants, except the anticipated rare request for their data to be deleted, will be included in the final analysis.

Adverse Events

It is not expected that participation in this study will lead to an increase in alcohol consumption. Nevertheless, in an adverse event, defined in this study as participants reporting (via the drinks diary or during contact with the research team) that they have consumed more than 25 UK units of alcohol within a 24-hour period, participants will be contacted by the research team, which includes the clinicians (Dr Dominic Murphy, Clinical Psychologist, Head of Research, Combat Stress and Dr Cerisse Gunasinghe, Counseling Psychologist, King's College London), to perform a clinical interview and risk assessment. If concerns remain, a signposting booklet to relevant charities will be provided to the participants. The study clinicians may register an adverse event and withdraw the participants from the study; however, any data collected before withdrawal will be used for analysis.

Follow-Up Procedure and Data Monitoring

The research team will monitor incoming data to ensure that the app is functioning correctly. The research team will not contact participants outside automatic messaging of the app unless they reach out to the research team with queries, for example technical issues, or if they are unsure of how to perform a task with the app.

Additional Data Collection

Additional data will be collected during this study for future research. Participants can opt out for additional data collection at any time.

Physical Activity Data Streams

Individual consent will be sought from participants at baseline (day 0) to collect physical activity data using Google Fit and Apple Health Application Programming Interface. The information to be extracted includes heart rate, distance travelled, activities, height, and weight. The aim of this study is to assess the feasibility of monitoring participants who consume alcohol at a hazardous or harmful level. The findings of this study will be reported elsewhere.

Statistical and Data Analysis Plan

Statistical analysis will be performed after completing the data-collection phase. No interim analysis will be undertaken. The threshold for statistical significance will be P=.05, and effect sizes will be reported. Descriptive statistics (eg, demographics and response rate) and independent sample t tests and chi-square tests will be carried out to explore and identify potential differences between the intervention and control arms at follow-up. An intention-to-treat method will be used for primary outcome analysis such that those who are lost to follow-up will be retained in the primary analysis. Multiple imputation will be performed to estimate missing data, where appropriate. The primary outcome analysis will examine whether there is a statistically significant difference between the intervention and control arms on change in self-reported TLFB UK units consumed (as stated earlier, a difference of 4 UK units will be considered meaningful). Repeated-measures mixed modeling analyses will be conducted to examine the primary hypothesis that those who receive the full functionality of *Drinks*:Ration will report a greater reduction in alcohol consumption compared with control participants from baseline to 3-month follow-up (day 84). For the secondary outcomes, changes in the AUDIT score and WHOQOL-BREF computed quality of adjusted life years will be assessed using repeated-measures mixed modeling. These analyses will be repeated to assess changes between baseline and 6-month follow-up and will serve as a secondary outcome to assess the longer-term impact of the intervention on participants. These analyses will be reported as secondary outcomes.

For process evaluation measures, app utilization will be assessed using descriptive statistics of frequency of engagement using a previously published procedure [62]. This will include the number of times the app is initialized (started when not running in the background), the average session duration (time spent using the app overall and for each page), the number of times a participant performs an interaction (synchronize data, add a drink, or add a message rating), and the number of weeks in which participants remain engaged with the app. Participant engagement is defined as having at least 3 interactions in a 7-day period, other than receiving push notifications or SMS text messages, and will be used as a proxy for usability. An independent sample analysis will be carried out to explore and identify differences between the intervention and control arms. Usability of *Drinks*:Ration will also be reported using descriptive statistics and thematic analysis of *debrief* sessions. Finally, analyses will be carried out to identify differences between the intervention and control arms in app experience (as measured by MAUQ). In the pursuit of open science, data and code syntax will be published alongside reporting of the trial. As this is a single-blinded RCT, an independent researcher (who will be blinded to allocation) will review all analyses and data before publication. This study will be reported following the Template for Intervention Description and Replication [63] and CONSORT (Consolidated Standards of Reporting Trials) checklist [64].

Results

Development of *Drinks*:Ration is complete. Owing to the lockdown as a result of COVID-19, the RCT will start in October 2020. As participants can start at different timepoints, we aim to complete all data collection by October 2021. The results of this study will be communicated via publication.

Discussion

Alcohol misuse is a persistent problem in the UK AF, with estimates forecasting that more than 50% of those who have left the AF meet the criteria for hazardous alcohol use. This is almost double that of the general population [65]. New and innovative modes of delivery and digital interventions are required to meet this demand [66]. At present, there are no smartphone-based alcohol interventions targeted toward the AF to reduce alcohol misuse, with estimates indicating that more than 50% of veterans misuse alcohol use [3]. Therefore, we have developed a theory-driven and user-centered smartphone app, which may help fill this gap in treatment. However, its efficacy, usability, and functionality need to be ascertained in a fully powered RCT. This study protocol describes the design of an RCT to determine the efficacy of *Drinks*:Ration within a treatment-seeking veteran population.

To our knowledge, this is one of the first studies to examine the efficacy of a smartphone app to reduce hazardous/harmful alcohol consumption in a treatment-seeking veteran population that has been developed based on empirical evidence, development guidelines, and co-design. Although this study uses a veteran sample recruited from Combat Stress, it is expected that the findings will be generalizable to the wider veteran community, as Combat Stress is a countrywide organization.

Previous research has shown that veteran alcohol misuse is often highly comorbid with other mental health conditions, which has been shown to have a negative impact on health treatment utilization and that veterans attend fewer health appointments

[11]. The use of a smartphone app combined with personalized messaging and formative feedback may provide a cost-effective strategy to deal with the barriers to improving drinking behaviors and increasing mental health care adherence in the UK AF community. These proposed methods may build self-efficacy and promote behavior change in reducing alcohol intake. A novel aspect of this study, which has the potential to improve health care engagement and utilization, is the use of push notifications combined with SMS text messages to support behavior change. To our knowledge, this is one of the first large trials of a text messaging intervention to promote reductions in alcohol consumption in the AF community.

A key strength of this study is the collaboration between the charitable sector, academia, and the UK AF, which has enabled the development of *Drinks*:Ration. A further strength includes remote delivery via smartphones, so that there will be no issues with availability or geographical limitations for participants. The app can also be used on iOS and Android devices. However, our app requires an active data connection for the app to function when logging questionnaires to generate normative feedback. This is to operate the personalization algorithms. We anticipate several challenges in this study. First, our ability to recruit and retain sufficient number of participants to power our analysis, as it is known that many of those who have alcohol-related problems are reluctant to seek help to ameliorate their problems. We planned our recruitment approach following the best practice to mitigate this issue. Further, the app has been designed to promote its active use, with frequent reminders, which is expected to promote adherence to the app. Second, we expect that some participants may encounter technical issues related to the app (eg, unable to log drinks and unable to receive notifications) or the mobile device. To mitigate potential technical or mobile device issues, we have undertaken extensive testing across a range of popular mobile devices and we will allow participants to provide in-app feedback that will be regularly monitored by the research team. Third, the impact of COVID-19 on the study, participant recruitment, engagement, or attrition is unknown. The research team will monitor the situation and handle issues as they arise. Finally, we acknowledge that our sample comprises participants who may be undergoing active treatment. To mitigate this risk, we will undertake statistical analyses to compare the control and intervention arms, and, where identified, these differences will be highlighted when reporting the trial.

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Conflicts of Interest

NTF sits on the Independent Group Advising on the Release of Data at NHS Digital. NTF is also a trustee of a military-related charity. AS is a full-time member of the Armed Forces seconded to King's College London. DM and CW are employed by Combat Stress, a national charity in the United Kingdom that provides clinical mental health services to veterans.

Multimedia Appendix 1
Behaviour Change Technique assignment to each *Drinks*:Ration component.
[DOCX File , 20 KB - resprot_v9i10e19720_app1.docx]

Multimedia Appendix 2
Questionnaire mark-up.
[DOCX File , 37 KB - resprot_v9i10e19720_app2.docx]

Multimedia Appendix 3
Drinks Menu Alcohol Unit Assignment.
[DOCX File , 26 KB - resprot_v9i10e19720_app3.docx]

References

1. Fear NT, Iversen A, Meltzer H, Workman L, Hull L, Greenberg N, et al. Patterns of drinking in the UK Armed Forces. Addiction 2007 Nov;102(11):1749-1759. [doi: 10.1111/j.1360-0443.2007.01978.x] [Medline: 17935583]
2. Fear NT, Jones M, Murphy D, Hull L, Iversen AC, Coker B, et al. What are the consequences of deployment to Iraq and Afghanistan on the mental health of the UK armed forces? A cohort study. The Lancet 2010 May 22;375(9728):1783-1797. [doi: 10.1016/S0140-6736(10)60672-1] [Medline: 20471076]

3. Rona RJ, Jones M, Fear NT, Hull L, Hotopf M, Wessely S. Alcohol misuse and functional impairment in the UK Armed Forces: a population-based study. Drug Alcohol Depend 2010 Apr 01;108(1-2):37-42. [doi: 10.1016/j.drugalcdep.2009.11.014] [Medline: 20047802]
4. Stevelink SA, Jones M, Hull L, Pernet D, MacCrimmon S, Goodwin L, et al. Mental health outcomes at the end of the British involvement in the Iraq and Afghanistan conflicts: a cohort study. B J Psychiatry 2018 Dec;213(6):690-697 [FREE Full text] [doi: 10.1192/bjp.2018.175] [Medline: 30295216]
5. Goodwin L, Norton S, Fear N, Jones M, Hull L, Wessely S, et al. Trajectories of alcohol use in the UK military and associations with mental health. Addict Behav 2017 Dec;75:130-137. [doi: 10.1016/j.addbeh.2017.07.010] [Medline: 28734152]
6. The Alcohol Use Disorders Identification Test: Interview Version. National Institute on Drug Abuse (NIDA). 2001. URL: https://www.who.int/publications/i/item/audit-the-alcohol-use-disorders-identification-test-guidelines-for-use-in-primary-health-care [accessed 2020-01-01]
7. Garnett C, Crane D, West R, Michie S, Brown J, Winstock A. Normative misperceptions about alcohol use in the general population of drinkers: a cross-sectional survey. Addict Behav 2015 Mar;42:203-206 [FREE Full text] [doi: 10.1016/j.addbeh.2014.11.010] [Medline: 25482365]
8. Hines LA, Goodwin L, Jones M, Hull L, Wessely S, Fear NT, et al. Factors affecting help seeking for mental health problems after deployment to Iraq and Afghanistan. Psychiatr Serv 2014 Jan 01;65(1):98-105. [doi: 10.1176/appi.ps.004972012] [Medline: 24037454]
9. Jones E, Fear NT. Alcohol use and misuse within the military: a review. Int Rev Psychiatry 2011 Apr;23(2):166-172. [doi: 10.3109/09540261.2010.550868] [Medline: 21521086]
10. Irizar P, Leightley D, Stevelink S, Rona R, Jones N, Gouni K, et al. Drinking motivations in UK serving and ex-serving military personnel. Occup Med (Lond) 2020 Jun 20;70(4):259-267 [FREE Full text] [doi: 10.1093/occmed/kqaa003] [Medline: 31961932]
11. Murphy D, Ashwick R, Palmer E, Busuttil W. Describing the profile of a population of UK veterans seeking support for mental health difficulties. J Ment Health 2019 Dec;28(6):654-661. [doi: 10.1080/09638237.2017.1385739] [Medline: 28982279]
12. Elbogen EB, Wagner HR, Johnson SC, Kinneer P, Kang H, Vasterling JJ, et al. Are Iraq and Afghanistan veterans using mental health services? New data from a national random-sample survey. Psychiatr Serv 2013 Feb 01;64(2):134-141 [FREE Full text] [doi: 10.1176/appi.ps.004792011] [Medline: 23475498]
13. Murphy D, Spencer-Harper L, Carson C, Palmer E, Hill K, Sorfleet N, et al. Long-term responses to treatment in UK veterans with military-related PTSD: an observational study. BMJ Open 2016 Sep 16;6(9):e011667 [FREE Full text] [doi: 10.1136/bmjopen-2016-011667] [Medline: 27638494]
14. Statistics on Alcohol, England, 2018 [PAS]. NHS Digital. 2020. URL: https://digital.nhs.uk/data-and-information/publications/statistical/statistics-on-alcohol/2018 [accessed 2020-01-01]
15. A summary of the Review of the Effectiveness of Treatment for Alcohol Problems. CORE – Aggregating the World's Open Access Research Papers. 2006. URL: https://core.ac.uk/download/pdf/34711278.pdf [accessed 2020-01-01]
16. Burton R, Henn C, Lavoie D, O'Connor R, Perkins C, Sweeney K, et al. The Public Health Burden of Alcohol and the Effectiveness and Cost-Effectiveness of Alcohol Control Policies: An Evidence Review. Government of UK Developer Documentation. 2016. URL: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/733108/alcohol_public_health_burden_evidence_review_update_2018.pdf [accessed 2020-01-01]
17. Abrams DB, Orleans CT, Niaura RS, Goldstein MG, Prochaska JO, Velicer W. Integrating individual and public health perspectives for treatment of tobacco dependence under managed health care: a combined stepped-care and matching model. Ann Behav Med 1996;18(4):290-304. [doi: 10.1007/BF02895291] [Medline: 18425675]
18. Kaner EF, Beyer F, Dickinson HO, Pienaar E, Campbell F, Schlesinger C, et al. Effectiveness of brief alcohol interventions in primary care populations. Cochrane Database Syst Rev 2007 Apr 18(2):CD004148. [doi: 10.1002/14651858.CD004148.pub3] [Medline: 17443541]
19. Doherty A, Mason C, Fear N, Rona R, Greenberg N, Goodwin L. Are brief alcohol interventions targeting alcohol use efficacious in military and veteran populations? A meta-analysis. Drug Alcohol Depend 2017 Sep 01;178:571-578. [doi: 10.1016/j.drugalcdep.2017.05.029] [Medline: 28750345]
20. Ballesteros J, Duffy JC, Querejeta I, Ariño J, González-Pinto A. Efficacy of brief interventions for hazardous drinkers in primary care: systematic review and meta-analyses. Alcohol Clin Exp Res 2004 Apr;28(4):608-618. [doi: 10.1097/01.alc.0000122106.84718.67] [Medline: 15100612]
21. Michie S, Whittington C, Hamoudi Z, Zarnani F, Tober G, West R. Identification of behaviour change techniques to reduce excessive alcohol consumption. Addiction 2012 Aug;107(8):1431-1440. [doi: 10.1111/j.1360-0443.2012.03845.x] [Medline: 22340523]
22. Kunz FM, French MT, Bazargan-Hejazi S. Cost-effectiveness analysis of a brief intervention delivered to problem drinkers presenting at an inner-city hospital emergency department. J Stud Alcohol 2004 May;65(3):363-370. [doi: 10.15288/jsa.2004.65.363] [Medline: 15222593]

23. Donoghue K, Patton R, Phillips T, Deluca P, Drummond C. The effectiveness of electronic screening and brief intervention for reducing levels of alcohol consumption: a systematic review and meta-analysis. J Med Internet Res 2014 Jun 02;16(6):e142 [FREE Full text] [doi: 10.2196/jmir.3193] [Medline: 24892426]
24. Garnett C, Crane D, Michie S, West R, Brown J. Evaluating the effectiveness of a smartphone app to reduce excessive alcohol consumption: protocol for a factorial randomised control trial. BMC Public Health 2016 Jul 08;16:536 [FREE Full text] [doi: 10.1186/s12889-016-3140-8] [Medline: 27392430]
25. Linke S, Brown A, Wallace P. Down your drink: a web-based intervention for people with excessive alcohol consumption. Alcohol Alcohol 2004;39(1):29-32. [doi: 10.1093/alcalc/agh004] [Medline: 14691071]
26. Lapham GT, Hawkins EJ, Chavez LJ, Achtmeyer CE, Williams EC, Thomas RM, et al. Feedback from recently returned veterans on an anonymous web-based brief alcohol intervention. Addict Sci Clin Pract 2012 Aug 28;7:17 [FREE Full text] [doi: 10.1186/1940-0640-7-17] [Medline: 23186354]
27. Christensen H, Griffiths KM, Farrer L. Adherence in internet interventions for anxiety and depression. J Med Internet Res 2009 Apr 24;11(2):e13 [FREE Full text] [doi: 10.2196/jmir.1194] [Medline: 19403466]
28. Kypri K, Langley JD, Saunders JB, Cashell-Smith ML, Herbison P. Randomized controlled trial of web-based alcohol screening and brief intervention in primary care. Arch Intern Med 2008 Mar 10;168(5):530-536. [doi: 10.1001/archinternmed.2007.109] [Medline: 18332300]
29. Wickersham A, Petrides PM, Williamson V, Leightley D. Efficacy of mobile application interventions for the treatment of post-traumatic stress disorder: A systematic review. Digit Health 2019;5:2055207619842986 [FREE Full text] [doi: 10.1177/2055207619842986] [Medline: 31019722]
30. Leightley D, McPhee JS, Yap MH. Automated analysis and quantification of human mobility using a depth sensor. IEEE J Biomed Health Inform 2017 Jul;21(4):939-948. [doi: 10.1109/jbhi.2016.2558540] [Medline: 27254874]
31. Leightley D, Williamson V, Darby J, Fear NT. Identifying probable post-traumatic stress disorder: applying supervised machine learning to data from a UK military cohort. J Ment Health 2019 Feb;28(1):34-41. [doi: 10.1080/09638237.2018.1521946] [Medline: 30445899]
32. Redfern J, Thiagalingam A, Jan S, Whittaker R, Hackett ML, Mooney J, et al. Development of a set of mobile phone text messages designed for prevention of recurrent cardiovascular events. Eur J Prev Cardiol 2014 Apr;21(4):492-499. [doi: 10.1177/2047487312449416] [Medline: 22605787]
33. Prestwich A, Perugini M, Hurling R. Can the effects of implementation intentions on exercise be enhanced using text messages? Psychol Health 2009 Jul;24(6):677-687. [doi: 10.1080/08870440802040715] [Medline: 20205020]
34. Müssener U, Thomas K, Linderoth C, Leijon M, Bendtsen M. A Text Message-Based Intervention Targeting Alcohol Consumption Among University Students: User Satisfaction and Acceptability Study. JMIR Hum Factors 2018 Jul 10;5(3):e23 [FREE Full text] [doi: 10.2196/humanfactors.9641] [Medline: 29991469]
35. Fowler LA, Holt SL, Joshi D. Mobile technology-based interventions for adult users of alcohol: A systematic review of the literature. Addict Behav 2016 Nov;62:25-34. [doi: 10.1016/j.addbeh.2016.06.008] [Medline: 27310031]
36. Drinkaware: Track And Calculate Units App. Drinkaware. URL: https://www.drinkaware.co.uk/tools/app/ [accessed 2018-05-21] [WebCite Cache ID 6zZtHhyXH]
37. Jones N. Mental health, stigmatising beliefs, barriers to care and help-seeking in a non-deployed sample of UK army personnel. J Psychol Psychother 2013;3(5):-. [doi: 10.4172/2161-0487.1000129]
38. Wooten NR, Tavakoli AS, Al-Barwani MB, Thomas NA, Chakraborty H, Scheyett AM, et al. Comparing behavioral health models for reducing risky drinking among older male veterans. Am J Drug Alcohol Abuse 2017 Sep;43(5):545-555 [FREE Full text] [doi: 10.1080/00952990.2017.1286499] [Medline: 28410002]
39. United Kingdom National Health Service. URL: https://www.nhs.uk/pages/home.aspx [accessed 2018-05-21] [WebCite Cache ID 6zZtobwPF]
40. Quanbeck A, Chih MY, Isham A, Gustafson D. Mobile Delivery of Treatment for Alcohol Use Disorders: A Review of the Literature. Alcohol Res 2014;36(1):111-122 [FREE Full text] [Medline: 26259005]
41. Kaner EF, Beyer FR, Garnett C, Crane D, Brown J, Muirhead C, et al. Personalised digital interventions for reducing hazardous and harmful alcohol consumption in community-dwelling populations. Cochrane Database Syst Rev 2017 Sep 25;9:CD011479 [FREE Full text] [doi: 10.1002/14651858.CD011479.pub2] [Medline: 28944453]
42. Products. The National Institute for Health and Care Excellence. URL: https://www.nice.org.uk/guidance/conditions-and-diseases/liver-conditions/alcohol-use-disorders/products?ProductType=Guidance&Status=Published [accessed 2020-01-19]
43. Sobell LC, Maisto SA, Sobell MB, Cooper A. Reliability of alcohol abusers' self-reports of drinking behavior. Behav Res Ther 1979;17(2):157-160. [doi: 10.1016/0005-7967(79)90025-1] [Medline: 426744]
44. Alcohol Guidelines Review: Report From the Guidelines Development Group to the UK Chief Medical Officers. Government of UK. URL: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/489797/CMO_Alcohol_Report.pdf [accessed 2020-09-08]
45. Parkin DM, Boyd L, Walker LC. 16. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. Br J Cancer 2011 Dec 06;105 Suppl 2(Suppl 2):S77-S81 [FREE Full text] [doi: 10.1038/bjc.2011.489] [Medline: 22158327]

46. Murphy D, Turgoose D. Exploring patterns of alcohol misuse in treatment-seeking UK veterans: A cross-sectional study. Addict Behav 2019 May;92:14-19. [doi: 10.1016/j.addbeh.2018.11.044] [Medline: 30572207]
47. Stevelink SA, Jones N, Jones M, Dyball D, Khera CK, Pernet D, et al. Do serving and ex-serving personnel of the UK armed forces seek help for perceived stress, emotional or mental health problems? Eur J Psychotraumatol 2019;10(1):1556552 [FREE Full text] [doi: 10.1080/20008198.2018.1556552] [Medline: 30693074]
48. Weijers MD, Busuttil PE. Exploring patterns in referrals to combat stress for UK veterans with mental health difficulties between 1994 and 2014. Int J Emerg Ment Health 2015;17(3):-. [doi: 10.4172/1522-4821.1000250]
49. Leightley D, Puddephatt J, Jones N, Mahmoodi T, Chui Z, Field M, et al. A Smartphone App and Personalized Text Messaging Framework (InDEx) to Monitor and Reduce Alcohol Use in Ex-Serving Personnel: Development and Feasibility Study. JMIR Mhealth Uhealth 2018 Sep 11;6(9):e10074 [FREE Full text] [doi: 10.2196/10074] [Medline: 30206054]
50. Leightley D, Puddephatt JS, Goodwin L, Rona R, Fear NT. InDEx: Open Source iOS and Android Software for Self-Reporting and Monitoring of Alcohol Consumption. J Open Res Softw 2018 Mar 23;6:13 [FREE Full text] [doi: 10.5334/jors.207] [Medline: 29795769]
51. Puddephatt J, Leightley D, Palmer L, Jones N, Mahmoodi T, Drummond C, et al. A Qualitative Evaluation of the Acceptability of a Tailored Smartphone Alcohol Intervention for a Military Population: Information About Drinking for Ex-Serving Personnel (InDEx) App. JMIR Mhealth Uhealth 2019 May 24;7(5):e12267 [FREE Full text] [doi: 10.2196/12267] [Medline: 31127726]
52. Gollwitzer P, Sheeran P. Implementation intentions and goal achievement: a meta ‐ analysis of effects and processes. Adv Experiment Soc Psychol 2006:119. [doi: 10.1016/S0065-2601(06)38002-1]
53. Arroll B, Goodyear-Smith F, Crengle S, Gunn J, Kerse N, Fishman T, et al. Validation of PHQ-2 and PHQ-9 to screen for major depression in the primary care population. Ann Fam Med 2010;8(4):348-353 [FREE Full text] [doi: 10.1370/afm.1139] [Medline: 20644190]
54. Kroenke K, Spitzer RL, Williams JB, Monahan PO, Löwe B. Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. Ann Intern Med 2007 Mar 06;146(5):317-325. [doi: 10.7326/0003-4819-146-5-200703060-00004] [Medline: 17339617]
55. Cloitre M, Shevlin M, Brewin CR, Bisson JI, Roberts NP, Maercker A, et al. The International Trauma Questionnaire: development of a self-report measure of ICD-11 PTSD and complex PTSD. Acta Psychiatr Scand 2018 Dec;138(6):536-546. [doi: 10.1111/acps.12956] [Medline: 30178492]
56. Readiness Ruler. The Center for Evidence-Based Practices at Case Western Reserve University. 2010. URL: https://www.centerforebp.case.edu/resources/tools/readiness-ruler [accessed 2020-09-15]
57. Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption--II. Addiction 1993 Jun;88(6):791-804. [doi: 10.1111/j.1360-0443.1993.tb02093.x] [Medline: 8329970]
58. -. Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group. Psychol Med 1998 May;28(3):551-558. [doi: 10.1017/s0033291798006667] [Medline: 9626712]
59. Zhou L, Bao J, Setiawan IM, Saptono A, Parmanto B. The mHealth App Usability Questionnaire (MAUQ): Development and Validation Study. JMIR Mhealth Uhealth 2019 Apr 11;7(4):e11500 [FREE Full text] [doi: 10.2196/11500] [Medline: 30973342]
60. Fiellin DA, McGinnis KA, Maisto SA, Justice AC, Bryant K. Measuring alcohol consumption using Timeline Followback in non-treatment-seeking medical clinic patients with and without HIV infection: 7-, 14-, or 30-day recall. J Stud Alcohol Drugs 2013 May;74(3):500-504 [FREE Full text] [doi: 10.15288/jsad.2013.74.500] [Medline: 23490581]
61. Donabedian A. Evaluating the quality of medical care. 1966. Milbank Q 2005;83(4):691-729 [FREE Full text] [doi: 10.1111/j.1468-0009.2005.00397.x] [Medline: 16279964]
62. Iacoviello BM, Steinerman JR, Klein DB, Silver TL, Berger AG, Luo SX, et al. Clickotine, A Personalized Smartphone App for Smoking Cessation: Initial Evaluation. JMIR Mhealth Uhealth 2017 Apr 25;5(4):e56 [FREE Full text] [doi: 10.2196/mhealth.7226] [Medline: 28442453]
63. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ 2014 Mar 07;348:g1687. [doi: 10.1136/bmj.g1687] [Medline: 24609605]
64. Rennie D. CONSORT revised--improving the reporting of randomized trials. JAMA 2001 Apr 18;285(15):2006-2007. [doi: 10.1001/jama.285.15.2006] [Medline: 11308440]
65. McManus S, Bebbington P, Jenkins R, Brugha T. Mental health and wellbeing in England: Adult Psychiatric Morbidity Survey 2014. NHS Digita. 2014. URL: https://digital.nhs.uk/data-and-information/publications/statistical/adult-psychiatric-morbidity-survey/adult-psychiatric-morbidity-survey-survey-of-mental-health-and-wellbeing-england-2014 [accessed 2020-09-15]
66. Coleman SJ, Stevelink SA, Hatch SL, Denny JA, Greenberg N. Stigma-related barriers and facilitators to help seeking for mental health issues in the armed forces: a systematic review and thematic synthesis of qualitative literature. Psychol Med 2017 Aug;47(11):1880-1892. [doi: 10.1017/S0033291717000356] [Medline: 28290262]

Abbreviations

AF: armed forces
AUDIT: Alcohol Use Disorders Identification Test
BCT: behavior change technique
MAUQ: mHealth App Usability Questionnaire
NHS: National Health Service
NIHR: National Institute for Health Research
PTSD: posttraumatic stress disorder
QR: quick response
RCT: randomized controlled trial
TLFB: Timeline Follow-back for alcohol consumption
WHOQOL-BREF: World Health Organization Quality of Life-BREF

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Protocol

Impact of Remote Titration Combined With Telemonitoring on the Optimization of Guideline-Directed Medical Therapy for Patients With Heart Failure: Protocol for a Randomized Controlled Trial

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Abstract

Background: Guideline-directed medical therapy (GDMT), optimized to maximum tolerated doses, has been shown to improve clinical outcomes in patients with heart failure (HF). Timely use and optimization of GDMT can improve HF symptoms, reduce the burden of hospitalization, and increase survival rates, whereas GDMT deferral may worsen the progression of HF, decrease survival rates, and predispose patients to poor outcomes. However, studies indicate that GDMT remains underused, with less than 25% of patients receiving target doses in clinical practice. Telemonitoring is a potential component in the management of HF that can provide reliable and real-time physiological data for clinical decision support and facilitate remote titration of medication.

Objective: The primary objective of this study is to evaluate the impact of remote titration facilitated by telemonitoring on health care outcomes, with a primary outcome measure being the proportion of patients achieving target doses. The secondary objective is to identify the barriers and facilitators that can affect the implementation and effectiveness of the intervention.

Methods: A mixed methods study of a smartphone-based telemonitoring system is being conducted at the Peter Munk Cardiac Centre (PMCC), University Health Network, Toronto. The study is based on an effectiveness-implementation hybrid design and incorporates process evaluations alongside the assessment of clinical outcomes. The effectiveness research component is assessed by a two-arm randomized controlled trial (RCT) aiming to enroll 108 patients. The RCT compares a remote titration strategy that uses data from a smartphone-based telemonitoring system with a standard titration program consisting of in-office visits. The implementation research component consists of a qualitative study based on semistructured interviews with a purposive sample of clinicians and patients.

Results: Patient recruitment began in January 2019 at PMCC, with a total of 76 participants recruited by February 24, 2020 (39 in the intervention group and 37 in the control group). The final analysis is expected to be completed by the winter of 2021.

Conclusions: This study will be among the first to provide evidence on the implementation of remote titration facilitated by telemonitoring and its impact on patient health outcomes. The successful use of telemonitoring for this purpose has the potential to alter the existing approach to titration of HF medication and support the development of a care delivery model that combines clinic visits with virtual follow-ups.

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International Registered Report Identifier (IRRID): DERR1-10.2196/19705

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KEYWORDS

telemonitoring; telemedicine; remote titration; mHealth; heart failure

Introduction

Background

Heart failure (HF) is a global public health problem affecting an estimated 26 million worldwide [1]. Researchers estimate that more than 1 million people in Canada are living with HF, about 50,000 new cases are diagnosed each year, and HF costs the Canadian health care system Can $2.8 (US $2.12) billion annually [2,3]. The rapidly aging population in developed countries and improved prognosis of HF are contributing to the increasing prevalence of people with HF. However, although HF prognosis has improved, the long-term mortality rates for the condition remain high. Approximately 1 in 3 patients admitted to the hospital with HF still die within a year and approximately 1 in 2 die within 5 years [4].

In addition, HF accounts for 1% to 2% of direct health care expenditure in developed countries [5] and the cost to our health care system is expected to grow with the aging of the population and rising prevalence of HF. In Canada alone, studies found that in 2013, HF hospitalizations accounted for Can $482 (US $364.34) million in spending. By 2030, the amount is estimated to increase to Can $722 (US $545.75) million [6].

Over the past few years, significant progress has been made in pharmacological therapies for HF. Guideline-directed medical therapy (GDMT) for patients with HF, comprising angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors (ARNIs), beta blockers (BBLs), and mineralocorticoid receptor antagonists (MRAs), has been shown through randomized controlled trials (RCTs) to improve symptoms, reduce the burden of hospitalization, and increase survival rates [7]. Conversely, a meta-analysis conducted in 2017 by Zaman et al [8] showed that a 1-year deferral of treatment could reduce the 1-year survival rate from 90% (if treated) to 78%. GDMT deferral may also worsen HF progression and predispose patients to worse outcomes [9]. Clinical guidelines recommend up-titrating these treatments to maximum tolerated doses [10]. However, these successes have not fully translated into clinical practice, as studies and registries consistently report that evidence-based pharmacotherapies for HF are severely underutilized [11,12].

Barriers including patient-related factors such as time constraints and financial limitations, physician-related issues such as knowledge of drug therapy optimization, and institution-related logistical issues surrounding clinic visits often complicate the titration process [13]. In addition, the dynamic nature of HF presents challenges in patient care and management, with patients receiving care in primary, acute, and community care settings and with frequent transitions between care providers [14]. These frequent transitions of care across multiple providers and multiple settings are poorly coordinated and often exacerbate the difficulty of medication titration [15]. All these factors impede timely optimization of vital therapy for patients with HF, which is particularly detrimental because delays in therapy can lead to significant disease progression that may have been preventable [9].

Telemonitoring is a potential component in the management of HF that can provide reliable and real-time physiological data for clinical decision support, alerting, and patient self-management. Telemonitoring enables patients to track vital signs and symptoms and receive automated instruction and clinical intervention during *teachable moments* (ie, clear actions are provided when the context is most appropriate). The acquired physiological and symptom data can also help inform clinical decisions by health care providers, such as remote titration of medication [16].

Objectives

This study aims to explore how the combination of remote titration and telemonitoring affects GDMT optimization compared with standard of care. The study takes a dual focus in assessing both the clinical effectiveness and implementation of the intervention. The primary objective of this study is to evaluate the impact of remote titration facilitated by telemonitoring on health care outcomes, including the proportion of patients achieving target doses, time to dose optimization, and patient health outcomes. The secondary objective of this study is to obtain a deeper understanding of the experiences of clinicians and patients with HF participating in the remote titration program to identify factors that affect the implementation of the intervention.

Methods

Study Design Overview

The study is based on a type 1 effectiveness-implementation hybrid design. In this type of study, the primary aim is to determine effectiveness, and the secondary aim is to explore the implementation of the innovation [17]. This is a mixed methods study with 108 patients with HF, consisting of an RCT and a qualitative study. The RCT predominantly addresses the effectiveness component while providing supporting data for the implementation component of the research. The qualitative study predominantly addresses the implementation component while providing supporting data for the effectiveness component. In addition, the study included an internal pilot [18] that aimed to identify the most suitable primary outcome measure and obtain more accurate data to inform an appropriate sample size calculation.

This study has received approval from the research ethics boards of the University of Toronto (research ethics board number 00036655) and the research ethics boards at the University Health Network (UHN; research ethics board number 18-5351), where patients are recruited and patient data are stored. The study has also been registered at ClinicalTrials.gov (NCT04205513).

Sample Size Calculation

One of the main outcome measures of this study, the number of visits required to complete titration, was used to calculate the initial sample size based on data obtained from the existing literature. Assuming biweekly titration over a period of 3 to 6 months (ie, 9±3 visits in total for the control group) as recommended by HF guidelines [10,19], a reduction of at least 35% in the number of visits for the intervention group, 80% power, and α=.05 (two-sided), the sample size per group was calculated to be 16. Furthermore, assuming that as much as 30% of the patients may be lost to follow-up or cannot be titrated, the sample size per group became 21. Hence, 42 patients were enrolled for the internal pilot portion of the study.

Data from the internal pilot and the literature were combined to perform the final sample size calculation. It was determined that the initially selected primary outcome measure of the number of visits required to achieve titration was not appropriate because clinic visits were strongly affected by external factors unrelated to the intervention. Many patients in the control group attended very sporadic clinic visits, which resulted in a slow and unpredictable titration process. Therefore, the new calculation was based on an alternative primary outcome measure, which was the proportion of patients achieving target doses. In the pilot cohort, 18 of 21 patients (86%) in the intervention group and 10 of 21 patients (48%) in the control group completed titration within 6 months of enrollment. According to an expert panel conducted by the Canadian Cardiovascular Society, most physicians (55%) believed that the entire triple therapy titration to maximum tolerated or target doses should be completed within 4 months, 93% believed that this should be done within 6 months, and all respondents agreed that every titration would not necessarily require a face-to-face visit [19]. The titration completion rates reported in the literature vary, and the timelines are not always clear. However, multiple studies reported that 17% to 43% of patients achieve target doses within 3 to 6 months [12,20,21].

In light of the varying ranges provided by available data and to ensure that the sample size of the full study would be sufficient to detect statistical significance, a higher completion rate among those available was used for the control group, and a slightly more conservative completion rate was used for the intervention group. Therefore, rates of 45% and 75% were used for the control and intervention groups, respectively. The calculation assumed a power of 80%. An alpha of .025 (two-sided) was used, instead of .05, to account for the single interim analysis conducted. On the basis of this, the sample size per group was calculated to be 49. Furthermore, assuming that up to 10% of the patients may be lost to follow-up or cannot be titrated (based on the observed attrition rate in the internal pilot), the sample size per group was calculated to be 54. Hence, the overall sample size of the study is 108 patients.

Medly Telemonitoring System

Medly, a mobile phone–based telemonitoring program for patients with HF was launched at UHN in 2016. This program is integrated into the Ted Rogers Centre of Excellence in Heart Function at the Peter Munk Cardiac Centre (PMCC) as part of the standard of care.

Medly enables patients with HF to take clinically relevant physiological measurements with wireless home medical devices in addition to answering symptom questions through the mobile phone app. The measurements are automatically and wirelessly transmitted to the mobile phone and then to a data server. Specifically, patients monitor daily weight, blood pressure, heart rate, and symptoms, and some patients monitor their activity as determined by their cardiologist. Daily reports are typically completed every morning (patients receive an automated reminder call if the measurements are not performed by 10 AM), and patients are instructed to record their blood pressure and symptoms if they feel unwell. Automated self-care instructions that have been carefully developed with health care specialists are sent to the patient in accordance with a rule-based algorithm that analyzes their measurements and reported symptoms [22]. If there are signs indicating deterioration in their status, an email alert is sent to a clinician at the Heart Function Clinic. Clinicians can also view alerts and the patient's telemonitoring data through a secure web portal. The data are monitored by a dedicated Medly nurse coordinator during working hours and an assigned clinician after hours and on weekends. Medly has a demonstrated positive impact on patient outcomes and patient experience. An RCT conducted with Medly at the Heart Function Clinic and an evaluation of the Medly Program as part of the standard of care found improvements in patient health outcomes and high patient and health care provider satisfaction. Adherence to daily monitoring was high, and the cardiologists and nurse practitioners indicated that Medly improved information transfer from their patients because they received real-time patient information and alerts that supported clinical decision making [23,24].

Therefore, Medly was chosen as the system to support the titration of HF medication for this study. Specifically, the intent was for Medly to be used to provide frequent and real-time data to support clinical decisions on the optimal modification of patients' medications remotely.

Study Protocol

Participant Enrollment and Randomization

RCT

Study participants are recruited from the PMCC Heart Function Clinic. Eligible participants are first identified by the cardiologist. During their usual visit to the Heart Function Clinic, all patients who meet the study's inclusion and exclusion criteria (listed in Textboxes 1 and 2, respectively), are told about the study and asked by a member of their circle of care if they are willing to speak to the nurse coordinator regarding participation. Patients who agree meet with the coordinator

immediately after their visit with the cardiologist, and a written informed consent is obtained from each patient. Patients are then randomized 1:1 into control and intervention groups. A web-based computer-generated randomization tool is used to perform block randomization in blocks of 4. The generated sequence is used to create randomization envelopes, and the nurse coordinator is provided with randomly generated treatment allocations within sealed opaque envelopes. Following enrollment, the envelopes are used to determine if the patient is in the intervention or control group. Cardiologists are notified into which group their patients are randomized.

Textbox 1. Patient inclusion criteria.

- Able to provide informed consent to participate in the program
- 18 years or older
- Diagnosed as having heart failure (HF) and followed up by a cardiologist at the Peter Munk Cardiac Centre Heart Function Clinic, who has the primary responsibility for management of the patient's HF
- New York Heart Association Classes I to III
- Stable HF defined as no hospitalization within 1 month
- Patient is not yet at target doses of guideline-directed medical therapy (angiotensin-converting-enzyme inhibitor, and/or angiotensin receptor blocker, and/or beta blocker, and/or angiotensin receptor-neprilysin inhibitors, and/or mineralocorticoid receptor antagonist at suboptimal doses), and hence qualifies for up-titration
- Patient or their informal caregiver speaks and reads English adequately to participate in the program and understand the alerts or prompts in the Medly application
- Ability to comply with using Medly (eg, able to stand on the weight scale, able to answer symptom questions)

Textbox 2. Patient exclusion criteria.

- Active acutely decompensated heart failure
- Already on target doses of guideline-directed medical therapy
- Inability to titrate medications due to adverse events including:
  - History of angioedema
  - Uncontrolled hypertension
  - Hypotension preventing up-titration
  - Heart rate at rest <56 beats per minute
- Congenital heart disease
- Previous heart transplant or currently awaiting heart transplant
- Acute coronary syndrome; stroke; transient ischemic attack; cardiac, carotid, or other major cardiovascular surgery; percutaneous coronary intervention; or carotid angioplasty within 6 weeks before randomization
- Obstructive or restrictive cardiomyopathy
- Second- or third-degree atrioventricular block without a pacemaker
- Presence of hemodynamically significant mitral and/or aortic valve disease, except mitral regurgitation
- Presence of other hemodynamically significant obstructive lesions of the left ventricular outflow tract, including aortic and subaortic stenosis, which are not controlled with suitable treatment
- Evidence of hepatic impairment defined as alanine aminotransferase or aspartate aminotransferase value >3-fold the upper normal limit. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 at randomization or >35% decline in eGFR between visits
- Known stenosis of both renal arteries
- Hyper- or hypothyroidism not controlled by treatment
- Hyperkalemia >5.5 mmol/L at randomization
- Hyponatremia <130 mmol/L at randomization
- History of severe asthma or pulmonary disease
- Presence of any other disease, which in the clinician's opinion would exclude the patient from the study or with a life expectancy of <1 year

Qualitative Study

Patients randomized into the intervention group will be invited to participate in individual interviews intended to assess their experience and perception of the program upon titration completion. Maximum variation sampling [25] will be used to interview a varied selection of people. Participants will be purposively selected to represent a range of experiences with the intervention and include men and women, old and young, and patients who reside at varying distances from the clinic.

All health care providers and study staff from the Heart Function Clinic who participate in the remote titration program during the RCT will also be invited to participate in semistructured interviews through an email. Written informed consent will be obtained before the start of any interview.

Semistructured interview guides will be developed to explore the participants' views on various aspects of the remote titration program. To ensure that the information generated is based on the participants' unique perspectives, questions will not follow any specific constructs. During the interview, participants will be asked open-ended questions to ascertain their comfort with the intervention and its delivery, any concerns or difficulties they may have had with respect to the intervention, and whether it met their goals or expectations. Follow-up questions will explore topics raised by participants.

Intervention Versus Control Groups

The recommended therapeutic approach for patients with HF and reduced left ventricular ejection fraction (LVEF<40%) consists of triple therapy with either an ACEI or ARB or ARNI, BBL, and MRA, titrated to target doses [10]. However, these doses are not often achieved in clinical practice [7]. Patients identified as receiving suboptimal doses of HF medications are enrolled and randomized at a ratio of 1:1 to 1 of 2 treatment groups:

- Control group—standard titration management strategy consisting of regular in-office visits.
- Intervention group—remote titration management strategy consisting of telephone contacts facilitated by data from the Medly system and in-office visits as deemed necessary by the patient's care team.

Both groups are titrated in accordance with the recommendations of the HF management guidelines. Participants in the intervention group, as per Medly standard of care, are asked to take daily weight and blood pressure readings and answer questions on symptoms. Patients are also provided with requisitions for blood work to be performed at local laboratories when requested. Titration checkpoints are scheduled biweekly unless specified otherwise by cardiologists. Patients are contacted by phone, and medication changes are performed during these calls based on data obtained through Medly and the latest blood work. Patients in the intervention group still visit the hospital for follow-ups at their cardiologist's discretion and to perform echocardiograms, electrocardiograms (ECGs), and cardiopulmonary exercise testing (CPET).

Participants in the control group attend regular visits and are provided with the current standard of care. As the Medly system is integrated into the PMCC Heart Function Clinic as part of the standard of care, patients in the control group are also monitored through Medly. However, no remote titrations occur, and medication changes are performed during clinic visits. At the clinic visit, patients have their measurements taken, such as their blood pressure, weight, and heart rate. The clinicians inquire about their symptoms, diet, exercise, and adherence to medication. Blood tests, echocardiograms, ECGs, and CPETs are performed as required. Medication changes are performed based on the data collected through these assessments.

The titration process is terminated when patients reach target doses or maximum tolerated doses. A follow-up clinic appointment is scheduled within 3 months of titration completion, as per the standard of care. Throughout this process, the importance of patients' adherence to program requirements in terms of daily measurements and symptom reporting is emphasized and strictly monitored to ensure prompt identification of potential changes in their condition.

Data Collection

RCT

The primary outcome measures will be the proportion of patients who achieve target doses and the time to dose optimization. Additional measures will include patient health outcomes (including, but not limited to, New York Heart Association [NYHA] class, LVEF, and brain natriuretic peptide [BNP] levels), the number of visits and/or calls required to achieve target doses, and health care resource utilization.

Information will be obtained by reviewing the patients' electronic patient record (EPR) charts and Medly data and documentation throughout the study by the study coordinator. Baseline and poststudy medications and dosages for each patient and baseline and poststudy clinical measures, including NYHA class, LVEF, and BNP levels, will be determined through manual EPR chart reviews. Health care utilization will primarily be determined through EPR chart reviews. However, this information will be supplemented through patient self-reporting to account for situations in which patients use services outside of UHN. Data regarding the titration process, such as the number of visits and/or phone calls performed, actions undertaken, and any adverse events that occurred throughout the study, will be documented by the study coordinator. The number of visits, phone calls, and total contact points will be recorded in detail for each group to determine the impact of remote titration on the GDMT optimization process.

Qualitative Study

The qualitative study will aim to identify the barriers to and facilitators for implementation. Semistructured one-on-one interviews will be conducted with participants to explore their views on various aspects of the remote titration program. Patients randomized into the intervention group will be interviewed in a quiet and private space within the clinic or over the telephone. Interviews are expected to last between 15 and 30 min. Additional interviews will be conducted until data saturation is reached and the interviewer determines that no new pertinent information is being collected. Health care providers from the Heart Function Clinic who participate in the remote

titration program will also be interviewed. The individual interviews are expected to last between 20 and 45 min and will be conducted in the clinician's office or over the telephone. All interviews will be audio-recorded and transcribed for subsequent analysis.

The schedule for data acquisition is shown in Table 1.

Table 1. Schedule for data acquisition indicated by checkmarks at the specified time point.

Data collected	Baseline	Interim analysis	Titration completion	3-month follow-up
Demographics	✓	N/A[a]	N/A	N/A
Health service utilization				
Number of HF[b]-related hospitalizations since enrollment	N/A	✓	✓	✓
Number of days in the hospital since enrollment	N/A	✓	✓	✓
Number of emergency department visits since enrollment	N/A	✓	✓	✓
Number of clinic visits or phone calls since enrollment	N/A	✓	✓	✓
Clinical outcomes				
BNP[c] levels	✓	✓	✓	✓
NYHA[d] class	✓	✓	✓	✓
LVEF[e] (%)	✓	N/A	N/A	✓
Qualitative data				
Clinician interviews	N/A	✓	✓	N/A
Patient interviews	N/A	✓	N/A	N/A

[a]N/A: not applicable.

[b]HF: heart failure.

[c]BNP: brain natriuretic peptide.

[d]NYHA: New York Heart Association.

[e]LVEF: left ventricular ejection fraction.

Data Analysis

RCT

Descriptive, parametric, and nonparametric statistics will be performed. Statistical analyses will be selected in accordance with the data under review and the required level of comparison: McNemar tests will be performed on binary baseline and poststudy data, whereas chi-square tests will be performed to compare binary poststudy data between the intervention group and the control group; paired Student *t* tests and Wilcoxon signed-rank tests will be performed on baseline and poststudy data for normally and not normally distributed data, respectively. Independent Student *t* tests and Mann-Whitney tests will be performed to compare poststudy data between the intervention group and the control group for normally and not normally distributed data, respectively.

Qualitative Study

Conventional content analysis [26] will be used to analyze the transcribed interviews, and coding will be performed using NVivo software (QSR International). A conventional inductive approach will first be used to gain direct information from study participants, without imposing preconceived categories or theoretical perspectives, and to ensure that knowledge generated from the content analysis is based on the participants' unique perspectives [27]. After themes have been derived through inductive content analysis, a deductive approach will be used as the final step to frame and structure the findings [26]. Therefore, the themes generated through inductive content analysis will be delineated and mapped in accordance with Chaudoir's multilevel framework for the assessment of factors affecting the implementation of health innovations [28].

Results

Patient recruitment began in January 2019 at PMCC, UHN, Toronto. The study is currently in progress, and a total of 76 participants have been recruited as of February 24, 2020 (39 in the intervention group and 37 in the control group). The final analysis is expected to be completed by the winter of 2021. This study will be among the first to substantiate the implementation of remote titration facilitated by telemonitoring and its impact on patient health outcomes.

Discussion

Principal Results

This study aims to determine how the combination of remote titration and telemonitoring affects GDMT optimization compared with the standard of care. Specifically, the objectives of this study are to assess the effectiveness and implementation of remote titration facilitated by telemonitoring. Telemonitoring is a potential component in the management of HF that allows patients to remotely provide reliable and real-time physiological

data for clinical decision support. Studies have demonstrated that the use of telemonitoring in the HF population is associated with a reduction in hospitalizations and readmissions and improved mortality [29-32]. Patient and clinician perceptions are positive, and telemonitoring is viewed as a useful and efficacious tool that can be used to promote positive outcomes in the HF population [33-35].

Despite this, only a few trials have attempted to use telemonitoring for the purpose of remote titration of HF medication. A study conducted by D'Onofrio et al [36] and Palmisano et al [37] assessed the effectiveness of a structured program for BBL titration and found that remote titration allowed 76% of patients in the intervention group to achieve target doses compared with only 38% of patients in the control group. Similarly, Spaeder et al [38] also performed a study that focused on rapid titration of the BBL carvedilol and compared in-office titration with a combined in-office and remote titration model. The study found no statistical difference in the proportion of patients who reached the target doses. However, the time frame required to reach the final dose was significantly shorter in the intervention group (mean 33.6, SD 16.6) than in the control group (mean 63.7, SD 20.2).

Of note, a few other studies that have attempted to perform remote medication titration did not contain any telemonitoring components, such as a smartphone-based app or a web platform. Instead, patients periodically called or were contacted by a clinician and relayed their measurements and symptom data over the phone. Two such trials by Steckler et al [39] and Moyer-Knox et al [40] assessed BBL titration over the phone. Steckler et al [39] found that the proportion of patients receiving BBLs at any dose increased from 61% at baseline to 97% after optimization, and the proportion of patients receiving target BBL doses increased from 12.5% at baseline to 40.6% after optimization. Moyer-Knox et al [40] found that 96% of patients reached therapeutic doses (6.25 mg twice daily) and 71% of patients reached target doses of 25 mg twice daily within approximately 8 weeks.

These trials provided preliminary evidence demonstrating that remote titration (with or without the aid of telemonitoring) of BBLs can be successful and results in a higher proportion of patients reaching target doses within shorter time frames.

Strengths and Limitations of the Study

Unlike previous studies that focused solely on the titration of BBLs, a strength of this study is that it encompasses the titration of full triple therapy for patients with HF. In addition, the mixed methods design of this study will allow triangulation of data from quantitative and qualitative assessments, thereby enhancing data validity. Methodological triangulation enables the validation of findings through the collection of data from multiple sources and via different methods. Specifically, data from interviews with clinicians and patients will be used to complement, confirm, and explain the results of the quantitative study. Furthermore, the previously existing evidence regarding remote titration and the currently available data on the effectiveness of Medly telemonitoring for patients with HF [22,23,33,41] make it possible to adopt an effectiveness-implementation hybrid design [17]. Therefore, implementation-related questions can be explored much earlier than could be achieved in separate sequential intervention and implementation study designs [17].

A limitation of this study is its single-center nature and the availability of dedicated specialized staff to support the intervention. The patient population enrolled in this study was recruited from a single specialized heart function clinic. The PMCC Heart Function Clinic has implemented telemonitoring as a standard of care. The Medly Program was launched at the clinic in 2016, and cardiologists are familiar with monitoring patients through Medly. The familiarity of the clinicians involved in this study with telemonitoring as well as the existing processes for alert management and communication of information obtained through the Medly system may contribute to the mitigation of challenges that could otherwise be encountered. Furthermore, the intervention is supported by a dedicated nurse coordinator. As access to multidisciplinary HF services varies between clinics, additional staffing limits the potential generalizability and external validity of the study. Finally, as our study investigates changes in the process of care, blinding could not be applied to clinicians. However, patient randomization is performed using sealed opaque envelopes containing randomly generated treatment allocations. Patients in the intervention group follow a structured predetermined remote titration schedule, whereas patients in the control group continue to be treated as per the standard of care by their respective cardiologists. Thus, the lack of clinician blinding is not expected to have an impact on the outcomes of the study.

Significance of the Research

The significant gap that still exists in adherence to guideline-recommended evidence-based therapies for HF emphasizes the need for novel approaches to the problem of medication titration. An intervention that can successfully promote optimal GDMT use in clinical practice may substantially improve clinical outcomes in patients and reduce the burden of HF on the health care system as a whole. Although information and research on remote titration of HF medication are somewhat limited, the results of previously conducted studies have been fairly positive, pointing to a favorable impact on titration rates and timelines. This study will be among the first to explore whether remote titration facilitated by telemonitoring may be able to promote optimal GDMT use. In addition, it will be the first study to provide insight on the implementation process as well as the perception of the intervention by both clinicians and patients.

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Conflicts of Interest

Members of the research team (ES and HR) have the intellectual property rights of the Medly system.

References

1. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. J Am Coll Cardiol 2014 Apr 1;63(12):1123-1133 [FREE Full text] [doi: 10.1016/j.jacc.2013.11.053] [Medline: 24491689]
2. Butrous H, Hummel SL. Heart failure in older adults. Can J Cardiol 2016 Sep;32(9):1140-1147 [FREE Full text] [doi: 10.1016/j.cjca.2016.05.005] [Medline: 27476982]
3. Blais C, Dai S, Waters C, Robitaille C, Smith M, Svenson LW, et al. Assessing the burden of hospitalized and community-care heart failure in Canada. Can J Cardiol 2014 Mar;30(3):352-358. [doi: 10.1016/j.cjca.2013.12.013] [Medline: 24565257]
4. Ponikowski P, Anker SD, AlHabib KF, Cowie MR, Force TL, Hu S, et al. Heart failure: preventing disease and death worldwide. ESC Heart Fail 2014 Sep;1(1):4-25 [FREE Full text] [doi: 10.1002/ehf2.12005] [Medline: 28834669]
5. Cook C, Cole G, Asaria P, Jabbour R, Francis DP. The annual global economic burden of heart failure. Int J Cardiol 2014 Feb 15;171(3):368-376. [doi: 10.1016/j.ijcard.2013.12.028] [Medline: 24398230]
6. Tran DT, Ohinmaa A, Thanh NX, Howlett JG, Ezekowitz JA, McAlister FA, et al. The current and future financial burden of hospital admissions for heart failure in Canada: a cost analysis. CMAJ Open 2016;4(3):E365-E370 [FREE Full text] [doi: 10.9778/cmajo.20150130] [Medline: 27730101]
7. Atherton J, Hickey A. Expert comment: is medication titration in heart failure too complex? Card Fail Rev 2017 Apr;3(1):25-32 [FREE Full text] [doi: 10.15420/cfr.2017:1:2] [Medline: 28785472]
8. Zaman S, Zaman SS, Scholtes T, Shun-Shin MJ, Plymen CM, Francis DP, et al. The mortality risk of deferring optimal medical therapy in heart failure: a systematic comparison against norms for surgical consent and patient information leaflets. Eur J Heart Fail 2017 Nov;19(11):1401-1409 [FREE Full text] [doi: 10.1002/ejhf.838] [Medline: 28597606]
9. Gracia E, Hamid A, Butler J. Timely management of new-onset heart failure. Circulation 2019 Aug 20;140(8):621-623. [doi: 10.1161/CIRCULATIONAHA.118.035452] [Medline: 31424994]
10. Ezekowitz JA, O'Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, et al. 2017 comprehensive update of the Canadian cardiovascular society guidelines for the management of heart failure. Can J Cardiol 2017 Nov;33(11):1342-1433. [doi: 10.1016/j.cjca.2017.08.022] [Medline: 29111106]
11. Maggioni AP, Anker SD, Dahlström U, Filippatos G, Ponikowski P, Zannad F, Heart Failure Association of the ESC. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC heart failure long-term registry. Eur J Heart Fail 2013 Oct;15(10):1173-1184 [FREE Full text] [doi: 10.1093/eurjhf/hft134] [Medline: 23978433]
12. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, et al. Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF registry. J Am Coll Cardiol 2018 Jul 24;72(4):351-366 [FREE Full text] [doi: 10.1016/j.jacc.2018.04.070] [Medline: 30025570]
13. Carroll R, Mudge A, Suna J, Denaro C, Atherton J. Prescribing and up-titration in recently hospitalized heart failure patients attending a disease management program. Int J Cardiol 2016 Aug 1;216:121-127. [doi: 10.1016/j.ijcard.2016.04.084] [Medline: 27153136]
14. Virani SA, Bains M, Code J, Ducharme A, Harkness K, Howlett JG, Board and Membership of the Canadian Heart Failure Society. The need for heart failure advocacy in Canada. Can J Cardiol 2017 Nov;33(11):1450-1454. [doi: 10.1016/j.cjca.2017.08.024] [Medline: 29111108]
15. Sevilla-Cazes J, Ahmad FS, Bowles KH, Jaskowiak A, Gallagher T, Goldberg LR, et al. Heart failure home management challenges and reasons for readmission: a qualitative study to understand the patient's perspective. J Gen Intern Med 2018 Oct;33(10):1700-1707 [FREE Full text] [doi: 10.1007/s11606-018-4542-3] [Medline: 29992429]
16. Cafazzo JA, Seto E. The hospital at home: advances in remote patient monitoring. Biomed Instrum Technol 2010;Suppl Home Healthcare:47-52. [Medline: 22049607]
17. Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. Med Care 2012 Mar;50(3):217-226 [FREE Full text] [doi: 10.1097/MLR.0b013e3182408812] [Medline: 22310560]
18. Wittes J, Brittain E. The role of internal pilot studies in increasing the efficiency of clinical trials. Stat Med 1990;9(1-2):65-71; discussion 71. [doi: 10.1002/sim.4780090113] [Medline: 2345839]
19. Howlett JG, Chan M, Ezekowitz JA, Harkness K, Heckman GA, Kouz S, Canadian Cardiovascular Society Heart Failure Guidelines Panels. The Canadian cardiovascular society heart failure companion: bridging guidelines to your practice. Can J Cardiol 2016 Mar;32(3):296-310. [doi: 10.1016/j.cjca.2015.06.019] [Medline: 26391749]
20. Fonarow GC, Albert NM, Curtis AB, Stough WG, Gheorghiade M, Heywood JT, et al. Improving evidence-based care for heart failure in outpatient cardiology practices: primary results of the registry to improve the use of evidence-based heart failure therapies in the outpatient setting (IMPROVE HF). Circulation 2010 Aug 10;122(6):585-596. [doi: 10.1161/CIRCULATIONAHA.109.934471] [Medline: 20660805]

21. Fowler MB, Lottes SR, Nelson JJ, Lukas MA, Gilbert EM, Greenberg B, COHERE Participant Physicians. Beta-blocker dosing in community-based treatment of heart failure. Am Heart J 2007 Jun;153(6):1029-1036. [doi: 10.1016/j.ahj.2007.03.010] [Medline: 17540206]
22. Seto E, Leonard KJ, Cafazzo JA, Barnsley J, Masino C, Ross HJ. Developing healthcare rule-based expert systems: case study of a heart failure telemonitoring system. Int J Med Inform 2012 Aug;81(8):556-565. [doi: 10.1016/j.ijmedinf.2012.03.001] [Medline: 22465288]
23. Seto E, Leonard KJ, Cafazzo JA, Barnsley J, Masino C, Ross HJ. Mobile phone-based telemonitoring for heart failure management: a randomized controlled trial. J Med Internet Res 2012 Feb 16;14(1):e31 [FREE Full text] [doi: 10.2196/jmir.1909] [Medline: 22356799]
24. Ware P, Ross HJ, Cafazzo JA, Boodoo C, Munnery M, Seto E. Outcomes of a heart failure telemonitoring program implemented as the standard of care in an outpatient heart function clinic: pretest-posttest pragmatic study. J Med Internet Res 2020 Feb 8;22(2):e16538 [FREE Full text] [doi: 10.2196/16538] [Medline: 32027309]
25. Palinkas LA, Horwitz SM, Green CA, Wisdom JP, Duan N, Hoagwood K. Purposeful sampling for qualitative data collection and analysis in mixed method implementation research. Adm Policy Ment Health 2015 Sep;42(5):533-544 [FREE Full text] [doi: 10.1007/s10488-013-0528-y] [Medline: 24193818]
26. Hsieh H, Shannon SE. Three approaches to qualitative content analysis. Qual Health Res 2005 Nov;15(9):1277-1288. [doi: 10.1177/1049732305276687] [Medline: 16204405]
27. Proctor E, Silmere H, Raghavan R, Hovmand P, Aarons G, Bunger A, et al. Outcomes for implementation research: conceptual distinctions, measurement challenges, and research agenda. Adm Policy Ment Health 2011 Mar;38(2):65-76 [FREE Full text] [doi: 10.1007/s10488-010-0319-7] [Medline: 20957426]
28. Chaudoir SR, Dugan AG, Barr CH. Measuring factors affecting implementation of health innovations: a systematic review of structural, organizational, provider, patient, and innovation level measures. Implement Sci 2013 Feb 17;8:22 [FREE Full text] [doi: 10.1186/1748-5908-8-22] [Medline: 23414420]
29. Clark RA, Inglis SC, McAlister FA, Cleland JG, Stewart S. Telemonitoring or structured telephone support programmes for patients with chronic heart failure: systematic review and meta-analysis. Br Med J 2007 May 5;334(7600):942 [FREE Full text] [doi: 10.1136/bmj.39156.536968.55] [Medline: 17426062]
30. Koehler F, Winkler S, Schieber M, Sechtem U, Stangl K, Böhm M, TIM-HF Investigators. Telemedical interventional monitoring in heart failure (TIM-HF), a randomized, controlled intervention trial investigating the impact of telemedicine on mortality in ambulatory patients with heart failure: study design. Eur J Heart Fail 2010 Dec;12(12):1354-1362 [FREE Full text] [doi: 10.1093/eurjhf/hfq199] [Medline: 21098580]
31. Kotb A, Cameron C, Hsieh S, Wells G. Comparative effectiveness of different forms of telemedicine for individuals with heart failure (HF): a systematic review and network meta-analysis. PLoS One 2015;10(2):e0118681 [FREE Full text] [doi: 10.1371/journal.pone.0118681] [Medline: 25714962]
32. Zhu Y, Gu X, Xu C. Effectiveness of telemedicine systems for adults with heart failure: a meta-analysis of randomized controlled trials. Heart Fail Rev 2020 Mar;25(2):231-243 [FREE Full text] [doi: 10.1007/s10741-019-09801-5] [Medline: 31197564]
33. Seto E, Leonard KJ, Masino C, Cafazzo JA, Barnsley J, Ross HJ. Attitudes of heart failure patients and health care providers towards mobile phone-based remote monitoring. J Med Internet Res 2010 Nov 29;12(4):e55 [FREE Full text] [doi: 10.2196/jmir.1627] [Medline: 21115435]
34. Ware P, Ross HJ, Cafazzo JA, Laporte A, Gordon K, Seto E. Evaluating the implementation of a mobile phone-based telemonitoring program: longitudinal study guided by the consolidated framework for implementation research. JMIR Mhealth Uhealth 2018 Jul 31;6(7):e10768 [FREE Full text] [doi: 10.2196/10768] [Medline: 30064970]
35. Fairbrother P, Ure J, Hanley J, McCloughan L, Denvir M, Sheikh A, Telescot programme team. Telemonitoring for chronic heart failure: the views of patients and healthcare professionals - a qualitative study. J Clin Nurs 2014 Jan;23(1-2):132-144. [doi: 10.1111/jocn.12137] [Medline: 23451899]
36. D'Onofrio A, Palmisano P, Rapacciuolo A, Ammendola E, Calò L, Ruocco A, et al. Effectiveness of a management program for outpatient clinic or remote titration of beta-blockers in CRT patients: the RESTORE study. Int J Cardiol 2017 Jun 1;236:290-295. [doi: 10.1016/j.ijcard.2017.02.015] [Medline: 28188000]
37. Palmisano P, Ammendola E, D'Onofrio A, Accogli M, Calò L, Ruocco A, et al. Evaluation of synergistic effects of resynchronization therapy and a β-blocker up-titration strategy based on a predefined patient-management program: the RESTORE study. Clin Cardiol 2015 Jan;38(1):2-7 [FREE Full text] [doi: 10.1002/clc.22352] [Medline: 25580847]
38. Spaeder J, Najjar SS, Gerstenblith G, Hefter G, Kern L, Palmer JG, et al. Rapid titration of carvedilol in patients with congestive heart failure: a randomized trial of automated telemedicine versus frequent outpatient clinic visits. Am Heart J 2006 Apr;151(4):844.e1-844.10. [doi: 10.1016/j.ahj.2005.06.044] [Medline: 16569544]
39. Steckler AE, Bishu K, Wassif H, Sigurdsson G, Wagner J, Jaenicke C, et al. Telephone titration of heart failure medications. J Cardiovasc Nurs 2011;26(1):29-36. [doi: 10.1097/JCN.0b013e3181ec1223] [Medline: 21127425]
40. Moyer-Knox D, Mueller TM, Vuckovic K, Mischke L, Williams RE. Remote titration of carvedilol for heart failure patients by advanced practice nurses. J Card Fail 2004 Jun;10(3):219-224. [doi: 10.1016/j.cardfail.2003.09.009] [Medline: 15190531]

41. Seto E, Leonard KJ, Cafazzo JA, Barnsley J, Masino C, Ross HJ. Perceptions and experiences of heart failure patients and clinicians on the use of mobile phone-based telemonitoring. J Med Internet Res 2012 Feb 10;14(1):e25 [FREE Full text] [doi: 10.2196/jmir.1912] [Medline: 22328237]

Abbreviations

ACEI: angiotensin-converting enzyme inhibitor
ARB: angiotensin receptor blocker
ARNI: angiotensin receptor-neprilysin inhibitor
BBL: beta blockers
BNP: brain natriuretic peptide
CPET: cardiopulmonary exercise testing
ECG: electrocardiogram
EPR: electronic patient record
GDMT: guideline- directed medical therapy
HF: heart failure
LVEF: left ventricular ejection fraction
MRA: mineralocorticoid receptor antagonist
NYHA: New York Heart Association
PMCC: Peter Munk Cardiac Centre
RCT: randomized controlled trial
UHN: University Health Network

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Protocol

Comparing Web-Based Mindfulness With Loving-Kindness and Compassion Training for Promoting Well-Being in Pregnancy: Protocol for a Three-Arm Pilot Randomized Controlled Trial

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Abstract

Background: Promoting psychological well-being and preventing distress among pregnant women is an important public health goal. In addition to adversely impacting the mother's health and well-being, psychological distress in pregnancy increases the risk of poor pregnancy outcomes, compromises infant socioemotional development and bonding, and heightens maternal and child vulnerability in the postpartum period. Mindfulness and compassion-based interventions show potential for prevention and early intervention for perinatal distress. As there is an established need for accessible, scalable, flexible, and low-cost interventions, there is increased interest in the delivery of these programs on the web. This project aims to pilot a three-arm randomized controlled trial (RCT) to determine the feasibility of a full-scale RCT comparing 2 web-based interventions (mindfulness vs loving-kindness and compassion) with a web-based active control condition (progressive muscle relaxation).

Objective: The primary objective of this study is to assess the feasibility of an RCT protocol comparing the 3 conditions delivered on the web as a series of instructional materials and brief daily practices over a course of 8 weeks. The second objective is to explore the experiences of women in the different intervention conditions. The third objective is to estimate SD values for the outcome measures to inform the design of an adequately powered trial to determine the comparative efficacy of the different conditions.

Methods: Pregnant women (n=75) participating in a longitudinal birth cohort study (the ORIGINS project) will be recruited to this study from 18 weeks of gestational age. We will assess the acceptability and feasibility of recruitment and retention strategies and the participants' engagement and adherence to the interventions. We will also assess the experiences of women in each of the 3 intervention conditions by measuring weekly changes in their well-being and engagement with the program and by conducting a qualitative analysis of postprogram interviews.

Results: This project was funded in September 2019 and received ethics approval on July 8, 2020. Enrollment to the study will commence in September 2020. Feasibility of a full-scale RCT will be assessed using ADePT (*a process for decision making after pilot and feasibility trials*) criteria.

Conclusions: If the study is shown to be feasible, results will be used to inform future full-scale RCTs. Evidence for flexible, scalable, and low-cost interventions could inform population health strategies to promote well-being and reduce psychological distress among pregnant women.

Trial Registration: Australian New Zealand Clinical Trials Registry Number 12620000672954p; http://anzctr.org.au/ACTRN12620000672954p.aspx

International Registered Report Identifier (IRRID): PRR1-10.2196/19803

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KEYWORDS

mindfulness; compassion; pregnancy; telemedicine; mental health; public health; intervention

Introduction

Background

Maternal mental health in pregnancy is an issue of substantial public health importance [1]. Anxiety and depression are the most common postpartum difficulties experienced by women globally [2], with an average prevalence of 10% to 15%, although rates as high as 64% have been reported in US samples [2]. Psychological distress during pregnancy is associated with adverse impacts for both the mother and child [3-6]. For example, prenatal symptoms of depression and anxiety are associated with impaired fetal growth [7], risk of child emotional and behavioral problems [8-13], and differences in child brain morphology [14]. These findings align with the Developmental Origins of Health and Disease model [15], which posits that the characteristics of the perinatal environment exert lifelong influences on offspring health risk and resilience. Maternal mental health difficulties in pregnancy can also increase the risk of adjustment difficulties in the postnatal period [16,17].

Despite the availability of accessible and effective treatments for mood disorders, approximately half of the women experiencing perinatal distress do not seek help [18-20]. Such findings demonstrate a need for universal mental health promotion efforts that complement targeted treatment programs and span prevention through early intervention. Nonpharmacological approaches to mood management are also preferred by pregnant women because of concerns about the effects of pharmacological interventions on the developing fetus [21]. Furthermore, research on mental health risk and resilience also illustrates the dual benefits of targeting subclinical symptoms of distress and increasing positive mental health and well-being. For example, although a history of psychiatric symptoms predisposes individuals to future psychopathology, positive mental health both supports recovery from distress and protects against poor mental health in the future [22-25]. Studies with pregnant women have found that prenatal positive mental health traits such as positive affect and optimism are protective of postpartum depression [26,27] and birth outcomes such as preterm delivery [28]. A dual approach aligns with two-factor models of mental health, which recognize distress and well-being as 2 distinct but interrelated continua [22,29,30].

Meditation-Based Interventions

Meditation-based interventions, including mindfulness-based interventions (MBIs) and compassion-based interventions (CBIs), are promising approaches for improving mental health and reducing psychological distress in the perinatal period. There is considerable evidence demonstrating the effectiveness of MBIs in reducing symptoms of psychological distress and promoting positive mental health in community populations [31,32] and clinical and at-risk groups [33,34]. CBIs (used here to denote meditation interventions focused on loving-kindness, self-compassion, and compassion for others) are similar to MBIs in that standardized protocols tend to be delivered over 8 weeks, with meditation practice considered an *active ingredient* in intervention effectiveness [35,36]. However, there are also important differences: although MBIs focus on cultivating nonjudgmental awareness and acceptance of all present-moment experiences [37], CBIs involve the intentional cultivation of positive affective states (eg, love, kindness, compassion, joy) [38].

Although the literature on CBIs is sparse relative to that for MBIs, reviews and meta-analyses also document positive effects of compassion and loving-kindness meditation practices on positive mental health [39] and psychological distress [35,40,41]. More recent work has demonstrated the greater efficacy of CBI protocols over MBI protocols for some outcomes. For example, Le Nguyen et al [42] reported the superior effects of loving-kindness training over mindfulness training for improving telomere length in novice meditators. Furthermore, Trautwein et al [37] demonstrated the differential benefits of different types of meditation training (attention and loving-kindness) on various cognitive and affective outcomes. Although these findings provide the basis for the development of more targeted intervention approaches, it is not clear which of these outcomes is most relevant for promoting mental health and well-being in pregnant women.

MBIs and CBIs in Pregnancy

Evidence drawn from observational and experimental studies illustrates the potential benefit of MBIs and CBIs in reducing distress and promoting mental health in the perinatal period. For example, longitudinal studies have found significant inverse associations between trait mindfulness during pregnancy and both depressed mood across pregnancy and low birth weight (<10th percentile, after adjusting for gestational age, parity, and sex) [43]. Preliminary evidence also indicates that maternal mindfulness during pregnancy is associated with better behavioral and regulatory outcomes in infants and children [44,45]. However, results from systematic reviews of perinatal MBIs have been variable [46-48]. Although the literature suggests that mindfulness training in the perinatal period reduces

perinatal stress and anxiety [48], there is mixed evidence regarding reductions in depression [48]. This is partly linked to heterogeneity in sample types and methodology as well as differences across intervention protocols.

Although initial evidence demonstrates associations among maternal self-compassion, well-being, and adjustment [49-51], there are only very few studies assessing CBIs in the perinatal period. Those that are available have reported encouraging results. For example, a proof-of-concept study compared a 2-week web-based CBI with web-based cognitive behavioral therapy (CBT) for perinatal women and those planning pregnancy (n=123) [52]. Participants in the 2 groups had similar outcomes in terms of affect, self-reassurance, self-criticism, and self-compassion. However, CBI was superior to CBT in terms of reducing symptoms of depression and anxiety. In another study, a 6-session, 3-week loving-kindness and compassion group program was compared with pregnancy yoga and an untreated control group in a sample of pregnant women (n=109) [53]. In this study, participants in the intervention group reported significant improvements in maternal-fetal attachment, mindfulness, and positive emotion relative to the control groups at posttest and follow-up. There are currently no head-to-head studies comparing the efficacy of MBIs and CBIs among pregnant women.

Web-Based Meditation-Based Interventions

There are a number of potential benefits of delivering MBIs and CBIs via the internet [52,54], such as the capacity to implement across populations, to reach individuals who might struggle to access face-to-face services, the potential to improve cost-efficiencies, and the ability to provide greater flexibility to service users [55]. Meta-analyses have found small-to-moderate effect sizes for web-based and self-guided MBIs in promoting well-being and reducing symptoms of psychological distress [56]. Although there are limited studies of internet-delivered CBIs, 1 RCT of web-based compassion training for self-critical individuals reported moderate-to-large effect sizes for reductions in distress, relative to usual care [57]. However, it is currently unclear whether MBIs and CBIs delivered on the web are a feasible and efficacious means of reducing stress and promoting well-being in the perinatal period [58]. Available evidence for internet-delivered MBIs highlights some issues with intervention feasibility. For example, 1 RCT found evidence that compared with waitlist control, a web-based, 8-week self-guided MBI was associated with significant reductions in stress and pregnancy distress among pregnant women who completed the intervention; however, attrition exceeded 50% [59]. In the study by Kelman et al [52] on web-based CBI versus web-based CBT for perinatal women and those planning pregnancy, retention at a 2-week follow-up was 62% for CBI versus 71% for CBT.

As the field of pre- and perinatal meditation training advances, questions are raised about the types of meditation training, their suitability, and expected outcomes. In addition, there are enduring questions about how best to engage pregnant women in internet-delivered mental health interventions. Initial findings regarding engagement and retention within studies suggest a need for attention to consumer-focused design in the developmental stage of the intervention protocols [60]. This pilot study is intended as a precursor to a larger study (the Mums' Minds Matter [MMM] study), in which we aim to address some of these issues. The MMM study will involve a three-arm RCT comparing web-based mindfulness training, web-based loving-kindness and compassion training (LKCT), and web-based progressive muscle relaxation (PMR; active control) to improve positive mental health and psychological distress among pregnant women. Both experimental conditions in the study were developed with input from consumers (ie, women who had been pregnant) and were designed in line with the instructional design framework for MBIs proposed by Lippmann et al [54]. PMR was selected as an active control condition as it is considered safe for pregnant women, is associated with physical and psychological benefits in the perinatal period, and could be matched to the format and duration of the experimental conditions [61].

Objectives

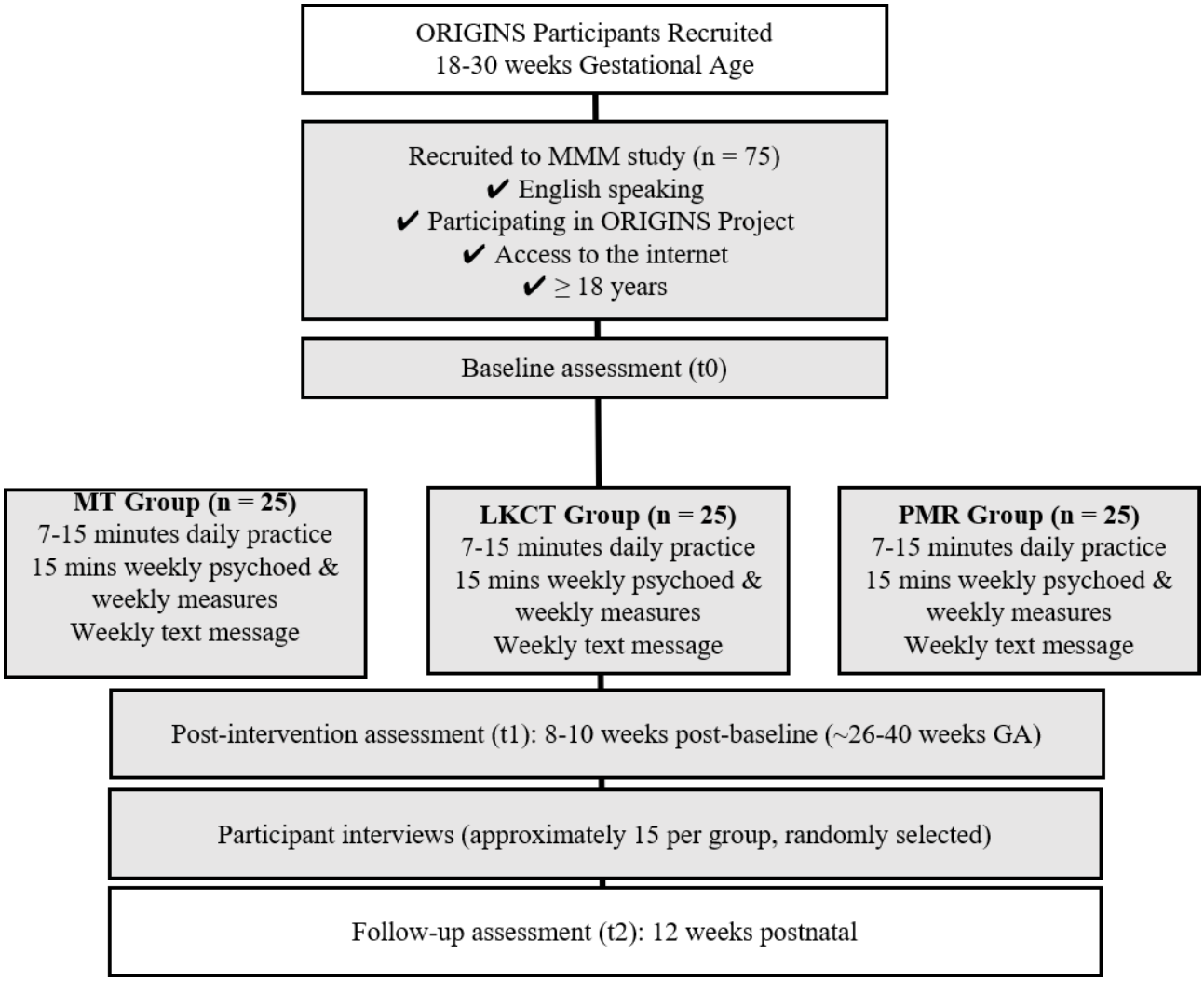
This study aims to pilot the overall MMM study design, including the recruitment, screening, randomization, assessment, and intervention methods to be used in the full-scale trial. In addition to piloting these methods, this study has 3 objectives: (1) to assess the feasibility of the full-scale trial by measuring recruitment to the trial and retention, engagement, and completion rates for each arm of the trial; (2) to explore the experiences of women in the study; and (3) to estimate the standard deviation values for each of the outcome measures to inform sample size calculations for the main trial.

Methods

Study Design

This is a randomized controlled trial (RCT) with 3 parallel groups: (1) mindfulness training, (2) LKCT, and (3) PMR and a repeated measure design. The trial is single blinded, with block randomization to have equal allocation of participants to groups stratified by parity. The trial is registered with the Australian New Zealand Clinical Trials Registry; the trial registration number of the study is 12620000672954p. This study was approved by the Joondalup Health Campus (JHC) Human Research Ethics Committee. An overview of the study design is shown in Figure 1.

Figure 1. Participant flow through the study.



Trial Site and Participating Centers

The MMM interventions are all web-based, and all data will be collected electronically. As the study will recruit women receiving antenatal care at JHC, this health campus is considered the physical trial site.

Participants

Eligibility Criteria

Eligible participants are pregnant women participating in the ORIGINS project (ORIGINS) and receiving antenatal care at a metropolitan health campus (JHC). ORIGINS is a longitudinal birth cohort study that recruits pregnant women and their partners from 12 weeks of gestational age and follows them and their child until 5 years postpartum. ORIGINS is open to any women who are birthing their baby at JHC [62]. Participants considered for inclusion in the MMM study will be women (1) at 18 to 30 weeks of pregnancy; (2) aged ≥18 years; (3) able to read, write, and understand English; and (4) able to access the internet.

Sample Size

We aim to recruit 25 participants per treatment arm (75 participants in total). The recommended sample sizes per treatment arm for pilot trials are between 15 and 25 when the standardized effect sizes for outcomes in the main trial are expected to be medium (0.5) to small (0.2) [63].

Recruitment

Participants will be recruited at or following their first antenatal assessment for ORIGINS. Participants will receive recruitment materials (a recruitment video and website link) via email and/or text message. Interested participants will be directed to the study website to complete electronic consent forms and web-based screening measures via REDCap (Vanderbilt University). In addition to assessing eligibility criteria and parity (for stratification), the screening assessment will include the Edinburgh Postnatal Depression Scale (EPDS). This is a valid tool for detecting symptoms of depression during pregnancy and postnatally [64]. Participants scoring above the thresholds for the risk of depression (total score ≥13) or reporting thoughts of self-harm (score of 1-3 on item 10) will receive a phone call from a registered psychologist to discuss referral to more targeted support services. They will not be excluded from participation in the study.

Randomization, Allocation, and Masking of the Intervention Conditions

Following screening, eligible participants will be asked to complete a web-based assessment battery comprising the

outcome measures for the main trial. Upon completion of this assessment battery, the REDCap randomization module will be used to randomize participants to 1 of the 3 conditions. Randomization will be stratified by parity (nulliparous or not). The research assistant (RA) will be notified by email when a participant has been randomized. Although participants will not be blinded to the intervention condition, the RA will code participants' condition allocation in the database so that the data analyst is blind to allocation. Minimal sufficient identifying data will be used to link MMM participant IDs to participant IDs in the ORIGINS study. This will be used to obtain the ORIGINS study data on participants' sociodemographic and birth outcome data.

Participant Procedure

Once a participant has been randomized, the RA will add the participant to their allocated intervention condition in Teachable, the web-based system used to deliver the programs. Participants will then receive an automated email from Teachable prompting them to create a password. Participants will also receive a phone call from the RA to confirm that they have successfully logged in to the program and to answer any participant questions. Participants will be asked to nominate a start date for the program within the next week.

Participants will access their allocated condition within the MMM program either on a computer (via the Teachable website) or on a smart device via the Teachable app. On the basis of their nominated start date, participants will receive an automated weekly text message with a link to the weekly outcome measures. These measures involve self-reports of stress, affect, and emotion regulation and are also designed to prompt self-reflection. There are also questions about daily practice, intentions to continue practice, and barriers and facilitators to practice. Participants who indicate that they do not intend to continue practice in the next week will be asked if they wish to opt out of the program. Participants choosing to opt out will be directed to a survey, which will ask them about the reasons for opting out of the program and request program feedback. At the conclusion of the 8-week intervention period, participants will be emailed a link to the t1 (posttest) assessment battery. Participants will be emailed again with a link to the t2 (follow-up) assessment battery 3 months after giving birth.

Interventions

All intervention conditions will be delivered on the web using the Teachable platform. The program is structured so that each day of the intervention is delivered as a separate *lesson*. The same intervention structure will be used for each condition: 8 weeks, with 1 formal practice (audio recording) to be practiced daily each week. Participants will also receive text instructions for 1 informal practice each week, which they are encouraged to practice as often as feasible. The informal practices are designed to support participants to integrate skills and learning into their daily activities.

Both the mindfulness training and LKCT interventions were developed following a two-step process. First, we conducted a scoping review of the literature to determine key components of MBIs and CBIs administered during the perinatal period. In addition to extracting data regarding intervention characteristics (eg, weekly themes, duration, mode of delivery, home practice), we also extracted data regarding specific considerations for delivering meditation-based interventions during pregnancy. These data were used to develop a draft intervention protocol for the mindfulness training and LKCT conditions. The protocol was developed by AF and AO, who have masters-level training in clinical psychology and are both certified teachers of MBIs and CBIs. The PMR condition was based on exercises described by Jacobson [65] and adapted for pregnancy by excluding muscle tension in the abdominal area.

The intervention protocol was also informed by prior theoretical and empirical work describing the proposed mechanisms by which mindfulness and loving-kindness and compassion training impacts positive mental health and distress. For example, dismantling studies have supported the theory that acceptance is a necessary component for MBIs to improve positive emotions [66], whereas perspectives and empirical data on loving-kindness and compassion meditation highlight the central role of self-soothing, caring motivations, and socioaffective processes (eg, directing loving thoughts toward another) [37,67-69]. Finally, the structure of the intervention conditions was informed by the instructional design model for internet-based MBIs proposed by Lippmann et al [54]. These include the use of formal and informal practices, provision of educational and supportive material, and the use of reminders (via text message) at least once a week. The core themes and practices for each condition are described in Table 1. Further information on the formal practices can be found in Multimedia Appendix 1.

Table 1. Outline of key themes and practices for each condition.

Components	Mindfulness training	Loving-kindness and compassion training	Progressive Muscle Relaxation
Themes	Nonjudgmental awareness of present-moment experiences (thoughts, feelings, and sensations); acceptance of present-moment experiences (thoughts, feelings, and sensations); using the breath as an anchor for attention; and how mindfulness can support perinatal health	Friendliness toward self; loving-kindness toward self, baby, and others; self-compassion; responding to difficulties with kindness and compassion; and how loving-kindness and compassion can support perinatal health	Relaxation and how relaxation can support perinatal health
Formal practices	Body scan, breath-focused meditation, walking meditation, and mountain meditation	Compassionate check-in, compassionate body scan, soothing image practice, loving-kindness practice, and responding to emotions with compassion	Progressive muscle relaxation exercise
Informal practice	Mindfulness of daily activities (chores, showering, and waking up), mindful communication, mindful walking in nature, and 3-min breathing space	Body softening practice, micromoments of soothing, on-the-spot loving kindness practice, and savoring practice	Informal relaxation applied in different contexts (eg, going to bed, driving, waking up)

Consumer testing and input for the mindfulness training and LKCT protocols were sought from a group of 16 women (8 per condition) who had a recent experience of pregnancy and had given birth in the past 5 years. Women accessed the meditation recordings and associated content on the web via the Teachable platform over the course of 4 weeks. They were asked to practice formal and informal practices and provide feedback on each practice using a web-based questionnaire. Reponses were collated and discussed in a series of focus groups (2 per treatment condition) where participants described their motivations and experiences with the intervention protocol and suggested revisions to the content and structure. For example, based on participant feedback, the practices in weeks 1 and 2 for each condition were changed from 15 min to 7 min and 10 min, respectively. Recordings were also amended to include background music. LKCT meditation practices were also slightly modified with regard to the terms used (eg, removal of the word *suffering*). The resulting intervention protocols involved daily practice of 7 min in week 1, 10 min in week 2, and 15 min in weeks 3 to 8, coupled with psychoeducation and 1 informal practice per week.

Data Collection

Study Outcomes

We will assess several metrics to determine the feasibility of the study across the following domains: recruitment, randomization, retention, and adherence (Table 2). To assess the feasibility of the assessment battery and calculate standard deviations on the measures, the main outcome measures for the full-scale RCT will be used (Table 3). Postintervention interviews will be conducted with a randomly selected sample of participants (n=approximately 15 in each condition) to gather further data on engagement with practice, reasons for attrition, satisfaction with the program, enjoyment and value of the program, and barriers and facilitators to engagement. Participants will be invited to partake in a semistructured interview by telephone, videoconference, or at the JHC clinic. Table 4 shows the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) schedule of enrollment, interventions, and assessment.

Table 2. Summary of outcomes and metrics for pilot study.

Outcome	Metrics
Recruitment	• Number of participants screened per week • Number of participants enrolled per week • Proportion of recruited ORIGINS participants electing to enroll
Randomization	• Proportion of eligible participants who access the web-based intervention following randomization • Proportion of eligible participants who complete at least one session (one day) of the web-based intervention
Retention	• Proportion of participants that complete t0 (baseline) measures after commencing them • Condition-specific completion rates following randomization (completion defined as ≥50% of modules accessed at least once) • Proportion of participants commencing baseline measures that complete time 1 (posttest) and time 2 (follow-up) measures
Adherence	• Self-reported completion of practice • Lesson completions in Teachable program
Acceptability	• Proportion of participant opt-outs from each intervention condition • Proportion of participant withdrawals from the study • Self-reported intervention and study satisfaction

Table 3. Summary of outcomes and measures for a full-scale randomized controlled trial.

Outcomes	Measures
Primary outcome	
Mental well-being	Mental Health Continuum–Short Form (14 items) [70]
Secondary outcomes	
Depression	Edinburgh Postnatal Depression Scale (10 items) [71]
Anxiety	Generalized Anxiety Disorder (7 items) [72]
Stress	Perceived Stress Scale (10 items) [73]
Self-compassion	Self-Compassion Scale–Short Form (12 items) [74]
Mindfulness	Mindful Attention and Awareness Scale (15 items) [75]
Emotion regulation	Difficulties in Emotion Regulation Scale (16 items) [76]
Affect	Positive and Negative Affect Scale–Short Form (10 items) [77]
Quality of life	EuroQol–5 Dimension (5 items) [78]
Tertiary outcomes	
Program satisfaction	Likert scale developed for the study to assess satisfaction with the assigned condition and the overall study (11 items)
Program engagement	Likert scale developed for the study to assess completion of daily practice, completion barriers and facilitators, and intention to complete practice in the following week (6 items)

Table 4. Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) schedule of enrollment, interventions, and assessment.

Study activities in each phase	Timepoint				
	Enrollment	Postallocation			
	Week 1 (t0)	Week 2	Week 9	Week 10 (t1)	3 months postpartum (t2)
Preintervention					
Eligibility screening	X[a]	N/A[b]	N/A	N/A	N/A
Informed consent	X	N/A	N/A	N/A	N/A
Allocation	X	N/A	N/A	N/A	N/A
Intervention					
Web-based mindfulness training	N/A	X	X	N/A	N/A
Web-based loving-kindness and compassion training	N/A	X	X	N/A	N/A
Web-based progress muscle relaxation	N/A	X	X	N/A	N/A
Assessments					
Demographics	X	N/A	N/A	N/A	N/A
Self-reported mental well-being, depression, anxiety, self-compassion, mindfulness, and quality of life	X	N/A	N/A	X	X
Self-reported affect, stress, and emotion regulation	X	N/A	N/A	X	X
Program engagement	N/A	X	X	N/A	N/A
Interviews	N/A	N/A	N/A	X	X

[a]X denotes when the study activity occurs.

[b]N/A: not applicable.

Data Management

On enrollment, all participants will be given a unique identifier that will be used in all database records. Although patient identifying information (first name and initials, date of birth, phone number, and email address) will be collected, this information will be stored separately to the outcome data and will be linkable only by the RA. Identifying information will be used for patient contact and linking with ORIGINS records.

Analytic Plan

Quantitative Analysis

The baseline characteristics of the participants will be reported to describe the sample. Descriptive statistics will be used to

summarize the quantitative data collected for each feasibility domain. Feasibility metrics will address the ADePT (*a process for decision making after pilot and feasibility trials*) framework [79]. This feasibility framework has been incorporated as part of a phased approach to the development and evaluation of the intervention. Feasibility assessment will use both quantitative feasibility data and qualitative data derived from the postprogram interviews. According to the ADePT framework, the progression criteria to move from a pilot to full-scale trial are divided into 3 categories: green, red, and amber (Table 5). Although the purpose of the study is not hypothesis testing, we will calculate the differences between the experimental groups and the control condition for primary and secondary outcomes.

Table 5. Decision-making criteria for full-scale randomized controlled trial, adapted from the "a process for decision making after pilot and feasibility trials" framework.

Outcome	Metrics
Green (proceed to full-scale RCT[a] without refinement)	• ≥50% of eligible participants consent to the pilot trial • ≥70% of consented participants commence each intervention arm • ≥50% of consented participants complete all intervention sessions in each intervention arm • Program satisfaction ratings and postprogram interventions demonstrate high satisfaction and acceptability of the program for ≥50% participants
Red (do not proceed to full-scale RCT)	• <30% of eligible participants consent to the pilot trial • <20% of consented participants commence each intervention arm • Program satisfaction ratings and postprogram interventions demonstrate low satisfaction or lack of acceptability of the program for ≥50% participants
Amber (consider proceeding to full-scale trial only after protocols have been refined)	• Neither red nor green criteria were met. Findings from qualitative and quantitative data will be used to determine whether a full-scale RCT should proceed with revisions

[a]RCT: randomized controlled trial.

Qualitative Analysis

Qualitative data collected during interviews will be analyzed to identify key themes regarding program engagement, acceptable and perceived impacts, and confidence in sustaining meditation practices. Using the approach by Braun and Clarke [80] to thematic analysis, transcripts will be iteratively coded, and codes will be collated into higher-level themes [80]. Transcripts will be reviewed to identify all instances of thematic codes, with codes expanded or collapsed as required. Qualitative data will be analyzed using qualitative content analysis [81], assigning a code to each concept using NVivo. Similar concepts will be identified and categorized into categories. Data will be analyzed using a phenomenological approach (ie, as a description of experiences as consciously experienced by participants), and narrative themes will be deducted until saturation. The coding process will be guided by the following deductive constructs: intervention acceptability, engagement, and application; mental health and well-being experiences; and suggestions for program revision.

Data Monitoring and Harms

Adverse events will be monitored weekly based on the self-reported data provided by participants at the weekly assessment and the data collected by the ORIGINS team. The key adverse event linked to the MMM study is deteriorating mental health; however, there is also a range of potential adverse events linked to pregnancy that are recorded by ORIGINS. In the MMM study, participants will be encouraged to contact the RA at any point if they have concerns about deteriorating mental health. They are asked weekly if they wish to continue with the program. If they select "no," they are asked about their reasons for discontinuation (including concerns about their mental or physical health). If participants report concerns about their mental health during the intervention or upon withdrawal from the study, they will be screened for depressive symptoms using the EPDS and for symptoms of traumatic stress using the abbreviated version of the Posttraumatic Stress Disorder Checklist–Civilian version (PCL-C) [82]. Participants who endorse item 10 on the EPDS or score 14 or more on the abbreviated PCL-C will receive a follow-up phone call from the study psychologist to discuss referral to more intensive or specialized support services. If a participant reports concerns about their mental or physical health, this will be reported to ORIGINS. ORIGINS has standard operating procedures for following up adverse events [62]. All adverse events in the MMM study will be recorded on an adverse event monitoring form, and all events and follow-up will be reported to an independent study monitor.

Results

This study was funded in September 2019 and received ethics approval on July 8, 2020. Enrollment to the study will commence in September 2020. A period of 1 year is scheduled for data collection, analysis, and publication of results. The results will inform the design of an adequately powered RCT.

Discussion

There is a need for scalable, flexible, and accessible interventions to promote the mental health of women during the perinatal period. Such interventions play an important role in supporting maternal resilience across pregnancy, potentially preventing the development of mental health problems and adjustment difficulties in the postpartum period. Although there is evidence to support the use of MBIs for improving psychological health in the perinatal period, data on the

feasibility and acceptability of web-based MBIs are limited. Furthermore, little is known about the comparative benefits of alternative meditation training programs such as those that aim to cultivate loving-kindness and compassion. As no prior studies have compared MBIs and CBIs in the perinatal period, this pilot study will provide important insights into how women might differentially experience these interventions. It will also provide data to support the design of a large-scale RCT.

Strengths

The proposed study has both strengths and limitations. The relative strength of the intervention approach is the involvement of mothers in the development of the intervention conditions. To our knowledge, there is limited literature documenting consumer involvement in the development of meditation-based interventions or in perinatal mental health promotion programs. Furthermore, the proposed trial will collect multiple measures of intervention engagement, experience, acceptability, adherence, perceived benefits, and harm. This comprehensive approach aligns with the recommendations made by Dimidjian and Segal [83] for progressing the clinical science of MBIs. In addition, the study is nested within a large longitudinal birth cohort, enabling future follow-up of study participants and their offspring. Finally, we have prespecified criteria for determining the feasibility of the study and determining whether to proceed with the full-scale RCT. Should the study proceed to a full-scale RCT, this will be one of few randomized trials of MBIs with pregnant women that use a well-matched active control condition.

Limitations

The situation of this study within a larger longitudinal birth cohort study also has limitations, namely that participants in the study are limited to those who have already consented to participate in a research project with a significant time investment. Accordingly, these women may not be representative of the general population, and insights into the accessibility and scalability of the MMM intervention are thus limited to this group. We propose to address this in the future by conducting consultation with women and service providers at other maternity hospitals not participating in ORIGINS and to study the effectiveness and implementation of the MMM study in women giving birth in these hospitals. A further limitation of the study is the potential confounding due to the capacity of participants in the study to seek psychological treatment while participating. To explore the impact of concurrent treatment, we will measure this at baseline and posttest, with the intention of analyzing these data in a full-scale RCT. Furthermore, it is anticipated that our sample will be heterogeneous with regard to the levels of psychological distress that participants experience and types of other support accessed during the study period. Despite these limitations, we believe that the proposed trial will provide important insights into the potential utility of web-based meditation-based training as a scalable public health intervention for promoting perinatal mental health.

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Authors' Contributions

AF, J Davis, AO, DS, JO, J Downs, and SP designed the study. AF and AO developed the intervention content with the support of RA. AF and KK drafted the manuscript, which was reviewed and approved by all authors.

Conflicts of Interest

AF is a trained and certified teacher of several different mindfulness and compassion-based programs and occasionally receives monetary reimbursement for delivering these programs.

Multimedia Appendix 1
Description of mindfulness and loving-kindness and compassion practices used in the Mums Minds Matter program.
[DOCX File , 16 KB - resprot_v9i10e19803_app1.docx]

References

1. Cornsweet BC, Steadman J. Distress levels in pregnancy and matched non-pregnant women. ANZJOG 2017;58(1):128-131.
2. Arifin SR, Cheyne H, Maxwell M. Review of the prevalence of postnatal depression across cultures. AIMS Public Health 2018;5(3):260-295 [FREE Full text] [doi: 10.3934/publichealth.2018.3.260] [Medline: 30280116]
3. Stone SL, Diop H, Declercq E, Cabral HJ, Fox MP, Wise LA. Stressful events during pregnancy and postpartum depressive symptoms. J Womens Health (Larchmt) 2015 May;24(5):384-393 [FREE Full text] [doi: 10.1089/jwh.2014.4857] [Medline: 25751609]
4. Salm Ward T, Kanu FA, Robb SW. Prevalence of stressful life events during pregnancy and its association with postpartum depressive symptoms. Arch Womens Ment Health 2017 Feb;20(1):161-171. [doi: 10.1007/s00737-016-0689-2] [Medline: 27785635]

5. Stein A, Pearson RM, Goodman SH, Rapa E, Rahman A, McCallum M, et al. Effects of perinatal mental disorders on the fetus and child. Lancet 2014 Nov;384(9956):1800-1819. [doi: 10.1016/s0140-6736(14)61277-0]
6. Dunkel Schetter C. Psychological science on pregnancy: stress processes, biopsychosocial models, and emerging research issues. Annu Rev Psychol 2011;62:531-558. [doi: 10.1146/annurev.psych.031809.130727] [Medline: 21126184]
7. Henrichs J, Schenk JJ, Roza SJ, van den Berg MP, Schmidt HG, Steegers EAP, et al. Maternal psychological distress and fetal growth trajectories: the Generation R Study. Psychol Med 2010 Apr;40(4):633-643. [doi: 10.1017/S0033291709990894] [Medline: 19656431]
8. Osborne S, Biaggi A, Chua T, Du Preez A, Hazelgrove K, Nikkheslat N, et al. Corrigendum to "Antenatal depression programs cortisol stress reactivity in offspring through increased maternal inflammation and cortisol in pregnancy: The Psychiatry Research and Motherhood - Depression (PRAM-D) study" [Psychoneuroendocrinology 98 (2018) 211-221]. Psychoneuroendocrinology 2020 Sep;119:104795. [doi: 10.1016/j.psyneuen.2020.104795] [Medline: 32709460]
9. van den Bergh BRH, van den Heuvel MI, Lahti M, Braeken M, de Rooij SR, Entringer S, et al. Prenatal developmental origins of behavior and mental health: The influence of maternal stress in pregnancy. Neurosci Biobehav Rev 2017 Jul 28. [doi: 10.1016/j.neubiorev.2017.07.003] [Medline: 28757456]
10. Lahti M, Savolainen K, Tuovinen S, Pesonen A, Lahti J, Heinonen K, et al. Maternal Depressive Symptoms During and After Pregnancy and Psychiatric Problems in Children. J Am Acad Child Adolesc Psychiatry 2017 Jan;56(1):30-39.e7. [doi: 10.1016/j.jaac.2016.10.007] [Medline: 27993226]
11. Wolford E, Lahti M, Tuovinen S, Lahti J, Lipsanen J, Savolainen K, et al. Maternal depressive symptoms during and after pregnancy are associated with attention-deficit/hyperactivity disorder symptoms in their 3- to 6-year-old children. PLoS One 2017;12(12):e0190248 [FREE Full text] [doi: 10.1371/journal.pone.0190248] [Medline: 29267405]
12. Van Batenburg-Eddes T, Brion MJ, Henrichs J, Jaddoe VW, Hofman A, Verhulst FC, et al. Parental depressive and anxiety symptoms during pregnancy and attention problems in children: a cross-cohort consistency study. J Child Psychol Psychiatry 2013 May;54(5):591-600 [FREE Full text] [doi: 10.1111/jcpp.12023] [Medline: 23215861]
13. O'Donnell KJ, Glover V, Barker ED, O'Connor TG. The persisting effect of maternal mood in pregnancy on childhood psychopathology. Dev Psychopathol 2014 May;26(2):393-403. [doi: 10.1017/S0954579414000029] [Medline: 24621564]
14. El Marroun H, Tiemeier H, Muetzel RL, Thijssen S, van der Knaap NJ, Jaddoe VW, et al. Prenatal Exposure to Maternal and Paternal Depressive Symptoms and Brain Morphology: A Population-based Prospective Neuroimaging Study in Young Children. Depress Anxiety 2016 Jul;33(7):658-666. [doi: 10.1002/da.22524] [Medline: 27163186]
15. Wadhwa P, Buss C, Entringer S, Swanson J. Developmental origins of health and disease: brief history of the approach and current focus on epigenetic mechanisms. Semin Reprod Med 2009 Sep;27(5):358-368 [FREE Full text] [doi: 10.1055/s-0029-1237424] [Medline: 19711246]
16. Moe V, von Soest T, Fredriksen E, Olafsen KS, Smith L. The Multiple Determinants of Maternal Parenting Stress 12 Months After Birth: The Contribution of Antenatal Attachment Style, Adverse Childhood Experiences, and Infant Temperament. Front Psychol 2018;9:1987 [FREE Full text] [doi: 10.3389/fpsyg.2018.01987] [Medline: 30405481]
17. Giallo R, Cooklin A, Wade C, D'Esposito F, Nicholson JM. Maternal postnatal mental health and later emotional-behavioural development of children: the mediating role of parenting behaviour. Child Care Health Dev 2014 May;40(3):327-336. [doi: 10.1111/cch.12028] [Medline: 23363326]
18. Da Costa D, Zelkowitz P, Nguyen T, Deville-Stoetzel J. Mental health help-seeking patterns and perceived barriers for care among nulliparous pregnant women. Arch Womens Ment Health 2018 Dec;21(6):757-764. [doi: 10.1007/s00737-018-0864-8] [Medline: 29846799]
19. Button S, Thornton A, Lee S, Shakespeare J, Ayers S. Seeking help for perinatal psychological distress: a meta-synthesis of women's experiences. Br J Gen Pract 2017 Oct;67(663):e692-e699 [FREE Full text] [doi: 10.3399/bjgp17X692549] [Medline: 28847773]
20. Woolhouse H, Brown S, Krastev A, Perlen S, Gunn J. Seeking help for anxiety and depression after childbirth: results of the Maternal Health Study. Arch Womens Ment Health 2009 Apr;12(2):75-83. [doi: 10.1007/s00737-009-0049-6] [Medline: 19214705]
21. Goodman JH. Women's attitudes, preferences, and perceived barriers to treatment for perinatal depression. Birth 2009 Mar;36(1):60-69. [doi: 10.1111/j.1523-536X.2008.00296.x] [Medline: 19278385]
22. Lamers SM, Westerhof GJ, Glas CA, Bohlmeijer ET. The bidirectional relation between positive mental health and psychopathology in a longitudinal representative panel study. J Posit Psychol 2015 May 27;10(6):553-560. [doi: 10.1080/17439760.2015.1015156]
23. Grant F, Guille C, Sen S. Well-being and the risk of depression under stress. PLoS One 2013;8(7):e67395 [FREE Full text] [doi: 10.1371/journal.pone.0067395] [Medline: 23840872]
24. Schotanus-Dijkstra M, Keyes CL, de Graaf R, Ten Have M. Recovery from mood and anxiety disorders: The influence of positive mental health. J Affect Disord 2019 Jun 01;252:107-113. [doi: 10.1016/j.jad.2019.04.051] [Medline: 30981053]
25. Keyes CL, Dhingra SS, Simoes EJ. Change in level of positive mental health as a predictor of future risk of mental illness. Am J Public Health 2010 Dec;100(12):2366-2371. [doi: 10.2105/AJPH.2010.192245] [Medline: 20966364]

26. Bos SC, Macedo A, Marques M, Pereira AT, Maia BR, Soares MJ, et al. Is positive affect in pregnancy protective of postpartum depression? Braz J Psychiatry 2013 Mar;35(1):5-12 [FREE Full text] [doi: 10.1016/j.rbp.2011.11.002] [Medline: 23567594]
27. Robakis TK, Williams KE, Crowe S, Kenna H, Gannon J, Rasgon NL. Optimistic outlook regarding maternity protects against depressive symptoms postpartum. Arch Womens Ment Health 2015 Apr;18(2):197-208 [FREE Full text] [doi: 10.1007/s00737-014-0446-3] [Medline: 25088532]
28. Voellmin A, Entringer S, Moog N, Wadhwa PD, Buss C. Maternal positive affect over the course of pregnancy is associated with the length of gestation and reduced risk of preterm delivery. J Psychosom Res 2013 Oct;75(4):336-340 [FREE Full text] [doi: 10.1016/j.jpsychores.2013.06.031] [Medline: 24119939]
29. Huppert FA, Whittington JE. Evidence for the independence of positive and negative well-being: implications for quality of life assessment. Br J Health Psychol 2003 Feb;8(Pt 1):107-122. [doi: 10.1348/135910703762879246] [Medline: 12643820]
30. Slade M. Mental illness and well-being: the central importance of positive psychology and recovery approaches. BMC Health Serv Res 2010 Jan 26;10:26 [FREE Full text] [doi: 10.1186/1472-6963-10-26] [Medline: 20102609]
31. Spijkerman M, Pots W, Bohlmeijer E. Effectiveness of online mindfulness-based interventions in improving mental health: A review and meta-analysis of randomised controlled trials. Clin Psychol Rev 2016 Apr;45:102-114 [FREE Full text] [doi: 10.1016/j.cpr.2016.03.009] [Medline: 27111302]
32. Galla BM, O'Reilly GA, Kitil MJ, Smalley SL, Black DS. Community-Based Mindfulness Program for Disease Prevention and Health Promotion: Targeting Stress Reduction. Am J Health Promot 2015;30(1):36-41. [doi: 10.4278/ajhp.131107-QUAN-567] [Medline: 25162319]
33. de Abreu Costa M, D'Alò de Oliveira GS, Tatton-Ramos T, Manfro GG, Salum GA. Anxiety and stress-related disorders and mindfulness-based interventions: a systematic review and multilevel meta-analysis and meta-regression of multiple outcomes. Mindfulness 2018 Nov 15;10(6):996-1005. [doi: 10.1007/s12671-018-1058-1]
34. Geschwind N, Peeters F, Drukker M, van Os J, Wichers M. Mindfulness training increases momentary positive emotions and reward experience in adults vulnerable to depression: a randomized controlled trial. J Consult Clin Psychol 2011 Oct;79(5):618-628. [doi: 10.1037/a0024595] [Medline: 21767001]
35. Kirby JN, Tellegen CL, Steindl SR. A Meta-Analysis of Compassion-Based Interventions: Current State of Knowledge and Future Directions. Behav Ther 2017 Nov;48(6):778-792. [doi: 10.1016/j.beth.2017.06.003] [Medline: 29029675]
36. Kang Y, Gray JR, Dovidio JF. The Head and the Heart: Effects of Understanding and Experiencing Lovingkindness on Attitudes Toward the Self and Others. Mindfulness 2014 Oct 25;6(5):1063-1070. [doi: 10.1007/s12671-014-0355-6]
37. Trautwein F, Kanske P, Böckler A, Singer T. Differential benefits of mental training types for attention, compassion, and theory of mind. Cognition 2020 Jan;194:104039 [FREE Full text] [doi: 10.1016/j.cognition.2019.104039] [Medline: 31450018]
38. Fredrickson BL, Boulton AJ, Firestine AM, van Cappellen P, Algoe SB, Brantley MM, et al. Positive emotion correlates of meditation practice: a comparison of mindfulness meditation and loving-kindness meditation. Mindfulness (N Y) 2017 Dec;8(6):1623-1633 [FREE Full text] [doi: 10.1007/s12671-017-0735-9] [Medline: 29201247]
39. Zeng X, Chiu CP, Wang R, Oei TP, Leung FY. The effect of loving-kindness meditation on positive emotions: a meta-analytic review. Front Psychol 2015;6:1693 [FREE Full text] [doi: 10.3389/fpsyg.2015.01693] [Medline: 26579061]
40. Hofmann SG, Grossman P, Hinton DE. Loving-kindness and compassion meditation: potential for psychological interventions. Clin Psychol Rev 2011 Nov;31(7):1126-1132 [FREE Full text] [doi: 10.1016/j.cpr.2011.07.003] [Medline: 21840289]
41. Graser J, Stangier U. Compassion and loving-kindness meditation: an overview and prospects for the application in clinical samples. Harv Rev Psychiatry 2018;26(4):201-215. [doi: 10.1097/HRP.0000000000000192] [Medline: 29975338]
42. Le Nguyen KD, Lin J, Algoe SB, Brantley MM, Kim SL, Brantley J, et al. Loving-kindness meditation slows biological aging in novices: Evidence from a 12-week randomized controlled trial. Psychoneuroendocrinology 2019 Oct;108:20-27. [doi: 10.1016/j.psyneuen.2019.05.020] [Medline: 31185369]
43. Nyklíček I, Truijens SE, Spek V, Pop VJ. Mindfulness skills during pregnancy: prospective associations with mother's mood and neonatal birth weight. J Psychosom Res 2018 Apr;107:14-19. [doi: 10.1016/j.jpsychores.2018.01.012] [Medline: 29502758]
44. van den Heuvel M, Johannes M, Henrichs J, van den Bergh B. Maternal mindfulness during pregnancy and infant socio-emotional development and temperament: the mediating role of maternal anxiety. Early Hum Dev 2015 Feb;91(2):103-108. [doi: 10.1016/j.earlhumdev.2014.12.003] [Medline: 25577496]
45. Braeken MA, Jones A, Otte RA, Nyklíček I, Van den Bergh BR. Potential benefits of mindfulness during pregnancy on maternal autonomic nervous system function and infant development. Psychophysiology 2017 Feb;54(2):279-288. [doi: 10.1111/psyp.12782] [Medline: 28118687]
46. Hall HG, Beattie J, Lau R, East C, Anne Biro M. Mindfulness and perinatal mental health: a systematic review. Women Birth 2016 Feb;29(1):62-71. [doi: 10.1016/j.wombi.2015.08.006] [Medline: 26346905]
47. Taylor BL, Cavanagh K, Strauss C. The effectiveness of mindfulness-based interventions in the perinatal period: a systematic review and meta-analysis. PLoS One 2016;11(5):e0155720 [FREE Full text] [doi: 10.1371/journal.pone.0155720] [Medline: 27182732]

48. Shi Z, MacBeth A. The effectiveness of mindfulness-based interventions on maternal perinatal mental health outcomes: a systematic review. Mindfulness (N Y) 2017;8(4):823-847 [FREE Full text] [doi: 10.1007/s12671-016-0673-y] [Medline: 28757900]
49. Townshend K, Caltabiano N. Self-compassion and mindfulness: modeling change processes associated with the reduction of perinatal depression. J Child Fam Stud 2019 Apr 17;28(7):1790-1802. [doi: 10.1007/s10826-019-01371-2]
50. Monteiro F, Fonseca A, Pereira M, Alves S, Canavarro MC. What protects at-risk postpartum women from developing depressive and anxiety symptoms? The role of acceptance-focused processes and self-compassion. J Affect Disord 2019 Mar 1;246:522-529. [doi: 10.1016/j.jad.2018.12.124] [Medline: 30599377]
51. Pedro L, Branquinho M, Canavarro MC, Fonseca A. Self-criticism, negative automatic thoughts and postpartum depressive symptoms: the buffering effect of self-compassion. J Reprod Infant Psychol 2019 Nov;37(5):539-553. [doi: 10.1080/02646838.2019.1597969] [Medline: 30947526]
52. Kelman AR, Evare BS, Barrera AZ, Muñoz RF, Gilbert P. A proof-of-concept pilot randomized comparative trial of brief Internet-based compassionate mind training and cognitive-behavioral therapy for perinatal and intending to become pregnant women. Clin Psychol Psychother 2018 Feb 23:608-619. [doi: 10.1002/cpp.2185] [Medline: 29473698]
53. Kim MJ, Heo JM, Gim WS. An Examination of the Possibility of Loving-Kindness and Compassion Meditation for Pregnant Women: A Preliminary Study. Korean J Str Res 2017 Jun 30;25(2):145-154. [doi: 10.17547/kjsr.2017.25.2.145]
54. Lippmann M, Laudel H, Heinzle M, Narciss S. Relating instructional design components to the effectiveness of internet-based mindfulness interventions: a critical interpretive synthesis. J Med Internet Res 2019 Nov 27;21(11):e12497 [FREE Full text] [doi: 10.2196/12497] [Medline: 31774413]
55. Bennett GG, Glasgow RE. The delivery of public health interventions via the internet: actualizing their potential. Annu Rev Public Health 2009;30:273-292. [doi: 10.1146/annurev.publhealth.031308.100235] [Medline: 19296777]
56. Cavanagh K, Strauss C, Forder L, Jones F. Can mindfulness and acceptance be learnt by self-help?: a systematic review and meta-analysis of mindfulness and acceptance-based self-help interventions. Clin Psychol Rev 2014 Mar;34(2):118-129. [doi: 10.1016/j.cpr.2014.01.001] [Medline: 24487343]
57. Krieger T, Reber F, von Glutz B, Urech A, Moser CT, Schulz A, et al. An internet-based compassion-focused intervention for increased self-criticism: a randomized controlled trial. Behav Ther 2019 Mar;50(2):430-445. [doi: 10.1016/j.beth.2018.08.003] [Medline: 30824257]
58. Ashford MT, Olander EK, Ayers S. Computer- or web-based interventions for perinatal mental health: a systematic review. J Affect Disord 2016 Jun;197:134-146. [doi: 10.1016/j.jad.2016.02.057] [Medline: 26991368]
59. Krusche A, Dymond M, Murphy SE, Crane C. Mindfulness for pregnancy: a randomised controlled study of online mindfulness during pregnancy. Midwifery 2018 Oct;65:51-57. [doi: 10.1016/j.midw.2018.07.005] [Medline: 30099285]
60. Hilgart MM, Ritterband LM, Thorndike FP, Kinzie MB. Using instructional design process to improve design and development of internet interventions. J Med Internet Res 2012 Jun 28;14(3):e89 [FREE Full text] [doi: 10.2196/jmir.1890] [Medline: 22743534]
61. Beddoe AE, Lee KA. Mind-body interventions during pregnancy. J Obstet Gynecol Neonatal Nurs 2008;37(2):165-175. [doi: 10.1111/j.1552-6909.2008.00218.x] [Medline: 18336440]
62. Hagemann E, Colvin L, Gibson LY, Miller SJ, Palmer DJ, Srinivas Jois R, et al. The ORIGINS Project. In: Sata F, Fukuoka H, Hanson M, editors. Pre-emptive Medicine: Public Health Aspects of Developmental Origins of Health and Disease. Singapore: Springer; 2019:99-116.
63. Whitehead AL, Julious SA, Cooper CL, Campbell MJ. Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable. Stat Methods Med Res 2016 Jun;25(3):1057-1073 [FREE Full text] [doi: 10.1177/0962280215588241] [Medline: 26092476]
64. Milgrom J, Ericksen J, Negri L, Gemmill AW. Screening for postnatal depression in routine primary care: properties of the Edinburgh postnatal depression scale in an Australian sample. Aust N Z J Psychiatry 2005 Sep;39(9):833-839. [doi: 10.1080/j.1440-1614.2005.01660.x] [Medline: 16168042]
65. Jacobson E. Progressive Relaxation. Chicago, IL: University of Chicago Press; 1938.
66. Lindsay EK, Chin B, Greco CM, Young S, Brown KW, Wright AG, et al. How mindfulness training promotes positive emotions: dismantling acceptance skills training in two randomized controlled trials. J Pers Soc Psychol 2018 Dec;115(6):944-973 [FREE Full text] [doi: 10.1037/pspa0000134] [Medline: 30550321]
67. Dahl CJ, Lutz A, Davidson RJ. Cognitive processes are central in compassion meditation. Trends Cogn Sci 2016 Mar;20(3):161-162. [doi: 10.1016/j.tics.2015.12.005] [Medline: 26762882]
68. Dahl CJ, Lutz A, Davidson RJ. Reconstructing and deconstructing the self: cognitive mechanisms in meditation practice. Trends Cogn Sci 2015 Sep;19(9):515-523 [FREE Full text] [doi: 10.1016/j.tics.2015.07.001] [Medline: 26231761]
69. Engen HG, Singer T. Affect and motivation are critical in constructive meditation. Trends Cogn Sci 2016 Mar;20(3):159-160. [doi: 10.1016/j.tics.2015.11.004] [Medline: 26686556]
70. Keyes CL. The mental health continuum: from languishing to flourishing in life. J Health Soc Behav 2002 Jun;43(2):207-222. [Medline: 12096700]
71. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh postnatal depression scale. Br J Psychiatry 1987 Jun;150:782-786. [doi: 10.1192/bjp.150.6.782] [Medline: 3651732]

72. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006 May 22;166(10):1092-1097. [doi: 10.1001/archinte.166.10.1092] [Medline: 16717171]
73. Cohen S. Perceived stress in a probability sample of the United States. In: Spacapan S, Oskamp S, editors. The Social Psychology of Health: The Claremont Symposium on Applied Social. Newbury Park, CA: Sage; 1988:31-67.
74. Raes F, Pommier E, Neff KD, Van Gucht D. Construction and factorial validation of a short form of the self-compassion scale. Clin Psychol Psychother 2011;18(3):250-255. [doi: 10.1002/cpp.702] [Medline: 21584907]
75. Brown KW, Ryan RM. The benefits of being present: mindfulness and its role in psychological well-being. J Pers Soc Psychol 2003 Apr;84(4):822-848. [doi: 10.1037/0022-3514.84.4.822] [Medline: 12703651]
76. Bjureberg J, Ljótsson B, Tull MT, Hedman E, Sahlin H, Lundh L, et al. Development and validation of a brief version of the difficulties in emotion regulation scale: the DERS-16. J Psychopathol Behav Assess 2016 Jun;38(2):284-296 [FREE Full text] [doi: 10.1007/s10862-015-9514-x] [Medline: 27239096]
77. Thompson ER. Development and validation of an internationally reliable short-form of the positive and negative affect schedule (PANAS). J Cross-Cult Psychol 2016 Jul 26;38(2):227-242. [doi: 10.1177/0022022106297301]
78. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011 Dec;20(10):1727-1736 [FREE Full text] [doi: 10.1007/s11136-011-9903-x] [Medline: 21479777]
79. Bugge C, Williams B, Hagen S, Logan J, Glazener C, Pringle S, et al. A process for decision-making after pilot and feasibility trials (ADePT): development following a feasibility study of a complex intervention for pelvic organ prolapse. Trials 2013 Oct 25;14:353 [FREE Full text] [doi: 10.1186/1745-6215-14-353] [Medline: 24160371]
80. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006 Jan;3(2):77-101. [doi: 10.1191/1478088706qp063oa]
81. Sandelowski M. Whatever happened to qualitative description? Res Nurs Health 2000 Aug;23(4):334-340. [doi: 10.1002/1098-240x(200008)23:4<334::aid-nur9>3.0.co;2-g] [Medline: 10940958]
82. Lang AJ, Stein MB. An abbreviated PTSD checklist for use as a screening instrument in primary care. Behav Res Ther 2005 May;43(5):585-594. [doi: 10.1016/j.brat.2004.04.005] [Medline: 15865914]
83. Dimidjian S, Segal ZV. Prospects for a clinical science of mindfulness-based intervention. Am Psychol 2015 Oct;70(7):593-620 [FREE Full text] [doi: 10.1037/a0039589] [Medline: 26436311]

Abbreviations

ADePT: A process for Decision making after Pilot and Feasibility Trials
CBI: compassion-based intervention
EPDS: Edinburgh Postnatal Depression Scale
JHC: Joondalup Health Campus
LKCT: loving-kindness and compassion training
MBI: mindfulness-based intervention
MMM: Mums' Mind Matter
PMR: Progressive Muscle Relaxation
RA: research assistant
RCT: randomized controlled trial

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Protocol

Repetitive Transcranial Magnetic Stimulation With and Without Internet-Delivered Cognitive-Behavioral Therapy for the Treatment of Resistant Depression: Protocol for Patient-Centered Randomized Controlled Pilot Trial

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Abstract

Background: Major depression is a severe, disabling, and potentially lethal clinical disorder. Only about half of patients respond to an initial course of antidepressant pharmacotherapy. At least 15% of all patients with major depressive disorder (MDD) remain refractory to any treatment intervention. By the time that a patient has experienced 3 definitive treatment failures, the likelihood of achieving remission with the fourth treatment option offered is below 10%. Repetitive transcranial magnetic stimulation (rTMS) is considered a treatment option for patients with MDD who are refractory to antidepressant treatment. It is not currently known if the addition of internet-delivered cognitive-behavioral therapy (iCBT) enhances patients' responses to rTMS treatments.

Objective: This study will evaluate the initial comparative clinical effectiveness of rTMS with and without iCBT as an innovative patient-centered intervention for the treatment of participants diagnosed with treatment-resistant depression (TRD).

Methods: This study is a prospective, two-arm randomized controlled trial. In total, 100 participants diagnosed with resistant depression at a psychiatric care clinic in Edmonton, Alberta, Canada, will be randomized to one of two conditions: (1) enrolment in rTMS sessions alone and (2) enrolment in the rTMS sessions plus iCBT. Participants in each group will complete evaluation measures (eg, recovery, general symptomatology, and functional outcomes) at baseline, 1 month, 3 months, and 6 months. The primary outcome measure will be the mean change to scores on the Hamilton Depression Rating Scale. Patient service utilization data and clinician-rated measures will also be used to gauge patient progress. Patient data will be analyzed with descriptive statistics, repeated measures, and correlational analyses.

Results: We expect the results of the study to be available in 24 months. We hypothesize that participants enrolled in the study who receive rTMS plus iCBT will achieve superior outcomes in comparison to participants who receive rTMS alone.

Conclusions: The concomitant application of psychotherapy with rTMS has not been investigated previously. We hope that this project will provide us with a concrete base of data to evaluate the practical application and efficacy of using a novel combination of these two treatment modalities (rTMS plus iCBT).

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KEYWORDS

repetitive transcranial magnetic stimulation; internet-delivered cognitive-behavioral therapy; treatment of resistant depression; cognitive-behavioral therapy; depression

Introduction

Background and Rationale

Major depression is a severe, disabling, and potentially lethal clinical disorder [1-3]. Although there are a wide variety of pharmaceutical agents available as treatments for major depression, only about half of patients respond to an initial course of antidepressant pharmacotherapy [4,5]. For these patients, the current standard of care involves an empirical series of treatment attempts, typically using medication switches, antidepressant combinations, or adjunctive therapy with mood stabilizers, benzodiazepines, atypical antipsychotics, or other agents [6]. The adverse event burden and tolerability of some of these more complex interventions are not trivial and are a significant factor that hinders patient adherence to treatment [7]. Similarly, although there is increasing evidence that at least some of the atypical antipsychotics are effective as adjuncts to antidepressants, the potential for side effects, including weight gain and dyslipidemia, warrants both caution and careful clinical management.

It has been conservatively estimated that at least 15% of all patients with major depressive disorder (MDD) remain refractory to any treatment intervention [5,6]. Although a complicated relationship exists between disease chronicity and ineffective treatment [8], clinical evidence suggests that the higher the number of treatment failures, the lower the likelihood of good treatment response to subsequent interventions [4,9]. The reported results of the STAR*D study are the most vivid example of this clinical phenomenon [10-16]. In that work, there was an increased likelihood of more reduced response with each successive treatment failure. For example, after the first treatment attempt, about 30% of patients remitted. By the time that a patient had experienced 3 definitive treatment failures, the likelihood of achieving remission with the fourth treatment option offered fell below 10%. Poor treatment adherence and high discontinuation rates represent a major challenge, particularly for pharmacotherapy. Strategies for enhancing adherence include patient education and supported self-management, as well as the use of collaborative care systems by practitioners. Treatment adherence should be discussed at an early stage and monitored frequently during treatment in a collaborative manner. A weak therapeutic alliance predicts poorer treatment adherence [17]. These facts underline the clinical urgency for physicians to identify treatment-resistant patients as early as possible so that alternative treatments with proven efficacies may be offered sooner. In turn, this will result in superior treatment outcomes for these treatment-resistant patients.

Technology and the internet have dramatically changed medicine. According to Statistics Canada, 83% of Canadians had internet access in 2012, and more than 70% use the internet daily; in addition, 62% were smartphone users [17]. E–mental health refers to the use of computers, internet, and mobile devices for mental health information and care provision [18]. E–mental health apps are now widely available for information, screening, assessment and monitoring, interactive self-management, psychotherapy, and social support. Clinicians should be aware that there are benefits and potential harms to using and recommending e–mental health apps and that few have good-quality evidence of effectiveness [18-20]. Meta-analyses and reviews of computer-based psychological treatment for the treatment of MDD, whether delivered over the internet or as a stand-alone program, demonstrate convincing support for these treatment modalities [21-27]. Internet- and computer-delivered cognitive behavioral therapy (iCBT) can also be helpful in relapse prevention [28].

In 2009, the Canadian Network for Mood and Anxiety Treatments (CANMAT), a not-for-profit scientific and educational organization, published a revision of evidence-based clinical guidelines for the treatment of depressive disorders [29]. CANMAT updated these guidelines in 2016 to reflect new evidence in the field [30-35]. These updated CANMAT guidelines cover a variety of treatments, including psychological treatments in general and cognitive-behavioral therapy (CBT) in particular, as well as pharmacological treatments, neurostimulation, and complementary and alternative medicine (CAM) treatments. Choosing a first-line treatment among these treatment choices remains a collaborative decision between patient and clinician. However, there continues to be greater evidence and clinical experience with traditional treatments (psychotherapy and pharmacotherapy) and few studies directly comparing these with neurostimulation or CAM treatments. In addition, many studies of neurostimulation include populations of patients who have failed at least one previous treatment. Therefore, first-line psychological and/or pharmacological treatments should usually be considered before neurostimulation or CAM treatments [17,31-35].

Neurostimulation, also referred to as neuromodulation, is an expanding area of research and clinical interest, driven in part by the increasing knowledge base on the neurocircuitry of depression [36]. Most of these neurostimulation treatments have been studied and are used in patients with TRD who have failed to respond to standard treatments [33]. However, no previous studies examined the effect of rTMS plus iCBT in comparison to rTMS alone. Our study hypothesis is to enhance the efficiency of the treatment and assess the initial comparative clinical effectiveness of rTMS treatments when used with and without iCBT in a patient population where an improvement in treatment effects is much needed.

Repetitive Transcranial Magnetic Stimulation

rTMS uses powerful (1.0-2.5 Tesla) focused magnetic field pulses to induce electrical currents in neural tissue noninvasively via an inductor coil placed against the scalp. Therapeutic rTMS is usually delivered by a trained technician or nurse under physician supervision. Unlike electroconvulsive therapy (ECT), no anesthesia is required. The therapeutic mechanism of rTMS is still under investigation, with mechanisms proposed at molecular, cellular, and network levels [37]. Standard protocols deliver rTMS once daily, 5 days/week. Stimulation 3 times/week has been reported as similarly effective, albeit with slower improvement and a similar number of sessions required overall [38]. "Accelerated" protocols with multiple daily sessions (2-10/day) are being explored to complete the course more rapidly [39,40]. Repeated rTMS sessions can exert therapeutic effects lasting several months [33]. Clinical trials and naturalistic studies have found maximal effects at 26-28 sessions [41,42]. Clinical experience concurs in suggesting 20 sessions before declaring treatment failure, with extension to 25-30 sessions if improvements occur [33].

More than 30 systematic reviews and meta-analyses have been conducted on rTMS in depression, with most studies involving participants with some degree of treatment resistance (ie, having failed at least 1 or 2 antidepressant trials). Overall, rTMS is considered a first-line treatment for MDD for participants who have failed at least 1 antidepressant treatment. Both high-frequency (10 Hz) rTMS of the left dorsolateral prefrontal cortex (DLPFC) and low-frequency (1 Hz) rTMS of the right DLPFC have demonstrated efficacy in numerous meta-analyses [43-46], with no differences in outcomes between them [43]. Hence both high-frequency left DLPFC and low-frequency right DLPFC are first-line rTMS protocol recommendations.

The efficacy of rTMS is established in patients with TRD defined by stringent criteria [47]. The most recent meta-analysis of high-frequency left DLPFC rTMS for TRD (23 trials, n=1156) illustrated significant efficacy of rTMS over sham, with a weighted mean difference of 2.31 and an effect size of 0.33 [48]. In addition, randomized controlled trials (RCTs) with adequate sessions (20-30) and treatment durations of 4 weeks or more achieved 40%-55% response and 25%-35% remission rates, and a real-world effectiveness study reported 58% response and 37% remission rates [42]. Similarly, for low-frequency right DLPFC rTMS, a meta-analysis (8 trials, n=263) revealed that patients who received the treatment had superior remission rates compared to sham (35% versus 10%, respectively, $P<.001$) [49]. Maintenance treatment is essential to prevent relapse following successful rTMS sessions. One study (n=204) reported median relapse time at 120 days, with relapse rates of 25%, 40%, 57%, and 77% at 2, 3, 4, and 6 months, respectively [50]. In another study (n=257), maintenance rTMS sessions were needed over 12 months for sustained remission in 71% of rTMS remitters and response in 63% of rTMS responders [51]. Moreover, a study found that without maintenance, 38% of rTMS responders relapsed within 24 weeks, at a mean of 109 days posttreatment [52]. With reintroduction of rTMS as needed, 73% met response criteria and 60% met remission criteria at 24 weeks [52]. Various rTMS maintenance schedules have been proposed [53,54], yet there is insufficient evidence to support any particular schedule of maintenance sessions.

Cognitive-Behavioral Therapy

Cognitive-behavioral therapy is an evidence-based, structured, intensive, time-limited, symptom-focused form of psychotherapy recommended for the treatment of major depression and anxiety disorders [55]. Internet-delivered CBT (iCBT) is structured CBT delivered via the internet. CBT helps people become aware of how certain negative automatic thoughts, attitudes, expectations, and beliefs contribute to feelings of sadness and anxiety. Specifically, "people undergoing CBT learn how their thinking patterns, which may have developed in the past to deal with difficult or painful experiences and negatively affect their behavior, can be identified and changed to reduce unhappiness" [56].

Barriers to conventional face-to-face treatment include stigmas around people seeking help in person, geography (distance from a health care professional), time, and cost. Increasingly, there is a desire to pursue internet delivery as an option to increase access to treatment [57].

ICBT consists of structured modules with clearly defined goals and is delivered via the internet [56]. Although there are many types of iCBT programs, each is a goal-oriented session that typically consists of 8-12 modules and can be guided or unguided [56]. ICBT programs are made available by computer, smartphone, or tablet, for a fee [56]. With unguided iCBT, participants are informed of a website through which they can participate in an online self-directed program. Guided iCBT involves support from a regulated health professional (eg, social worker, psychologist, psychotherapist, occupational therapist, nurse, or physician). In guided iCBT, people complete modules and communicate (via email, text messages, or telephone calls) their progress to a regulated health care professional [56].

MoodGYM is the iCBT program that will be used in this study. Its stated aims are to help participants identify and overcome emotional problems and demonstrate how patients can develop good coping skills for good mental health. It is a modular program developed by the Centre for Mental Health Research at the Australian National University [58]. Each module explores topics including the following: why someone feels the way they do, changing the way they think, changing "warped" thoughts, knowing what makes an individual upset, assertiveness, and interpersonal skills training [58]. Once registered, individuals work through a series of modules or workbooks, which can be undertaken piecemeal depending on the time available. Many studies have demonstrated the effectiveness of MoodGYM for MDD and anxiety in both outpatients and inpatients in different clinical settings [19,21,59-67]. In addition, it is effective for the mitigation of burnout, depression, and suicidality among health care students and professionals [68].

Objectives

The goal of this project is to evaluate the initial comparative clinical effectiveness of rTMS treatments when used with and without iCBT.

Due to the limited availability of data in this specific area, another goal of the study is to generate effect size data for these interventions, which will help inform sample size and power calculations for a full randomized clinical trial. Patient outcomes are organized according to recovery variables (eg, recovery and stigma), functional variables (quality of life and employment), symptom variables (psychological symptoms and overall outcomes), and service variables (eg, health service utilization, cost, and satisfaction).

Methods

Ethics and Dissemination

The study will be conducted per the Declaration of Helsinki (Hong Kong Amendment) and the Canadian guidelines for Good Clinical Practice. All participants will provide informed consent before study inclusion. The results will be disseminated at several levels, including participants, practitioners, academics/researchers, and health care organizations.

The study will be a prospective, parallel design, two-arm, rater-blinded randomized controlled pilot trial with a recruitment period of 12 months. It will involve active treatment for six weeks and an observation period of 6 months for each participant. An overview of the timeline for the project is in Table 1. The research will be carried out in an Addiction and Mental Health clinic in a large, sociodemographically diverse city in Western Canada (Edmonton, Alberta).

Table 1. Gantt chart timeline.

Milestones	Year 1				Year 2	
	Q1	Q2	Q3	Q4	Q1	Q2
Milestone 1: Recruiting and training of trainee in psychiatry, setting up of infrastructure for iCBT[a]						
1.1. Advertising and recruitment of a trainee in psychiatry who will support the research/evaluation of the project component, apply rTMS[b], and facilitate iCBT.	✓					
Milestone 2: The recruitment of study participants						
2.1. Recruitment, baseline assessment, and randomization		✓	✓			
2.2. Assignment into one of the two arms of the study		✓	✓			
2.3. Delivery of iCBT and rTMS to participants		✓	✓	✓		
Milestone 3: Follow-up assessment of study participants						
3.1. Follow-up assessments of individual study participants				✓	✓	
3.2. Follow-up satisfaction survey of participants, all groups				✓	✓	
Milestone 4: Data compilation, data analysis, and preparation of reports, publications, and presentations						
4.1. Data compilation		✓	✓	✓	✓	✓
4.2. Data analysis		✓	✓	✓	✓	✓
4.3. Preparation of reports, publications, and presentations						✓

[a]iCBT: internet-based cognitive-behavioral therapy.

[b]rTMS: repetitive transcranial magnetic stimulation.

Inclusion Criteria

Study participants should meet the following inclusion criteria:

- Aged 18-65 years
- Suffering from a major depressive episode based on Diagnostic and Statistical Manual of Mental Disorders (DSM) 5 criteria and having failed two or more standard antidepressant treatments during the current episode.
- Hamilton Depression Rating Scale (17-HAM-D) score of 10 or more
- Participant may be on psychotropic medications including antidepressants, antipsychotics, benzodiazepines, and anticonvulsants
- Have a good understanding of the English language with fair computer/internet skills, and able and willing to provide informed consent.

Exclusion Criteria

The exclusion criteria for this study are the following:

- Diagnosis with the following conditions (current unless otherwise stated):
- - A neurological disorder, including a history of seizures, cerebrovascular disease, primary or secondary tumors in the central nervous system, stroke, cerebral aneurysm, movement disorder, or any lifetime history of loss of consciousness due to head injury.
  - Any current Axis 1 psychotic disorder (including substance-induced psychosis, psychotic disorder due to a medical condition, or major depression with psychotic features), as defined by the Mini-International Neuropsychiatric Interview [69] at the screening visit.
  - Any current Axis II personality disorder that would interfere with participation in the study or might affect cognition and ability to participate meaningfully, as

well as mental retardation identified through medical history or by the investigator.
    - A current amnestic disorder, dementia, or delirium as defined by a Montreal Cognitive Assessment score of ≤16, or any other neurological or mental disease that might affect cognition or the ability to participate in CBT meaningfully.
- Participation in any drug or device clinical trial in the six weeks (42 days) prior to the screening visit and/or participation in another clinical trial for the duration of the study.
- Participants who are pregnant/breastfeeding.
- Discovery and/or the sudden appearance of any condition or circumstance from the above list that, in the opinion of the investigator, has the potential to prevent study completion and/or to have a confounding effect on outcome assessments.

The rTMS-trained health care practitioners' team will determine a participant's eligibility for the rTMS treatments. Once the individual has been accepted into the rTMS program, a member of our research team will introduce the study to him/her, give them a copy of the information leaflet, and ask if they would also be interested in enrolling in our study. The recruitment and an informed consent process will involve a face-to-face meeting with the eligible participant during the week of their rTMS eligibility assessment, which occurs 1 week before beginning the rTMS sessions. Participants can also withdraw from the study at any time without providing a reason. To withdraw, participants can contact the research coordinator to let him/her know. If participants leave the study, we will not collect new health information about them, and they may ask the research coordinator to withdraw any data we have already collected from them before data analysis and dissemination.

Interventions

Participants would be randomly assigned to receive either rTMS alone or rTMS plus iCBT. Participants in both arms of the study will attend an introductory visit to introduce the rTMS system to them and explain the procedure that will be carried out in each visit. Participants will be asked to complete standard questionnaires as part of their participation in the rTMS program. A week before the start of rTMS sessions, the participants will be invited into the clinic for motor threshold (MT) assessments, which are important for selection of stimulation intensities for each patient, and assessment for inclusion in the study. MT is roughly a measure of the TMS intensity necessary to evoke a peripheral motor response. These assessments will be done by the rTMS team, which includes health care practitioners trained on how to assess and use rTMS. Each of the assessments will take 3-5 minutes, and the total time will be 35-45 minutes. The timeline for visits will be the same for all participants. All participants will be scheduled to receive 30 sessions of rTMS treatments over 6 weeks as predetermined by Alberta Health Services' Strategic Clinical Network for Addiction and Mental Health. In addition, participants in the rTMS plus iCBT arm of the study will be assisted in registering for the iCBT program (MoodGYM) to receive unique login information. They will be assisted in participating in 12 one-hour sessions of iCBT at the clinic followed by rTMS treatments on the same day. These in-clinic iCBT sessions will be scheduled at about three-day intervals (ideally Tuesdays and Thursdays) so that participants receive two iCBT sessions each week. These in-clinic iCBT sessions are necessary to avoid poor treatment adherence and high discontinuation rates, as conducting these sessions by themselves at home may represent a major challenge for patients with TRD. Participants would also be encouraged to continue with iCBT treatments on their own at home, outside the sessions delivered in the clinic. The personal information relating to the MoodGYM website that will be collected consists of age group, gender, email address, password, answers to secret questions nominated, and the information the participants submit when using the MoodGYM website (including quizzes, workbooks, and diaries). In addition, the following information about participants' usage of the MoodGYM website will be collected by using transient cookies: participants' browser's internet address, the date and time the site was visited, the pages that were accessed and the documents that were downloaded, the type of browser used, the number of bookmarks created, the last viewed date, the time of visit, and details about participant's subscription excluding credit card details. MoodGYM has its own privacy policy that controls the personal information obtained from all participants under their respective User Data profile. There is no risk that a participant's diagnosis could be exposed to the public should a breach at MoodGYM occur.

All participants will be followed up for 6 months and will be encouraged to continue to receive whatever community clinic/program treatments or supports are part of their usual care.

Sample Size

Consistent with the idea that this is a pilot study, with no established effect size data available to aid in power and sample size calculations, the research will use data that can be elicited from participants who can be enrolled within existing operational resources. This method is acceptable for pilot studies involving novel interventions and has been described by Haynes et al [70] as using "the participants I can get." Therefore, the study will be limited to a sample size of 100, with about 50 participants recruited into each arm of the study. Patients with TRD are vulnerable to severe depressive attacks, and it can reasonably be expected that only a small number of eligible participants will enroll in and complete the study.

Results

We hypothesize that participants enrolled in the rTMS plus iCBT treatment arm of the study will achieve superior outcomes compared with participants enrolled in the rTMS alone arm of the study on each outcome measure used.

Outcomes

Outcome measures and time points are detailed in Table 2 and follow from the aim and objectives of the study. All measures (except patient experience questionnaire, interviews, and data extraction) are objective measures with published information regarding reliability and validity. The Hamilton Depression

Rating Scale (HAM-D) [71,72] will be the primary outcome and all other measures will be secondary outcomes. These measures include the following: Columbia Suicide Severity Rating Scale (CSSRS) [73,74], Young Mania Rating Scale (YMRS) [75], Quick Inventory of Depressive Symptomatology Self Report-16 (QIDS SR-16) [76], Frequency, Intensity, and Burden of Side Effects Ratings (FIBSER; edited for rTMS) [77], Patient Rated Inventory of Side Effects (PRISE) [78], EuroQoL 5-Dimension 5-Level (EQ-5D-5L) [79,80], and World Health Organization Disability Assessment 2.0 (WHODAS 2.0) [81]. The primary outcome measure will be the mean change in the scores on the Hamilton Depression Rating Scale. Patient service utilization data and clinician-rated measures will also be used to gauge patient progress. Patient data will be analyzed with descriptive statistics, repeated measures, and correlational analyses. All quantitative data will be analyzed using SPSS (Version 26; IBM Corp) [82].

Table 2. Client-oriented outcome measures.

Outcome measures			Time points assessed			
Variable type and construct	Tool	Rater	Baseline	1 month	3 months	6 months
Symptom variables						
Depression	Hamilton Depression Rating Scale (HAM-D)	Clinician	✓	✓	✓	✓
Depression	Quick Inventory of Depressive Symptomatology Self Report-16 (QIDS SR-16)	Client	✓	✓	✓	✓
Suicidal ideation	Columbia Suicide Severity Rating Scale (CSSRS)	Clinician	✓	✓	✓	✓
Mania	Young Mania Rating Scale (YMRS)	Clinician	✓	✓	✓	✓
Functional variables						
Side effects	Frequency, Intensity, and Burden of Side Effects Ratings (FIBSER; edited for rTMS)	Client	✓	✓	✓	✓
Side effects	Patient Rated Inventory of Side Effects (PRISE)	Client	✓	✓	✓	✓
Disability measures	World Health Organization Disability Assessment 2.0 (WHODAS 2.0)	Client	✓	✓	✓	✓
Quality of life	EuroQoL 5-Dimension 5-Level (EQ-5D-5L)	Client	✓	✓	✓	✓

Randomization and Blinding

A simple randomization technique will be used based on a single sequence of random assignments. A computer-generated Excel sheet (Microsoft Corp) will be used for simple randomization of subjects. Randomization will be stratified by using permuted blocks to ensure balance (1:1) between the two follow-up treatment groups. The randomization codes will be transmitted by an independent statistician via text message directly to a researcher's password-protected phone line with a secure online backup. This will commence as soon as participants sign the consent forms.

As it will not be possible for participants to be blinded, treatment allocation will be made explicit to them as soon as randomization is concluded. Primary outcome assessors will be blinded to treatment group allocation by not involving them in discussions about study participants and not granting them access to the database that contains the randomization code. After data collection is complete, all data will undergo a blind review for the purposes of finalizing the planned analysis.

Follow-up Assessment

At 1, 3, and 6 months, a blinded researcher will contact all study participants and help them complete a range of assessment tools relating to the primary and secondary outcome measures. They will be offered the opportunity to complete the assessments face-to-face or over the phone. Qualitative data collection will be in the form of a patient experience questionnaire and a focus group workshop, which will be conducted at 3 and 6 months. At 6 months, data related to each person's clinic/program attendance rates and utilization of health services will be compiled from administrative records by the blinded researcher.

Patient and Public Involvement

This study was designed to address the clinical urgency to identify and respond to early evidence of treatment resistance using treatments that have proven efficacy in these more difficult-to-treat psychiatric patients. The study is designed as patient-oriented research with the active involvement of a patient representative who will be a coauthor of the study protocol. Our randomized trial offers participants the opportunity to provide feedback regarding the burden of the intervention through a focused group workshop involving a cross-section of participants from the two arms of the study.

Ethics and Dissemination

The study will be conducted per the Declaration of Helsinki (Hong Kong Amendment) and Good Clinical Practice (Canadian Guidelines). Written informed consent will be obtained from each participant. The study has received ethical clearance from the Health Ethics Research Board of the University of Alberta (Pro00094208). The study is registered with ClinicalTrials.gov (registration number NCT04239651; preresult). The study results, expected 18 months after commencement of recruitment, will be disseminated at several levels, including participants,

practitioners, academics/researchers, and health care organizations.

The investigator's team will plan an organizational engagement strategy to advance discussions about practicability and effectiveness before the conclusion of the trial. This will help ensure the findings are a relevant part of decision-making processes in a way that is aligned with study findings as they emerge. This may facilitate the planning of a more extensive study that is endorsed at both leadership and operational levels so that the potential benefits of the interventions can reach participants in a timelier fashion.

Discussion

Overview

The results of the study will provide the data required to evaluate the initial effectiveness of rTMS plus iCBT for patients diagnosed with resistant depression. The majority of RCTs support the efficacy of rTMS for major depression. The data collected on rTMS is significant only as a single intervention. The concomitant application of psychotherapy with rTMS has not been investigated previously. We hope that this project will provide us with a concrete base of data to evaluate the practical application and efficacy of using a novel combination of these two treatment modalities (rTMS plus iCBT). To our knowledge, no clinical trials have applied these two new treatment interventions together before. Due to the limited availability of data in this specific area, another aim is to generate effect size data for these interventions, which will help in sample size and power calculations for a full randomized clinical trial.

Strengths of This Study

The strengths of this study include the following:

- Randomization of participants will ensure that participants in the two treatment arms have somewhat similar psychiatric morbidity at baseline.
- Blinding of primary outcome assessors for the primary outcome measures will ensure the elimination of bias in outcome measures.

Limitation of This Study

The limitations of this study include the following:

- The small sample size may reduce the study power, which will limit the ability of the study to detect differences in outcome measures between participants in the two treatment arms.
- Possible variability in concomitant treatments (medication and/or psychotherapy) being received by patients outside the rTMS clinic as well as the differing lengths of treatment time between the two arms of the study could have confounding effects on the outcomes of our interventions.

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Conflicts of Interest

None declared.

References

1. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 2003 Jun 18;289(23):3095-3105. [doi: 10.1001/jama.289.23.3095] [Medline: 12813115]
2. Murray CA, Lopez AD. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Geneva, Switzerland: WJO; 1996:A.
3. American Foundation for Suicide Prevention. You are not alone. Mental health conditions and suicide.: American Foundation for Suicide Prevention; 2009. URL: http://www.afsp.org/index.cfm?fuseaction_ [accessed 2019-12-11]
4. Sackeim HA. The definition and meaning of treatment-resistant depression. J Clin Psychiatry 2001;62 Suppl 16:10-17 [FREE Full text] [Medline: 11480879]
5. Rush AJ, Thase ME, Dubé S. Research issues in the study of difficult-to-treat depression. Biol Psychiatry 2003 Apr 15;53(8):743-753. [doi: 10.1016/s0006-3223(03)00088-x] [Medline: 12706958]
6. Greden JF. Unmet need: what justifies the search for a new antidepressant? J Clin Psychiatry 2002;63 Suppl 2:3-7 [FREE Full text] [Medline: 15453007]
7. Papakostas GI. Tolerability of modern antidepressants. J Clin Psychiatry 2008;69 Suppl E1:8-13. [Medline: 18494538]
8. Leon AC, Solomon DA, Mueller TI, Endicott J, Rice JP, Maser JD, et al. A 20-year longitudinal observational study of somatic antidepressant treatment effectiveness. Am J Psychiatry 2003 Apr;160(4):727-733. [doi: 10.1176/appi.ajp.160.4.727] [Medline: 12668362]
9. Prudic J, Haskett RF, Mulsant B, Malone KM, Pettinati HM, Stephens S, et al. Resistance to antidepressant medications and short-term clinical response to ECT. Am J Psychiatry 1996 Aug;153(8):985-992. [doi: 10.1176/ajp.153.8.985] [Medline: 8678194]

10. Nierenberg AA, Fava M, Trivedi MH, Wisniewski SR, Thase ME, McGrath PJ, et al. A comparison of lithium and T(3) augmentation following two failed medication treatments for depression: a STAR*D report. Am J Psychiatry 2006 Sep;163(9):1519-30; quiz 1665. [doi: 10.1176/ajp.2006.163.9.1519] [Medline: 16946176]
11. Fava M, Rush AJ, Wisniewski SR, Nierenberg AA, Alpert JE, McGrath PJ, et al. A comparison of mirtazapine and nortriptyline following two consecutive failed medication treatments for depressed outpatients: a STAR*D report. Am J Psychiatry 2006 Jul;163(7):1161-1172. [doi: 10.1176/appi.ajp.163.7.1161] [Medline: 16816220]
12. McGrath PJ, Stewart JW, Fava M, Trivedi MH, Wisniewski SR, Nierenberg AA, et al. Tranylcypromine versus venlafaxine plus mirtazapine following three failed antidepressant medication trials for depression: a STAR*D report. Am J Psychiatry 2006 Sep;163(9):1531-41; quiz 1666. [doi: 10.1176/ajp.2006.163.9.1531] [Medline: 16946177]
13. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006 Jan;163(1):28-40. [doi: 10.1176/appi.ajp.163.1.28] [Medline: 16390886]
14. Rush AJ, Trivedi MH, Wisniewski SR, Stewart JW, Nierenberg AA, Thase ME, STAR*D Study Team. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. N Engl J Med 2006 Mar 23;354(12):1231-1242. [doi: 10.1056/NEJMoa052963] [Medline: 16554525]
15. Trivedi MH, Fava M, Wisniewski SR, Thase ME, Quitkin F, Warden D, STAR*D Study Team. Medication augmentation after the failure of SSRIs for depression. N Engl J Med 2006 Mar 23;354(12):1243-1252. [doi: 10.1056/NEJMoa052964] [Medline: 16554526]
16. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006 Nov;163(11):1905-1917. [doi: 10.1176/appi.ajp.163.11.1905] [Medline: 17074942]
17. Lam RW, McIntosh D, Wang J, Enns MW, Kolivakis T, Michalak EE, CANMAT Depression Work Group. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 1. Disease Burden and Principles of Care. Can J Psychiatry 2016 Sep;61(9):510-523 [FREE Full text] [doi: 10.1177/0706743716659416] [Medline: 27486151]
18. Lal S, Adair CE. E-mental health: a rapid review of the literature. Psychiatr Serv 2014 Jan 1;65(1):24-32. [doi: 10.1176/appi.ps.201300009] [Medline: 24081188]
19. Karasouli E, Adams A. Assessing the Evidence for e-Resources for Mental Health Self-Management: A Systematic Literature Review. JMIR Ment Health 2014;1(1):e3 [FREE Full text] [doi: 10.2196/mental.3708] [Medline: 26543903]
20. Grist R, Porter J, Stallard P. Mental Health Mobile Apps for Preadolescents and Adolescents: A Systematic Review. J Med Internet Res 2017 May 25;19(5):e176 [FREE Full text] [doi: 10.2196/jmir.7332] [Medline: 28546138]
21. Andrews G, Basu A, Cuijpers P, Craske MG, McEvoy P, English CL, et al. Computer therapy for the anxiety and depression disorders is effective, acceptable and practical health care: An updated meta-analysis. J Anxiety Disord 2018 Apr;55:70-78 [FREE Full text] [doi: 10.1016/j.janxdis.2018.01.001] [Medline: 29422409]
22. Arnberg FK, Linton SJ, Hultcrantz M, Heintz E, Jonsson U. Internet-delivered psychological treatments for mood and anxiety disorders: a systematic review of their efficacy, safety, and cost-effectiveness. PLoS One 2014;9(5):e98118 [FREE Full text] [doi: 10.1371/journal.pone.0098118] [Medline: 24844847]
23. Vallury KD, Jones M, Oosterbroek C. Computerized Cognitive Behavior Therapy for Anxiety and Depression in Rural Areas: A Systematic Review. J Med Internet Res 2015;17(6):e139 [FREE Full text] [doi: 10.2196/jmir.4145] [Medline: 26048193]
24. Titov N. Internet-delivered psychotherapy for depression in adults. Curr Opin Psychiatry 2011 Jan;24(1):18-23. [doi: 10.1097/YCO.0b013e32833ed18f] [Medline: 20827199]
25. Richards D, Richardson T. Computer-based psychological treatments for depression: a systematic review and meta-analysis. Clin Psychol Rev 2012 Jun;32(4):329-342. [doi: 10.1016/j.cpr.2012.02.004] [Medline: 22466510]
26. Eells TD, Barrett MS, Wright JH, Thase M. Computer-assisted cognitive-behavior therapy for depression. Psychotherapy (Chic) 2014 Jun;51(2):191-197. [doi: 10.1037/a0032406] [Medline: 24059735]
27. Renton T, Tang H, Ennis N, Cusimano MD, Bhalerao S, Schweizer TA, et al. Web-based intervention programs for depression: a scoping review and evaluation. J Med Internet Res 2014;16(9):e209 [FREE Full text] [doi: 10.2196/jmir.3147] [Medline: 25249003]
28. Holländare F, Anthony SA, Randestad M, Tillfors M, Carlbring P, Andersson G, et al. Two-year outcome of internet-based relapse prevention for partially remitted depression. Behav Res Ther 2013 Nov;51(11):719-722. [doi: 10.1016/j.brat.2013.08.002] [Medline: 24021360]
29. Patten SB, Kennedy SH, Lam RW, O'Donovan C, Filteau MJ, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical Guidelines for the Management of Major Depressive Disorder in Adults. I. Classification, Burden and Principles of Management. Journal of Affective Disorders 2009 Oct;117:S5-S14. [doi: 10.1016/j.jad.2009.06.044]
30. Patten SB. Updated CANMAT Guidelines for Treatment of Major Depressive Disorder. Can J Psychiatry 2016 Sep;61(9):504-505 [FREE Full text] [doi: 10.1177/0706743716660034] [Medline: 27534886]
31. Parikh SV, Quilty LC, Ravitz P, Rosenbluth M, Pavlova B, Grigoriadis S, CANMAT Depression Work Group. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with

Major Depressive Disorder: Section 2. Psychological Treatments. Can J Psychiatry 2016 Dec;61(9):524-539 [FREE Full text] [doi: 10.1177/0706743716659418] [Medline: 27486150]
32. Kennedy SH, Lam RW, McIntyre RS, Tourjman SV, Bhat V, Blier P, CANMAT Depression Work Group. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments. Can J Psychiatry 2016 Sep;61(9):540-560 [FREE Full text] [doi: 10.1177/0706743716659417] [Medline: 27486148]
33. Milev RV, Giacobbe P, Kennedy SH, Blumberger DM, Daskalakis ZJ, Downar J, CANMAT Depression Work Group. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 4. Neurostimulation Treatments. Can J Psychiatry 2016 Sep;61(9):561-575 [FREE Full text] [doi: 10.1177/0706743716660033] [Medline: 27486154]
34. Ravindran AV, Balneaves LG, Faulkner G, Ortiz A, McIntosh D, Morehouse RL, CANMAT Depression Work Group. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 5. Complementary and Alternative Medicine Treatments. Can J Psychiatry 2016 Sep;61(9):576-587 [FREE Full text] [doi: 10.1177/0706743716660290] [Medline: 27486153]
35. MacQueen GM, Frey BN, Ismail Z, Jaworska N, Steiner M, Lieshout RJV, CANMAT Depression Work Group. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 6. Special Populations: Youth, Women, and the Elderly. Can J Psychiatry 2016 Sep;61(9):588-603 [FREE Full text] [doi: 10.1177/0706743716659276] [Medline: 27486149]
36. Hallett M. Transcranial magnetic stimulation: a primer. Neuron 2007 Jul 19;55(2):187-199 [FREE Full text] [doi: 10.1016/j.neuron.2007.06.026] [Medline: 17640522]
37. Noda Y, Silverstein WK, Barr MS, Vila-Rodriguez F, Downar J, Rajji TK, et al. Neurobiological mechanisms of repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex in depression: a systematic review. Psychol Med 2015 Dec;45(16):3411-3432. [doi: 10.1017/S0033291715001609] [Medline: 26349810]
38. Galletly C, Gill S, Clarke P, Burton C, Fitzgerald PB. A randomized trial comparing repetitive transcranial magnetic stimulation given 3 days/week and 5 days/week for the treatment of major depression: is efficacy related to the duration of treatment or the number of treatments? Psychol Med 2012 May;42(5):981-988. [doi: 10.1017/S0033291711001760] [Medline: 21910937]
39. McGirr A, Van den Eynde F, Tovar-Perdomo S, Fleck MPA, Berlim MT. Effectiveness and acceptability of accelerated repetitive transcranial magnetic stimulation (rTMS) for treatment-resistant major depressive disorder: an open label trial. J Affect Disord 2015 Mar 01;173:216-220. [doi: 10.1016/j.jad.2014.10.068] [Medline: 25462419]
40. George MS, Raman R, Benedek DM, Pelic CG, Grammer GG, Stokes KT, et al. A two-site pilot randomized 3 day trial of high dose left prefrontal repetitive transcranial magnetic stimulation (rTMS) for suicidal inpatients. Brain Stimul 2014;7(3):421-431. [doi: 10.1016/j.brs.2014.03.006] [Medline: 24731434]
41. McDonald WM, Durkalski V, Ball ER, Holtzheimer PE, Pavlicova M, Lisanby SH, et al. Improving the antidepressant efficacy of transcranial magnetic stimulation: maximizing the number of stimulations and treatment location in treatment-resistant depression. Depress Anxiety 2011 Nov;28(11):973-980 [FREE Full text] [doi: 10.1002/da.20885] [Medline: 21898711]
42. Carpenter LL, Janicak PG, Aaronson ST, Boyadjis T, Brock DG, Cook IA, et al. Transcranial magnetic stimulation (TMS) for major depression: a multisite, naturalistic, observational study of acute treatment outcomes in clinical practice. Depress Anxiety 2012 Jul;29(7):587-596. [doi: 10.1002/da.21969] [Medline: 22689344]
43. Kedzior KK, Azorina V, Reitz SK. More female patients and fewer stimuli per session are associated with the short-term antidepressant properties of repetitive transcranial magnetic stimulation (rTMS): a meta-analysis of 54 sham-controlled studies published between 1997-2013. Neuropsychiatr Dis Treat 2014;10:727-756 [FREE Full text] [doi: 10.2147/NDT.S58405] [Medline: 24855360]
44. Berlim MT, van den Eynde F, Tovar-Perdomo S, Daskalakis ZJ. Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. Psychol Med 2014 Jan;44(2):225-239. [doi: 10.1017/S0033291713000512] [Medline: 23507264]
45. Hovington CL, McGirr A, Lepage M, Berlim MT. Repetitive transcranial magnetic stimulation (rTMS) for treating major depression and schizophrenia: a systematic review of recent meta-analyses. Ann Med 2013 Jun;45(4):308-321. [doi: 10.3109/07853890.2013.783993] [Medline: 23687987]
46. Leggett LE, Soril LJJ, Coward S, Lorenzetti DL, MacKean G, Clement FM. Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression in Adult and Youth Populations: A Systematic Literature Review and Meta-Analysis. Prim Care Companion CNS Disord 2015;17(6) [FREE Full text] [doi: 10.4088/PCC.15r01807] [Medline: 27057417]
47. Gaynes BN, Lloyd SW, Lux L, Gartlehner G, Hansen RA, Brode S, et al. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis. J Clin Psychiatry 2014 May;75(5):477-89; quiz 489 [FREE Full text] [doi: 10.4088/JCP.13r08815] [Medline: 24922485]

48. Health Quality Ontario. Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Ont Health Technol Assess Ser 2016;16(5):1-66 [FREE Full text] [Medline: 27099642]
49. Berlim MT, Van den Eynde F, Jeff Daskalakis Z. Clinically meaningful efficacy and acceptability of low-frequency repetitive transcranial magnetic stimulation (rTMS) for treating primary major depression: a meta-analysis of randomized, double-blind and sham-controlled trials. Neuropsychopharmacology 2013 Mar;38(4):543-551 [FREE Full text] [doi: 10.1038/npp.2012.237] [Medline: 23249815]
50. Cohen RB, Boggio PS, Fregni F. Risk factors for relapse after remission with repetitive transcranial magnetic stimulation for the treatment of depression. Depress Anxiety 2009;26(7):682-688. [doi: 10.1002/da.20486] [Medline: 19170101]
51. Dunner DL, Aaronson ST, Sackeim HA, Janicak PG, Carpenter LL, Boyadjis T, et al. A multisite, naturalistic, observational study of transcranial magnetic stimulation for patients with pharmacoresistant major depressive disorder: durability of benefit over a 1-year follow-up period. J Clin Psychiatry 2014 Dec;75(12):1394-1401 [FREE Full text] [doi: 10.4088/JCP.13m08977] [Medline: 25271871]
52. Janicak PG, Nahas Z, Lisanby SH, Solvason HB, Sampson SM, McDonald WM, et al. Durability of clinical benefit with transcranial magnetic stimulation (TMS) in the treatment of pharmacoresistant major depression: assessment of relapse during a 6-month, multisite, open-label study. Brain Stimul 2010 Oct;3(4):187-199. [doi: 10.1016/j.brs.2010.07.003] [Medline: 20965447]
53. Richieri R, Guedj E, Michel P, Loundou A, Auquier P, Lançon C, et al. Maintenance transcranial magnetic stimulation reduces depression relapse: a propensity-adjusted analysis. J Affect Disord 2013 Oct;151(1):129-135. [doi: 10.1016/j.jad.2013.05.062] [Medline: 23790811]
54. Fitzgerald PB, Grace N, Hoy KE, Bailey M, Daskalakis ZJ. An open label trial of clustered maintenance rTMS for patients with refractory depression. Brain Stimul 2013 May;6(3):292-297. [doi: 10.1016/j.brs.2012.05.003] [Medline: 22683273]
55. Hazlett‐Stevens H, Craske MG. Brief cognitive-behavioral therapy: definition and scientific foundations. In: Bond FW, Craske MG, editors. Handbook of Brief Cognitive Behaviour Therapy. Hoboken, NJ, USA: John Wiley & Sons; 2002.
56. Gratzer D, Khalid-Khan F. Internet-delivered cognitive behavioural therapy in the treatment of psychiatric illness. CMAJ 2016 Mar 01;188(4):263-272. [doi: 10.1503/cmaj.150007] [Medline: 26527829]
57. Olthuis JV, Watt MC, Bailey K, Hayden JA, Stewart SH. Therapist-supported Internet cognitive behavioural therapy for anxiety disorders in adults. Cochrane Database Syst Rev 2015;3:CD011565. [doi: 10.1002/14651858.CD011565] [Medline: 25742186]
58. Haldane D. MoodGYM. 2006. URL: http://moodgym.anu.edu.au [accessed 2020-09-11]
59. Kaltenthaler E, Shackley P, Stevens K, Beverley C, Parry G, Chilcott J. A systematic review and economic evaluation of computerised cognitive behaviour therapy for depression and anxiety. Health Technol Assess 2002;6(22):1-89 [FREE Full text] [Medline: 12433315]
60. Kaltenthaler E, Brazier J, De NE, Tumur I, Ferriter M, Beverley C, et al. Computerised cognitive behaviour therapy for depression and anxiety update: a systematic review and economic evaluation. Health Technol Assess 2006 Sep;10(33):iii, xi-ixiv, 1 [FREE Full text] [Medline: 16959169]
61. Kaltenthaler E, Parry G, Beverley C. Computerized Cognitive Behaviour Therapy: A Systematic Review. Behav Cogn Psychother 2004 Feb 18;32(1):31-55. [doi: 10.1017/s135246580400102x]
62. Kaltenthaler E, Parry G, Beverley C, Ferriter M. Computerised cognitive-behavioural therapy for depression: systematic review. Br J Psychiatry 2008 Sep;193(3):181-184. [doi: 10.1192/bjp.bp.106.025981] [Medline: 18757972]
63. Spek V, Cuijpers P, Nyklícek I, Riper H, Keyzer J, Pop V. Internet-based cognitive behaviour therapy for symptoms of depression and anxiety: a meta-analysis. Psychol Med 2007 Mar;37(3):319-328. [doi: 10.1017/S0033291706008944] [Medline: 17112400]
64. Andersson G, Cuijpers P. Internet-based and other computerized psychological treatments for adult depression: a meta-analysis. Cogn Behav Ther 2009;38(4):196-205. [doi: 10.1080/16506070903318960] [Medline: 20183695]
65. Griffiths K, Christensen H. Review of randomised controlled trials of Internet interventions for mental disorders and related conditions. Clinical Psychologist 2006;10:16-29. [doi: 10.1080/13284200500378696]
66. Griffiths KM, Farrer L, Christensen H. The efficacy of internet interventions for depression and anxiety disorders: a review of randomised controlled trials. Med J Aust 2010 Jun 7;192(11 Suppl):S4-11. [Medline: 20528707]
67. Wade AG. Use of the internet to assist in the treatment of depression and anxiety: a systematic review. Prim Care Companion J Clin Psychiatry 2010 Aug;12(4) [FREE Full text] [doi: 10.4088/PCC.09r00876blu] [Medline: 21085550]
68. Pospos S, Young IT, Downs N, Iglewicz A, Depp C, Chen JY, et al. Web-Based Tools and Mobile Applications To Mitigate Burnout, Depression, and Suicidality Among Healthcare Students and Professionals: a Systematic Review. Acad Psychiatry 2017 Dec 18;42(1):109-120. [doi: 10.1007/s40596-017-0868-0]
69. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59 Suppl 20:22-33 [FREE Full text] [Medline: 9881538]
70. Haynes R, Guyatt G, Tugwell P. Clinical epidemiology: how to do clinical practice research. Philadelphia PA: Lippincott, Williams, Wilkins; 2005:-78174524.

71. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960 Feb;23:56-62. [Medline: 14399272]
72. Carroll BJ, Fielding JM, Blashki TG. Depression rating scales. A critical review. Arch Gen Psychiatry 1973 Mar;28(3):361-366. [doi: 10.1001/archpsyc.1973.01750330049009] [Medline: 4688625]
73. Posner K, Brent D, Lucas C, Gould M, Stanley B, Brown G, et al. Columbia-suicide severity rating scale (C-SSRS). New York, NY, USA: Columbia University Medical Center; 2008.
74. Shahid A, Wilkinson K, Marcu S, Shapiro C. Columbia-Suicide Severity Rating Scale (C-SSRS). In: STOP, THAT and One Hundred Other Sleep Scales. New York, NY, USA: Springer; 2011:131-135.
75. Young R, Biggs J, Ziegler V, Meyer D. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 1978 Nov;133:429-435 [FREE Full text] [doi: 10.1192/bjp.133.5.429] [Medline: 728692]
76. Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry 2003 Sep 01;54(5):573-583. [Medline: 12946886]
77. Wisniewski SR, Rush AJ, Balasubramani GK, Trivedi MH, Nierenberg AA, STARD Investigators. Self-rated global measure of the frequency, intensity, and burden of side effects. J Psychiatr Pract 2006 Mar;12(2):71-79. [doi: 10.1097/00131746-200603000-00002] [Medline: 16728903]
78. Rush A, Asberg M. Unpublished rating scale. In: Patient Rated Inventory of Side Effects (PRISE). Dallas, TX, USA: University of Texas; 1999.
79. Szende A, Williams A. Measuring self-reported population health: An international perspective based on EQ-5D. 2004. URL: https://euroqol.org/wp-content/uploads/2016/10/Measuring_Self-Reported_Population_Health_-_An_International_Perspective_based_on_EQ-5D.pdf [accessed 2020-10-16]
80. Brooks R, Rabin R, De Charro F. The measurement and valuation of health status using EQ-5D: a European perspective. Evidence from the EuroQol BIOMED Research Programme. New York, NY, USA: Springer Science & Business Media; 2013.
81. Ustün TB, Chatterji S, Kostanjsek N, Rehm J, Kennedy C, Epping-Jordan J, WHO/NIH Joint Project. Developing the World Health Organization Disability Assessment Schedule 2.0. Bull World Health Organ 2010 Nov 01;88(11):815-823 [FREE Full text] [doi: 10.2471/BLT.09.067231] [Medline: 21076562]
82. IBM Corp. IBM SPSS Statistics for Macintosh, Version 26.0. URL: https://www.ibm.com/products/spss-statistics [accessed 2020-10-16]

Abbreviations

CAM: complementary and alternative medicine
CANMAT: Canadian Network for Mood and Anxiety Treatments
CBT: cognitive-behavioral therapy
DLPFC: left dorsolateral prefrontal cortex
DSM: Diagnostic and Statistical Manual of Mental Disorders
ECT: electroconvulsive therapy
iCBT: internet-delivered cognitive-behavioral therapy
MDD: major depressive disorder
rTMS: repetitive transcranial magnetic stimulation
TRD: treatment-resistant depression

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Protocol

A Systematic Framework for Analyzing Observation Data in Patient-Centered Registries: Case Study for Patients With Depression

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Abstract

Background: Patient-centered registries are essential in population-based clinical care for patient identification and monitoring of outcomes. Although registry data may be used in real time for patient care, the same data may further be used for secondary analysis to assess disease burden, evaluation of disease management and health care services, and research. The design of a registry has major implications for the ability to effectively use these clinical data in research.

Objective: This study aims to develop a systematic framework to address the data and methodological issues involved in analyzing data in clinically designed patient-centered registries.

Methods: The systematic framework was composed of 3 major components: visualizing the multifaceted and heterogeneous patient-centered registries using a data flow diagram, assessing and managing data quality issues, and identifying patient cohorts for addressing specific research questions.

Results: Using a clinical registry designed as a part of a collaborative care program for adults with depression at Mayo Clinic, we were able to demonstrate the impact of the proposed framework on data integrity. By following the data cleaning and refining procedures of the framework, we were able to generate high-quality data that were available for research questions about the coordination and management of depression in a primary care setting. We describe the steps involved in converting clinically collected data into a viable research data set using registry cohorts of depressed adults to assess the impact on high-cost service use.

Conclusions: The systematic framework discussed in this study sheds light on the existing inconsistency and data quality issues in patient-centered registries. This study provided a step-by-step procedure for addressing these challenges and for generating high-quality data for both quality improvement and research that may enhance care and outcomes for patients.

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KEYWORDS

patient-centered registry; collaborative care model; care coordination management; integrated behavior health; systematic framework

Introduction

Background

Patient-centered registries can complement standard electronic health records (EHRs) for the purpose of coordinating an organized response to a subgroup of patients with the goal of improving health care quality and value [1]. The National Institute of Health defines a clinical registry as “a collection of information about individuals, usually focused around a specific diagnosis or condition” [2]. Properly designed and executed registries can play essential roles in enabling patient-centered

care, assessing disease burden, evaluating disease management and health care services, disseminating and using information about targeted diseases and health services, and conducting comparative effectiveness outcomes research [3-5].

The EHR has revolutionized the capture and storage of clinical data. However, as patients often seek care across multiple health systems, use multiple pharmacies, and change insurance carriers, the data captured in EHRs may be limited to better characterize patient cohorts or evaluate longitudinal clinical care [3]. To enable a comprehensive view of a patient and enable research that can guide policy and best practices, there is a need for patient-centered registries to be integrated with the EHR, administrative claims data, and pharmacy databases [6]. Additionally, there is a need for registry oversight to ensure data integrity and the conceptual and methodological frameworks for generating and evaluating data-driven hypotheses. In this study, the patient-centered registries primarily consisted of patients' clinical outcomes, self-management ratings, and measures of satisfaction with care.

Mental health disorders are common (46.6 million of the US population in 2017) [7], create significant disability and losses in productivity [8], and lead to substantial health costs. The majority of patients in the United States, however, do not receive effective mental health care [9]. The majority of patients with mental health problems present in primary care settings [10], where collaborative care models (CCMs) have been tested and implemented with positive outcomes in over 75 randomized controlled trials [11]. CCMs for mental health problems address the lack of access to specialty care with an evidence-based model. CCM has several critical elements that typically include (1) a care coordinator to connect with and manage the patient with a given illness, (2) a method of identification and tracking of these patients using a patient-centered registry, (3) the participation of a specialist providing a regular review of these patients with oversight of the care coordinator, and (4) a primary care provider who continues to care for these patients. Depression in adults is a very common target for CCM, based on the improving mood-promoting access to collaborative treatment (IMPACT) model [12]. New sources of reimbursement for this model from the Center for Medicare and Medicaid Studies provide incentives for clinical practices to adopt collaborative care. Each practice must create its own patient-centered registry for clinical management of those patients in collaborative care, assessing outcomes, and potentially a clinical research.

In 2008, the division of Integrated Behavioral Health (IBH) at the Mayo Clinic began implementing CCM for adult depression in primary care. As a part of that effort, a patient-centered registry was built with the ability to track both clinical outcomes and care engagement for the patient population over time. The registry was designed to support the implementation of CCM to deliver integrated and coordinated treatment for depression [13]. Outcomes and changes in treatments for patients were systematically captured and summarized in a transparent and actionable manner, which promoted more rapid changes in treatment for patients who were not improving compared with practice as usual [14]. The integrated nature of the CCM enabled providers to systematically take into account the complex medical, psychological, social, and cultural factors affecting a patient's illness and provide personalized treatment plans to ensure that treatment goals were met.

The depression registry included information on diverse patients with respect to disease severity, treatment protocols, comorbidities, and socioeconomic and ethnic backgrounds. The Mayo Clinic system is a multispecialty practice in a city of 100,000 with both primary and specialty care included within the same EHR along with hospital and emergency room data. For this implementation, the capacity has existed to potentially integrate the registry data with administrative, pharmacy, emergency, and hospitalization databases as well as patients' social determinants of health and personal health records. Despite the robust design and implementation of the depression registry, there were inherent data limitations that impeded effective research. Specifically, as the registry has prevalent data quality issues (data inconsistency, accuracy, and completeness), defining or utilizing longitudinal outcomes for research has been challenging. Additionally, identifying patient cohorts (group of patients sharing similar clinical or utilization characteristics) in the registry for a retrospective study is a challenging process.

Objectives

Previous studies have discussed the challenges of evaluating data-driven hypotheses using data accumulated in patient-centered registries and have offered general guidelines to address these challenges. For example, Gliklich et al [15] provided an overview of data quality issues including data completeness, missing values, and data accuracy in registries and listed available solutions for the problems. In another study, Kodra et al [16] discussed 6 dimensions of data quality such as data usefulness, accessibility, and timeliness in registries for rare diseases. They also proposed methods for evaluating the quality of data against the 6 dimensions. Although helpful in identifying problems and strategies, these studies did not propose a systematic framework to address the methodological challenges of identifying patient cohorts in the patient registries, specifically in patient-centered registries for mental disorders. For the purpose of this study, we defined the systematic framework as an analytical tool, consisting of structured components that addressed the challenges of evaluating a data-driven hypothesis using accumulated data in a patient-centered registry.

To demonstrate the general applicability of the systematic framework, we applied it to generate an analytic sample of patients from the depression registry and used the sample to describe the structure and characteristics of the implemented CCM.

Methods

The major components of the systematic framework include (1) development of a data flow diagram (DFD) to visualize components of the registry; (2) data quality assessment, which focused on the analysis of data errors (accuracy) and missingness (completeness); and (3) identification of patient cohorts, which covered the challenges of identifying comparable patient cohorts

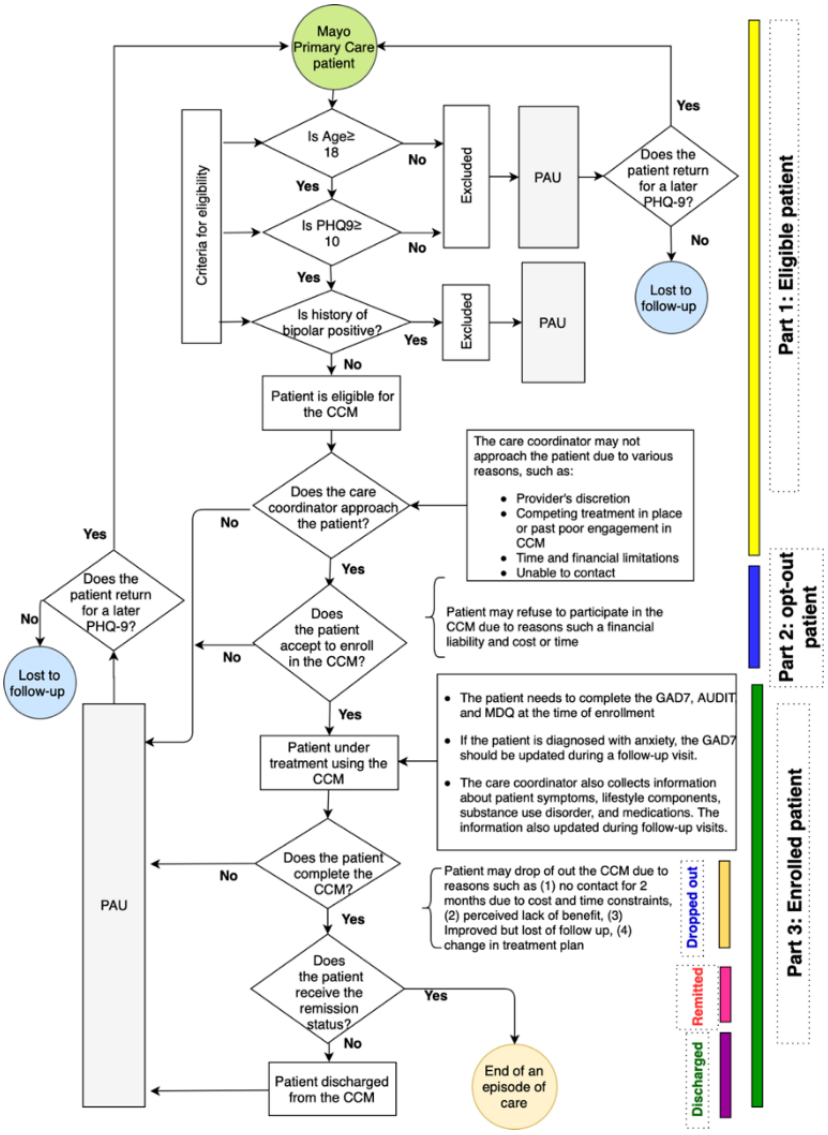
in longitudinal clinical care. We demonstrated the feasibility and usefulness of this framework using the depression registry. By following the analytical steps of this framework, we produced high-quality data and identified major patient subgroups for subsequent cross-sectional or longitudinal studies. This study was reviewed and approved by the Institution Review Board at the Mayo Clinic. See Multimedia Appendix 1 for more information about the depression registry.

Patient Registry DFD

In exploring the use of patient-centered registries for research, a DFD [17] provides research teams with a high-level view of the scope and focus of the registry. Additionally, a DFD allows the reader to visualize the interaction between different components of the registry and the clinical decision-making process designed to manage patient care. This visualization subsequently facilitates the process of generating rules for data quality assessment and defining patient cohorts for a specific research question. Designing a DFD for a patient-centered registry should include 3 major parts. First, the eligibility portion of the DFD needs to present information about the criteria and evaluation models for identifying eligible patients in the registry. Second, an enrollment section of a DFD should include information about enrollment, specifically the patients' decision to enroll in the registry after being approached by clinicians and a list of patients who met eligibility requirements but were not approached. Finally, the third section of a DFD should provide information about the flow of enrolled patients in the registry during and after receiving the intervention. This part can also include information on the process of data collection at the initial and follow-up visits for enrolled patients.

We used the DFD to visualize components of the depression registry and the CCM intervention (Figure 1). The first part of the depression DFD presents criteria for identifying eligible patients for the CCM intervention, including a clinical diagnosis of depression with a Patient Health Questionnaire (PHQ-9) ≥10 [18], age ≥18 years, and no history of bipolar disorder. The second part of the DFD focused on eligible patients, including those who refused to enroll in the CCM. The patient's refusal of the intervention was recorded as an *opt-out* status in the depression registry. A patient may refuse to enroll in the CCM for various reasons, including cost or time commitment. Additionally, a patient may not be approached for reasons including lack of space in the program, perceptions that the patient was already involved in analogous services, and past lack of interest in participating. Finally, the last part of the DFD demonstrated that an enrolled patient could experience 3 potential outcomes: *drop out* (stopping the CCM without completing a course of treatment), *remitted* (remission from depression), and *discharged* (discharged from the CCM without reaching the remission status). The enrolled patients were required to complete questionnaires related to anxiety symptoms [19], bipolar disorder [20], and alcohol use disorder [21] and to provide information about lifestyle components and medication use. This information was updated in follow-up visits and was used for assessing the patient's treatment plan.

Figure 1. Data flow diagram of the Integrated Behavioral Health registry. AUDIT: Alcohol Use Disorders Identification Test; CCM: Care Coordination Model; GAD7: General Anxiety Disorder-7; MDQ: Mood Disorder Questionnaire; PAU: Practice As Usual.



Overall, the DFD provided insight into the underlying structure of the data, the main patient cohorts available in the registry, and the potential limitations of retrospective studies based on data from the patient-centered registries. For example, the DFD showed that the depression registry included 3 major patient cohorts: nonapproached, opt out, and enrolled. Additionally, the patient information in the registry consisted of both structured and unstructured data (clinical notes), creating additional variables for interpretation.

Data Quality Assessment

Identifying the data quality issues and adopting appropriate solutions to solve those issues are a critical part of data processing in patient-centered registries that evolve over time. The research team may use available frameworks of data analysis errors, such as those described by Tallentire et al [22] or Kahn et al [23] to evaluate the quality of observation data in the registry against 6 dimensions: accuracy, completeness, consistency, timeliness, validity, and uniqueness. The frameworks also help the research team focus on potential errors in the data sets and to generate rules to address those errors. We use the term observation data because the primary goal for collecting the data from patients was for clinical care not for research purposes.

To facilitate the process of identifying and refining data errors in the depression registry, we used the Kahn framework. This framework consists of 5 components: (1) attribute domain constraints, (2) relational integrity rules, (3) historical data rules, (4) state-dependent object rules, and (5) attribute dependency rules. Using these components, we were able to measure the accuracy, validity, consistency, uniqueness, and completeness of data in the registry. Although evaluating the quality of data for the timeliness was out of the scope of this study, Table 1 shows the rules we generated for each component to identify and solve the data errors in the depression registry.

Table 1. Framework for analysis of data errors.

Dimensions of data quality	Components	Generated rules with examples
Accuracy, consistency, validity, and completeness	Attribute domain constraints	• Define the domain of elements in the registry • Use the frequency analysis to identify data elements with values out of the range of the domain • Identify inconsistencies in the data elements' domain Examples: • All items in the PHQ-9[a]-questionnaire should have a value between 0-3. • All answers to the question about the "current employment status" should be recorded as Yes or No. All other answers such as "I am employed" or "I am looking for a job" should be converted to Yes and No, respectively.
Consistency, uniqueness, and completeness	Relational integrity rules	• Identify unique identifiers (primary keys) in each data set for mapping different data sets. • Define appropriate strategies for mapping data sets. Example: • The variables Medical-record-number, eligibility- date, and activation-date can be used as identifiers for mapping patients across different data sets.
Accuracy, consistency, validity, and completeness	Historical data rules	• Identify data elements capturing date and time (date-time) of events in the IBH[b] registry. • Identify data elements that their differences present duration for an event (eg, duration of the CCM[c]). • Identify date-time elements that needed to be recorded in a specific time interval. Examples: • Date of birth should be recorded before all events associated with an individual patient in the registry. • The difference between the activation-date (start date) and the end-date indicates the duration of the intervention. • Each enrolled patient should have at least one contact date, otherwise the contact date should be labeled as a missing value.
Completeness, consistency, uniqueness, and accuracy	State-dependent objects rules	• Identify a set of events whose occurrence depends on other events in the registry. • Identify a set of events whose occurrence is concurrent with other events in the registry. Examples: • Patients with an end date for the CCM intervention should also have a start-date and eligibility-date; otherwise, the start date and eligibility date would be labeled as missing values. • The recording date for completing the PHQ-9, MDQ[d], GAD7[e], and AUDIT[f] questionnaires should be before or at the same date of enrollment date.
Accuracy	Attribute dependency rules	• Evaluate accuracy of events that follow other events. • Identify data elements having aggregated values of associated components of the data elements. Examples: • The total score of the PHQ-9 should be equal to the sum of the values of 9 items of the questionnaire.

[a]PHQ-9: Patient Health Questionnaire.

[b]IBH: Integrated Behavioral Health.

[c]CCM: care coordination model.

[d]MDQ: Mood Disorder Questionnaire.

[e]GAD7: General Anxiety Disorder-7.

[f]AUDIT: Alcohol Use Disorders Identification Test.

Addressing Missing Data in Patient-Centered Registries

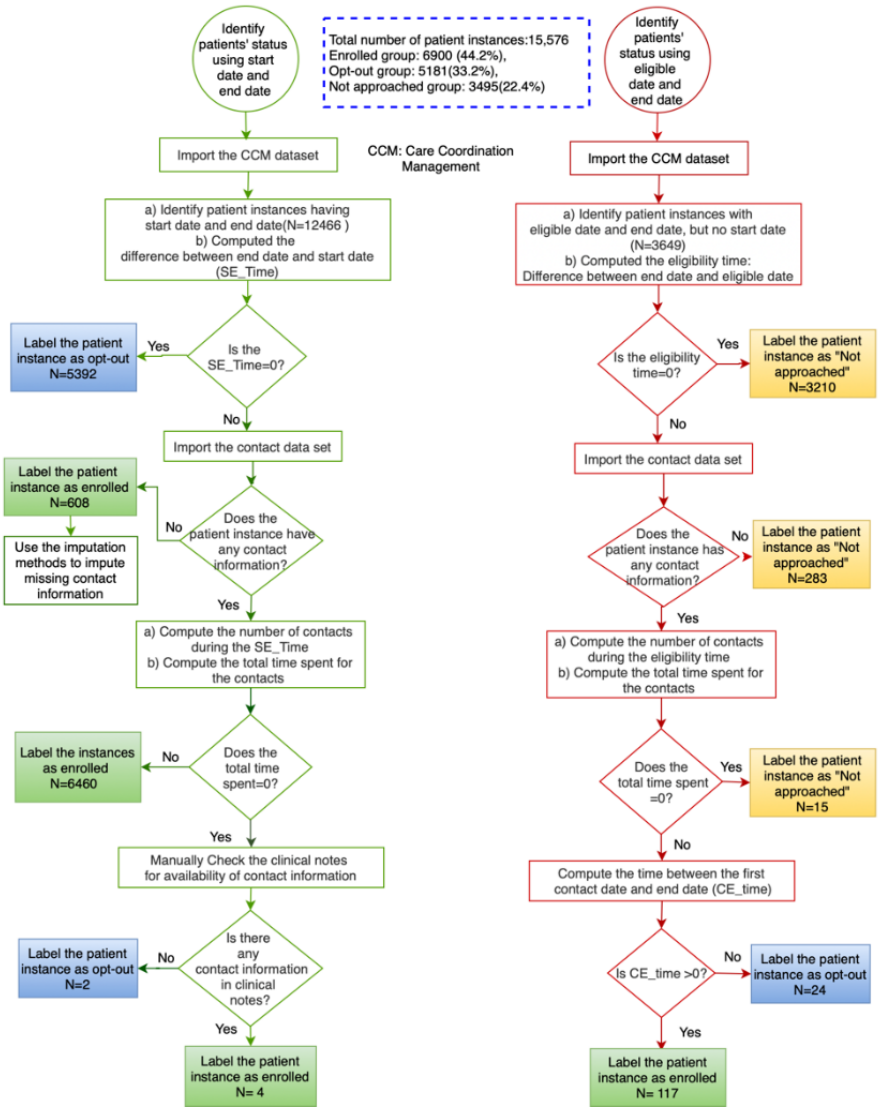
Addressing the missing data in patient-centered registries depends on (1) frequency of missing data; (2) the source of missing data, which might be due to reasons such as patients' unwillingness to share the requested information with clinicians, clinicians' failure to collect the required information, data entry and processing error, and changing the guidelines of data collection of the registry; and (3) the type of missing data that can be summarized as missing completely at random (MCAR), missing at random, and missing not at random. See Multimedia

Appendix 2 [24] for more information on the source and type of missing data. There are different approaches to handling the missing data with complete case analysis and imputation methods using machine learning or aggregation methods as common solutions.

The following are examples of our methods for handling missing values in the depression registry:

1. Using the complete case analysis for handling missing data in the CCM intervention data set: According to the guidelines of the depression registry, all patients enrolled in the CCM intervention should have an eligibility date, a start date, and an end date. Patient instances with a start date but without an end date were marked as missing data. As the number of missing data was low (0.4% or 90 out of a total of 18,716) and the source and type of the missing data were data entry error and MCAR, respectively, we simply dropped these patients from inclusion in the registry.
2. Developing an algorithm to identify and handle patient instances with a missing start date for the CCM intervention: To identify patient instances with a missing start date, we first computed the eligibility-time (end date minus eligibility date). If eligibility-time >0, we computed the total number of contacts and total time spent on communication between clinicians and patients during the eligibility-time. For patient instances with contact information, the first date of contact was marked as the start date. Overall, we identified 154 patient instances with a missing start date for the CCM intervention. Figure 2 visualizes the steps of this algorithm.

Figure 2. Identifying patient subgroups in the depression registry. CCM: collaborative care model.



Identifying Patient Cohorts in Patient-Centered Registries

To conduct comparative effectiveness research and health outcome studies using longitudinal data collected for clinical purposes, the research team needs to identify comparable patient cohorts and to define proper observational and outcome windows before entering the phase of data modeling and analysis. This is more complicated in registry data collected over long periods of time, as patients may have a wide variety of interactions recorded. In this section, we discuss the challenges of identifying patient cohorts and defining outcome

windows in patient-centered registries, and then, we provide an approach to address these challenges based on the depression registry.

Excluding Ineligible Patients Based on the Specifications of the Research Question

Commonly, the first step in defining patient cohorts in registries for a specific research question is to define inclusion and exclusion criteria related to the aims of the study. For example, using the data in the depression registry, we were interested in investigating the effectiveness of the CCM intervention in improving health care outcomes in patients with depression. To answer this research question, we started with the inclusion and exclusion criteria, which, as illustrated in the DFD (Figure 1), was defined as all adult patients (≥18 years) who had a clinical diagnosis of major depression, with no prior diagnosis of bipolar disorder and with moderate to severe symptoms of depression (PHQ ≥10) before or on the start date of the enrollment for the CCM intervention. Patients who did not meet these criteria were excluded from the study sample.

Identifying Major Patient Subgroups in Patient-Centered Registries

The second step in defining patient cohorts in a patient registry is to identify major patient subgroups. The DFD of the registry can be very helpful in providing information about the different patient statuses (eg, enrolled or opt out), which can provide an insight into the possible patient subgroups in the database. Consultation with clinicians can also be helpful in identifying the subgroups.

In our case study, the DFD (Figure 1) shows that an individual patient may experience 3 possible statuses in the depression registry: enrolled, opt out, and not approached. After a discussion with the research clinicians, we utilized 2 data sets, the CCM data set and the contact data set to design 2 algorithms (algorithms A and B in Figure 2) to identify the 3 patient statuses in the registry. The CCM data set recorded the eligibility date of the patients for the intervention of CCM (eligible date), the date that a patient was recruited by a care coordinator (start date), and the date that the intervention ended (end date). All patient instances in the CCM data set were required to have an eligible date and end date, but the start date could be missing if the patient was not approached by clinicians for the CCM intervention. We computed 2 variables, activation-time (SE_Time) and eligibility-time using this data set, indicating the time that the patient status was open in the CCM intervention and in the registry, respectively. The contact data set included the number of contacts that occurred between care coordinators and patients for the CCM intervention and the associated time spent for each communication. Using these data sets, we computed the frequency and time of contacts (total time spent) between care coordinators and patients if the patients' activation-time or eligibility-time was greater than 0. If the frequency=0 or total-time-spent=0, the patient was considered not enrolled in the CCM intervention. Table 2 presents the description, counts, and min/max distribution of the key date variables in the CCM and contact data sets used in algorithms A and B (Figure 2) for identifying major patient subgroups as well as some derived variables.

Table 2. Descriptions of and statistics of variables used in algorithms A and B (Figure 2).

Variables	Description	No.	No missing	Minimum	Maximum
CCM[a] database					
Eligibility date	The date that the patient was eligible for the CCM intervention.	15,576 (patient instances)	0	March 3, 2008	May 17, 2018
Start date	The date that the care coordinator offered the CCM to the patient.	15,576 (patient instances)	3649 (23.42); patient instances having missing start-date	March 6, 2008	May 14, 2018
End date	The end date of the CCM intervention.	15,576 (patient instances)	0	March 3, 2008	May 15, 2018
Computed variables using the CCM database					
Activation-time (SE_Time)	Difference between the start date and the end date.	11,927 (76.57); patient instances having start-date	0	0 (days)	1263 (days)
Eligibility-time	Difference between the eligibility date and the end date, if the start date is missing.	3649 (23.42) patient instances having eligibility date but without start date	0	0 (days)	900 (days)
Contact database					
Contact date (date of contact)	The date of contact between the patient and the care coordinator.	121,435 instances of contact	206 (0.17)	March 7, 2008	September 28, 2018
Time spent	The time spent for each contact.	121,435 instances of contact	0	0	990 min
Computed contact variables for patient instances with activation-time >0					
Total number of contacts for each patient instance (algorithm A)	Total number of contacts between the clinician and the patient with activation-time >0.	6824; total number of enrolled patient instances having contact information	90 (1.32); total number of patient instances with no contact information	1 (number of contact)	123 (number of contact)
Total time spent for each patient instance (algorithm A)	The total time that the clinician spent for communicating with the patients with activation-time >0.	6824; total number of enrolled patient instances having contact information	90 (1.32); total number of enrolled patient instances with no contact information	0 (min)	3375 (min)
Computed contact variables for patient instances with eligibility-time >0					
Total number of contacts for each patient instance (algorithm B)	Total number of contacts between clinicians and patients with eligibility-time >0.	433; total number of patient instances with eligibility time >0	263 (60.73); total number of patient instances with eligibility time >0 and having no contact information	1 (number of contacts)	27 (number of contacts)
Total time spent for each patient instance (algorithm B)	The total time that the clinician spent for communicating with patients with eligibility-time >0.	433; total number of patient instances with eligibility time >0	263 (60.73); total number of patient instances with eligibility time >0 and having no contact information	0 (min)	645 (min)
CE_Time (algorithm B)	Duration between the first contact date (in the contact data set) and the end date (in the CCM data set).	154 (35.56); total number of patient instance s having at least one contact date	0	0	616

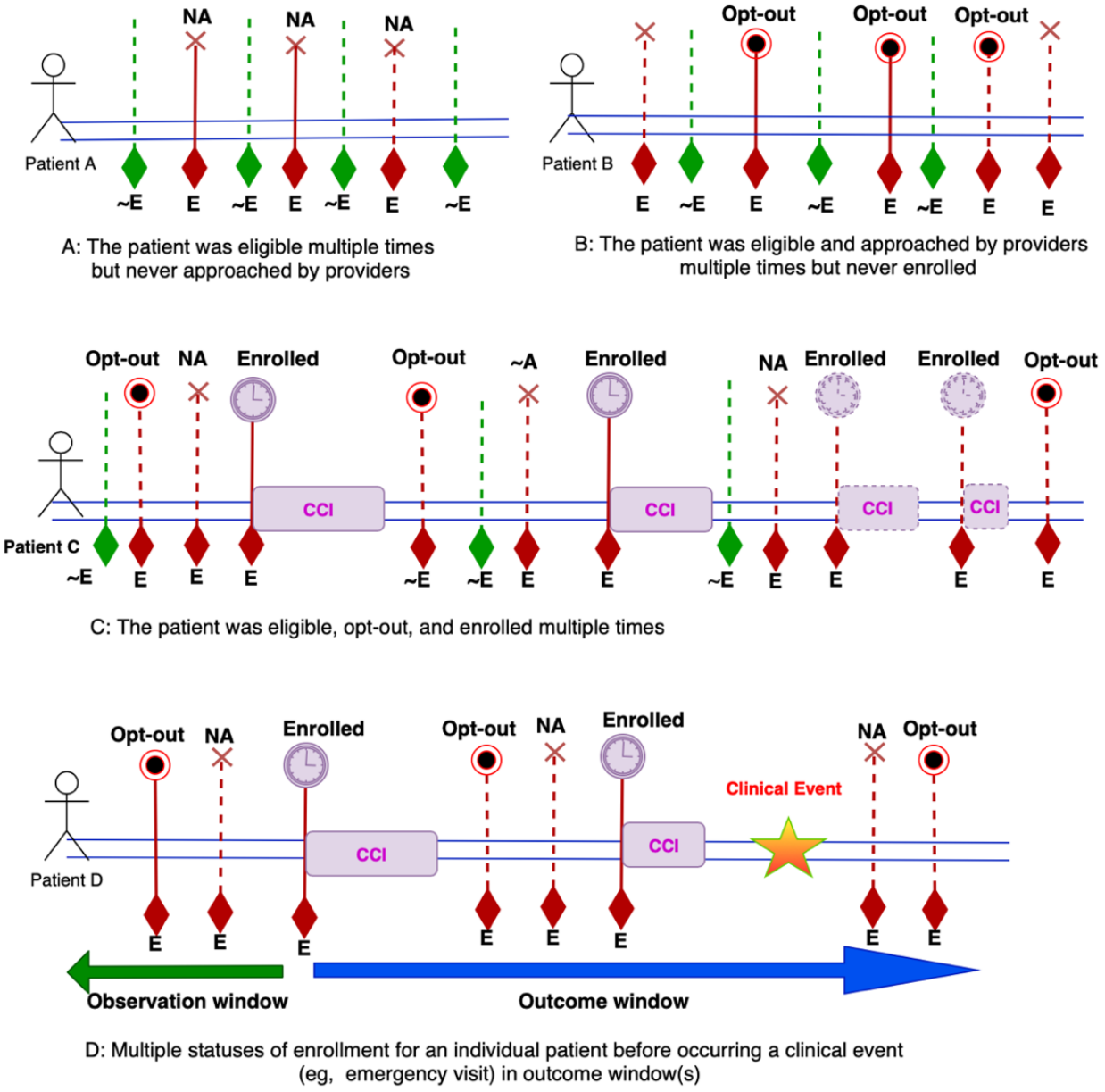
[a]CCM: care coordination model.

Identifying Observation and Outcome Windows for Patients With Multiple Statuses in the IBH Registry

The third step for defining patient cohorts in a patient registry for a specific research question is to identify proper observation and outcome windows of patients with chronic illnesses who are followed over several years and have multiple points of eligibility due to the fluctuating nature of their condition. In chronic disease research where patients are followed over time, choosing observation and outcome windows can be difficult, primarily due to the heterogeneous behavior of the patients and the clinical program. For example, in the depression registry, a

patient may be eligible multiple times for the intervention but never approached (nonapproached patients) by providers to enroll in the CCM intervention (part A in Figure 3). On the other hand, an eligible patient may be approached by the provider multiple times but refused to enroll in the intervention (opt-out patient, part B in Figure 3). However, some eligible patients may enroll in the intervention multiple times (part C in Figure 3). It is possible for multiple variations to occur with the patient not approached for one occurrence, opt out for another, and then enroll for another.

Figure 3. An illustration of a patient with multiple statuses in the Integrated Behavioral Health registry. CCI: care coordination intervention; ~E: not eligible; E: eligible; NA: not approached.



If the focus of the research question is on measuring the effectiveness of an intervention for a specific outcome such as an emergency department visit or rehospitalization, it is often unclear how to optimally define an index date (start of follow-up) for the 3 subgroups (enrolled, opt out, and not approached) identified in Section *Patient Registry DFD* and presented in Figure 3 parts A, B, and C. For example, for patients with multiple enrolled statuses, the index date can be defined as the start date of the first enrollment or it could be the start of a later enrollment. Each of the selected index dates may not necessarily lead to the same conclusion about the effectiveness of the intervention. Changes in practice (eg, the introduction of a new antidepressant or clinical service) may happen over time, which could impact clinical outcomes for patients starting CCM during a given period versus another one. Similarly, for patients with multiple opt-out statuses and who have never enrolled, their index date can be taken as the first, the last, or an interim opt-out date. It is not clear which is optimal; the different index dates may lead to different conclusions. In complex situations, setting an arbitrary index date to define observation and outcome windows could increase the risk of measurement bias (part D of Figure 3).

Our solution for identifying a proper index date to define patient cohorts for a cross-sectional study focused on measuring the coverage and effectiveness of the intervention for a specified follow-up time window (eg, 6 months) using the depression registry data. Thus, identifying a proper index date for a longitudinal study with a focus on health care outcomes would be part of our future study.

Identifying Patient Cohorts for a Cross-Sectional Study in the Depression Registry

To identify patient cohorts for a cross-sectional study, the focus was on measuring the effectiveness of CCM interventions in treating eligible registry patients with moderate to severe symptoms of depression. The depression database contains a PHQ-9 table containing all the questionnaires completed by those primary care patients who were treated at Mayo Clinic since 2008 and who completed at least one PHQ-9 in the course of their care. Patients were selected for the study if they were diagnosed with depression and met the inclusion/exclusion criteria (Figure 1) and completed at least two PHQ-9 questionnaires. Patients not meeting these criteria were excluded from the study.

For 6-month follow-up, there were 3 possible ways of specifying an appropriate index date for defining outcomes. In the first option, the index date would be the same for the entire cohort (intervention and comparison groups) and would be the first date on which a patient met the eligibility criteria. The advantage of this method was that all patients had a similar window of comparison. The disadvantage was that the time between the eligibility and enrollment dates may vary, such that the treatment effect was diluted with patients in the intervention group by being enrolled late in the observation window. The second option was to use an index date that was linked with enrollment into the CCM program. For the treatment group, this would be an intent-to-treat group where all enrolled patients were included regardless of completing or dropping out or reaching remission in treatment. For the comparison (usual care) group, however, the choice of an index date would be challenging. An eligibility date could be chosen, but if there were several, which one to choose? An additional concern is how to account for variation in the time between eligibility and enrollment in the treatment group as compared to the nontreatment group where (by definition) there was no enrollment. In the treatment arm, there is a possibility that patients began receiving some sort of treatment outside of the CCM program between their eligibility date and enrollment, which might bias results in favor of the treatment arm. The third option would be to look at the average time between eligibility and enrollment in the treatment cohort and add that time to each of the comparison cohort's eligibility date to create an equivalent 6-month window.

Choosing any of the index dates would result in generating different patient cohorts. In the special case where the index date was the date where the patient first became eligible, we identified 4 patient cohorts in the depression registry presented in Figure 4. Figure 4 parts A-D illustrates the patient cohorts with *not approached* status, *opt-out* status, *completed enrollment* status, and *incomplete enrollment* status at the 6-month window. Using these 4 cohorts, we aimed to test the following hypotheses in our next study:

Figure 4. The identified patient cohorts for a cross-sectional study. CCI: care coordination intervention; E: eligible; ~E: not eligible; NA: not approached.

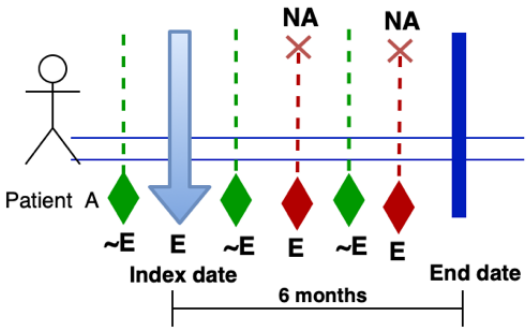


Figure 5. A: Patient cohort with not approached status during six months

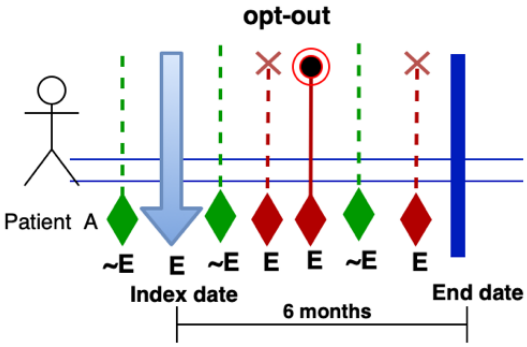


Figure 5. B: Patient cohort with opt-out status during six months

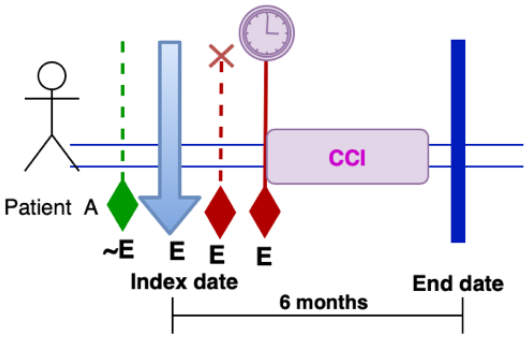


Figure 5. C: Patient cohort with completed enrollment status during six months

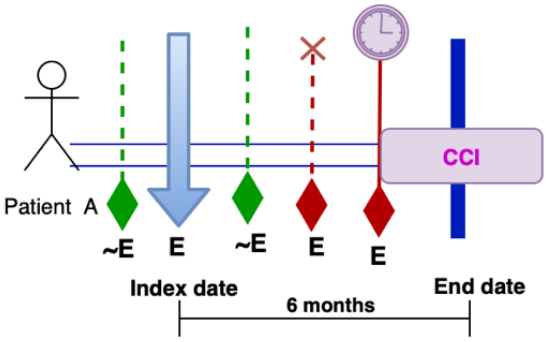


Figure 5. D: Patient cohort with incomplete enrollment status during six months

1. Effectiveness will be higher in patients with enrolled status (vs others) as measured by the percentage of patients reaching remission in 6 or 12 months and/or time to remission. Those patients who choose to enroll in care coordination are different (by age, etc) than those who either are not approached or opt out, suggesting a need for changes in the program or in recruitment efforts to better impact the population of depressed patients. There is a significant difference between demographic information (age, employment, education, and marital status) and comorbidities in patients with *enrolled* status compared with patients without *enrolled* status (*not approached* and *opt-out* status).
2. There is a significant difference between the frequency of emergency department visits and hospitalizations in patients with *enrolled* status compared with patients with *not approached* and *opt-out* status in the outcome window of 12 months after the index date (the 6 months after the index date).

Results

Summary of the Components of the Analytical Framework

The primary result of this project was the development of a clean data set with descriptors of the data and patient cohorts for a research project. Table 3 summarizes the main steps in taking a clinically created patient-centered registries and getting the data ready for research.

Table 3. A summary of the analytical framework suggested in this study.

Problem	Solution	Advantages	Limitations	Other options
Patient care programs evolve based on clinical and reimbursement changes without regard to research leading to confusion about the flow of data for research	Create a data flow diagram	• Provides insight into the underlying structure of data • Identifies the main patient cohorts available in the registry	Not suitable for registries that are lack of the component of patient-centered care for chronic disease	• Unified Modeling Language [25] • Conceptual Modeling [26]
Data collected in clinical settings is prone to many data quality issues	Use the Kahn et al [23] framework to evaluate the quality of accumulated data in the registry against 5 dimensions: accuracy, completeness, consistency, validity, and uniqueness	Provides specific operational approaches to determine the quality of data in a patient-centered registry	• Not appropriate for multisite registries • Not appropriate for cleaning unstructured data set (eg, text cleaning)	Achilles Heel Data Quality Tool [27]
Patients may flow in and out of clinical care based on clinical needs leading to confusion when creating cohorts	Use visualization techniques to visualize all possible instances (having no, single, or multiple enrollment status) in the registry	• Helps the research team define key points of time in a patient's flow (eg, eligibility date and start date) that account for the majority of patients • Helps create rule-based algorithms to create comparable patient cohorts for a study	Needs a deep understanding of patients' flow in the registry and standard definitions that are adhered to in clinical practice as patients enter and leave treatment.	Use unsupervised machine learning algorithms (eg, deep learning) for creating initial patient cohorts for human review [28]

A Descriptive Summary of Patients' Demographic Information and PHQ-9 Data Available in the Depression Registry

The total number of patients registered in the depression registry was 18,716 patients as of 2008. Consent is sought and obtained annually by the clinical practice as a part of regular care and documented in the EHR for retrospective patient research at the Mayo Clinic. In this project, 7.01% (1312/18,716) of the registry patients (n=1310) did not consent to share their data for research purposes and were excluded from the study. Out of 17,406 patients with informed consent, about 1830 (10.51%) did not meet the inclusion criteria (a history of bipolar disorder, age 18 years or greater, or a PHQ-9<10) and were excluded from the study. Overall, out of 15,576 eligible patients, we identified 6900 (44.2%) instances with enrolled status, 5181(33.2%) with opt-out status, and 3495 (22.4%) with nonapproached status. Table 4 summarizes the key baseline characteristics of these subgroups. The mean age of the enrolled, opt out, and nonapproached subgroups was 41.3 (SD 16.2), 40.2 (SD 16.5), and 41.6 (SD 17.5), respectively. The proportion of females in all 3 subgroups was significantly higher than that of males, which is in line with the findings of the Centers for Disease Control and Prevention, indicating that two times as many women use antidepressants as men [29]. Whites comprised a large fraction (>90%) of patients in the 3 groups. Similarly, the majority of the patients in all 3 groups were married (enrolled: 3377/6900,48.94%; opt out: 44.85%, 2324/5181; and not approached: 1461/3495, 41.80%), followed by single patients (enrolled: 2102/6900,30.46%; opt out: 1841/5181,35.53%; and not approached: 1354/3495, 38.74%). Table 3 also includes the depression score as measured by the PHQ-9 questionnaire for the 3 subgroups. The majority of patients in all 3 groups had moderate depression (PHQ-9 between 10 and 19) at both the eligibility date and start date of the CCM intervention. Patients with severe depression (PHQ-9≥20) were more likely to be enrolled in the CCM intervention. In future studies, we will evaluate the association of demographic information and the PHQ score with patients' willingness to accept or refuse to participate in the CCM intervention.

Table 4. Statistics on major patient subgroups in the depression registry.

Variables	Enrolled	Opt out	Not approached
Total number of instances, n (%)	6900 (44.30)	5181 (33.30)	3495 (22.40)
Age (years), mean (SD)	41.27 (16.18)	40.17 (16.46)	41.59 (17.54)
Sex, n (%)			
Female	4936 (71.50)	3758 (72.50)	2402 (68.70)
Missing	10 (0.14)	6 (0.10)	1 (0.02)
Race, n (%)			
White	6347 (91.98)	4675 (90.23)	3197 (91.47)
Black or African American	157 (2.27)	152 (2.93)	91 (2.60)
Asian	116 (1.68)	92 (1.77)	32 (0.91)
Native American	28 (0.40)	26 (0.50)	28 (0.80)
Others	188 (2.72)	184 (3.55)	109 (3.12)
Unknown	55 (0.79)	45 (0.87)	37 (1.10)
Missing	9 (0.13)	7 (0.13)	1 (0.02)
Marital status, n (%)			
Married	3377 (48.94)	2324 (44.85)	1461 (41.8)
Single	2102 (30.46)	1841 (35.53)	1354 (38.74)
Divorced	1084 (15.71)	802 (15.48)	487 (13.93)
Widowed	320 (4.63)	203(3.92)	177 (5.06)
Unknown	7 (0.10)	4 (0.07)	15 (0.40)
Missing	10 (0.14)	7 (0.13)	1 (0.2)
PHQ-9[a] at start-date, n (%)			
≤5[b]	69 (1.00)	153 (2.95)	No start date is available
>5, <10[b]	260 (3.78)	134 (2.58)	No start date is available
≥10, <15	2956 (42.84)	2401 (46.34)	No start date is available
≥15, <20	2309 (33.46)	1593 (30.74)	No start date is available
≥20 (severe depression)	1228 (17.79)	824 (15.90)	No start date is available
Missing	78 (1.13)	76 (1.46)	No start date is available
PHQ-9 at eligibility date, n (%)			
≤5[b]	17 (0.25)	0	0
>5, <10[b]	49 (0.71)	0	0
≥10, <15	3055 (44.27)	2537 (48.97)	1976 (56.54)
≥15, <20	2491 (36.10)	1751 (33.80)	1011 (28.93)
≥20 (severe depression)	1288 (18.67)	893 (12.23)	508 (14.53)

[a]PHQ-9: Patient Health Questionnaire.

[b]The enrolled patients with PHQ-9<10 at the point of enrollment were included in the data set of the study due to the health care providers' discretion. The patients met other eligibility criteria and were diagnosed with depression. The clinical reasons for inclusion of these subthreshold patients were varied and included a previous pattern of relapse or a concern that the patient was minimizing their symptoms.

Discussion

Principal Findings

A well-designed and implemented registry that ensures comprehensive, consistent, accurate, and complete data about patients is critical for accurate assessment of disease burden, evaluation of disease management and health care services, and conducting comparative effectiveness and outcomes research. The success of retrospective research studies utilizing data from patient registries depends on the underlying structure of the registry, the implemented data preparation steps, and the

research question(s). This study focused on the data preparation steps (DFD and data quality) to support statistical or machine learning data analysis applications and selection of patient cohorts to address specific research questions in mental health. The feasibility and usefulness of the proposed framework was demonstrated using the depression patient-centered registries at the Mayo Clinic, which was designed for the CCM [30] to manage primary care patients diagnosed with moderate to severe depression. By following the data cleaning and refining procedure discussed in this framework, we produced high-quality data for potential research questions that can be answered using the data in the depression registry. We also generated cohorts of patients available for testing hypotheses related to the effectiveness of the CCM for primary care patients with depression.

In patient registries developed to follow patients with chronic diseases over multiple years, identifying appropriate patient cohorts for cross-sectional or longitudinal studies can be very challenging. In the case of the CCM, a patient can have multiple points of enrollment for the intervention due to the fluctuating nature of chronic conditions. A potential solution, as discussed in this study, is to first identify major patient subgroups (eg, enrolled, opt out, not approached) in the registry and set the index date as the first date of eligibility for all subgroups and limit the outcome window to a relatively short period (eg, 6 months) after the index date. Although this solution can help select the right patients (intervention and control) for a cross-sectional study, it may not be appropriate for longitudinal studies because some patients may have multiple eligibility and enrollment statuses. One possible solution would be to use multiple outcome windows (eg, every 6 months after the index date). In this case, information collected in a previous outcome window can be included as patient history to assess the effectiveness of the intervention in the next outcome window.

An additional area of consideration for practices embarking on adopting or creating a patient-centered registry in their setting would be to reduce the potential challenges we identified upstream of the point at which research is done. Data collected in clinical practice as compared with data collected in research settings are complicated by who does the data entry and changes in staff. Tools such as the EHR and patient workflows evolve and can lead to a lack of oversight. Data may be gathered to report quality outcomes or to support billing, but it is often rare to see practices that ensure data quality for quality improvement and retrospective research. Practices might consider creating a DFD during patient-centered registries design, along with standard definitions of critical elements (eg, eligibility vs start date and graduation vs recovery). Monitoring data integrity and assigning oversight of the registry, highlighting the importance of data maintenance, would vastly reduce the time involved in preparing clinical data for research and allow for more rapid feedback to the practice about which programs are or are not effective.

Lessons Learned

A summary of lessons learned during the process of developing this systematic framework and testing its feasibility using data in the depression registry was as follows:

1. Data cleaning and refining of accumulated data in a patient-centered registry is a time-consuming process and unexpectedly challenging. Researchers need to plan to dedicate sufficient time and resources to understand the underlying structure of the data and develop effective procedures to identify and manage data quality issues in the registry.
2. Visualizing multiple statuses of an individual patient over a period of time would highlight the challenges of defining appropriate observation and outcome windows for this group of patients. Therefore, it would help the research team to adopt a proper strategy for defining appropriate patient cohorts and consequently reduce the risk of measurement bias in the study.
3. Involving stakeholders of the patient registry (eg, care coordinators and primary care providers) in the process of addressing data quality issues, specifically missing data, would substantially assist the research team in adopting appropriate strategies for handling the issues and consequently would provide high-quality data for subsequent research projects.

Limitations

We acknowledge some limitations of our proposed framework:

1. The first component of data analysis is mostly suitable for designing a DFD in registries with a focus on patient-centered interventions for managing chronic diseases. Therefore, the DFD might not be appropriate for other types of health care registries with a different focus or patient group.
2. Data quality has many different dimensions. In this study, we discussed 5 dimensions of data quality: accuracy, completeness, consistency, timeliness, validity, and uniqueness. Information about other dimensions such as timeliness or accessibility can be found in the study by Kodra et al [16].
3. The second component of the registry is mostly developed with a focus on cleaning and refining structured data. If unstructured data (eg, clinical notes or images) are also part of the analyses, then the research team needs to implement the applicable methods for the unstructured data.
4. Registries vary in their strengths with regard to being linked to pharmacy data, administrative data, and care in multiple sites. Some of these methods would vary as data from other sources are included.

Conclusions

There is a need for a conceptual and methodological framework for generating and evaluating data-driven hypotheses using data in patient-centered registries created for clinical reasons to enhance care and outcomes for patients. The systematic framework introduced in this study provides a clear step-by-step process for identifying and managing data quality issues in the registries and identifying appropriate patient cohorts for a specific research question. Overall, it is unrealistic to aim for data in a registry that is completely free of errors. Some errors will remain undetected and uncorrected regardless of the completeness of the data quality assessment framework. Utilization of a data analytics framework can merely lead to an

improvement in data quality. We selected the components of data quality and identified patient cohorts in this framework to be practically feasible and facilitate detecting and correcting common errors in the registries. This implies that this framework can be expected to be effective in providing high-quality data to evaluate data-driven hypotheses using data in patient-centered registries. In future studies, we aim to use the data in the depression registry to estimate the risk of hospitalization and emergency department visits, measuring the effectiveness of the CCM on clinical outcomes and health care services cost.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Integrated Behavioral Health registry.
[DOCX File , 14 KB - resprot_v9i10e18366_app1.docx]

Multimedia Appendix 2
Missing data.
[DOCX File , 13 KB - resprot_v9i10e18366_app2.docx]

References

1. What is an electronic health record (EHR)? Office of the National Coordinator for Health Information Technology. 2020. URL: https://www.healthit.gov/faq/what-electronic-health-record-ehr [accessed 2020-09-14]
2. Rare Diseases Registry Program (RaDaR). National Center for Advancing Translational Sciences. 2020. URL: https://ncats.nih.gov/radar [accessed 2020-05-01]
3. Franklin PD, Ayers DC, Berliner E. The essential role of patient-centered registries in an era of electronic health records. NEJM Catal 2018;4(5).
4. Agency for Health Care Research and Quality. In: Gliklich RE, Dreyer NA, Leavy MB, editors. Registries for Evaluating Patient Outcomes: A User's Guide. 3rd Edition. Rockville, MD: Agency for Healthcare Research and Quality (US); 2014.
5. World Health Organization. Mental Health Information Systems: WHO Mental Health Policy and Service Guidance Package - Module 12. Geneva, Switzerland: World Health Organization; 2005. URL: https://www.who.int/mental_health/policy/services/essentialpackage1v12/en/
6. Bellgard MI, Napier K, Render L, Radochonski M, Lamont L, Graham C, et al. A registry framework enabling patient-centred care. Stud Health Technol Inform 2015;214:8-14. [Medline: 26210411]
7. Mental Illness. National Institute of Mental Health. 2020. URL: https://www.nimh.nih.gov/health/statistics/mental-illness.shtml [accessed 2020-05-01]
8. Harnois G, Gabriel P. Mental health and work: impact, issues and good practices. World Health Organization. Geneva, Switzerland: World Health Organization; 2000. URL: https://www.who.int/mental_health/media/en/712.pdf [accessed 2020-09-29]
9. Lake J, Turner MS. Urgent need for improved mental health care and a more collaborative model of care. Perm J 2017;21:17-24 [FREE Full text] [doi: 10.7812/TPP/17-024] [Medline: 28898197]
10. Bagayogo IP, Turcios-Wiswe K, Taku K, Peccoralo L, Katz CL. Providing mental health services in the primary care setting: the experiences and perceptions of general practitioners at a New York City clinic. Psychiatr Q 2018 Dec;89(4):897-908. [doi: 10.1007/s11126-018-9587-2] [Medline: 29968148]
11. Archer J, Bower P, Gilbody S, Lovell K, Richards D, Gask L, et al. Collaborative care for depression and anxiety problems. Cochrane Database Syst Rev 2012 Oct 17;10:CD006525. [doi: 10.1002/14651858.CD006525.pub2] [Medline: 23076925]
12. Unützer J, Katon W, Callahan CM, Williams Jr JW, Hunkeler E, Harpole L, IMPACT Investigators. Improving Mood-Promoting Access to Collaborative Treatment. Collaborative care management of late-life depression in the primary care setting: a randomized controlled trial. J Am Med Assoc 2002 Dec 11;288(22):2836-2845. [doi: 10.1001/jama.288.22.2836] [Medline: 12472325]
13. Unützer J, Harbin H, Schoenbaum M, Druss B. The collaborative care model: an approach for integrating physical and mental health care in Medicaid health homes. Health Home Information Resource Center. 2013. URL: https://www.chcs.org/media/HH_IRC_Collaborative_Care_Model__052113_2.pdf [accessed 2020-09-29]
14. Dejesus RS, Angstman KB, Cha SS, Williams MD. Antidepressant medication use among patients with depression: comparison between usual care and collaborative care using care managers. Clin Pract Epidemiol Ment Health 2013 May 31;9:84-87 [FREE Full text] [doi: 10.2174/1745017901309010084] [Medline: 23847688]
15. Gliklich RE, Dreyer NA, Leavy MB, editors. Analysis, interpretation, and reporting of registry data to evaluate outcomes. In: Registries for Evaluating Patient Outcomes: A User's Guide. 3rd edition. Rockville, MD: Agency for Healthcare Research and Quality (US); 2014.

16. Kodra Y, de la Paz MP, Coi A, Santoro M, Bianchi F, Ahmed F, et al. Data quality in rare diseases registries. Adv Exp Med Biol 2017;1031:149-164. [doi: 10.1007/978-3-319-67144-4_8] [Medline: 29214570]
17. DeMarco T. Structure analysis and system specification. In: Broy M, Denert E, editors. Pioneers and Their Contributions to Software Engineering. Berlin, Heidelberg: Springer; 1979:255-288.
18. Moriarty AS, Gilbody S, McMillan D, Manea L. Screening and case finding for major depressive disorder using the Patient Health Questionnaire (PHQ-9): a meta-analysis. Gen Hosp Psychiatry 2015;37(6):567-576. [doi: 10.1016/j.genhosppsych.2015.06.012] [Medline: 26195347]
19. Williams N. The GAD-7 questionnaire. Occup Med 2014 Apr 3;64(3):224. [doi: 10.1093/occmed/kqt161]
20. Miller C, Klugman J, Berv DA, Rosenquist KJ, Ghaemi SN. Sensitivity and specificity of the Mood Disorder Questionnaire for detecting bipolar disorder. J Affect Disord 2004 Aug;81(2):167-171. [doi: 10.1016/S0165-0327(03)00156-3] [Medline: 15306144]
21. Conigrave K, Hall WD, Saunders JB. The AUDIT questionnaire: choosing a cut-off score. Alcohol Use Disorder Identification Test. Addiction 1995 Oct;90(10):1349-1356. [doi: 10.1046/j.1360-0443.1995.901013496.x] [Medline: 8616463]
22. Tallentire VR, Smith SE, Skinner J, Cameron HS. Exploring patterns of error in acute care using framework analysis. BMC Med Educ 2015 Jan 16;15:3 [FREE Full text] [doi: 10.1186/s12909-015-0285-6] [Medline: 25592440]
23. Kahn MG, Raebel MA, Glanz JM, Riedlinger K, Steiner JF. A pragmatic framework for single-site and multisite data quality assessment in electronic health record-based clinical research. Med Care 2012 Jul;50 Suppl:S21-S29 [FREE Full text] [doi: 10.1097/MLR.0b013e318257dd67] [Medline: 22692254]
24. Mack C, Su Z, Westreich D. Managing Missing Data in Patient Registries Addendum to Registries for Evaluating Patient Outcomes: A User's Guide. Third Edition. Rockville, MD: Agency for Healthcare Research and Quality (US); 2018.
25. Bell D. An introduction to the Unified Modeling Language. IBM Developer. 2020. URL: https://developer.ibm.com/articles/an-introduction-to-uml/ [accessed 2020-06-01]
26. Powell-Morse A. Conceptual models – what are they and how can you use them? Airbrake: Full-Stack Application Monitoring Software. 2020. URL: https://airbrake.io/blog/sdlc/conceptual-model [accessed 2020-06-01]
27. Huser V, Li X, Zhang Z, Jung S, Park RW, Banda J, et al. Extending Achilles heel data quality tool with new rules informed by multi-site data quality comparison. Stud Health Technol Inform 2019 Aug 21;264:1488-1489. [doi: 10.3233/SHTI190498] [Medline: 31438195]
28. Segura-Bedmar I, Raez P. Cohort selection for clinical trials using deep learning models. J Am Med Inform Assoc 2019 Nov 1;26(11):1181-1188 [FREE Full text] [doi: 10.1093/jamia/ocz139] [Medline: 31532478]
29. Pratt LA, Brody DJ, Gu Q. Antidepressant use among persons aged 12 and over:United States,2011-2014. NCHS Data Brief 2017 Aug(283):1-8 [FREE Full text] [Medline: 29155679]
30. Angstman KB, Williams MD. Patients in a depression collaborative care model of care: comparison of 6-month cost utilization data with usual care. J Prim Care Community Health 2010 Apr 1;1(1):12-16. [doi: 10.1177/2150131909359414] [Medline: 23804062]

Abbreviations

CCM: collaborative care model
DFD: data flow diagram
EHRs: electronic health records
IBH: Integrated Behavioral Health
MCAR: missing completely at random
PHQ-9: Patient Health Questionnaire

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Protocol

App-Delivered Self-Management Intervention Trial selfBACK for People With Low Back Pain: Protocol for Implementation and Process Evaluation

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Abstract

Background: Implementation and process evaluation is vital for understanding how interventions function in different settings, including if and why interventions have different effects or do not work at all.

Objective: This paper presents the protocol for an implementation and process evaluation embedded in a multicenter randomized controlled trial conducted in Denmark and Norway (the selfBACK project). selfBACK is a data-driven decision support system that provides participants with weekly self-management plans for low back pain. These plans are delivered through a smartphone app and tailored to individual participants by using case-based reasoning methodology. In the trial, we compare selfBACK in addition to usual care with usual care alone.

Methods: The aim of this study is to conduct a convergent mixed-methods implementation and process evaluation of the selfBACK app by following the reach, effectiveness, adoption, implementation, and maintenance framework. We will evaluate the process of implementing selfBACK and investigate how participants use the intervention in daily life. The evaluation will also cover the reach of the intervention, health care provider willingness to adopt it, and participant satisfaction with the intervention. We will gather quantitative measures by questionnaires and measures of data analytics on app use and perform a qualitative exploration of the implementation using semistructured interviews theoretically informed by normalization process theory. Data collection will be conducted between March 2019 and October 2020.

Results: The trial opened for recruitment in February 2019. This mixed-methods implementation and evaluation study is embedded in the randomized controlled trial and will be collecting data from March 2019 to October 2020; dissemination of trial results is planned thereafter. The results from the process evaluation are expected 2021-2022.

Conclusions: This study will provide a detailed understanding of how self-management of low back pain can be improved and how a digital health intervention can be used as an add-on to usual care to support patients to self-manage their low back pain.

We will provide knowledge that can be used to explore the possibilities of extending the generic components of the selfBACK system and key drivers that could be of use in other conditions and diseases where self-management is an essential prevention or treatment strategy.

Trial Registration: ClinicalTrials.gov NCT03798288; https://www.clinicaltrials.gov/ct2/show/NCT03798288

International Registered Report Identifier (IRRID): DERR1-10.2196/20308

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KEYWORDS

randomized controlled trial; implementation; process evaluation; low back pain; digital health intervention; mHealth; decision support system; RE-AIM

Introduction

Self-management is often recommended as an important element of living with a chronic health condition. Self-management is defined varyingly in the literature, but key elements are "structured, multicomponent interventions that support autonomy and involve education and training with the aim of promoting adherence to self-management behaviors to achieve improved physical, psychological, and economic outcomes" [1]. Self-management involves work that many patients find challenging without support [2]. With the increased integration of digital technologies in our daily lives, digital health interventions such as smartphone apps have been suggested as promising platforms for supporting self-management [3,4], and they are increasingly being used to help people manage their chronic conditions [5]. Digital health interventions may encourage patients to engage in preventive health activities, promote communication between health care providers and patients, and improve patient adherence to treatment protocols and self-care of chronic conditions [6].

Individuals who aspire to be healthy or have more choice and control over managing their well-being are especially likely to engage with digital health interventions [7], whereas others experience barriers to engagement in digital health interventions such as poor digital literacy or negative experiences with impersonal digital health interventions [7]. Barriers and facilitators to digital health engagement are complex, and there are many interrelated factors that affect patients' and the public's ability to engage with digital health interventions [6,7]. Digital health interventions are more likely to achieve their full potential if they are user friendly and tailored to individual user needs [7]. However, we need to enhance our understanding of factors that hinder or promote uptake and use of digital health interventions, especially for individual conditions [6]. To gain this knowledge, systematic evaluations of implementation processes are vital for investigating how participants engage with and use digital health interventions in daily life. These evaluations consist of multiple components, which together can help distinguish between interventions that are inherently faulty (failure of intervention concept or theory) and those that are poorly delivered (implementation failure) [8]. Information regarding implementation (eg, delivery and receipt of the intervention) is an important aspect in a process evaluation [9] and can provide valuable insights regarding likely future implementation ability of the digital health intervention in real-world settings.

Low back pain is a very common condition and the most significant contributor to years lived with disability and disability-adjusted life years globally [10,11]. In addition to the individual health consequences, low back pain poses an enormous economic burden on the European economy [10,11], which is only expected to increase as the European population ages. In most people a specific cause of low back pain will not be identified; thus, most low back pain is termed nonspecific, and for many, the condition becomes recurrent or long-lasting [12]. Evidence-based guidelines for treatment of nonspecific low back pain consistently endorse self-management as a central part of low back pain care [13-16]. Self-management in chronic conditions may be supported by digital health interventions, but in relation to low back pain the current evidence is weak [17]. Published studies have been heterogeneous with poor descriptions of interventions and limited theoretical underpinnings suggesting the need for further research in this sphere [17,18]. In the burgeoning field of digital health interventions, it therefore seems relevant to develop high-quality digital self-management interventions for people with low back pain [17-19] and evaluate the process of implementing the interventions to gain insights into why digital self-management interventions work or do not work, and how they can be optimized to increase likelihood of success [7,20].

The selfBACK study aims to create and implement a smartphone app with high-quality, evidence-based content that provides self-management support to people with low back pain [21,22]. This paper describes the protocol for an implementation and process evaluation study embedded in a multicenter, randomized controlled trial (RCT) of the selfBACK app compared with usual care. The focus of this paper is the planned evaluation of the implementation processes. A detailed protocol concerning the design of the RCT and a feasibility study have been reported elsewhere [23,24]. Results of the pilot study will be reported separately.

Methods

Aims of This Study

We will conduct a convergent mixed-methods implementation and process evaluation of the selfBACK app by following the reach, effectiveness, adoption, implementation, and maintenance (RE-AIM) framework [25].

The specific aims of the study according to the RE-AIM framework are as follows:

- Describe the proportion and characteristics of participants and nonparticipants in selfBACK and the recruitment pathways
- Evaluate self-perceived effect and user acceptability and satisfaction using quantitative measures combined with interview-based explorations of both participant and health care provider appraisals of selfBACK
- Describe health care provider recruitment strategies of potential participants and identify factors affecting uptake of health care provider adoption of selfBACK
- Explore the implementation of selfBACK and how participants embed and integrate use of the app in daily routines, and compare participants with different levels of engagement and use
- Explore participants' intended future use and sustained engagement with the selfBACK app

selfBACK Overview

The selfBACK project is a 5-year project (2016-2020) funded by the European Union Horizon 2020 Research and Innovation Programme. In brief, the selfBACK intervention is a data-driven decision support system that provides participants with tailored, weekly updated self-management plans delivered through a smartphone app. The app content builds on clinical guidelines for treatment of low back pain and has three main components: (1) physical activity advice and step counting using input from an activity-detecting wristband, (2) education based on a cognitive behavioral approach, and (3) instructions on physical strength and flexibility exercises. The content of the app used is described in detail in the protocol paper [21-23]. Tailoring of the self-management plans is achieved by using the case-based reasoning methodology, which is an artificial intelligence method. In selfBACK, the case-based reasoning system takes data about the current case (participant) and compares it with data from previous successful ones to find similar cases (participants) that are used to tailor the self-management plan for the current case (participant). The intervention will be tested in a multicenter RCT with two parallel arms conducted in Denmark and Norway. The trial period is 9 months with primary outcome (pain-related disability) assessed at 3 months. The control arm will receive usual care (ie, follow any diagnostic or treatment-related pathway as instructed by their health care provider). The intervention arm will use the selfBACK app in addition to usual care. The trial will include 350 participants allocated 1:1 to the usual care arm and intervention arm (selfBACK as an add-on to usual care) [21-23]. Eligible participants for the RCT are individuals who seek care from a primary health care practice or an outpatient hospital facility for nonspecific low back pain.

In both Norway and Denmark, participants are recruited from general practice, physiotherapy, and chiropractic clinics. Additionally, in Denmark participants are also recruited from the Spine Centre in the region of Southern Denmark. The Spine Centre is a specialized outpatient hospital facility that reviews patients with back pain referred from primary care. The Spine Centre provides diagnostic assessment of patients and prescribes treatment plans according to national treatment guidelines. Patients seen at the Spine Centre without serious pathologies may be referred to the selfBACK study.

The recruitment period for the RCT started in March 2019. In each country, collaborations with local clinics and health care providers were established to facilitate recruitment. Health care providers refer potentially eligible participants based on a short description of eligibility. Final eligibility is assessed by the research team during a screening phone call.

Ethical Approval and Consent to Participate

National ethics approvals have been granted for both the Danish (Regional Scientific Ethical Committee for Southern Denmark, S-20182000-24) and Norwegian (Regional Committee for Medical and Health Research Ethics, 2017/923-6) sites of the RCT, including the process evaluation. Regarding collecting, managing, and storage of data, approval was granted from the Danish Data Protection Agency through application to the University of Southern Denmark's legal office (201-57-0008) and from the Norwegian National Data Protection Authority and the Centre for Research Data through ethics approval. The trial was registered with ClinicalTrials.gov [NCT03798288].

All participants are asked for informed consent, assigned after the principles of the Helsinki Declaration II. All data will be treated confidentially and stored in pseudoanonymized form. The quantitative data will be stored on a server in Norway, while the interview data will be stored in Denmark. Both servers are secure and firewall-protected, and backups are performed daily. In both countries, data handling and storage is consistent with the European regulations on data protection.

Guiding Theoretical Frameworks

This implementation and process evaluation study integrates three published frameworks to guide the design of the intervention and formative evaluation: (1) intervention mapping [26], used to conceive and develop the intervention; (2) the RE-AIM framework [25,27], used to guide the overall evaluation of the study and assess implementation success of the selfBACK app [25,27]; and (3) normalization process theory [28], used to guide the evaluation of barriers and facilitators that may affect implementation, providing a more detailed understanding of how and why the trial achieves the observed results.

Intervention Mapping

Complex innovations such as digital health behavior change interventions can be conceived and developed using this comprehensive framework [26]. Intervention mapping has been described as "providing a systematic and stepwise approach to planning interventions" [29]. Intervention mapping enables identification of behavioral and environmental determinants likely to influence engagement with and operationalization of recommended self-management behaviors, thus enhancing the potential for intervention success. The development of the intervention using intervention mapping is described in brief elsewhere [23].

RE-AIM Framework

Our overall evaluation is guided by the RE-AIM framework and investigates all five elements of the framework: reach, effectiveness, adoption, implementation, and maintenance [25,27]. The RE-AIM framework is an evaluation framework that aims to determine the success of an intervention

implementation within a given context [25,30]. It has been extensively used in RCTs to evaluate the external validity and sustainability of effective practices [31] including digital health interventions in diabetes [32] and mental disorders [33].

Normalization Process Theory

Normalization process theory [28] is an implementation theory [30] that provides a framework for the collection and analysis of data and a coherent set of explanations of implementation processes [34]. Using this theoretical framework will enable us to identify, characterize, and explain mechanisms that shape the implementation process of selfBACK, which will in turn influence outcomes [34]. Normalization process theory has increasingly been used as a framework in prospective evaluations of health care innovations or interventions, particularly digital health interventions [35], as part of service deployments or clinical trials. Normalization process theory provides a conceptual framework that enables increased understanding of the factors that influence how new technologies or therapies become implemented, embedded, and integrated, or not, into routine use or everyday life [34]. It has also been used extensively to understand self-management practices of patients [36].

Data Collection and Analysis

This mixed-methods implementation and evaluation study is embedded in the RCT and will be collecting data from March 2019 to October 2020. We will gather self-reported data by questionnaires (including characteristics of the participants such as age, sex, and working status), retrieve data analytics on app use, and perform a theoretically informed qualitative exploration involving semistructured interviews with participants and health care providers.

Interview Participants

Intervention arm participants in both Denmark and Norway will be selected for interview based on a simple measure of adherence to the intervention: number of weekly self-management plans generated during the first 3 months of the intervention period. During this period and dependent on participants' adherence, between 1 and 14 plans may be generated. Cut points for 3 adherence level groups will be based on pilot data of participant app use and defined as 1 to 7 plans (low or nonuse), 8 to 12 plans (moderate use), and 13 to 14 plans (high use). Approximately 6 to 8 participants from each of the 3 groups in the intervention arm will be interviewed [37]—up to 24 interviews or until data saturation is reached.

In addition, 6 to 8 participants in the usual care group will be interviewed. Even though the intervention group allocation in the RCT will be 1:1, the number of participants interviewed from the usual care arm will be lower since interviews will only pertain to general experiences of low back pain self-management and perceived effect of participation in the trial. The majority of the interviews will be conducted in Denmark as this is the primary country of patient recruitment.

The number of health care providers to be interviewed will be determined based on the number of recruitment sites needed for the RCT. To secure maximum variation, we will interview health care providers from all participating professions and aim to identify health care providers with varying success in terms of recruitment to the RCT. The estimated sample size is approximately 10 health care providers. Interviews will be undertaken either in person or via telephone and will be audiotaped with participant or health care provider consent and transcribed verbatim to provide data for the qualitative analyses.

RE-AIM Components

Textbox 1 provides a detailed description of the activities related to each of the five elements in the RE-AIM framework.

Textbox 1. Description of quantitative and qualitative data collection strategies.

Reach

- Quantitative:
  - Participant recruitment flow: number of referred, screened, enrolled, and randomized; reason for nonparticipation or exclusion
  - Participant characteristics: sociodemographic data; fear avoidance; self-efficacy; illness perception
  - Recruitment strategy: description of recruitment pathways into selfBACK
- Qualitative:
  - Semistructured interviews, intervention arm: experience of enrollment in selfBACK
  - Semistructured interviews, usual care arm: experience of enrollment in selfBACK

Effectiveness

- Quantitative:
  - User satisfaction, intervention arm: Virtual Care Climate Questionnaire plus overall rating items
- Qualitative:
  - Semistructured interviews, intervention arm: motivation for participating; perception of self-management; change in self-management behavior; effect of participating; satisfaction and appraisal of selfBACK app
  - Semistructured interviews, usual care arm: motivation for participating; perception of self-management; change in self-management behavior; effect of participating (if any)
  - Semistructured interviews or focus groups, health care providers: perception and appraisal of selfBACK

Adoption

- Quantitative:
  - Recruiter flow: numbers of invited and accepting health care providers; number of patients informed about the selfBACK study per health care provider or clinic
  - Characteristics of health care providers: type; number of health care providers per clinic
  - Recruitment strategy: description of how clinics or health care providers were recruited to selfBACK
- Qualitative:
  - Semistructured or focus groups interviews, health care providers: role in patient engagement; success of engagement; barriers and facilitators for informing patients about the study

Implementation

- Quantitative:
  - App use data, 0 to 3 months: frequency of use; number of app visits; time spent using the app; number of days with visits; number of plans generated; goal achievement scores
  - Participant characteristics: sociodemographic data; fear avoidance; self-efficacy; illness perception
- Qualitative:
  - Semistructured interviews, intervention arm: attitude toward self-management of low back pain and the selfBACK app; barriers and facilitators for engagement; experience of using selfBACK app; challenges of engaging with selfBACK app and what helped; embedment in daily routine

Maintenance

- Quantitative:
  - App use data, 4 to 9 months: frequency of use; number of app visits; time spent using the app; number of days with visits; number of plans generated; goal achievement scores
- Qualitative:
  - Semistructured interviews, intervention group: perspectives on intended sustained engagement with selfBACK app

Reach

The first dimension of interest in the RE-AIM framework is the reach of the intervention, which refers to the proportion of the target population participating in the intervention [25]. This will provide valuable information about interest in the intervention, eligibility rates among those interested in using the selfBACK system, and details on why some interested respondents are deemed ineligible.

The selfBACK RCT follows the recommendations outlined in the Consolidated Standards on Reporting Trials (CONSORT) guidelines [38]: number of invitations for trial participation and acceptance rates and basic sociodemographic variables for all patients screened for eligibility. Recruitment pathways and flow of recruitment (eg, invitations and acceptance rates) will be examined to see how many people fail the eligibility screening and how many proceed to the trial. During the interviews, we will ask participants about their experience in the enrollment process.

Effectiveness

The second dimension of the RE-AIM framework is effectiveness, which refers to the impact, including potential negative effects, of the intervention on important outcomes [25]. We evaluate effectiveness from the participant perspective using measures of self-perceived effect and user acceptability and satisfaction. This will be investigated both quantitatively, through self-reported patient questionnaires, and qualitatively, through questionnaire data and semistructured interviews. The primary outcome of the RCT, pain-related disability measured by the Roland Morris Disability Questionnaire [39,40] at 3 months, and a range of secondary outcomes [23] will be reported separately from the implementation evaluation.

Quantitatively, we will collect data on effectiveness approximately 4 months after baseline using a web-based questionnaire including the 15-item version of the Virtual Care Climate Questionnaire (VCCQ), which evaluates how participants perceive the effectiveness of the autonomy-supportive communication for health behavior change offered in a virtual care setting [41].

The VCCQ has a 7-point response scale with totally disagree and totally agree as end points. Further, 3 items on overall rating of the selfBACK app, ease of use of the app, and recommendation to others will be used, rated using a 5-point rating system in the same way commercial apps often do. The VCCQ and the rating items will be sent only to the intervention group. To complement participant perspectives on effectiveness, health care provider perceptions and appraisals of the selfBACK system in terms of its value to practice will also be investigated through interviews. Semistructured interviews with participants from the intervention arm will be performed to investigate their motivation for participating in the trial, perceptions of self-management, views on acceptability and satisfaction with the app, and appraisal of the effects, if any, of use of the selfBACK system. Usual care arm interviews will likewise elucidate participant motivation for participating in the trial, their perception of self-management, and any effect participation has induced.

Adoption

Adoption—the third dimension of the RE-AIM framework—refers the willingness of health care providers to inform patients about the selfBACK intervention along with perceived barriers and facilitators to participation and recruitment [25]. Adoption will be assessed by investigating which potential clinical sites adopt the intervention (ie, agree to participate in the trial and inform patients about the study). Semistructured interviews with purposefully sampled health care providers will be undertaken to explore how the health care providers engaged patients (eg, what informal criteria they used for selecting which participants to inform about the study and what barriers and facilitators for engaging patients they experienced). Further, strategies employed by the researchers to recruit health care providers to the selfBACK trial and sustain health care provider engagement of patients into the trial will be described narratively.

Implementation

Implementation is the fourth dimension of the RE-AIM framework and describes to what extent the intervention is implemented as intended [25]. This is usually described as examining how effectively and consistently an intervention is delivered in a specific context (eg, primary or secondary care) by staff. As the selfBACK intervention is not being delivered by staff but instead through a self-management app, we will focus on how the selfBACK app becomes embedded and integrated into the daily routines of participants with low back pain.

When assessing implementation, we will focus on the first 4 months of the intervention. Semistructured interviews with participants in the intervention group will be undertaken with participants with different levels of use of the app (ie, high, moderate, low, and nonuse). The interviews will focus on how and why the participants embed and integrate the selfBACK app in daily life or do not (eg, their attitude toward self-management of low back pain, barriers and facilitators for engagement, and experience with using the selfBACK app). Interviews will be conducted approximately 4 months after inclusion (ie, after participants have completed the follow-up questionnaires that feature the primary outcome and VCCQ). The interviewer will be blinded to the outcome measures.

Implementation will also be assessed quantitatively by investigating app use analytics data (eg, frequency of use and goal achievement scores) throughout the first 3 months after inclusion. Information on individual participant app use will be drawn from the backend system serving selfBACK. The app use data will also be used to compare the groups of participants with different adherence levels on characteristics such as sociodemographic data, fear avoidance, self-efficacy, and illness perception.

Maintenance

Maintenance is the fifth dimension of the RE-AIM framework and refers to the extent to which engagement with the intervention is sustained at the individual and system level over time [25]. Due to the nature of the selfBACK intervention, our focus will be on the concept of maintenance at the individual

level: use of the app beyond 3 months and up to 9 months (full trial period). We will examine this with app analytics for the trial period 4 to 9 months after baseline and explore participants' intended future use beyond the 3 months through semistructured interviews with intervention arm participants.

Normalization Process Theory Components

In Figure 1, we have outlined the four main constructs of normalization process theory that will guide the collection and analysis of interview data in the selfBACK RCT.

Figure 1. Four constructs of normalization process theory and associated questions from the process evaluation.

Coherence refers to the sense-making work individuals undertake that influences whether they are willing to embed a new practice in their lives and will influence initial adoption of the intervention by health care providers and participants using the app. Specifically, we will explore whether participants understand the purpose of the selfBACK app and if they like the idea.

Cognitive participation is the work individuals undertake to engage with the new practice and will influence implementation. Participants will be prompted to consider their level of buy-in of the selfBACK app concept and potential for sustained engagement.

Collective action refers to the work individuals do to enact a new practice, which will be related to implementation and maintenance. We will elucidate participant confidence in using the app and integrating use in their daily lives. Further, any contextual issues that help or hinder the participant will be highlighted.

Reflexive monitoring is the appraisal work individuals undertake to determine whether the new practice is worth sustaining or how it must be reconfigured to fit their needs and will relate particularly to maintaining their use of the intervention. Participants will be asked about the perceived benefits, if any, of using the app, its value to them, and the need for any modifications.

Analysis

Quantitative Data Analysis

Simple descriptive statistics will be used to do comparisons and test for differences on questionnaire and app use data. Statistical analyses will be performed in the most recent version of SPSS Statistics (IBM Corporation).

Qualitative Data Analysis

Qualitative data will be analyzed using a framework approach underpinned by normalization process theory. In terms of usual care participants, normalization process theory will serve to help understand experiences of low back pain and facilitators and barriers to low back pain self-management in general. The analyses will follow the five stages of framework analysis described by Ritchie [42]: familiarization, identifying a thematic framework, indexing, charting, and mapping and interpretation. The distribution of codes will be recorded and, importantly, any data that fall outside of the coding frame will be identified and examined to determine if important concepts or ideas are being missed by using the chosen theoretical framework. Transcripts will be analyzed and coded in their original language. To ensure consensus on themes and coding, coding meetings will be arranged to discuss coding among key researchers. At the meetings, the coding framework and a proportion of the data will be double coded to ensure data analysis is robust and coders are open to identifying themes that fall outside the normalization

process theory framework. In this way, coding will be iterative and responsive to the data and inappropriate shoe-horning of the qualitative data collected will be avoided.

Results

Recruitment to the trial started in early 2019 and ran until the end of 2019. Data collection started in March 2019 and is expected to be complete by October 2020; dissemination of trial results is planned thereafter. The results from the process evaluation are expected in 2021-2022.

Discussion

This mixed-methods implementation and process evaluation embedded in an RCT will assess the factors that influence uptake and use of a digital health intervention for self-management of low back pain as an addition to usual care. In addition to identification of factors that influence the effect of the selfBACK intervention, we will explore participant acceptance and patterns of use of the selfBACK app in the intervention arm and attempt to understand current self-management strategies for those in the usual care arm. In preparation for this study, we aimed to ensure high usability of selfBACK by involving people with low back pain and health care providers during the development phase of the project. In our evaluation, we will extend on the development process and assess health care provider experiences with the selfBACK system and their views on future implementability. Further, we have undertaken an intervention mapping process, developed logic models of change (described elsewhere) [43] and described the theoretical underpinnings for the selfBACK system. However, our process evaluation will enable an in-depth examination of factors identified as key by the normalization process theory, particularly factors that influence uptake of a digital health intervention directed at self-management and factors related to the integration of the selfBACK intervention into daily life.

This study will provide a detailed understanding of how self-management of low back pain can be improved and how a digital health intervention can be used as an add-on to usual care to support patients to self-manage their low back pain. We will provide knowledge that can be used to explore the possibilities of extending the generic components of the selfBACK system and key drivers that could be of use to other conditions and diseases where self-management is an essential prevention or treatment strategy such as diabetes, osteoarthritis, rheumatoid arthritis, cardiovascular disease, or chronic obstructive pulmonary disorders. It will also provide valuable insights into health care provider views and likely improve future implementability of the selfBACK system at scale to support self-management of low back pain. Last, this thorough implementation and process evaluation integrated in the RCT will enhance the credibility of the findings from our trial and provide important input for improving the selfBACK system in order to enhance its future impact.

Acknowledgments

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Authors' Contributions

CDNR provided the first draft of the manuscript. MaJS and MeJS critically scrutinized the first draft and provided comments. BIN, FM, and KW drafted the initial protocol and gave specific input to the qualitative interviews and theoretical framework. KB gave specific input to app use data. LFS, PJM, BIN, FSM, and KS gave specific input to the quantitative measures of effectiveness. All authors participated in the design and content of the process evaluation, and all authors read, commented on, and approved the final manuscript prior to submission.

Conflicts of Interest

The overall aim of the selfBACK project is to develop a digital decision support system and mobile app to support participants to self-manage their low back pain. The results and experiences from the pilot and RCT will inform the further development of the selfBACK system, which may be introduced into the commercial market. If the selfBACK system is introduced into the commercial market, it will be done by a separate company that will have obtained a license to take the app to market. Any profit from such a transaction is received by the participating universities and not by individual authors. In order to secure an unbiased interpretation and dissemination of the RCT, the interpretation of the results will be performed blind to group allocation. Upon publication of study results, this commercial potential in the app development will be clearly stated and the publication will undergo peer review to ensure methodological and scientific rigor. Additionally, the overall conduct of the trial is overseen with a semiannual review by the European Union, which is funding the project.

References

1. Toomey E, Currie-Murphy L, Matthews J, Hurley DA. The effectiveness of physiotherapist-delivered group education and exercise interventions to promote self-management for people with osteoarthritis and chronic low back pain: a rapid review part I. Man Ther 2015 Apr;20(2):265-286. [doi: 10.1016/j.math.2014.10.013] [Medline: 25466293]

2. Newson JT, Huguet N, Ramage-Morin PL, McCarthy MJ, Bernier J, Kaplan MS, et al. Health behaviour changes after diagnosis of chronic illness among Canadians aged 50 or older. Health Rep 2012 Dec;23(4):49-53 [FREE Full text] [Medline: 23356045]
3. Zhao J, Freeman B, Li M. Can mobile phone apps influence people's health behavior change? An evidence review. J Med Internet Res 2016 Oct 31;18(11):e287 [FREE Full text] [doi: 10.2196/jmir.5692] [Medline: 27806926]
4. Beatty L, Lambert S. A systematic review of internet-based self-help therapeutic interventions to improve distress and disease-control among adults with chronic health conditions. Clin Psychol Rev 2013 Jun;33(4):609-622. [doi: 10.1016/j.cpr.2013.03.004] [Medline: 23603521]
5. Georgsson M, Staggers N. Quantifying usability: an evaluation of a diabetes mHealth system on effectiveness, efficiency, and satisfaction metrics with associated user characteristics. J Am Med Inform Assoc 2016 Jan;23(1):5-11. [doi: 10.1093/jamia/ocv099] [Medline: 26377990]
6. Lupton D. The digitally engaged patient: self-monitoring and self-care in the digital health era. Soc Theory Health 2013 Jun 19;11(3):256-270. [doi: 10.1057/sth.2013.10]
7. O'Connor S, Hanlon P, O'Donnell CA, Garcia S, Glanville J, Mair FS. Understanding factors affecting patient and public engagement and recruitment to digital health interventions: a systematic review of qualitative studies. BMC Med Inform Decis Mak 2016 Sep 15;16(1):120 [FREE Full text] [doi: 10.1186/s12911-016-0359-3] [Medline: 27630020]
8. Oakley A, Strange V, Bonell C, Allen E, Stephenson J. Process evaluation in randomised controlled trials of complex interventions. BMJ 2006 Feb 18;332(7538):413-416 [FREE Full text] [doi: 10.1136/bmj.332.7538.413] [Medline: 16484270]
9. Linnan L, Steckler A. Process Evaluation for Public Health Interventions and Research. San Francisco: Jossey-Bass; 2002.
10. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012 Dec;380(9859):2163-2196. [doi: 10.1016/S0140-6736(12)61729-2]
11. GBD 2013 DALYsHALE Collaborators, Murray CJL, Barber RM, Foreman KJ, Abbasoglu OA, Abd-Allah F, et al. . [doi: 10.1016/S0140-6736(15)61340-X] [Medline: 26321261]
12. Hartvigsen J, Hancock MJ, Kongsted A, Louw Q, Ferreira ML, Genevay S, Lancet Low Back Pain Series Working Group. What low back pain is and why we need to pay attention. Lancet 2018 Mar 20;391:2356-2367. [doi: 10.1016/S0140-6736(18)30480-X] [Medline: 29573870]
13. de Campos T. Low back pain and sciatica in over 16s: assessment and management NICE Guideline NG59. J Physiother 2017. [doi: 10.1016/j.jphys.2017.02.012] [Medline: 27929617]
14. Qaseem A, Wilt TJ, McLean RM, Forciea MA, Clinical Guidelines Committee of the American College of Physicians. Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2017 Apr 04;166(7):514-530. [doi: 10.7326/M16-2367] [Medline: 28192789]
15. Wong JJ, Côté P, Sutton DA, Randhawa K, Yu H, Varatharajan S, et al. Clinical practice guidelines for the noninvasive management of low back pain: a systematic review by the Ontario Protocol for Traffic Injury Management (OPTIMa) Collaboration. Eur J Pain 2017 Feb;21(2):201-216. [doi: 10.1002/ejp.931] [Medline: 27712027]
16. Stochkendahl MJ, Kjaer P, Hartvigsen J, Kongsted A, Aaboe J, Andersen M, et al. National Clinical Guidelines for non-surgical treatment of patients with recent onset low back pain or lumbar radiculopathy. Eur Spine J 2017 Apr 20;27:60-75. [doi: 10.1007/s00586-017-5099-2] [Medline: 28429142]
17. Nicholl BI, Sandal LF, Stochkendahl MJ, McCallum M, Suresh N, Vasseljen O, et al. Digital support interventions for the self-management of low back pain: a systematic review. J Med Internet Res 2017 May 21;19(5):e179 [FREE Full text] [doi: 10.2196/jmir.7290] [Medline: 28550009]
18. Machado GC, Pinheiro MB, Lee H, Ahmed OH, Hendrick P, Williams C, et al. Smartphone apps for the self-management of low back pain: a systematic review. Best Pract Res Clin Rheumatol 2016 Dec;30(6):1098-1109. [doi: 10.1016/j.berh.2017.04.002] [Medline: 29103552]
19. Dario AB, Moreti CA, Almeida L, Ferreira ML, Refshauge K, Simic M, et al. Effectiveness of telehealth-based interventions in the management of non-specific low back pain: a systematic review with meta-analysis. Spine J 2017 Sep;17(9):1342-1351. [doi: 10.1016/j.spinee.2017.04.008] [Medline: 28412562]
20. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: Medical Research Council guidance. BMJ 2015;350:h1258 [FREE Full text] [Medline: 25791983]
21. Mork PJ, Bach K, selfBACK Consortium. A decision support system to enhance self-management of low back pain: protocol for the selfBACK project. JMIR Res Protoc 2018 Dec 20;7(7):e167 [FREE Full text] [doi: 10.2196/resprot.9379] [Medline: 30030208]
22. Mork PJ, Bach K, SelfBACK Consortium. Metadata correction: a decision support system to enhance self-management of low back pain: protocol for the selfBACK project. JMIR Res Protoc 2019 Jan 03;8(1):e12180 [FREE Full text] [doi: 10.2196/12180] [Medline: 30609979]
23. Sandal LF, Stochkendahl MJ, Svendsen MJ, Wood K, Øverås CK, Nordstoga AL, et al. An app-delivered self-management program for people with low back pain: protocol for the selfback randomized controlled trial. JMIR Res Protoc 2019 Dec 03;8(12):e14720 [FREE Full text] [doi: 10.2196/14720] [Medline: 31793897]

24. Sani S, Wiratunga N, Massie S, Cooper K. A decision support system for self-management of low back pain: results from WP2 pilot study and empirical evaluation of algorithms. 2018. URL: https://www.selfback.eu/uploads/1/0/7/1/107154065/d2_5_pilot_deliverable_pu_300918.pdf [accessed 2020-10-21]
25. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. Am J Public Health 1999 Sep;89(9):1322-1327. [Medline: 10474547]
26. Eldredge L, Markham C, Ruiter R, Fernández M, Kok G, Parvel G. Planning Health Promotion Programs: An Intervention Mapping Approach. 4th Edition. San Francisco: Jossey-Bass; 2016.
27. Gaglio B, Shoup JA, Glasgow RE. The RE-AIM framework: a systematic review of use over time. Am J Public Health 2013 Jun;103(6):e38-e46. [doi: 10.2105/AJPH.2013.301299] [Medline: 23597377]
28. May C, Finch T. Implementing, embedding, and integrating practices: an outline of normalization process theory. Sociology 2009 Jun 15;43(3):535-554. [doi: 10.1177/0038038509103208]
29. Fernandez ME, Ruiter RAC, Markham CM, Kok G. Intervention mapping: theory- and evidence-based health promotion program planning: perspective and examples. Front Public Health 2019;7:209 [FREE Full text] [doi: 10.3389/fpubh.2019.00209] [Medline: 31475126]
30. Nilsen P. Making sense of implementation theories, models and frameworks. Implement Sci 2015;10:53 [FREE Full text] [doi: 10.1186/s13012-015-0242-0] [Medline: 25895742]
31. Mazzucca S, Tabak RG, Pilar M, Ramsey AT, Baumann AA, Kryzer E, et al. Variation in research designs used to test the effectiveness of dissemination and implementation strategies: a review. Front Public Health 2018;6:32 [FREE Full text] [doi: 10.3389/fpubh.2018.00032] [Medline: 29515989]
32. Pihlajamäki J, Männikkö R, Tilles-Tirkkonen T, Karhunen L, Kolehmainen M, Schwab U, StopDia study group. Digitally supported program for type 2 diabetes risk identification and risk reduction in real-world setting: protocol for the StopDia model and randomized controlled trial. BMC Public Health 2019 Mar 01;19(1):255 [FREE Full text] [doi: 10.1186/s12889-019-6574-y] [Medline: 30823909]
33. Kaylor-Hughes CJ, Rawsthorne M, Coulson NS, Simpson S, Simons L, Guo B, REBOOT Notts Lived Experience Advisory Panel, et al. Direct to public peer support and e-therapy program versus information to aid self-management of depression and anxiety: protocol for a randomized controlled trial. JMIR Res Protoc 2017 Dec 18;6(12):e231 [FREE Full text] [doi: 10.2196/resprot.8061] [Medline: 29254909]
34. May CR, Cummings A, Girling M, Bracher M, Mair FS, May CM, et al. Using Normalization Process Theory in feasibility studies and process evaluations of complex healthcare interventions: a systematic review. Implement Sci 2018 Dec 07;13(1):80 [FREE Full text] [doi: 10.1186/s13012-018-0758-1] [Medline: 29879986]
35. Lennon MR, Bouamrane M, Devlin AM, O'Connor S, O'Donnell C, Chetty U, et al. Readiness for delivering digital health at scale: lessons from a longitudinal qualitative evaluation of a national digital health innovation program in the United Kingdom. J Med Internet Res 2017 Feb 16;19(2):e42 [FREE Full text] [doi: 10.2196/jmir.6900] [Medline: 28209558]
36. Gallacher K, Morrison D, Jani B, Macdonald S, May CR, Montori VM, et al. Uncovering treatment burden as a key concept for stroke care: a systematic review of qualitative research. PLoS Med 2013;10(6):e1001473 [FREE Full text] [doi: 10.1371/journal.pmed.1001473] [Medline: 23824703]
37. Malterud K, Siersma VD, Guassora AD. Sample size in qualitative interview studies: guided by information power. Qual Health Res 2015 Nov 27;26:1753-1760. [doi: 10.1177/1049732315617444] [Medline: 26613970]
38. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c332 [FREE Full text] [Medline: 20332509]
39. Roland M, Morris R. A study of the natural history of back pain. Part I: development of a reliable and sensitive measure of disability in low-back pain. Spine (Phila Pa 1976) 1983 Mar;8(2):141-144. [Medline: 6222486]
40. Jordan K, Dunn KM, Lewis M, Croft P. A minimal clinically important difference was derived for the Roland-Morris Disability Questionnaire for low back pain. J Clin Epidemiol 2006 Jan;59(1):45-52. [doi: 10.1016/j.jclinepi.2005.03.018] [Medline: 16360560]
41. Smit ES, Dima AL, Immerzeel SAM, van den Putte B, Williams GC. The Virtual Care Climate Questionnaire: development and validation of a questionnaire measuring perceived support for autonomy in a virtual care setting. J Med Internet Res 2017 May 08;19(5):e155 [FREE Full text] [doi: 10.2196/jmir.6714] [Medline: 28483743]
42. Ritchie J. Qualitative Research Practice: A Guide for Social Science Students and Researchers. 2nd Edition. Los Angeles: Sage Publishers; 2014.
43. Svendsen M, Rasmussen C, Sandal L, Stochkendahl M, Søgaard K, Hartvigsen J. A decision support system for self-management of low back pain: intervention mapping protocol (IMAP). 2018. URL: https://www.selfback.eu/uploads/1/0/7/1/107154065/d3_8_imap_deliverable_pu_300918.pdf [accessed 2020-10-21]

Abbreviations

CONSORT: Consolidated Standards on Reporting Trials
RCT: randomized controlled trial
RE-AIM: reach, effectiveness, adoption, implementation, and maintenance

VCCQ: Virtual Care Climate Questionnaire

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Protocol

Safety and Efficacy of Convalescent Plasma to Treat Severe COVID-19: Protocol for the Saudi Collaborative Multicenter Phase II Study

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Abstract

Background: The COVID-19 pandemic is expected to cause significant morbidity and mortality. The development of an effective vaccine will take several months to become available, and its affordability is unpredictable. Transfusion of convalescent plasma (CP) may provide passive immunity. Based on initial data from China, a group of hematologists, infectious disease specialists, and intensivists drafted this protocol in March 2020.

Objective: The aim of this study is to test the feasibility, safety, and efficacy of CP in treating patients with COVID-19 across Saudi Arabia.

Methods: Eligible patients with COVID-19 will be recruited for CP infusion according to the inclusion criteria. As COVID-19 has proven to be a moving target as far as its management is concerned, we will use current definitions according to the Ministry of Health (MOH) guidelines for diagnosis, treatment, and recovery. All CP recipients will receive supportive management including all available recommended therapies according to the available MOH guidelines. Eligible CP donors will be patients with COVID-19 who have fully recovered from their disease according to MOH recovery criteria as detailed in the inclusion criteria. CP donors have to qualify as blood donors according to MOH regulations except for the history of COVID-19 in the recent past. We will also test the CP donors for the presence of SARS-CoV-2 antibodies by a rapid test, and aliquots will be archived for future antibody titration. Due to the perceived benefit of CP, randomization was not considered. However, we will compare the outcome of the cohort treated with CP with those who did not receive CP due to a lack of consent or lack of availability. In this national collaborative study, there is a likelihood of not finding exactly matched control group patients. Hence, we plan to perform a propensity score matching of the CP recipients with the comparator group patients for the major characteristics. We plan to collect demographic, clinical, and laboratory characteristics of both groups and compare the outcomes. A total sample size of 575 patients, 115 CP recipients and 460 matched controls (1:4 ratio), will be sufficient to detect a clinically important hospital stay and 30-day mortality difference between the two groups with 80% power and a 5% level of significance.

Results: At present, patient recruitment is still ongoing, and the interim analysis of the first 40 patients will be shared soon.

Conclusions: In this paper, we present a protocol for a national collaborative multicenter phase II study in Saudi Arabia for assessing the feasibility, safety, and potential efficacy of CP in treating patients with severe COVID-19. We plan to publish an interim report of the first 40 CP recipients and their matched comparators soon.

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International Registered Report Identifier (IRRID): PRR1-10.2196/23543

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KEYWORDS

coronaviruses; SARS-CoV-2; COVID-19; antibodies; convalescent plasma; treatment; immunology; feasibility; safety; efficacy; infectious disease

Introduction

Background

The COVID-19 pandemic, caused by SARS-CoV-2, is a major health and economic concern worldwide due to its morbidity and mortality. Coronaviruses are a large family of RNA viruses that cause illnesses ranging from the common cold to more severe diseases such as Middle East respiratory syndrome–related coronavirus (MERS-CoV) and severe acute respiratory syndrome–related coronavirus (SARS-CoV) [1]. The new strain of coronavirus identified in December 2019 in Wuhan City, Hubei Province of China was called the 2019 novel coronavirus. The International Committee on Taxonomy of Viruses determined that SARS-CoV-2 is the same species as SARS-CoV. The World Health Organization (WHO) has named the disease associated with SARS-CoV-2 infections COVID-19.

Clinical features of SARS-CoV-2 infection typically include fever and respiratory symptoms like cough and shortness of breath; in severe cases, the infection can cause pneumonia, severe acute respiratory distress syndrome (ARDS), kidney failure, and even death. SARS-CoV-2 has a higher transmission rate with an approximate fatality rate of 3% [2]. The final diagnosis of SARS-CoV-2 infection depends on laboratory detection of the SARS-CoV-2 viral RNA by real-time reverse transcription–polymerase chain reaction (rRT-PCR) [1-4].

The concept of using convalescent plasma (CP) is not new since it has been tried in limited numbers of patients during recent viral crises, including the 2003 severe acute respiratory syndrome epidemic, the 2009 “swine flu” epidemic, and the 2012 outbreak of Middle East respiratory syndrome [5]. CP treatment reduced mortality in patients with severe pandemic influenza A 2009 virus infection [6]. Patients with a resolved viral infection typically develop a polyclonal antibody immune response to different viral antigens. Some of these polyclonal antibodies will likely neutralize the virus and prevent new rounds of infection. Patients who recovered from COVID-19 can donate plasma, and then, this plasma can be transfused into patients who are actively infected [7]. Indeed, the same rationale was used in the treatment of several patients with Ebola with convalescent serum during the outbreak in 2014-2015 [8].

Therefore, CP therapy is expected to improve the clinical, laboratory, and radiological features of the patients severely affected by COVID-19. Decreasing the morbidity and mortality of COVID-19 in a cost-effective manner, leading to improved quality of health care and self-sufficiency in the treatment of serious diseases affecting the masses, is in line with the top priorities in Vision 2030 of the Kingdom of Saudi Arabia.

SARS-CoV-2–Specific Immunoglobulins Containing CP

Among the most attractive intuitive options, during this fast-kinetic pandemic, is treating the patients who are sick with COVID-19 with SARS-CoV-2–specific immunoglobulins found in patients who have fully recovered from COVID-19 and are considered no longer infected. We know from prior research that antibodies against viral antigens render people immune, but we do not know yet how long the immunity will last. However, Zhao et al [9] showed seroconversion in 173 patients with COVID-19 appeared for total antibody, immunoglobulin M (IgM), and immunoglobulin G (IgG) at 11, 12, and 14 days [9]. The presence of antibodies was <40% in the first 7 days and then rapidly increased to 100%, 94.3%, and 79.8% for antibodies, IgM, and IgG, respectively, by day 15. In contrast, viral RNA decreased from 66.7% before day 7 to 45.5% in days 15-39. Moreover, a higher titer of antibodies was independently associated with clinically worse COVID-19 (P=.006) [9].

Antibodies Detection by a Rapid Serological Method and Their Kinetics

In those patients who have passed the viremic phase, the presence of antibodies is highly desirable and provides evidence of the immunity to combat COVID-19 (Table 1). Fortunately, the Saudi Food and Drug Authority (SFDA) has recently approved a needed rapid test kit made by BIOZEK company and other brands in the Saudi market that qualitatively detect IgG and IgM antibodies against SARS-CoV-2 from whole blood, serum, or plasma using a single-use cassette. This kit uses lateral flow chromatographic immunoassay and can produce results within 10 minutes. The combination use of the IgM and IgG tests can reflect virus infection and the immune status of the body effectively (Table 1).

Table 1. How to interpret the results of PCR and antibody results.[a]

Test results			Clinical Significance
PCR[b]	IgM[c]	IgG[d]	
✓[e]	—[f]	—	The patient may be in the window period of infection.
✓	✓	—	The patient may be in the early stage of infection.
✓	✓	✓	The patient is in the active phase of infection.
✓	—	✓	The patient may be in the late or recurrent stage of infection.
—	✓	—	The patient may be in the early stage of infection. PCR result may be false-negative.
—	—	✓	The patient may have had a past infection and has recovered.
—	✓	✓	The patient may be in the recovery stage of an infection, or the PCR result may be false-negative.

[a]Adapted from [10,11].

[b]PCR: polymerase chain reaction.

[c]IgM: immunoglobulin M.

[d]IgG: immunoglobulin G.

[e]Indicates a positive result.

[f]Indicates a negative result.

Role of CP in Treating Severe COVID-19

Casadevall and Pirofski [12] suggested that convalescent sera from individuals with COVID-19 may be an option for treating the highest-risk patients with COVID-19 and possibly for prophylaxis of infection in individuals at high risk of COVID-19. This passive antibody administration concept to prevent disease is already used in patients exposed to hepatitis B and rabies viruses, and to prevent severe respiratory syncytial virus disease in high-risk infants [12]. The proposed use of convalescent sera in the COVID-19 epidemic would rely on preparations of high titers of neutralizing antibodies against SARS-CoV-2.

In the first pilot Chinese study reported by Duan et al [13], CP therapy in 10 patients showed a potential therapeutic effect and low risk in the treatment of patients with severe COVID-19. One dose of CP with a high concentration of neutralizing antibodies can rapidly reduce the viral load and tends to improve clinical outcomes [13]. The optimal dose and treatment time point, as well as the definite clinical benefits of CP therapy, need to be further investigated in randomized clinical studies. Out of 40 donors (recovered patients with COVID-19), 39 showed a high antibody titer of at least 1:160. After receiving CP therapy, 9 out of 10 recipients were found to have neutralizing antibody titers >1:640 [13]. Although small, it is a pivotal study to prove the safety and efficacy of CP therapy. All patients showed an increase in oxygen saturation within 3 days. Other parameters that improved were increased absolute lymphocyte counts (ALCs) and decreased C-reactive protein (CRP). Varying degrees of resolution of lung lesions were also seen on radiological examinations within 7 days. In 7 patients who previously had viremia, the viral load was undetectable after transfusion [13].

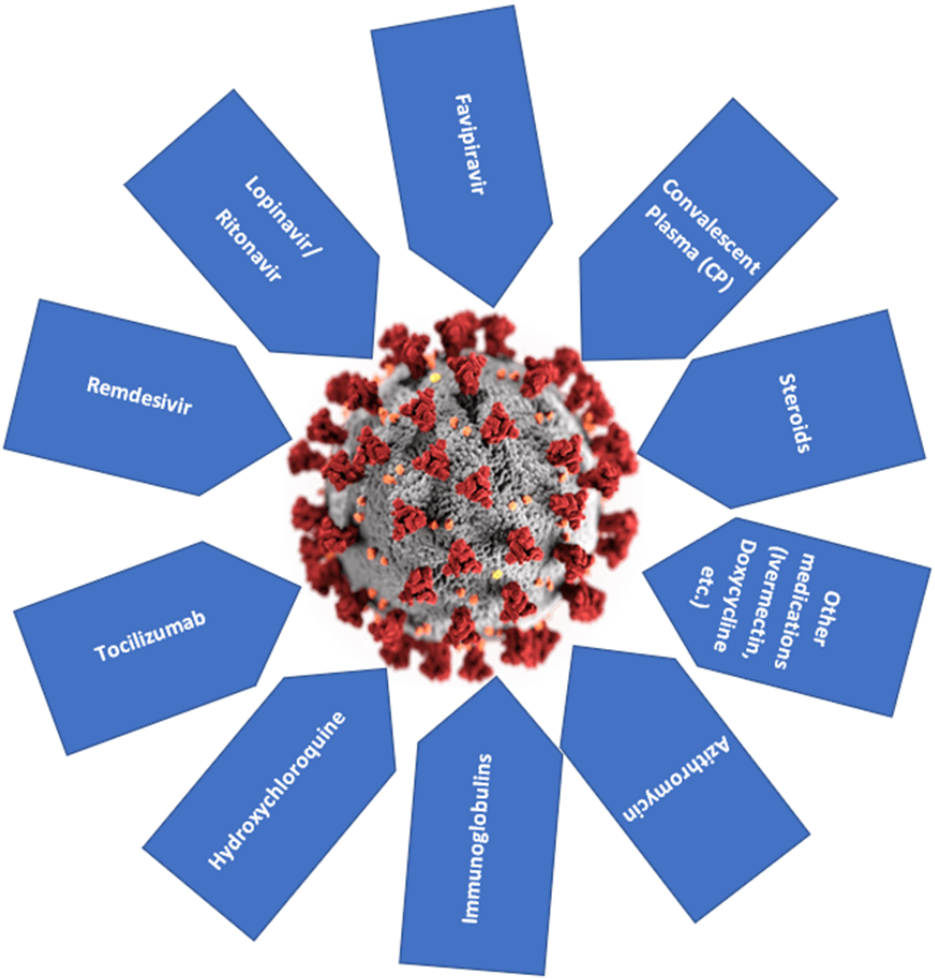
Currently Available Therapeutic Options for COVID-19

According to the WHO, the management of COVID-19 has mainly focused on infection prevention, case detection, monitoring, and supportive care, although there are reports on the efficacy of new potential therapeutic agents (Figure 1).

However, no specific anti–SARS-CoV-2 treatment is recommended because of conflicting evidence. Evidence shows that CP from patients who have recovered from viral infections can be used as a treatment without the occurrence of severe adverse events (SAE). Therefore, it might be worthwhile to test the safety and efficacy of CP transfusion in patients infected with SARS-CoV-2 [14].

Our study aims to test the feasibility, safety, and efficacy of CP in treating patients with COVID-19 across Saudi Arabia.

Figure 1. Some therapeutic options for treating COVID-19.



Methods

This is a national, phase II, multicenter trial evaluating the safety and potential efficacy of CP to treat severe COVID-19 and patients at high risk of developing severe COVID-19. Detailed bilingual informed consent forms (ICFs) approved by the Ministry of Health (MOH) and institutional review boards (IRBs) will be used for both CP donors and CP recipients.

Time of the Study

The proposed duration of 3 months was considered ideal for recruiting the first 40 CP recipients for our proposed prospective study. If interim analysis shows the benefit of CP, we will increase the sample size and extend the trial period.

Inclusion Criteria

The inclusion criteria for recipients is as follows:

- 18 years or older
- Patients with COVID-19 confirmed by positive rRT-PCR test for SARS-CoV-2 “using one of the SFDA approved kits used in the Kingdom of Saudi Arabia” as per current MOH guidelines
- Must have required intensive care unit (ICU), severe, or immediately life-threatening care:
  - Patient requiring ICU care or admission
  - Severe disease is defined as dyspnea, respiratory frequency≥30/min, blood oxygen saturation≤93%, the partial pressure of arterial oxygen to fraction of inspired oxygen ratio<300, or lung infiltrates>50% within 24-48 hours.
  - Life-threatening disease is defined as respiratory failure, septic shock, or multiple organ dysfunction or failure.

The inclusion criteria for the donors was as follows:

- 18 years or older
- Prior confirmed COVID-19 diagnosis as per current MOH guidelines
- Complete clinical recovery from COVID-19 before donation (at least 14 days from the last SARS-CoV-2 negative

polymerase chain reaction or 28 days from the initial symptoms) [15-18]
- All MOH criteria for blood donation will be followed.
- All transfusion transmissible infections markers on the donor's blood are negative as per current MOH routine blood donor screening regulations.
- Positive rapid serology test for antibodies (IgG) against SARS-CoV-2 indicating immunity against COVID 19

Exclusion Criteria

The exclusion criteria for recipients was a negative or nonconclusive COVID-19 rRT-PCR test for SARS-CoV-2, mild symptoms, and hospitalization not requiring ICU care or admission. The exclusion criteria for donors was being unfit for blood donation or a multiparous or pregnant female.

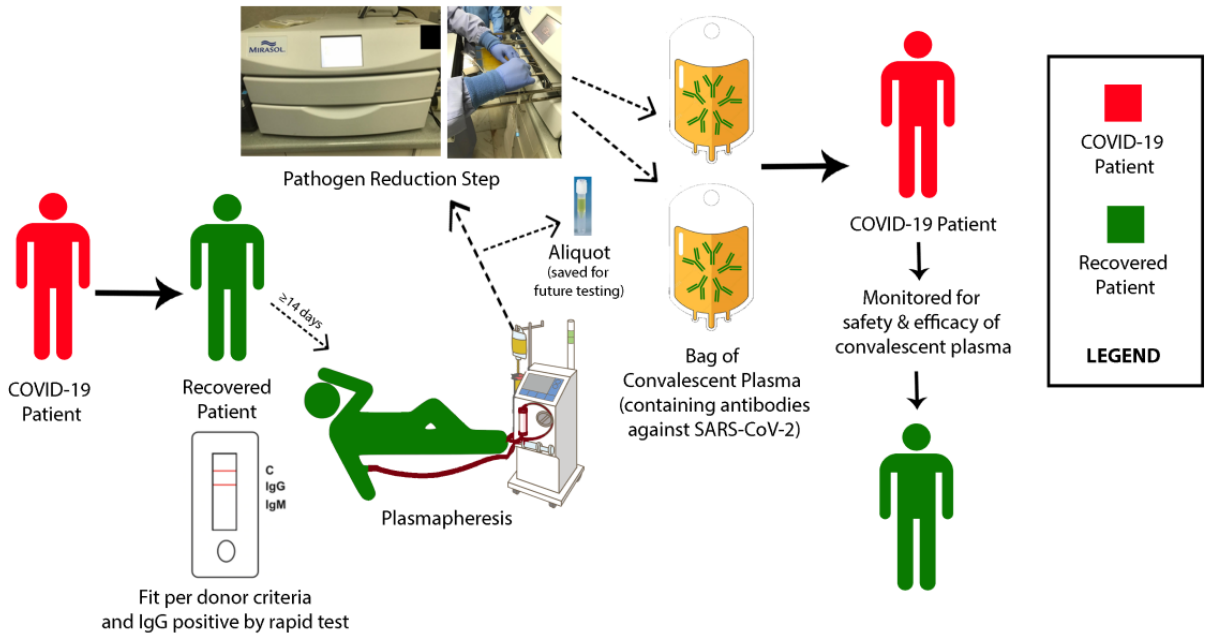
Collection of CP Infusion for Treatment of COVID-19

As antibody kinetics show IgG levels are highest around day 28 and decline around day 42 to complete disappearance in many months, we will try to get plasma donation from fully recovered patients soon after day 28 of the onset of symptoms (that usually last for 7-10 days). For the recovery definition, we will continue to follow the MOH's current precautionary protocol to prevent the spread of the virus causing COVID-19 that requires blood donor abstinence from donation for 28 days from exposure [17,18].

Plasmapheresis to collect plasma from the donors (using Trima, Hemonetics, or alike machines) is a commonly used procedure. Donors are required to be in an acceptable health state and pass through a multistep screening (donor history questionnaire, vital signs check, laboratory tests, etc) before CP donation. The arrangement for plasmapheresis and collection will start after obtaining the donor's informed consent. The collected plasma will undergo an additional safety step of pathogen reduction using Mirasol or Intercept Pathogen Reduction Technology, which is SFDA and CE (Conformité Européenne) approved (Figure 2). The Mirasol system uses vitamin B2 (riboflavin) and ultraviolet light. Mirasol-treated fresh frozen plasma (FFP) maintains a good quality of therapeutic proteins as demonstrated in multiple external validation studies [19-21]. After passing through the pathogen reduction system, the CP will be sent to the COVID-19 recipients, or it can be stored in a dedicated FFP freezer at ≤–18 °C. The shelf life of frozen CP should be similar to normal FFP according to the storage conditions (1 year at ≤–18 °C or 24 hours at 1-6 °C). The CP units will be labeled, stored, and shipped as per Central Board for Accreditation of Healthcare Institutes (CBAHI), American Association of Blood Banks (AABB), and Joint Commission International guidelines for blood products handling and management.

CP will be used only for eligible patients who have COVID-19. The common side effects of FFP transfusion include side effects of blood product transfusion (eg, allergic or febrile reactions, transfusion-related acute lung injury [TRALI], and transfusion-associated circulatory overload [TACO]) while the infectious risk is minimal. Plasma volume to be collected from each donor can be up to 15% of the total blood volume (TBV; TBV = weight in kg x 70 ml). For example, from a CP donor who weighs 65 kg, we can collect up to ~682 ml plasma (15 / 100 x 65 x 70). CP donors can donate more than once as per the regulations of the CBAHI and AABB, which allows healthy donors to donate plasma twice in a month up to a maximum of 24 donations in a year. Special International Society of Blood Transfusion labels will be affixed on the plasma bags indicating COVID-19 CP (Figure 2).

Figure 2. Logistic cycle of convalescent plasma procurement from donor, processing, and infusion to patient with COVID-19. IgG: immunoglobulin G; IgM: immunoglobulin M.



ICF

The ICF will be used for both the CP donor and the recipient (Approved Donor ICF [Arabic and English] and Approved Recipient ICF [Arabic and English]).

Transfusion of CP for Treatment of COVID-19

After obtaining informed consent, eligible patients who have severe COVID-19 and have not recovered yet will be infused with the donated CP 300 ml (200-400 ml/treatment dose) at least once and, if needed, daily for up to 5 sessions (Figure 3).

Other supportive and therapeutic measures should continue according to the locally approved protocols with due diligence. Patients will be monitored after FFP transfusion for the usual side effects of blood product transfusion (eg, allergic or febrile reactions, TRALI, and circulatory overload). We will then assess the response after the infusion of the plasma in these patients as detailed in the Response Assessment section.

As with other plasma therapies, attention should be given to ABO compatibility. For plasma selection, we will consider ABO compatibility (Table 2) regardless of Rh status. To minimize the risk of TRALI, preference will be given to plasma from male donors and nulliparous women.

Figure 3. Schematic for the proposed process of CP donation and infusion. CP: convalescent plasma; PCR: polymerase chain reaction.

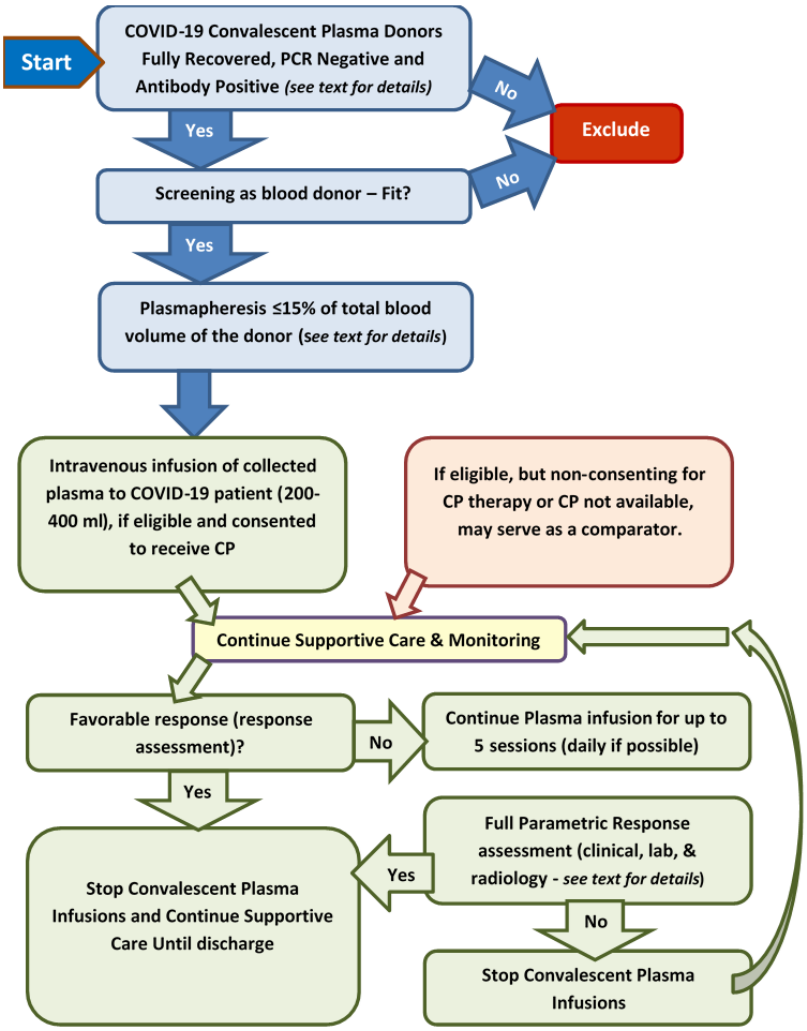


Table 2. ABO group selection order for transfusion of plasma.[a]

Patient's ABO group	Fresh frozen plasma
O	
First choice	O
Second choice	A or B
Third choice	AB
A	
First choice	A
Second choice	AB
Third choice	B[b]
B	
First choice	B
Second choice	AB
Third choice	A[b]
AB	
First choice	AB
Second choice	A[b]
Third choice	B[b]

[a]Adapated from [22].

[b]Tested and negative for high titer anti-A and/or anti-B (should be less than 1:64).

Data Collection

Clinical information of all enrolled patients will be retrieved from the hospital electronic or paper records system, including the following:

- Baseline demographic data
- Days of illness duration
- Presenting symptoms
- Radiological findings (chest x-ray and computed tomography [CT] scan chest, if possible) on the day of hospital admission; on the day of ICU admission; on the day of CP infusion (day 0); and on days 3, 7, 14, and 30
- Laboratory infectious marker testing results like respiratory, urinary, or blood culture
- Laboratory inflammatory markers: CRP (day of CP infusion [day 0] and then on days 3, 7, 14, and 30)
- Application of assisted mechanical ventilation and their modes, intranasal oxygen inhalation, number of days of intubation, or nasal oxygen support
- Medication regimen (eg, hydroxychloroquine, azithromycin, any antiviral therapies, steroids, tocilizumab)
- Complications including acute renal failure, acute coronary syndrome, myocarditis, ARDS, gastrointestinal complication, and nosocomial infection
- The SARS-CoV-2 RNA from the serum sample will be monitored during treatment and at day 14 of recovery or discharge, whichever is later.

We plan to test for all of the following parameters for patients with COVID-19:

- Complete blood count (CBC) differential to include percent and ALC, and percent and absolute neutrophil count
- Chemistry panel to include total protein, albumin, lactate dehydrogenase, alanine aminotransferase and aspartate aminotransferase, and procalcitonin
- Cardiac biomarkers (eg, cardiac troponins)
- Creatine phosphokinase
- Ferritin
- Full coagulation profile to include partial thromboplastin (PT), activated PT time, fibrinogen, and D-dimer
- CRP
- Oxygen saturation
- Radiological examination
- ABO RhD grouping and antibody screening
- rRT-PCR test for SARS-CoV-2
- Test for IgG and IgM antibodies against SARS-CoV-2

CP donors will essentially undergo routine blood donation processes such as donor history questionnaire, clinical examination, and testing for the infectious marker (serology and nucleic acid testing methods) along with ABO RhD grouping, antibody screening, and CBC. They will also undergo a test for IgG and IgM antibodies against SARS-CoV-2, which should be positive for IgG.

Data collection forms have been developed to collect data for CP donors, recipients, and controls (comparators).

Response Assessment

The response assessment includes daily clinical assessment by a physician; vital signs including temperature, blood pressure, respiratory rate, and heart rate; oxygen saturation; oxygen

requirement; ventilator requirement and the modes employed; inotrope medications requirement; CBCs, liver function tests, urea, creatinine, and electrolytes daily; Apache score; Sequential Organ Failure Assessment score; fluid balance; x-ray or CT changes, repeated every 3-5 days; organs functions assessment; plasma doses and frequency requirement; transfusion-related side effects including TRALI, TACO, etc; and the SARS-CoV-2 RNA will be tested on recovery (or deterioration to determine alternative etiology).

Study Endpoint and Outcome Measures

Our primary endpoints are ICU (or designated area for critical patients) length of stay; safety of CP; and reporting of SAE such as anaphylaxis, TRALI, and TACO.

Our secondary endpoints will include number of days on mechanical ventilation, 30-day mortality, and days to clinical recovery as defined by the MOH.

Study Population

A total sample size of 575 patients, 115 CP recipients and 460 matched controls (1:4 ratio), will be sufficient to detect a clinically important difference of 11.6% between two groups (CP recipients vs matched controls) in 30-day mortality using a two-tailed *z* test of proportions and chi-square test with 80% power and a 5% level of significance. This 11.6% difference represents a 12.4% mortality in the CP recipient group and 24.4% mortality in the matched control patients [23].

The treatment group (CP recipients group) will have 115 patients who have COVID-19 but have not recovered yet as per the inclusion criteria. The control group (comparator group) will have 460 patients who are either not consenting to receive CP or those who will not be able to receive CP due to nonavailability to compare the efficacy of the CP. Control group patients will be subjected to propensity score (PS) matching based on age, gender, diabetes mellitus (DM), hypertension (HTN), and intubation.

Statistical Analysis

Descriptive and inferential statistics will be used to characterize the study sample and test the hypotheses. Descriptive results for all quantitative variables such as age will be presented as mean (SD; for normally distributed data) or median with interquartile range (for data not normally distributed), while numbers (percentage) will be reported for all qualitative variables such as gender.

To assess the independent effect of CP transfusion safety and survival, we will conduct a PS-matching (based on age, gender, DM, HTN, and intubation) analysis. Among the predictors, exact matching will be enforced to achieve the balance for all predictors between the plasma and control groups.

The bivariate analysis will be performed using independent sample *t* test, Mann-Whitney *U* test, Pearson chi-square test, or Fisher exact test whenever appropriate to compare the demographic characteristics (eg, age, gender, nationality) and clinical characteristics (improvement in oxygenation, laboratory parameters, radiological findings, complications, and length of hospital stay) between those who will receive the CP and those who will not receive this therapy.

The multiple binary logistic regression model will be used to assess the effect of CP transfusion on 30-day mortality after adjusting for potential confounding factors compared to matched controls patients. The adjusted odds ratio and 95% confidence interval for the adjusted odds ratio will be reported. The Hosmer-Lemeshow goodness-of-fit statistics will be used to determine whether the model adequately describes the data.

The time-to-event analysis will be measured from the date of diagnosis. The overall survival at 30 days and 3 months will be evaluated using the Kaplan-Meier estimator and compared between the two groups (plasma recipients vs matched control patients) using the log-rank test. A Cox proportional hazard model will also be used to estimate the hazard ratio for in-hospital 30-day mortality for the plasma group compared with matched control group patients after adjusting for potential confounding factors. In addition, interactions between CP administration and all the predictors will be tested to see if the plasma effects will be the same in subgroups. A $P<.05$ (two-tailed) will be considered statistically significant. All statistical analyses will be performed using SPSS version 24 (IBM Corp).

Interim Analysis

An interim analysis will be performed after enrolling 40 CP recipients and 40 PS-matched controls. A similar statistical analysis will be performed as previously described.

Monitoring and Safety

Plasma infusion is a routine practice in health care facilities. All known adverse events and SAE of CP infusion, such as anaphylaxis, TRALI, and TACO, will be collected as per the SFDA reporting standard. SAE or death of a study participant due to any cause will be reported by the study team to the IRB chairman and principal investigator within 24 hours of the event.

Confidentiality Statement

All subject-related personal information will be saved in password-protected files, which will only be accessed by the study research team. All data will be archived in our archiving facility within the hospital once the study has come to an end. This will be in accordance with the standard requirement for the clinical trial archival.

Patient and Family Education, and Donor Recruitment Strategy

A variety of methods will be used to recruit CP donors for the study. These include referrals of the recovered patients from various hospitals, dissemination of messages to the public through social media platforms, and a website set up specifically for the study for general information and communication [24].

We will be using the following Twitter account: @Plasma4CovidKSA for public information only. Approved videos will be used on the website and Twitter account. In addition, multilingual advertisement statements and links to the videos by international physicians may be shared with non-Arabic speaking patients. Detailed bilingual ICFs approved

by the MOH and IRBs will be used for both CP donors and CP recipients.

Results

We are still collecting data and recruiting patients for our ongoing national clinical trial. We will soon share the results of an interim analysis of the first 40 CP recipients and PS-matched controls. Once the study is completed, the final results will be published.

The following approvals have been obtained in addition to IRB approvals of the participating centers: MOH Central IRB log No 20-COVID-19-01M (approved on April 2, 2020); SFDA Saudi Clinical Trials Registry No 20041102 (approved on April 14, 2020); and the ClinicalTrials.gov identifier is NCT04347681 (updated and under process).

Discussion

The study of the Saudi population at risk of severe COVID-19 has some distinct features, as Saudi Arabia was recently challenged by related coronaviruses including MERS-CoV that might lead to distinct immunological responses to SARS-CoV-2. The intention overriding the scientific merit of a randomized controlled trial during this pandemic is an attempt to add CP in the armamentarium against COVID-19, as this readily available agent has historically shown benefit in the treatment of related coronaviruses. There are multiple theoretical and scientific reasons to support our thinking that CP may turn out to be an effective treatment. However, the bottom line is that we do not have enough data to be certain. CP trials that have been published so far have limitations and conflicting data. Our group and others are working hard during this time to establish evidence that could support the therapeutic use of CP for patients with COVID-19.

Limitations of our study include, first, the design of the study, as we could not find it feasible to make the study a randomized controlled trial with our patient population due to the strong perceived benefit of CP in the minds of the patients and treating physicians in this situation. Second, our collaborating centers are of various levels from secondary to tertiary care hospitals with limitation of experience uniformity in conducting such a collaborative study. However, we intend to be a mutually supportive group and keep our study elements uniform. In addition, currently, anti–SARS-CoV-2 antibodies titration facilities are not available countrywide in Saudi Arabia. However, we plan to save aliquots of collected convalescent plasmas to test antibody titers whenever such facilities will be available. Last, we could not include the investigation of some biomarkers like interleukin-6 during treatment in our protocol, due to nonavailability in some centers. Nonetheless, treatment with CP seems promising to treat patients with COVID-19, and a national clinical trial to explore the efficacy and safety of CP is justified.

Conflicts of Interest

None declared.

References

1. World Health Organization. Middle East respiratory syndrome coronavirus (MERS-CoV). Krankenhaushyg Infektionsverhut 2014 Mar;36(1):34-35 [FREE Full text] [doi: 10.1016/j.khinf.2014.01.014] [Medline: 32288154]
2. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. Vital surveillances: the epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) - China, 2020. China CDC Weekly 2020;2(8):113-122. [doi: 10.46234/ccdcw2020.032]
3. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020 Feb 22;395(10224):565-574 [FREE Full text] [doi: 10.1016/S0140-6736(20)30251-8] [Medline: 32007145]
4. COVID-19 coronavirus pandemic. Worldometer. 2020. URL: https://www.worldometers.info/coronavirus/ [accessed 2020-04-02]
5. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, Cleary P, Khaw F, Lim WS, Convalescent Plasma Study Group. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis 2015 Jan 01;211(1):80-90 [FREE Full text] [doi: 10.1093/infdis/jiu396] [Medline: 25030060]
6. Hung IF, To KK, Lee C, Lee K, Chan K, Yan W, et al. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. Clin Infect Dis 2011 Feb 15;52(4):447-456. [doi: 10.1093/cid/ciq106] [Medline: 21248066]
7. Marano G, Vaglio S, Pupella S, Facco G, Catalano L, Liumbruno GM, et al. Convalescent plasma: new evidence for an old therapeutic tool? Blood Transfus 2016 Mar;14(2):152-157. [doi: 10.2450/2015.0131-15] [Medline: 26674811]
8. Kraft CS, Hewlett AL, Koepsell S, Winkler AM, Kratochvil CJ, Larson L, Nebraska Biocontainment Unit and the Emory Serious Communicable Diseases Unit. The use of TKM-100802 and convalescent plasma in 2 patients with Ebola virus disease in the United States. Clin Infect Dis 2015 Aug 15;61(4):496-502 [FREE Full text] [doi: 10.1093/cid/civ334] [Medline: 25904375]
9. Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. Clin Infect Dis 2020 Mar 28 [FREE Full text] [doi: 10.1093/cid/ciaa344] [Medline: 32221519]

10. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. Ann Intern Med 2020 May 05;172(9):577-582. [doi: 10.7326/M20-0504] [Medline: 32150748]
11. Diagnosis and treatment protocol for COVID-19 (trial version 7). National Health Commission of the People's Republic of China. URL: http://en.nhc.gov.cn/2020-03/29/c_78469.htm [accessed 2020-04-04]
12. Casadevall A, Pirofski L. The convalescent sera option for containing COVID-19. J Clin Invest 2020;130(4):1545-1548. [doi: 10.1172/jci138003]
13. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, et al. The feasibility of convalescent plasma therapy in severe COVID-19 patients: a pilot study. medRxiv 2020 Mar 16:6145. [doi: 10.1101/2020.03.16.20036145]
14. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. Lancet Infect Dis 2020 Apr;20(4):398-400. [doi: 10.1016/s1473-3099(20)30141-9]
15. Investigational COVID-19 convalescent plasma - emergency INDs. U.S. Food And Drug Administration. 2020 Mar 25. URL: https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds [accessed 2020-04-04]
16. COVID-19 convalescent plasma collection: donor eligibility, processing, labeling, and distribution. American Association of Blood Banks. 2020 Apr 04. URL: https://abhh.org.br/wp-content/uploads/2020/04/AABB_COVID-19-Convalescent-Plasma-Collection.pdf [accessed 2020-04-04]
17. Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with COVID-2019. Nature 2020 May;581(7809):465-469. [doi: 10.1038/s41586-020-2196-x] [Medline: 32235945]
18. COVID-19 Investigation Team. Clinical and virologic characteristics of the first 12 patients with coronavirus disease 2019 (COVID-19) in the United States. Nat Med 2020 Jun;26(6):861-868. [doi: 10.1038/s41591-020-0877-5] [Medline: 32327757]
19. Hornsey V, Drummond O, Morrison A, McMillan L, MacGregor I, Prowse C. Pathogen reduction of fresh plasma using riboflavin and ultraviolet light: effects on plasma coagulation proteins. Transfusion 2009 Oct;49(10):2167-2172. [doi: 10.1111/j.1537-2995.2009.02272.x] [Medline: 19555414]
20. Larrea L, Calabuig M, Roldán V, Rivera J, Tsai H, Vicente V, et al. The influence of riboflavin photochemistry on plasma coagulation factors. Transfus Apher Sci 2009 Dec;41(3):199-204 [FREE Full text] [doi: 10.1016/j.transci.2009.09.006] [Medline: 19782644]
21. Smith J, Rock G. Protein quality in Mirasol pathogen reduction technology-treated, apheresis-derived fresh-frozen plasma. Transfusion 2010 Apr;50(4):926-931. [doi: 10.1111/j.1537-2995.2009.02517.x] [Medline: 20051060]
22. Norfolk D, editor. The ABO system. In: Handbook of Transfusion Medicine, fifth edition. UK: TSO Information & Publishing Solutions; 2013.
23. Liu STH, Lin HM, Baine I, Wajnberg A, Gumprecht JP, Rahman F, et al. Convalescent plasma treatment of severe COVID-19: a matched control study. medRxiv 2020 May 20:2236. [doi: 10.1101/2020.05.20.20102236]
24. Plasma For COVID. URL: https://plasmaforcovid.com

Abbreviations

AABB: American Association of Blood Banks
ALC: absolute lymphocyte count
ARDS: acute respiratory distress syndrome
CBAHI: Central Board for Accreditation of Healthcare Institutes
CBC: complete blood count
CE: Conformité Européenne
CP: convalescent plasma
CRP: C-reactive protein
CT: computed tomography
DM: diabetes mellitus
FFP: fresh frozen plasma
HTN: hypertension
ICF: informed consent form
ICU: intensive care unit
IgG: immunoglobulin G
IgM: immunoglobulin M
IRB: institutional review board
MERS-CoV: Middle East respiratory syndrome–related coronavirus
MOH: Ministry of Health
PS: propensity score
PT: partial thromboplastin
rRT-PCR: real-time reverse transcription–polymerase chain reaction

SAE: serious adverse events
SARS-CoV: severe acute respiratory syndrome–related coronavirus
SFDA: Saudi Food and Drug Authority
TACO: transfusion-associated circulatory overload
TBV: total blood volume
TRALI: transfusion-related acute lung injury
WHO: World Health Organization

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Protocol

Career Crafting Training Intervention for Physicians: Protocol for a Randomized Controlled Trial

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Abstract

Background: Physicians work in a highly demanding work setting where ongoing changes affect their work and challenge their employability (ie, their ability and willingness to continue working). In this high-pressure environment, physicians could benefit from proactively managing or *crafting* their careers; however, they tend not to show this behavior. The new concept of career crafting concerns proactively making choices and adapting behavior regarding both short-term job design (ie, job crafting) as well as longer-term career development (ie, career self-management). However, so far, no intervention studies have aimed at enhancing career crafting behavior among physicians. Given that proactive work and career behavior have been shown to be related to favorable outcomes, we designed an intervention to support career crafting behavior and employability of physicians.

Objective: The objectives of this study were to describe (1) the development and (2) the design of the evaluation of a randomized controlled career crafting intervention to increase job crafting, career self-management, and employability.

Methods: A randomized controlled intervention study was designed for 141 physicians in two Dutch hospitals. The study was designed and will be evaluated based on parts of the intervention mapping protocol. First, needs of physicians were assessed through 40 interviews held with physicians and managers. This pointed to a need to support physicians in becoming more proactive regarding their careers as well as in building awareness of proactive behaviors in order to craft their current work situation. Based on this, a training program was developed in line with their needs. A number of theoretical methods and practical applications were selected as the building blocks of the training. Next, participants were randomly assigned to either the waitlist-control group (ie, received no training) or the intervention group. The intervention group participated in a 4-hour training session and worked on four self-set goals. Then, a coaching conversation took place over the phone. Digital questionnaires distributed before and 8 weeks after the intervention assessed changes in job crafting, career self-management, employability, and changes in the following additional variables: job satisfaction, career satisfaction, work-home interference, work ability, and performance. In addition, a process evaluation was conducted to examine factors that may have promoted or hindered the effectiveness of the intervention.

Results: Data collection was completed in March 2020. Evaluation of outcomes and the research process started in April 2020. Study results were submitted for publication in September 2020.

Conclusions: This study protocol gives insight into the systematic development and design of a career crafting training intervention that is aimed to enhance job crafting, career self-management, and employability. This study will provide valuable information to physicians, managers, policy makers, and other researchers that aim to enhance career crafting.

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KEYWORDS

career crafting; job crafting; career self-management; intervention study; employability; physicians; intervention mapping

Introduction

Physicians work in a highly demanding work setting where ongoing changes affect their work. Physicians' work environment is characterized by high work pressure and other stressors [1]. This challenges physicians' ability and willingness to continue to work until the retirement age in their current profession [2] (ie, their employability [3]). Recent studies show that the employability profile of physicians and other workers in the health care sector is relatively low compared to employees in other sectors. Specifically, in a study among 42,613 health care workers in the Netherlands, 47% of them thought it was possible to find employment beyond their current employer, compared to 57% of employees in other sectors; 52% of health care workers regularly perceive a high physical workload, compared to 38% of employees in other sectors; and 19% of health care workers often perceive a high emotional workload, compared to 7% of employees in other sectors [4].

In order for employees to successfully navigate within this complex environment, they must proactively take control over their working life by creating a resourceful, healthy, and motivating environment for themselves [5]. This can be done through career crafting, which is a relatively new concept in the literature, and is defined as "individuals' proactive behaviors aimed at optimizing career outcomes through improving person-career fit" [6]. Career crafting entails both choices and changes to the current work environment (ie, job crafting) as well as actions focused on longer-term career design (ie, career self-management) [6]. Job crafting refers to the self-initiated behaviors that employees take to shape, mold, and change their jobs [7-9]. For example, people can craft social resources such as support or they can optimize tasks or situations that are hindering. An example of job crafting is limiting tasks that drain energy, such as reducing the time spent on meetings by 15 minutes per meeting. Career self-management is defined as the extent to which employees proactively develop their careers as expressed by diverse career behaviors [10]. An example of career self-management is networking behavior, in which someone proactively approaches others who can be helpful in shaping their career. Career crafting entails the combination of both types of behaviors. For example, an employee may reduce energy-draining activities (ie, through job crafting) by communicating firmer boundaries in meetings (eg, "I have 30 minutes for this meeting; what are our highest priorities?"). The time thus gained is used to proactively network with someone from another organization (ie, career self-management), who is employed in a position that is of interest to the employee, to learn about how he or she managed to get that position.

Career crafting is considered an important individual behavior aimed at safeguarding the sustainability of one's career over time [6]. This suggests that career crafting may possibly enhance employability. However, empirical evidence about the antecedents and consequences of career crafting is lacking and requires further examination. Previous studies have found that career crafting behaviors such as job crafting and career self-management fulfil important roles in contemporary careers and result in beneficial outcomes [11,12]. Previous studies found that career crafting behaviors are beneficial to the individual, as reflected in enhanced work engagement [13], well-being [14], meaningfulness, and job satisfaction [15], as well as to the organization, as reflected in enhanced performance [16]. This makes it worthwhile to invest in an intervention program that enhances physicians' career crafting and employability, which is urgent in today's health care career context.

Three gaps exist in the current literature. First, despite the increasing importance of proactive career behaviors, to our knowledge, as yet no intervention studies have aimed at enhancing career crafting. Career adaptability training for graduates [17] focused on facilitating the school-to-work transition but did not examine how to stay employable within a work context. That study and other existing career interventions had a different focus (eg, career coaching or counseling) than the subject of our study or showed methodological weaknesses [18]. These studies, for instance, used a cross-sectional study design [19], lacked a control group [20-22], or did not assign participants randomly to a control or treatment group, as shown in a meta-analysis by Whiston et al [23].

Second, career studies have mainly focused on employees in general [24], while employees in different jobs have been shown to have different career trajectories and employment opportunities [25]. Paying attention to physicians' careers is important for two reasons. First, some studies describe their career choices as serendipitous or circumstantial [26] and mention that physicians are neither actively engaged in career planning nor being stimulated to do so [27,28]. Other studies have shown that attention on careers is beneficial for employee job satisfaction [22] and may help employees to keep up with a fast-changing work environment [29]. Second, physicians' career trajectories are different from those of other employees. Physicians usually finish their medical training around the age of 30 years and work as medical specialists for the next 30-35 years of their career. Although their high level of education may stimulate career possibilities, the specialized nature of their work tends to reduce their employment opportunities and may, thus, result in physicians often having the same job until retirement [25]. Relevant career opportunities for physicians should, therefore, not only focus on promotion, since possibilities for this are limited, or on external opportunities (eg, changing jobs or organizations), but they should also include possibilities of internal career opportunities (eg, changing work content or tasks). Focusing on physicians' career content may help physicians in developing coping skills to effectively deal with the challenges presented by their work environment. This seems important as research has shown that some physicians are insecure about their competencies to fulfil nonclinical tasks, such as teaching, managerial skills, and financial skills, for which they are not primarily educated [30,31]. The career crafting training developed in this study is likely to fit physicians' needs, since their needs have been identified and because the content of the training has been developed in collaboration with physicians.

Third, most intervention studies mainly focus on the analysis of outcomes and lack a systematic process evaluation [32,33]. This may be partly explained by the absence of an evidence-based framework that describes the elements that need

to be included in process evaluations. Nevertheless, process evaluation is important as it helps us to understand why parts of an intervention result in a certain outcome and shows how research findings can be used to guide practice [32].

In responding to these knowledge gaps, this study makes the following contributions. This study contributes to the literature on proactive career behavior by elaborating on the development and design of the evaluation of a career crafting training intervention. In doing so, the specific needs and challenges that physicians face are taken into account, which increases the practical utility of this intervention. This paper elaborates on the systematic process in which this career intervention is developed for, and in collaboration with, physicians. Furthermore, the research protocol discusses a framework to conduct a process evaluation, based on the current literature. The objectives of this study are to describe (1) the development and (2) the design of the evaluation of a randomized controlled career crafting intervention developed for physicians to increase job crafting, career self-management, and employability.

Methods

Overview

The intervention was developed in a systematic way, using elements of the intervention mapping (IM) protocol. IM is a widely accepted methodology for planning theory-based and evidence-based health promotion programs [34] and has been used in numerous studies, eg [35], [36]. IM consists of six steps: (1) needs assessment, (2) definition of program objectives, (3) methods and practical applications, (4) intervention program development and pilot test, (5) adoption and implementation, and (6) evaluation. The completion of every step creates a product that is the guide for the subsequent step [34]. Although these steps suggest that this is a linear process, moving back and forth between the steps is part of the process.

Step 1: Needs Assessment

The first step of IM was to assess and understand the problem and needs of the participants [34]. This intervention was custom-made in close collaboration with potential participants, physicians, and other stakeholders, such as managers of physicians who also work as physicians. There is widespread agreement that a participative approach in the design of interventions is promising. Employees are often familiar with the problems and the best solutions in their work context, and people can identify better with a project if they perceive themselves to be the agents of change rather than the objects of change [37].

In an earlier stage of this study, 40 face-to-face exploratory interviews were conducted to examine physicians' experiences with job crafting, career self-management behavior, and employability. Out of the 40 interviews, 27 (68%) were done with the target population, namely physicians, and 13 (33%) were conducted with their managers who also worked as physicians. The results of these interviews were discussed and interpreted by a planning group. This group consisted of the researchers of this study, a senior board member and a physician who also worked as a manager in the academic hospital, and two physicians and a senior board member of the general hospital. The reflections of the planning group were also discussed in both hospitals with people from the human resources department who were familiar with current policies and trainings for physicians. The interviews revealed that physicians lack attention for job crafting and career self-management. Moreover, employability was hardly discussed or thought of in this occupational group. Despite this, physicians and their managers emphasized the importance of finding ways to increase physicians' employability. They described several challenges: dealing with a high workload, rapid technological developments, finding a healthy work-life balance, the need to fulfil nonmedical-related tasks (eg, educational tasks or being part of certain committees), and the repetitive character of their tasks, which challenged their motivation in the longer run. Both physicians and managers mentioned that these challenges affected their ability and/or willingness to continue to work in their profession. Some physicians also indicated that support in these areas would be helpful, since a focus on these themes was not part of their standard medical training. Career crafting training, which helps them to cope with their current work environment and prepare them for their further career, is therefore expected to be in line with their needs.

Step 2: Definition of Program Objectives

The next step involved specifying the change objectives. This included what must be changed and who must make the change [34]. These were formulated based on the needs that physicians and managers expressed in step 1. The following three program objectives were chosen: the intervention will increase physicians' (1) job crafting behavior, (2) career self-management behaviors, and (3) employability. Following the IM approach, three personal determinants were identified to realize behavioral change in order to reach these objectives [38]. These were awareness of the importance of investing in job crafting, career self-management, and employability; knowledge about these topics; and learning the skills to know how these investments can be made.

Step 3: Methods and Practical Applications

In the third step, methods and practical applications were chosen to achieve the objectives [34], based on existing literature and the stakeholder interviews. Multimedia Appendix 1 shows the theoretical methods and the practical applications for each determinant.

Step 4: Intervention Program Development and Pilot Test

Step 4 included a description of the intervention, completed program materials, and program protocols. The intervention consisted of a 4-hour group training session for diverse groups of physicians with a pre- and postmeasure. This half-day session was a combination of theory, reflection, exercises, and goal setting (see Multimedia Appendix 1). Participants learned the principles of proactive work and career behaviors, and all participants left the session with a plan outlining four small actions for the following 4 weeks.

In order to be successful, the program required pilot testing with intended implementers and recipients [34]. The survey was

created and pilot-tested by the first author in 4 face-to-face interviews with physicians and with managers who also worked as physicians. A *think-aloud* method was used, meaning that participants were asked to think out loud when reading the texts and answering the questions. At the end of the interview, some open-ended questions were asked about the survey's content, wording, and style of addressing physicians. If needed, introduction texts and items were adapted. Then, a list was made including program themes, assignments, and time frame planning. A training program and protocol was drafted, which was pretested in a pilot training session with intended users. A total of 5 physicians participated, who varied as much as possible on variables that might affect the variables of interest (eg, gender and age). The physicians followed the pilot training session and evaluated the training session at the end in a group discussion, based on the following: content, wording, suitability of given examples, and types of exercises. This resulted in optimization of the training content through some adaptations in allocated time and wording to make the content better suited to the perspectives of physicians. Moreover, examples of job crafting and career self-management were added, based on experiences of the physicians.

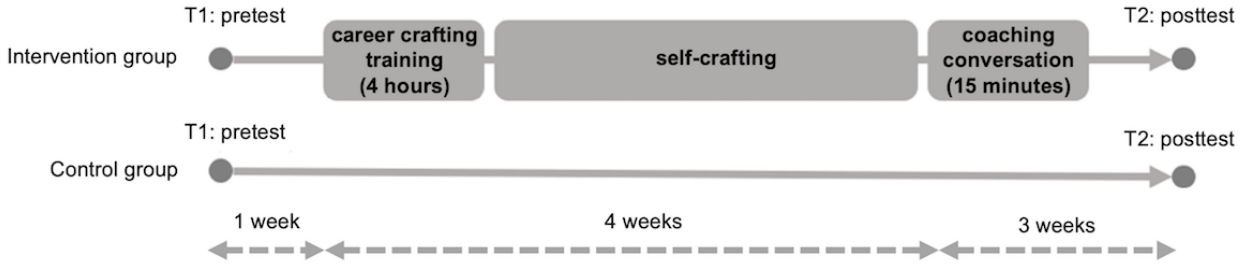
Step 5: Implementation

In this step, participants were recruited via presentations in physicians' staff meetings, word-of-mouth communication in existing networks, and promotions of the training via email. An email with information on the intervention (ie, goal, content, and duration of the intervention) was sent to the heads of departments, who were asked to share the email with physicians on their team. At the same time, the emails were sent to the representatives of physicians, who were asked to send the email to physicians in their department. In addition, accreditation was requested and granted. This means that physicians earned accreditation points (ie, professional development points) when participating in this training, which they need to stay registered. This will likely increase physicians' extrinsic motivation to participate in this training.

This intervention study started with randomly assigning participants to the waitlist-control group or the intervention group. Two independent randomizations were done using the randomizer function in Microsoft Excel (version 16.41): one for physicians in the academic hospital who were either assigned to the waitlist-control group or intervention group, and one for physicians in the general hospital who were randomized in a waitlist-control group or intervention group. Two independent randomizations enhanced the probability of equally dividing physicians in one hospital to the control or intervention group. This is important given the expectation that physicians from both hospitals differ on characteristics that might affect their career crafting behavior, such as type of contract and the degree of specialization. The advantage of the waitlist-control group is that all physicians received the intervention in the end. They were blind to the condition (ie, waitlist-control group or intervention group) to which they were assigned.

Figure 1 shows the procedure of this experiment. Participants in both the intervention and control groups received an email inviting them to complete the pretest. A total of 1 week after receiving the digital survey, which was sent through the program Qualtrics (version April 2020), physicians in the intervention group received a 4-hour training intervention. In total, 7-14 physicians were planned to attend each training session. After that, they worked on their self-set goals for the next 4 weeks. Then, a coaching conversation took place on the phone. A total of 3 weeks after the coaching conversation, which was 8 weeks after the pretest, physicians in both groups received a link to the posttest.

Figure 1. Design of the career crafting intervention.



Step 6: Evaluation of the Results

Overview

Both the effectiveness as well as the implementation process of the career crafting intervention will be systematically evaluated. The effectiveness of the intervention program will be evaluated quantitatively, by analyzing the variables of interest. The implementation process of the intervention will be examined through a process evaluation, both quantitatively, by examining the answers to survey items, and qualitatively, by asking for experiences of participants after the coaching session on the phone and in an open-ended question at the end of the last survey.

Effectiveness and Outcomes

The effectiveness of the career crafting training intervention will be examined by comparing the intervention and control groups on the outcomes that were gathered in the pre- and posttests. The main outcome measures of this study were job crafting, career self-management behavior, and employability. Perceptions on job crafting regarding personal resources were measured (9 items) [39], and perceptions on job crafting to change work aspects were measured (10 items) [7]. Perceptions on career self-management behavior were measured [10] by examining general career behaviors, career planning, career self-exploration, environmental career exploration, networking, voluntary human capital and skill development, and positioning

behavior (9 items). Perceived employability was measured by asking for physicians' willingness and mental and physical ability to continue working in their current profession until the retirement age (3 items) [3]. Additional outcome measures were job satisfaction [40], career satisfaction [41], work-home interference [42], work ability [43], and performance [44]. Additionally, background information was gathered on age, gender, type of employment contract, hours worked according to the contract, organizational tenure, and functional tenure. Data from the pre- and posttests of individuals could be linked with unique codes that were generated by the program Qualtrics.

Participants

The sample size was calculated on the basis of 95% power to reject the null hypothesis with a 2-tailed significance level of 5%. Assigning equal numbers of participants to the intervention and control groups, and based on the effects of job crafting training interventions on job crafting behavior [45,46], a total of 120 physicians (60 in each group) were needed. We aimed for 150 participants, to allow for 20% dropout. We widely communicated the possibility of participating in this intervention study to physicians, as explained in step 5. However, we did not reach all physicians (ie, 685 physicians in the academic hospital and 225 physicians in the general hospital), as we were not invited into all the departments of the hospital to give a presentation about the training content. In the end, 141 physicians participated; 107 physicians (76%) were employed by the academic hospital and 34 physicians (24%) worked in the general hospital.

Data Analysis

Depending on the assumptions for outliers, normality, and sphericity, we are planning to conduct 2-way, repeated-measures multivariate analyses of variance in SPSS (version 25.0 (IBM Corp)), to assess the *time* × *group* interaction effects of the intervention on the main and additional outcome measures. Subsequently, if the tests for assumptions are not violated, we will perform repeated-measures analyses of variance to further examine the effects within the control and intervention groups.

Process Evaluation

A process evaluation will be done during the process of implementing the study, providing insight into factors that may have helped or hindered the effectiveness of the intervention [32]. Despite the lack of an evidence-based framework describing the elements that need to be included in process evaluations [32], three dimensions are often mentioned: (1) context, (2) implementation process, and (3) participant mental models and mechanisms [32,47]. The elements examined within these dimensions are described in Multimedia Appendix 2. Both quantitative and qualitative methods will be used to examine these process evaluation elements, since both methods and the combination of them are shown to be effective [32,37,48].

Ethics

The University Medical Center Utrecht confirmed that this study falls outside the scope of the Dutch Medical Scientific Research Involving Human Subjects Act (*Wet medisch-wetenschappelijk onderzoek met mensen* [WMO], in Dutch) and, therefore, formal ethical approval was not required (METc 2019, 19/109). Nevertheless, ethical guidelines were applied as follows: all participants signed a written consent form stating that participation is voluntary, outcomes are held confidentially, and they can withdraw from the study at any time; they were also told that they could change their answers (ie, through a back button) before submitting the survey and were reminded of this at every contact moment. All study material was anonymized and saved on a protected server.

Results

Data collection was completed in March 2020. Evaluation of outcomes started in April 2020. One researcher conducted the primary analyses; these results were discussed with the research team in July 2020, which resulted in some adjustments and additional analyses. The process evaluation of the qualitative data that were obtained in the coaching interviews was done after the evaluation of the outcomes. Study results were submitted for publication in September 2020.

Discussion

This article describes (1) the development and (2) the evaluation design of the first career crafting training intervention aimed at increasing job crafting, career self-management behavior, and employability of physicians. This study protocol describes the systematic development of the intervention using parts of the IM protocol.

The strengths of this study boil down to three main points. First, this study addresses a novel concept, career crafting, which refers to proactive work and career behaviors that are linked to positive employee outcomes, such as well-being and employability. An intervention approach seems timely and relevant given the work and career-related challenges that physicians are facing. The intervention can potentially help them to cope with ongoing changes in their work environment [49] and might enhance the sustainability of their careers over time [6]. In order to fit the intervention's content with physicians' needs, needs are assessed through 40 interviews. This needs assessment forms the basis of the intervention program, which is further developed in close collaboration with physicians and other relevant stakeholders (eg, managers of physicians). Second, a robust research design is used, namely a randomized controlled field experiment, which is a high-quality approach to examine the causal effects of an intervention [50]. The effect and process evaluation help us to understand the outcomes of the intervention study and can be used to guide practice [32]. A third strength is that we designed the training to take place in 4-hour sessions, which kept the time investment low. The practical applicability of this study, therefore, seems high and the training could possibly be administered in an online format as well. Future studies could use this study protocol to examine such an intervention study in other occupational contexts to gain more insight into the effectiveness of a career crafting training intervention across different contexts with varying cultures.

Apart from the above strengths, this study has some limitations. First, contamination may occur when participants in the

intervention group communicate with waitlist-control participants about the content of the training. However, the chances of contamination are small, since physicians are widely spread across the organization. Second, because we use a field experiment, our control is limited. This means that participants might not adhere to the instructions, might be unable to attend the assigned training, might not complete both surveys, or could drop out completely. We deal with these problems by (1) keeping track of participants that want to change groups and (2) sending two reminders by email to complete the survey and four reminders to work on the self-set goals after the training.

A third limitation is that in order to minimize dropout, we did not include a long-term follow-up measurement. A second follow-up measurement could have revealed the extent to which findings can be generalized across longer time periods.

In conclusion, the systematic development of the intervention based on parts of the IM protocol has resulted in a 4-hour career crafting group training intervention to support physicians in developing proactive work and career behaviors. Subsequent analyses in a follow-up study can provide valuable insights to physicians, managers, and policy makers about the intervention's effectiveness for physicians.

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Authors' Contributions

All authors conceptualized the research project. EvL coordinated the study and gathered participants. EvL drafted the manuscript together with MvdH. All authors reviewed and provided comments and revisions. EK and TT secured funding for the project. MvdH designed the training content and pilot-tested the intervention together with EvL. All authors read and approved the final manuscript. EvL and MvdH were involved in conducting the intervention.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Theory-based methods and practical applications of the career crafting intervention.
[PDF File (Adobe PDF File), 20 KB - resprot_v9i10e18432_app1.pdf]

Multimedia Appendix 2
Elements of the process evaluation.
[PDF File (Adobe PDF File), 19 KB - resprot_v9i10e18432_app2.pdf]

References

1. Dunn PM, Arnetz BB, Christensen JF, Homer L. Meeting the imperative to improve physician well-being: Assessment of an innovative program. J Gen Intern Med 2007 Nov;22(11):1544-1552 [FREE Full text] [doi: 10.1007/s11606-007-0363-5] [Medline: 17891503]
2. Valcour M. Facilitating the crafting of sustainable careers in organizations. In: de Vos A, van der Heijden BIJM, editors. Handbook of Research on Sustainable Careers. Cheltenham, UK: Edward Elgar Publishing; 2015:20-34.
3. Oude Hengel KM, Blatter BM, Geuskens GA, Koppes LLJ, Bongers PM. Factors associated with the ability and willingness to continue working until the age of 65 in construction workers. Int Arch Occup Environ Health 2012 Oct;85(7):783-790. [doi: 10.1007/s00420-011-0719-3] [Medline: 22109674]
4. Houtman I, Hooftman W, de Vroome E. Duurzame inzetbaarheid van werknemers in de sector zorg en welzijn. Tijdschr voor Arb 2017;33(2):126-144.
5. Grant AM, Parker SK. Redesigning work design theories: The rise of relational and proactive perspectives. Acad Manage Ann 2009 Jan;3(1):317-375. [doi: 10.5465/19416520903047327]
6. de Vos A, Akkermans J, van der Heijden B. From occupational choice to career crafting. In: Gunz H, Lazarova M, Mayrhofer W, editors. The Routledge Companion to Career Studies. London, UK: Routledge; 2019:128-142.
7. Tims M, Bakker AB, Derks D. Development and validation of the job crafting scale. J Vocat Behav 2012 Feb;80(1):173-186. [doi: 10.1016/j.jvb.2011.05.009]
8. Tims M, Bakker AB. Job crafting: Towards a new model of individual job redesign. SA J Ind Psychol 2010 Dec 02;36(2):1-9 [FREE Full text] [doi: 10.4102/sajip.v36i2.841]
9. Wrzesniewski A, Dutton JE. Crafting a job: Revisioning employees as active crafters of their work. Acad Manage Rev 2001 Apr;26(2):179-201. [doi: 10.5465/amr.2001.4378011]

10. Hirschi A, Freund PA, Herrmann A. The career engagement scale. J Career Assess 2013 Dec 12;22(4):575-594. [doi: 10.1177/1069072713514813]
11. van der Heijde C. Employability and self-regulation in contemporary careers. In: Coetzee M, editor. Psycho-Social Career Meta-Capacities. Cham, Switzerland: Springer International Publishing; 2014:7-17.
12. King Z. Career self-management: Its nature, causes and consequences. J Vocat Behav 2004 Aug;65(1):112-133. [doi: 10.1016/s0001-8791(03)00052-6]
13. Rudolph CW, Katz IM, Lavigne KN, Zacher H. Job crafting: A meta-analysis of relationships with individual differences, job characteristics, and work outcomes. J Vocat Behav 2017 Oct;102:112-138. [doi: 10.1016/j.jvb.2017.05.008]
14. van den Heuvel M, Demerouti E, Peeters MCW. The job crafting intervention: Effects on job resources, self-efficacy, and affective well-being. J Occup Organ Psychol 2015 Jul 14;88(3):511-532. [doi: 10.1111/joop.12128]
15. Lazazzara A, Tims M, de Gennaro D. The process of reinventing a job: A meta-synthesis of qualitative job crafting research. J Vocat Behav 2019;116:1-18. [doi: 10.31234/osf.io/a9wf7]
16. Oprea BT, Barzin L, Vîrgă D, Iliescu D, Rusu A. Effectiveness of job crafting interventions: A meta-analysis and utility analysis. Eur J Work Organ Psychol 2019 Aug 05;28(6):723-741. [doi: 10.1080/1359432x.2019.1646728]
17. Koen J, Klehe UC, Van Vianen AEM. Training career adaptability to facilitate a successful school-to-work transition. J Vocat Behav 2012 Dec;81(3):395-408. [doi: 10.1016/j.jvb.2012.10.003]
18. Masdonati J, Massoudi K, Rossier J. Effectiveness of career counseling and the impact of the working alliance. J Career Dev 2009 Aug 04;36(2):183-203. [doi: 10.1177/0894845309340798]
19. Barnett BR, Bradley L. The impact of organisational support for career development on career satisfaction. Career Dev Int 2007 Oct 30;12(7):617-636. [doi: 10.1108/13620430710834396]
20. Fouad N, Cotter EW, Kantamneni N. The effectiveness of a career decision-making course. J Career Assess 2009 Jan 26;17(3):338-347. [doi: 10.1177/1069072708330678]
21. Rehfuss MC. The future career autobiography: A narrative measure of career intervention effectiveness. Career Dev Q 2009;58(1):82-90. [doi: 10.1002/j.2161-0045.2009.tb00177.x]
22. Spurk D, Kauffeld S, Barthauer L, Heinemann NS. Fostering networking behavior, career planning and optimism, and subjective career success: An intervention study. J Vocat Behav 2015 Apr;87:134-144. [doi: 10.1016/j.jvb.2014.12.007]
23. Whiston SC, Brecheisen BK, Stephens J. Does treatment modality affect career counseling effectiveness? J Vocat Behav 2003 Jun;62(3):390-410. [doi: 10.1016/s0001-8791(02)00050-7]
24. Litano ML, Major DA. Facilitating a whole-life approach to career development. J Career Dev 2015 Feb 05;43(1):52-65. [doi: 10.1177/0894845315569303]
25. van Harten J. Employable Ever After: Examining the antecedents and outcomes of sustainable employability in a hospital context [doctoral thesis]. Utrecht, the Netherlands: Utrecht University; 2016. URL: https://dspace.library.uu.nl/handle/1874/340549 [accessed 2020-09-28] https://dspace.library.uu.nl/handle/1874/340549
26. Borges NJ, Navarro AM, Grover A, Hoban JD. How, when, and why do physicians choose careers in academic medicine? A literature review. Acad Med 2010;85(4):680-686. [doi: 10.1097/acm.0b013e3181d29cb9]
27. Löyttyniemi V. Doctors drifting: Autonomy and career uncertainty in young physicians' stories. Soc Sci Med 2001 Jan;52(2):227-237. [doi: 10.1016/s0277-9536(00)00223-9]
28. Kragten H. Bouw uw carrière tijdig af: Op dr. Uitgeput, dr. Tegenstem en dr. Houdtnooitop zit niemand te wachten. Medisch Contact. 2016 Sep 21. URL: https://www.medischcontact.nl/nieuws/laatste-nieuws/artikel/bouw-uw-carriere-tijdig-af.htm [accessed 2020-09-28]
29. Tims M, Akkermans T. Job and career crafting to fulfill individual career pathways. In: Hedge JW, Carter GW, editors. Career Pathways: From School to Retirement. Oxford, UK: Oxford University Press; 2020:165-190.
30. Teunissen PW, Westerman M. Opportunity or threat: The ambiguity of the consequences of transitions in medical education. Med Educ 2011 Jan;45(1):51-59. [doi: 10.1111/j.1365-2923.2010.03755.x] [Medline: 21155868]
31. Westerman M. Mind the Gap: The transition to hospital consultant [doctoral thesis]. Amsterdam, the Netherlands: Vrije Universiteit Amsterdam; 2012. URL: https://research.vu.nl/files/42104788/complete%20dissertation.pdf [accessed 2020-09-28]
32. Nielsen K, Randall R. Opening the black box: Presenting a model for evaluating organizational-level interventions. Eur J Work Organ Psychol 2013 Oct;22(5):601-617. [doi: 10.1080/1359432X.2012.690556]
33. Murta SG, Sanderson K, Oldenburg B. Process evaluation in occupational stress management programs: A systematic review. Am J Health Promot 2007;21(4):248-254. [doi: 10.4278/0890-1171-21.4.248] [Medline: 17375490]
34. Bartholomew Eldredge LK, Markham CM, Ruiter RAC, Fernández ME, Kok G, Parcel GS. Planning health promotion programs: An intervention mapping approach. 4th edition. San Francisco, CA: Jossey-Bass; 2016.
35. Dumas A, Lemieux S, Lapointe A, Provencher V, Robitaille J, Desroches S. Development of an evidence-informed blog to promote healthy eating among mothers: Use of the intervention mapping protocol. JMIR Res Protoc 2017 May 19;6(5):e92 [FREE Full text] [doi: 10.2196/resprot.7147] [Medline: 28526669]
36. Boekhout JM, Peels DA, Berendsen BA, Bolman CA, Lechner L. An eHealth intervention to promote physical activity and social network of single, chronically impaired older adults: Adaptation of an existing intervention using intervention mapping. JMIR Res Protoc 2017 Nov 23;6(11):e230 [FREE Full text] [doi: 10.2196/resprot.8093] [Medline: 29170146]

37. Semmer NK. Job stress interventions and the organization of work. Scand J Work Environ Health 2006 Dec;32(6):515-527 [FREE Full text] [doi: 10.5271/sjweh.1056] [Medline: 17173207]
38. Kok G, Gottlieb NH, Peters GY, Mullen PD, Parcel GS, Ruiter RAC, et al. A taxonomy of behaviour change methods: An intervention mapping approach. Health Psychol Rev 2016 Sep;10(3):297-312 [FREE Full text] [doi: 10.1080/17437199.2015.1077155] [Medline: 26262912]
39. Kooij DTAM, van Woerkom M, Wilkenloh J, Dorenbosch L, Denissen JJA. Job crafting towards strengths and interests: The effects of a job crafting intervention on person-job fit and the role of age. J Appl Psychol 2017 Jun;102(6):971-981. [doi: 10.1037/apl0000194] [Medline: 28277726]
40. Wanous JP, Reichers AE, Hudy MJ. Overall job satisfaction: How good are single-item measures? J Appl Psychol 1997 Apr;82(2):247-252. [doi: 10.1037/0021-9010.82.2.247] [Medline: 9109282]
41. Martins LL, Eddleston KA, Veiga JF. Moderators of the relationship between work-family conflict and career satisfaction. Acad Manage J 2002 Apr 01;45(2):399-409. [doi: 10.2307/3069354]
42. Geurts SAE, Taris TW, Kompier MAJ, Dikkers JSE, Van Hooff MLM, Kinnunen UM. Work-home interaction from a work psychological perspective: Development and validation of a new questionnaire, the SWING. Work Stress 2005 Oct;19(4):319-339. [doi: 10.1080/02678370500410208]
43. Ilmarinen J. The Work Ability Index (WAI). Occup Med 2007 Mar;57(2):160 [FREE Full text] [doi: 10.1093/occmed/kqm008]
44. Schoorman FD, Mayer RC. The value of common perspectives in self-reported appraisals. Organ Res Methods 2007 Jul 23;11(1):148-159. [doi: 10.1177/1094428107307168]
45. Demerouti E, Xanthopoulou D, Petrou P, Karagkounis C. Does job crafting assist dealing with organizational changes due to austerity measures? Two studies among Greek employees. Eur J Work Organ Psychol 2017 May 29;26(4):574-589. [doi: 10.1080/1359432x.2017.1325875]
46. Gordon HJ, Demerouti E, Le Blanc PM, Bakker AB, Bipp T, Verhagen MA. Individual job redesign: Job crafting interventions in healthcare. J Vocat Behav 2018 Feb;104:98-114. [doi: 10.1016/j.jvb.2017.07.002]
47. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: Medical Research Council guidance. BMJ 2015 Mar 19;350:h1258 [FREE Full text] [doi: 10.1136/bmj.h1258] [Medline: 25791983]
48. Randall R, Cox T, Griffiths A. Participants' accounts of a stress management intervention. Hum Relat 2016 Apr 22;60(8):1181-1209. [doi: 10.1177/0018726707081660]
49. Petrou P, Demerouti E, Peeters MCW, Schaufeli WB, Hetland J. Crafting a job on a daily basis: Contextual correlates and the link to work engagement. J Organ Behav 2012 Feb 23;33(8):1120-1141. [doi: 10.1002/job.1783]
50. Morton RB, Williams KC. Experimental Political Science and the Study of Causality: From Nature to the Lab. Cambridge, UK: Cambridge University Press; 2010.

Abbreviations

IM: intervention mapping
WMO: Wet medisch-wetenschappelijk onderzoek met mensen (Dutch Medical Scientific Research Involving Human Subjects Act)

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Protocol

Intravital Microscopy (IVM) in Human Solid Tumors: Novel Protocol to Examine Tumor-Associated Vessels

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Abstract

Background: Intravital microscopy (IVM) allows the real-time, direct visualization of microscopic blood vessels. This pilot clinical trial will elucidate the physical and functional characteristics of vessels associated with solid tumors.

Objective: The main objective of this study is to determine the feasibility of performing IVM in patients with solid tumors during the standard course of surgical resection. IVM will also be performed when vasopressors or fluid boluses are administered during the standard course of the operation.

Methods: This is an open-label, nonrandomized, single-center, pilot study of IVM observation in subjects with solid tumors undergoing surgical resection.

Results: This study was active on January 1, 2019 (NCT03823144) and funded by the Mayo Clinic Florida Cancer Focused Research Team Award. As of September 27, 2020, we had enrolled 20 patients. Accrual period is expected to end by December 31, 2021.

Conclusions: This trial will support the development of interventions to improve patient treatment by extending the application of IVM to the tumor microenvironment. IVM observations during volume and pressor management at the time of surgery may aid in the development of strategies to augment responses to systemic treatments.

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KEYWORDS

intravital microscopy; solid tumors; microvasculature

Introduction

Intravital microscopy (IVM) is the microscopic observation of living tissue in real-time. IVM has been used to show that tumor vessels lack the sequential hierarchy of normal vessels such that arterioles, capillaries, and venules typically cannot be discriminated within tumor tissues [1,2]. This disorganization of aberrant tumor vessels was demonstrated in a previous clinical trial [3]. These tumor-associated vessels were also characterized by irregular diameters, aberrant branching patterns, abnormal blood flow rates, and anastomotic strictures. These characteristics could have profound influence on the delivery of agents (ie, chemotherapy or cellular immunotherapy) to the tumor microenvironment [4].

Human IVM was used first in the investigation of melanoma primary tumors. IVM has also been used to directly examine the hemodynamic properties of tumor vessels in preclinical mouse models [5-8]. Recent studies in B16 murine melanoma have used IVM to demonstrate that the abnormal, tortuous vascular structure in tumors represents a bottleneck to adoptive cell transfer immunotherapy because of poor trafficking of cytotoxic effector T cells at this site [5]. Others have used different forms of IVM to observe lymphatics or metastatic disease in real-time in mouse models [9,10]. There has also been reported real-time imaging of human tumor and lymphatics using different techniques such as multiphoton imaging, high-resolution ultrasound, or optical coherence tomography [11,12].

Our trial has the strong potential to expand upon novel tumor imaging techniques and not only form a directly observed basis of the tumor vasculature as a barrier to systemic drug efficacy in humans but also establish a rationale to overcome this barrier. To this end, this trial has the following objectives.

Objectives

Primary Objective – Part I (10 Patients)

The main objective is to determine the feasibility of performing IVM in patients with deep space solid tumors during the standard course of surgical treatment (resection). A successful intravital microscopic observation will include the ability to complete each of the following:

1. Identify and measure vessels associated with tumor.
2. Determine vessel density per 10x field.
3. Visualize vital dyes within the vessels (fluorescein).
4. Calculate the blood flow velocity of the vessels and tissue penetration of fluorescein as a marker of vessel permeability.

Secondary Objective – Part II (40 Patients)

To assess the secondary objectives, we will:

1. Compare the microscopic observation of the tumor-associated vessels with normal tissue (peritoneal surface) in each individual subject.
2. Correlate the microscopic observations of the tumor-associated vessels with pathologic grade of tumor.
3. Correlate the microscopic observation of the microvasculature with tumor-specific and overall survival.

Primary and Secondary Endpoints

Primary Endpoint

A patient observation will be deemed a success if each of the following parameters was measured:

1. Identify tumor-associated vessels and measure vessel diameters.
2. Determine vessel density per 10x field.
3. Visualize vital dyes within the tumor-associated vessels (fluorescein).
4. Calculate the blood flow velocity of the tumor-associated vessels and tissue penetration of fluorescein as a marker of vessel permeability.

Measurements will be obtained before and after any tumor vessel manipulation with either bolus fluids or vasopressors.

Secondary Endpoints

Measurements to assess the secondary endpoints include the following:

1. Postoperative comparison of the microvasculature of tumor with normal tissue (eg, peritoneum) in each individual subject using vessel diameters, vessel density, detection of intravital dye, and flow rates.
2. Postoperative correlation of the microvasculature with pathologic features of the tumor (ie, tumor grade) at the time of the final pathology report (5-7 days after surgery).
3. Postoperative correlation of the microscopic observation of the tumor microvasculature tumor-specific and overall survival.

Methods

Study Design

This is an open-label, nonrandomized, single-center study of IVM observation in conjunction with fluorescein in subjects with deep space solid tumors undergoing surgical resection. The first part is a pilot study of feasibility. Subjects will be treated on an inpatient basis.

Study Protocol

Surgical resection will be performed as part of standard of care. Approach may include open, laparoscopic, or robotic, as the IVM microscope can be used through any of these approaches.

The IVM technology consists of a high-resolution confocal endomicroscope (Cell Vizio) supplied by Mauna Kea Technologies. This apparatus has the ability to provide single cell resolution and high-quality images of the microvasculature. While the typical application of this device is to investigate gastrointestinal mucosal surfaces (ie, esophagus or colon), it can be easily applied to any surface. It can be sterilized via standard STERRAD techniques or used with a sterile sleeve in order to interface with the peritoneal surface, as currently used in NCT03517852: Intravital Microscopy (IVM) in Patients with Peritoneal Carcinomatosis (PC) [13].

The microscope is positioned in the operating room table by the operating surgeon after the tumor is exposed. Once the microscope is in the proper position, the epifluorescent light source is turned on, and digital video recording commences. Then, 1-2 mL of 25% fluorescein is injected intravenously, and observation continues until loss of fluorescence is observed over 2-4 areas of both grossly normal and tumor tissue. The fluorescein is almost immediately visible within the microscopic field, and the vessels are quickly outlined in great detail. The fluorescence lasts for a few minutes (2-3 minutes) and then either fades or begins to permeate through the tissue. The extravasation of dye will be determined by visualizing fluorescence outside of the defined vessels for a total time of approximately 5 minutes. On average, the total obervation time per field is 1-2 minutes.

During the course of the surgery, if fluid boluses or vasopressors (eg, vasopressin or phenylephrine) are required and administered to maintain blood pressure during the resection, another round of IVM observations will be performed with a second dose of 1-2 mL of fluorescein. Communication with anesthesia will indicate when fluid boluses or vasopressors are administered, in order to coordinate the observation.

Technical difficulties with the microscope apparatus (eg, malfunction of the software or structural damage to any of the microscope components) or unforeseen events during the course of surgery that are unrelated to the study intervention but that result in the termination of the surgery (eg, adverse reaction to anesthetic prior to administration of fluorescein or hemodynamic instability from a complication of the surgery) will not be considered failures of the primary objective. If vasopressors are not administered during surgery, the patient data will still be included in the study as they address the primary objective, which is to determine the feasibility of IVM.

Offline analysis of digitally recorded live video will be performed using parameters and statistical methods that have been developed in our preclinical imaging studies [5]. Lumenal cross-sectional diameter (D) of vessels and velocity (V) of dye-labeled cells will be measured in offline observations. Wall shear rate (γ) will be calculated as 8(V/D) [14]. Vessel density will be determined by measuring the calculated blood vessel area as a percent of the total visual field area. If visible, the uptake of fluorescein will be measured as a diffusion rate (distance from tumor vessel over time) and as a percent of the total tumor field observed (percent of visual field expressed as surface area with dye detected). Blood flow velocity will be determined by the equation Q = (red blood cell velocity/1.6) x (d/2) x pi.

Target Accrual and Study Duration

A maximum of 50 subjects (Part I, 10 patients; Part II, 40 patients) will be enrolled. The number of subjects required is a function of the expected feasibility. Accrual is expected to take up to 2 years.

Inclusion Criteria

Patients who are aged ≥18 years will be included in this trial. Additionally, these patients must have an ECOG Performance ≤2. Patients with a measurable tumor by direct visualization (visible lesion typically >0.5 cm in maximal diameter) and deep space tumors that meet indications for resection also require a negative skin-prick test to fluorescein. Tumors can be benign or malignant.

Exclusion Criteria

Patients who are experiencing uncontrolled intercurrent illnesses including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, psychiatric illness, or social situations will be excluded. Other factors for exclusion include renal dysfunction, as defined as a glomerular filtration rate <45; liver dysfunction, as defined by Child-Pugh score >5 or liver function tests 1.5 times above the normal average; any known allergy or allergic reaction to fluorescein or positive skin-prick test to fluorescein; and pregnant or nursing female subjects.

Study Procedure

Baseline Evaluations

The standard presurgical assessment with labs and studies as determined by the preoperative anesthesia clinic will be used. A summary of the evaluations that should be performed during the preoperative visit, surgery, and postoperative visit is provided in Figure 1.

If determined to be eligible for the study and after giving informed consent, a skin-prick test to determine sensitivity and risk of anaphylaxis to fluorescein will be performed by the principal investigator. For testing allergic response to fluorescein, a sterile Duotip® lancet (Lincoln Medical, Decatur, IL) is used in 2 separate areas of skin on the forearm. The skin pricks will include approximately 4 µL of 25% fluorescein administered in areas of skin prepped with an alcohol pad. After 30 minutes, the appearance of a wheal greater than 3 mm in diameter is considered a positive test result. If a positive test is noted, the patient will no longer be eligible for this study. For comfort and relief of any skin irritation or pruritis, the patient will be offered an antihistamine (one 30-mg fexofenadine [Allegra] by mouth) following the skin-prick test if necessary.

Figure 1. Summary of the evaluations performed during the protocol. IVM: intravital microscopy.

	Preoperative Visit	Surgery	Postoperative Visit
History and physical	X		
Informed consent	X		
Fluorescein skin prick test	X		
Tests as medically indicated	X		
Surgical resection with IVM		X	
Postsurgical monitoring in recovery and inpatient stay		X	
Review of pathology			X
Routine cancer surveillance			X

Posttreatment Follow-Up Evaluations

The standard follow-up and safety evaluations from surgery includes a postoperative visit at 2-3 weeks and scheduled follow-up based upon final staging of the patient's cancer. Follow-up will be based upon current National Comprehensive Cancer Network guidelines.

At the completion of the surgery, if gross tumor is entirely debulked (R0 resection), then patients are considered disease-free. Treatment response will be based upon the presence of a recurrence of tumor at either the primary site, locoregional recurrence (peritoneum), or metastatic sites.

The time to recurrence will determine the standard length of clinical follow-up. However, for this study, a 10-year limit will be placed on clinical data collection during the standard clinical follow-up. After a patient is enrolled, the duration of data collection will end at 10 years from the time of microscopic observation (surgery). These data (time of recurrence or survival) will be correlated with findings from the one-time, initial IVM observation for the defined 10-year period of data collection.

Results

This study was active on January 1, 2019 (NCT03823144) and funded by the Mayo Clinic Florida Cancer Focused Research Team Award. As of September 27, 2020, we had enrolled 20 patients. Accrual period is expected to end by December 31, 2021.

Discussion

We anticipate that this study will elucidate the structural and hemodynamic properties of vessels associated with solid tumors, building on previous studies that used IVM in human cancers [3,15]. In order to model the effects of tumor-associated vessel function on patient outcomes, direct examination of the microvasculature is essential and critical to be performed in humans. Thus, the significance of our trial lies in the opportunity to develop interventions that improve patient care. Specifically, the detection of blood flow parameters (including vessel diameter, flow rates, vessel density, and fluorescent markers of tissue diffusion) in human solid tumors is expected to have utility in predicting clinical response to systemically delivered therapies. This is because, in order for effective intravenous therapies to reach target tumors, they must have functional tumor-associated vessels to travel through. Therefore, it is anticipated that the investigation of tumor-associated vessels in real-time through IVM will lead to a better understanding of factors influencing systemic drug efficacy and perhaps generate a more complete picture of the tumor-associated locoregional vasculature.

In addition, by adding IVM observations during the course of volume and pressor management during the course of surgery, further data regarding tumor vessel dynamics will be obtained, which may offer a means to augment responses to systemic treatments. Ongoing studies by our group are investigating whether tumor-associated vessels can be manipulated in order to augment drug delivery. However, the first step in reaching this innovative goal is to establish the feasibility and safety of IVM in human solid tumors, which is the primary objective of this trial.

Indeed, novel approaches using IVM have the potential to provide advances in the field of personalized medicine by identifying patients who may respond to systemically delivered chemotherapeutic drugs or immunotherapeutic agents. IVM has been applied to the endoscopic evaluation of gastrointestinal tumors, the cystoscopic evaluation of bladder urothelial cancer, and most recently to melanoma [3]. The superficial or endoluminal location of these tumor types facilitates IVM, and from these studies, advances have been made in the understanding of tumor vasculature and the diagnosis of endoluminal cancers [15]. Our current trial will take these studies another step further through investigation of deep space solid tumors, both benign and malignant.

We anticipate completion of trial enrollment by December 31, 2020. IVM results will be correlated with oncologic outcomes. While the microscope is used to observe tumor-associated vessels, the procedure is not anticipated to cause iatrogenic spread of tumors. This is because the microscope does not puncture the tumors but is only used to examine the tumor-associated vessels. Furthermore, digital and instrument manipulation, both blunt and sharp, is used to resect the tumor, which provides more force than the microscope. In addition, this study may be limited in that mainly surface tumor vessels will be observed, whereas deeper vessels will not be observed. Observation of deeper vessels will not be performed as this would require incision into the tumor, which is contraindicated.

In conclusion, our trial will support the development of interventions to improve patient treatment by extending the application of IVM to the tumor microenvironment. IVM observations during volume and pressor management at the time of surgery may also aid in the development of strategies to augment responses to systemic treatments.

Acknowledgments

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Conflicts of Interest

None declared.

References

1. Nagy JA, Chang S, Shih S, Dvorak AM, Dvorak HF. Heterogeneity of the tumor vasculature. Semin Thromb Hemost 2010 Apr;36(3):321-331 [FREE Full text] [doi: 10.1055/s-0030-1253454] [Medline: 20490982]
2. Nagy JA, Chang S, Dvorak AM, Dvorak HF. Why are tumour blood vessels abnormal and why is it important to know? Br J Cancer 2009 Mar 24;100(6):865-869 [FREE Full text] [doi: 10.1038/sj.bjc.6604929] [Medline: 19240721]
3. Fisher DT, Muhitch JB, Kim M, Doyen KC, Bogner PN, Evans SS, et al. Intraoperative intravital microscopy permits the study of human tumour vessels. Nat Commun 2016 Feb 17;7:10684 [FREE Full text] [doi: 10.1038/ncomms10684] [Medline: 26883450]
4. Abdollahi A, Folkman J. Evading tumor evasion: current concepts and perspectives of anti-angiogenic cancer therapy. Drug Resist Updat 2010;13(1-2):16-28. [doi: 10.1016/j.drup.2009.12.001] [Medline: 20061178]
5. Fisher DT, Chen Q, Skitzki JJ, Muhitch JB, Zhou L, Appenheimer MM, et al. IL-6 trans-signaling licenses mouse and human tumor microvascular gateways for trafficking of cytotoxic T cells. J Clin Invest 2011 Oct;121(10):3846-3859 [FREE Full text] [doi: 10.1172/JCI44952] [Medline: 21926464]
6. Fukumura D, Duda DG, Munn LL, Jain RK. Tumor microvasculature and microenvironment: novel insights through intravital imaging in pre-clinical models. Microcirculation 2010 Apr;17(3):206-225 [FREE Full text] [doi: 10.1111/j.1549-8719.2010.00029.x] [Medline: 20374484]
7. Skitzki JJ, Chen Q, Wang WC, Evans SS. Primary immune surveillance: some like it hot. J Mol Med (Berl) 2007 Dec;85(12):1361-1367. [doi: 10.1007/s00109-007-0245-7] [Medline: 17704903]
8. Jain RK, Munn LL, Fukumura D. Dissecting tumour pathophysiology using intravital microscopy. Nat Rev Cancer 2002 Apr;2(4):266-276. [doi: 10.1038/nrc778] [Medline: 12001988]
9. Murooka TT, Mempel TR. Multiphoton intravital microscopy to study lymphocyte motility in lymph nodes. Methods Mol Biol 2012;757:247-257. [doi: 10.1007/978-1-61779-166-6_16] [Medline: 21909917]
10. Entenberg D, Kedrin D, Wyckoff J, Sahai E, Condeelis J, Segall JE. Imaging tumor cell movement in vivo. Curr Protoc Cell Biol 2013 Mar;Chapter 19:Unit19.7 [FREE Full text] [doi: 10.1002/0471143030.cb1907s58] [Medline: 23456602]
11. McLaughlin RA, Scolaro L, Robbins P, Hamza S, Saunders C, Sampson DD. Imaging of human lymph nodes using optical coherence tomography: potential for staging cancer. Cancer Res 2010 Apr 01;70(7):2579-2584. [doi: 10.1158/0008-5472.CAN-09-4062] [Medline: 20233873]
12. Patsialou A, Bravo-Cordero JJ, Wang Y, Entenberg D, Liu H, Clarke M, et al. Intravital multiphoton imaging reveals multicellular streaming as a crucial component of in vivo cell migration in human breast tumors. Intravital 2013 Apr 01;2(2):e25294 [FREE Full text] [doi: 10.4161/intv.25294] [Medline: 25013744]
13. NCT03517852: Intravital Microscopy (IVM) in Patients With Peritoneal Carcinomatosis (PC). clinicaltrials.gov. 2020 Jan 29. URL: https://clinicaltrials.gov/ct2/show/NCT03517852 [accessed 2020-09-24]
14. Wu NZ, Klitzman B, Dodge R, Dewhirst MW. Diminished leukocyte-endothelium interaction in tumor microvessels. Cancer Res 1992 Aug 01;52(15):4265-4268. [Medline: 1638539]
15. Gabriel EM, Fisher DT, Evans S, Takabe K, Skitzki JJ. Intravital microscopy in the study of the tumor microenvironment: from bench to human application. Oncotarget 2018 Apr 13;9(28):20165-20178 [FREE Full text] [doi: 10.18632/oncotarget.24957] [Medline: 29732011]

Abbreviations

D: cross-sectional diameter
IVM: intravital microscopy
V: velocity

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Protocol

Effects of Acute Exercise on Drug Craving, Self-Esteem, Mood, and Affect in Adults with Polysubstance Use Disorder: Protocol for a Multicenter Randomized Controlled Trial

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Abstract

Background: Novel treatments for substance use disorders are needed. Acute bouts of exercise can improve mood states and craving in nonclinical populations. Exercise effects in those with polysubstance dependence are understudied; controlled trials are needed.

Objective: This protocol describes a clinical study examining the short-term psychological effects of 2 types of physical activity, soccer and circuit training, in patients with substance use disorders. Effects will be compared with a nonexercise control group. Specific aims are to investigate whether there are differences between the activities and the duration of changes.

Methods: This study is a short-term multicenter randomized control trial with a crossover design. Patients consecutively admitted to 4 inpatient treatment centers were invited to participate in 3 conditions, each lasting 45 minutes, within one week. The order of the conditions was randomized. There were a total of 5 assessments, taken at baseline, immediately before each condition, immediately after each condition, and 1, 2, and 4 hours postintervention, enabling patterns of change over time to be observed. Psychological effects were assessed with self-report questionnaires, which included scales for craving, state anxiety, positive and negative affect, self-esteem, and mood. Exercise intensity was assessed with the Borg Rating of Perceived Exertion scale and a heart rate monitor (Polar M200; Polar Electro Ltd). Cortisol was assessed in saliva before and 4 hours after the intervention.

Results: A total of 39 patients were included in the study. Data collection was completed in 2019.

Conclusions: We anticipate larger improvements in the intervention groups than among controls, indicating positive psychological effects during and after exercise. The study will add clinically relevant information about the short-term psychological effects of exercise in the treatment of substance use disorders, using activities that are easily accessible in different clinical settings.

Trial Registration: German Clinical Trials Register DRKS00018869; https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00018869

International Registered Report Identifier (IRRID): DERR1-10.2196/18553

(JMIR Res Protoc 2020;9(10):e18553) doi:10.2196/18553

KEYWORDS

exercise; acute; substance abuse; physical activity; drug addiction

Introduction

Substance use disorders (SUD) have wide-reaching impacts on health and well-being and contribute substantially to the global disease burden [1]. They are associated with shorter life expectancy, and comorbid medical conditions are common [2]. The prevalence of co-occurring personality and other psychiatric disorders is high, with estimates ranging from 50% to 90% [3]. Mood and anxiety disorders are prevalent and affect both the severity and outcome of treatment [4]. Current treatment options for SUDs include cognitive behavioral therapy, motivational interviewing, and medication. Although documented as effective, these methods do not help all patients. Relapse rates range between 40% and 60% [5], and dropout rates from in-patient treatment is around 30% [6].

Despite their high prevalence, few people with SUDs ever receive treatment, and there is a need for more treatment options [7,8]. One potential explanation for poor help seeking is the perceived stigma associated with traditional treatments [9,10]. Lifestyle-focused interventions have potential to increase help seeking by reducing this stigma.

Physical activity has been suggested as an alternative or complementary treatment option for SUDs [11-13]. The rationale is that physical exercise might be effective due to its beneficial effects on factors related to relapse and the maintenance of the disorder, such as comorbid mental disorders, craving, and emotional dysregulation [14-17].

Regular physical activity increases fitness and lowers the probability of chronic diseases [18,19]. It has been proposed as a strategy for alleviating symptoms of psychiatric disorders in general [20,21], and its application in the mental health care system is increasing. Regular physical activity has been shown to be effective in the prevention and treatment of common mental health conditions [22]. Studies also indicate that physical activity alleviates symptoms in people suffering from severe mental disorders [23]. Acute bouts of exercise have cognitive and mood-enhancing benefits, including improved executive functioning and lower state anxiety and stress reactivity [24,25]. The mechanisms behind the psychological benefits of exercise in SUDs are not well established, but one tenable hypothesis is that they are partly mediated by changes in the stress hormone cortisol [24].

While the effects of exercise are well documented for common mental disorders, there has been less research focus on SUDs. Most studies have addressed the effect of chronic exercise interventions on smoking cessation or alcohol misuse. Long-term exercise programs might affect smoking behavior [26] and lower tobacco cravings [27]. A meta-analysis of 21 exercise studies for alcohol use disorder concluded that, while regular exercise did not seem to affect consumption, it had beneficial effects on depression and physical fitness [28]. In another meta-analysis, Wang et al [29] found that exercise was associated with greater abstinence rates among illicit drug users compared with those using alcohol and nicotine. The effect of exercise on withdrawal symptoms, anxiety, and depression was not moderated by the type of substance used. Colledge et al [30] reviewed the effects of anaerobic exercise on SUDs. The results were mixed, with some evidence of a positive effect on abstinence from nicotine. No conclusions could be drawn regarding the effects of exercise among illicit drug users.

One plausible explanation for the beneficial long-term effects of an exercise program is that many single sessions have a cumulative long-term benefit. Few studies have addressed the short-term effects of physical activity in SUDs. A study of 45 regular smokers found that bouts of moderate and vigorous exercise provided relief from withdrawal symptoms, while moderate exercise relieved distress and improved mood [31]. Studies addressing alcohol urges or cravings show promising results, with lower craving after low-to-moderate intensity exercise [13,32]. Wang et al [33] studied the development of craving for amphetamines and found a reduction in cravings during and immediately after stationary cycle exercise. Results suggest that the intensity of the exercise may affect craving, with the lowest craving following moderate-to-vigorous exercise [34].

The misuse of a single substance is exceptional in SUDs [35]. Whether acute exercise can benefit people with polysubstance dependencies is unclear. Most studies have assessed aerobic forms of exercise, often in laboratory conditions using stationary bicycles [12,28]; little is known about other forms of exercise in clinical settings. With some exceptions [25], psychological benefits across different forms of exercise have not been compared, and it is unclear how long the changes last following a single exercise session. Studies have mostly used pre- and postassessments only, which is a limitation.

To address these questions, we conducted a feasibility study to compare the short-term effects of 3 different exercises (soccer, circuit training, and walking) conducted in nonlaboratory settings [36]. Findings suggested that moderately intense exercise activities performed in natural settings may increase mood, help attenuate drug cravings, increase positive affect, decrease negative affect, and improve self-esteem. The results were promising but need to be replicated with a larger sample and a randomized design.

In this study, we are conducting a multicenter randomized controlled trial to compare the short-term effects of 2 forms of exercise (soccer and circuit training) with a control condition (a lecture on the health benefits of physical activity) in polydrug-dependent inpatients. We chose to compare the effects of exercise to a nonexercising control group (lecture) instead of a walking-based intervention, as previous studies have shown that even light physical activity can have mood-enhancing effects [37]. We are also performing biomarker analyses of cortisol to better understand the underlying mechanisms.

Key research questions that will be addressed include (1) What are the short-term effects of soccer and circuit training on mood (primary outcome), drug craving, positive and negative affect, state anxiety, and self-esteem in adults with SUD? (2) How long do the effects last after the exercise sessions end? (3) Are there differences between the two forms of exercise? (4) Do the effects differ with the intensity of the exercise? and (5) Are the study outcomes associated with changes in the stress hormone cortisol?

Based on previous studies [33,38], we hypothesize that there will be positive psychological effects on the study outcomes after exercise, with a reduction in craving and an improvement in mood and affects. We expect to find larger improvements in the intervention groups than in the control group.

Methods

We adhered to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines in the preparation of this protocol. The study will be reported according to CONSORT (Consolidated Standards of Reporting Trials) ethical guideline recommendations.

Ethics Approval and Consent to Participate

The trial is approved by the Regional Committee for Medical and Health Research Ethics in South East Norway (2018/1275) and was retrospectively registered with the German Clinical Trials Register on November 11, 2019 (DRKS00018869). Before inclusion in the study, participants were asked to sign an informed consent form. All patients agreed to participate voluntarily and were told they were free to withdraw from the study at any time.

Setting and Participants

Inpatients from 4 treatment facilities were invited to participate. The main site for the study was the Department of Addiction Treatment - Adult, Division of Mental Health and Addiction, Oslo University Hospital. In addition, 3 other treatment centers were asked to participate (2 accepted): the Department of Addiction Treatment - Youth, Oslo University Hospital; an inpatient treatment center at the Division of Mental Health and Addiction, Vestfold Hospital Trust; and the Blue Cross Treatment Center, Slemdal, Oslo. The study was conducted in a clinical setting, where the participants received treatment.

The treatment centers are staffed by medical doctors, nurses, psychologists, and social workers. Treatment includes individual and group counseling and pharmacotherapy. Patients participate in structured group sessions and practice activities of daily living, including routines for house cleaning, eating, and sleeping. They receive individual sessions with psychologists, doctors, and social workers and participate in team meetings and social training. Physical exercise, including strength training, ball games, walks, and running, are part of the usual treatment program. Before admission to treatment, all patients complete detoxification.

Recruitment took place at the treatment centers, where patients were given information and invited to participate in the study by members of the research group and a local project coordinator. All participants were diagnosed with a SUD based on the International Classification of Diseases, Tenth Revision (ICD-10), were inpatients at one of the treatment centers, and were 18 years or older.

Study Design and Randomization

This study is a short-term, multicenter randomized controlled trial with a single pretest and multiple posttests. Using a crossover design, changes in mood, craving, state anxiety, affect, and self-esteem were assessed by comparing the initial measurement (taken immediately before exercise) with 4 follow-up assessments, first immediately after exercise, then at 1, 2, and 4 hours postintervention. The design allows the pattern of change over time to be seen.

Participants completed 3 sessions—2 supervised group exercise sessions (soccer and circuit training) and 1 control condition (attending a lecture about the health benefits of physical activity)—within the same week. All the sessions were performed in a group setting.

The order of the study conditions was determined by a random number generator and placed in sealed envelopes at a site separate from the study location. When a group of suitable patients (5-10 patients) was recruited at a site, a sealed envelope with the order of exercise and control conditions was drawn by a person outside of the research group.

Procedure

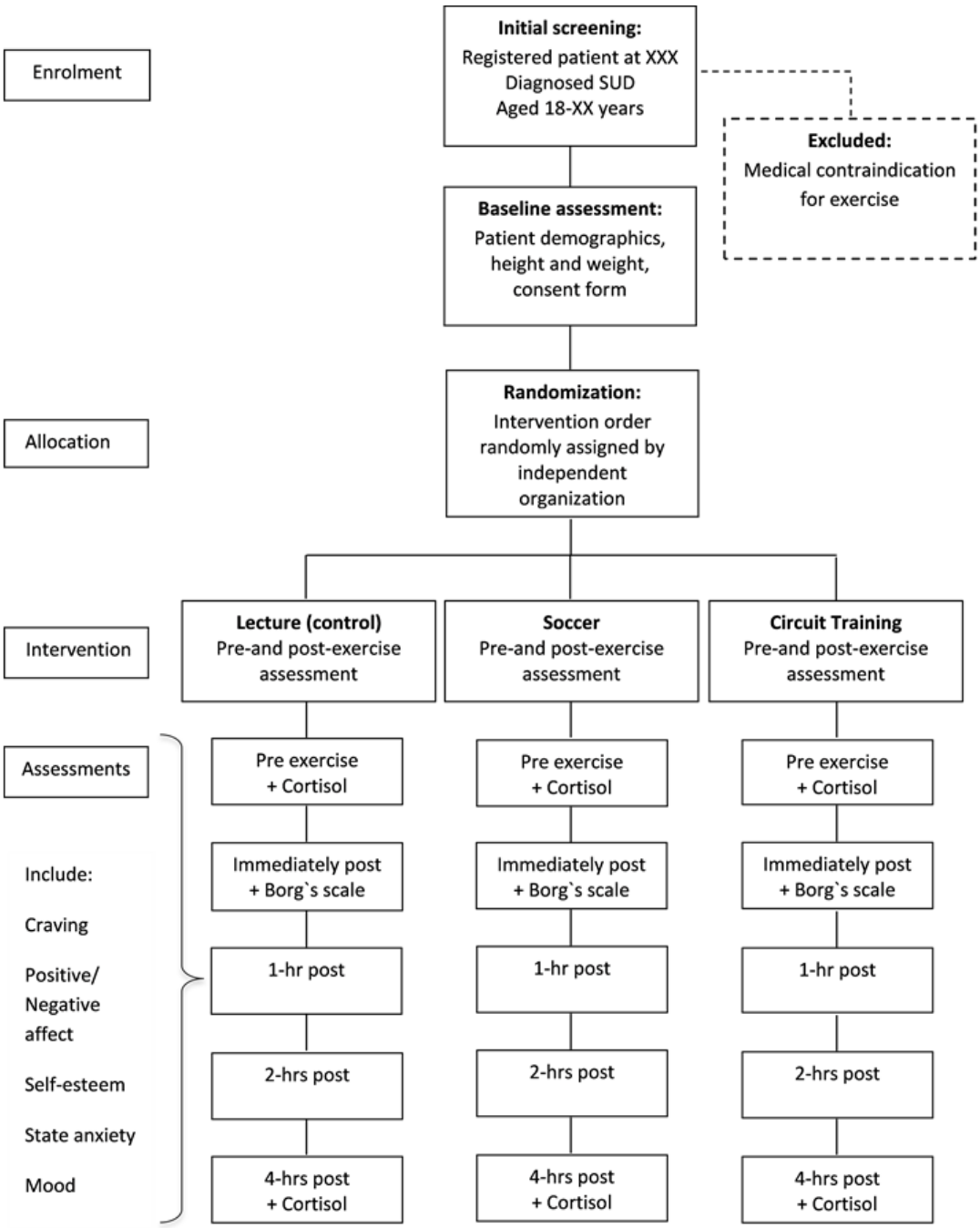
Patients were invited to attend an information meeting, where members of the research group explained the purpose of the study in detail and handed out written information. To minimize dropout, the recruitment took place a maximum of two weeks ahead of the trial. A member of the research group visited the treatment center 1 week before the study to answer questions.

After giving informed consent, eligible participants were gathered to perform the interventions and assessments. These sessions were undertaken on-site at the clinics starting at 9:30 AM on Monday, Wednesday, and Friday within one week. The participants were asked to refrain from doing exercise on the days of the trial and on the days in between the interventions to give a 1-day washout period between the sessions. All sessions lasted 45 minutes. During the week of the trial, all participants received treatment as usual between the sessions.

The following exercise activities and control condition were tested in random order: (1) indoor soccer, (2) circuit training in a gymnasium using body weight, and (3) the control condition, attending a lecture on exercise and mental health.

Across all trial days, the participants were advised to eat breakfast about an hour before starting the trial. They were advised to have a light meal or snack after training, have lunch on all trial days, and keep hydrated throughout the day. Participants were also asked to limit the use of caffeine and nicotine during the test period. The flow of participants through the trial is shown in Figure 1.

Figure 1. Flow of participants through the study. SUD: substance use disorder.



Exclusion Criteria

Patients admitted to the treatment centers typically have comorbid ICD-10 mental disorders. None of these served as exclusion criteria as long as the participant was able to give informed consent. All patients at the clinics were invited to join; the only exclusion criterion was having a physical condition or injury that would impede physical activity participation. Some patients relapsed to substances during treatment. Patients who were suspected to be under the influence of drugs were asked to discontinue.

Measures

Background Information

Therapists collected background information about the participants during an interview. The therapists filled in a questionnaire covering sociodemographic and treatment-related variables, ICD-10 substance use and mental disorders diagnosed

during treatment, duration of problematic drug use, treatment history, level of activity before admission, and attitude toward physical activity. Height and weight were recorded. For most participants, this was based on measures taken at the treatment centers. A minority were self-reported.

Baseline and Follow-up Assessments

Mood (primary outcome), craving, affect, self-esteem, and state anxiety were measured with self-report questionnaires. The same questionnaires were repeated for baseline and follow-up assessments. The questionnaires chosen could be completed in 5 minutes, were amenable to repeated administration, and had sound psychometric properties.

The self-report questionnaires and saliva samples collected immediately before the sessions were the baseline assessment. Following the sessions, participants filled in self-report questionnaires on 4 occasions: immediately after the session and 1, 2, and 4 hours after the session. Immediately after the exercise sessions, participants were also asked to rate the perceived intensity. A saliva sample was gathered 4 hours after all sessions. Figure 2 illustrates the SPIRIT figure, study measures, and assessment time points.

Self-report measures were (1) the Feeling Scale, (2) drug craving, (3) the Positive and Negative Affect Schedule (PANAS), (4) the Rosenberg Self-Esteem Scale, (5) state anxiety, and (6) the Borg Rating of Perceived Exertion (RPE) scale.

First, changes in mood related to exercise were assessed with the Feeling Scale [39] (primary outcome), a single-item Likert scale ranging from –5 (very bad) to 5 (very good). Participants were instructed to indicate how they felt “at this moment.” The scale has been used extensively in acute exercise studies [40].

Second, drug craving was assessed using a single-item visual analog scale (VAS) ranging from 0 (no craving for drugs) to 10 (strong craving for drugs). Participants were instructed to indicate how strong their craving for drugs felt “at this moment.” The instrument has been used in previous studies of acute exercise [41] and it was tested in our recent pilot study [36], where it was shown to be sensitive to change.

Third, the PANAS assesses 2 dimensions of affect [42]. Participants self-rate 20 items on a 5-point Likert scale ranging from 1 (very slightly/not at all) to 5 (extremely). Ten of the items represent positive affect and the others represent negative affect.

Fourth, self-esteem was measured using the 10-item Rosenberg Self-Esteem Scale [43], which measures global feelings about oneself (that is, both positive and negative feelings). All items are answered using a 4-point Likert scale ranging from strongly agree to strongly disagree.

Fifth, state anxiety was assessed by a single-item VAS-scale ranging from 0 (no anxiety) to 10 (intensive anxiety/full panic).

Sixth, the Borg RPE scale [44] was administered 5 minutes after each exercise session to assess how strenuous the exercises were perceived by participants. The single-item scale ranges from 6 (no exertion at all) to 20 (maximal exertion).

Figure 2. SPIRIT figure, study measures, and assessment time points. FS: Feeling Scale; HR: heart rate; PANAS: Positive and Negative Affect Schedule; RCT: randomized controlled trial; RPE: Rating of Perceived Exertion; RSES: Rosenberg Self-Esteem Scale; VAS: visual analog scale.

		Study period									
	Assessment name	Therapist-rated	Objective measure	Patient-rated	Enrollment	Baseline immediately pre-exercise	During	Immediately postexercise	1 hour postexercise	2 hours postexercise	4 hours postexercise
Time point					Week -1	Week 0	Week 0	Week 0	Week 0	Week 0	Week 0
Enrollment:											
Eligibility screen					√						
Informed consent						√					
Allocation					√						
Interventions:											
Soccer						←	—	→			
Circuit training						←	—	→			
Control condition (lecture)						←	—	→			
Assessments (RCT):											
Demographics	Questionnaire	√		√	√				√	√	√
Substance use disorder	Questionnaire	√		√	√			√	√	√	√
Smoking	Questionnaire	√		√	√				√	√	√
Mental disorders	Questionnaire	√		√	√				√	√	√
Previous treatment	Questionnaire	√		√	√						
Medical treatment	Questionnaire	√		√	√						
Years of substance use	Questionnaire	√		√	√						
Anabolic androgenic steroids	Questionnaire	√		√	√						
Weight	Questionnaire	√		√	√						
Height	Questionnaire	√		√	√				√	√	√
Previous physical activity	Questionnaire	√		√	√						
Attitudes towards physical activity	Questionnaire	√		√	√						
Stress	Cortisol		√			√					√
Heart rate (during conditions)	Polar HR monitor		√				√				
Self-esteem	RSES			√		√		√	√	√	√
Affect	PANAS		√	√		√		√	√	√	√
State anxiety	VAS			√		√		√	√	√	√
Mood	FS			√		√		√	√	√	√
Perceived exertion	RPE			√				√			
Drug craving	VAS			√		√		√	√	√	√

Device-Based Assessment of Physical Activity

In addition to collecting self-reports on how strenuous the exercises were perceived to be, data on the average and maximum heart rate were collected using a heart rate monitor (Polar M200; Polar Electro Ltd) during all of the conditions.

Biomarkers

Cortisol level was measured immediately before and 4 hours after the interventions. Saliva samples were collected using cotton swabs (Salivette; Sarstedt Inc). Collected samples were stored in a freezer until the end of the study. The cortisol level in saliva will be measured by liquid chromatographic–tandem mass spectrometry. The analyses will be performed at the Hormone Laboratory at Oslo University Hospital.

Consistent with Salivette recommendations, participants were asked not to eat or drink, use tobacco, or brush their teeth 60 minutes before the saliva samples were taken.

Exercise Interventions

The aerobic and anaerobic exercises included in the study were chosen on the basis of participant feedback given during the pilot study. All exercise sessions were supervised by a qualified staff member, a nurse with formal education in physical activity for people with mental health and addiction disorders.

Soccer

Soccer was played with 5 participants on each team, including the goalkeeper. It was arranged in gyms that the treatment centers normally use for physical activity sessions. The participants were randomly divided into 2 teams. If fewer than 10 patients participated in the study at one site, staff from that treatment center were asked to join. The field was 20 × 40 m and the goal was 3 × 2 m.

Participants were asked to play a friendly match where goals were counted. They were told their soccer competency was not important and that all participation in the match was valuable for the team, and they were asked to try to give it their best. The match lasted for 45 minutes, with a 2-minute break after 15 and 30 minutes.

Circuit Training

Circuit training was performed in the same gymnasium as the soccer intervention. Due to the low cost and limited need for equipment, we used body weight exercises only. Participants completed 4 circuits consisting of 8 individual exercise stations. They spent 40 seconds exercising at each station, then 20 seconds resting before transitioning to the next station. Between each circuit there was a 2-minute rest. As participants were new to the training environment, the first circuit took slightly longer to complete. Thus, the average duration of training for most participants was 45 minutes (42-48 minutes). The 8 exercises were air squats, inch worms, bench dips, frog jumps, sit-ups, push-ups, walking lunges, and back extensions.

During the first circuit, participants performed the exercises together to make sure they did them correctly. This circuit functioned as a warm-up and was undertaken at lower intensity. If a participant had a physical disability or was restricted from performing an exercise, an alternative or adjusted exercise was substituted. Participants were asked to give their best effort at each station and to perform as many repetitions as they could within 40 seconds. They were also told that if the exercises felt easy, they should try to increase the number of repetitions, whereas if they felt they were too strenuous, they could decrease the number.

Control Condition

Participants attended a 45-minute lecture with a PowerPoint (Microsoft Corp) presentation on the benefits of physical activity for physical and mental health. The lecture format was similar to what the patients would normally receive during conventional treatment. The lecture was given by a member of the research group in a meeting room at the treatment centers.

Adherence

A member of the research group was on-site during the interventions to remind participants about the assessment times and to motivate them to participate in the conditions. The same staff member was also available to answer any questions about the questionnaires.

Statistical Analyses and Power Calculation

Statistical power was estimated using G*Power (version 3.1.9.7; Heinrich-Heine-Universität Düsseldorf). Parameters were based on results from our feasibility study [36] and also took into account previous studies demonstrating medium effect sizes for acute exercise on mood states [38,45]. Assuming an effect size of 0.3 and power (β) of .8, with 3 groups and 5 measurement points, we estimate needing at least 21 participants to test our hypotheses. We planned to include one group of 5 to 10 participants from each site, which would give us 20 to 40 participants. Due to the experimental study design and the inclusion of only inpatients, we anticipate minimal missing data. Descriptive data will be calculated for each measure. Changes over time will be assessed using mixed (group × time) repeated-measures analysis of variance with post hoc contrasts. If participants return questionnaires with missing data, the missing items will be imputed using the last observation carried forward method. If questionnaires are returned with more than 50% of data missing, the questionnaire will be excluded from the analysis.

Safety, Data Management, and Confidentiality

During the trial, all patient data will be kept in a secure room accessible only by the research group. All data will be deidentified and treated according to the standards set by the Norwegian Data Inspectorate (Datatilsynet), in compliance with the Health Research Act and the Personal Data Act.

Results

Data collection was completed in August 2019. In total, 39 patients admitted at 3 treatment centers participated in the study. Data will be analyzed during 2020.

Discussion

Many SUD clinics have begun to implement physical activity as part of routine inpatient treatment due to its reported benefits. This study on acute exercise will add clinically relevant information about the short-term effects of soccer and circuit training on mood, craving, state anxiety, and self-esteem in this population. Most previous studies have performed pre-exercise and postexercise assessments only. The current study will add information on how the effects develop beyond the immediate

cessation of exercise. The activities in the study are readily available, inexpensive, and popular in the general population. If the interventions are effective, they can easily be integrated into different clinical settings, for both inpatients and outpatients, and adapted to the participant's fitness level.

The study is designed to reflect the clinical realities of inpatient treatment for SUDs. Typically, patients use multiple substances [3,35]. The inclusion of patients with comorbid SUD and mental disorders will give the study a high ecological validity but might also make the results difficult to interpret. Different drugs and various mental disorders might be affected in different ways by the interventions. Gathering information on the participants' co-occurring disorders will potentially enable subgroup analyses to differentiate exercise effects in those with different combinations of substance and mental health problems.

Craving is highly relevant in clinical settings, even though the nature of it and the items included in instruments that assess craving have been debated [15,46,47]. By using a single-item scale, it will not be possible to capture changes in different aspects of craving. The participants might have different perceptions of craving, varying from a subjective desire to consume a substance to various bodily sensations. This is a potential limitation. However, previous studies assessing acute craving have used single-item VAS scales [48,49]. As the aim of the present study is to assess changes in participants' overall subjective experience of craving and whether exercise can help attenuate it, we believe that a single-item scale can adequately capture this.

Using saliva samples is a noninvasive method for assessing cortisol levels. There is no need for medical staff, and saliva can be stored at room temperature for several hours before freezing. The drawback of saliva cortisol (versus serum cortisol) is that the use of tobacco and the presence of blood in the samples may lead to falsely elevated cortisol levels [50]. To control for this, the laboratory will not analyze samples with traces of blood. Samples with cortisol levels above reference levels will be excluded from analysis.

Dropout rates from treatment studies of SUDs are often high [6,28]. To minimize the risk of dropout, a member of the research group visited the treatment center 1 week before the study to answer questions. The recruitment took place a maximum of two weeks ahead of the trial. We tried to minimize dropout by keeping the overall intervention period short and integrating the interventions into the usual treatment routines at the treatment centers. This also minimized interference in the patients' usual treatment.

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Authors' Contributions

MME, EWM, SLJ, and MH were involved in designing the trial and developed the intervention. MME and SLJ were responsible for implementing the trial. MME and MH will oversee the data analysis. All authors will be involved in interpretation of the results. MME and EWM wrote the first draft. SLJ and SRD contributed to writing and reviewing. MME, EWM, and MH contributed to writing, reviewing, and editing. EWM and MH supervised.

Conflicts of Interest

None declared.

References

1. Degenhardt L, Whiteford H, Ferrari A, Baxter AJ, Charlson FJ, Hall WD, et al. Global burden of disease attributable to illicit drug use and dependence: findings from the Global Burden of Disease Study 2010. The Lancet 2013 Nov 09;382(9904):1564-1574. [doi: 10.1016/S0140-6736(13)61530-5] [Medline: 23993281]
2. Walker ER, Druss BG. Mental and Addictive Disorders and Medical Comorbidities. Curr Psychiatry Rep 2018 Aug 28;20(10):86. [doi: 10.1007/s11920-018-0956-1] [Medline: 30155583]
3. Demetrovics Z. Co-morbidity of drug addiction: An analysis of epidemiological data and possible etiological models. 2009 Aug 13;17(4):420-431. [doi: 10.1080/16066350802601324]
4. Lai HMX, Cleary M, Sitharthan T, Hunt GE. Prevalence of comorbid substance use, anxiety and mood disorders in epidemiological surveys, 1990-2014: A systematic review and meta-analysis. Drug Alcohol Depend 2015 Sep 01;154:1-13. [doi: 10.1016/j.drugalcdep.2015.05.031] [Medline: 26072219]
5. Principles of drug addiction treatment: A research-based guide (Third Edition). National Institute on Drug Abuse. URL: https://www.drugabuse.gov/publications/principles-drug-addiction-treatment-research-based-guide-third-edition/ [accessed 2019-09-30]
6. Lappan S, Brown A, Hendricks P. Dropout rates of in-person psychosocial substance use disorder treatments: a systematic review and meta-analysis. Addiction 2020 Feb;115(2):201-217. [doi: 10.1111/add.14793] [Medline: 31454123]

7. Kuramoto SJ, Martins SS, Ko JY, Chilcoat HD. Past year treatment status and alcohol abuse symptoms among US adults with alcohol dependence. Addict Behav 2011 Jun;36(6):648-653 [FREE Full text] [doi: 10.1016/j.addbeh.2011.01.017] [Medline: 21315517]
8. Cunningham JA, Breslin F. Only one in three people with alcohol abuse or dependence ever seek treatment. Addictive Behaviors 2004 Jan;29(1):221-223. [doi: 10.1016/S0306-4603(03)00077-7]
9. Schuler MS, Puttaiah S, Mojtabai R, Crum R. Perceived Barriers to Treatment for Alcohol Problems: A Latent Class Analysis. Psychiatr Serv 2015 Nov;66(11):1221-1228 [FREE Full text] [doi: 10.1176/appi.ps.201400160] [Medline: 26234326]
10. Probst C, Manthey J, Martinez A, Rehm J. Alcohol use disorder severity and reported reasons not to seek treatment: a cross-sectional study in European primary care practices. Subst Abuse Treat Prev Policy 2015 Aug 12;10:32 [FREE Full text] [doi: 10.1186/s13011-015-0028-z] [Medline: 26264215]
11. Giesen E, Deimel H, Bloch W. Clinical exercise interventions in alcohol use disorders: a systematic review. J Subst Abuse Treat 2015 May;52:1-9. [doi: 10.1016/j.jsat.2014.12.001] [Medline: 25641736]
12. Zschucke E, Heinz A, Ströhle A. Exercise and physical activity in the therapy of substance use disorders. ScientificWorldJournal 2012;2012:901741 [FREE Full text] [doi: 10.1100/2012/901741] [Medline: 22629222]
13. Manthou E, Georgakouli K, Fatouros I, Gianoulakis C, Theodorakis Y, Jamurtas A. Role of exercise in the treatment of alcohol use disorders. Biomed Rep 2016 May;4(5):535-545 [FREE Full text] [doi: 10.3892/br.2016.626] [Medline: 27123244]
14. Weinstock J, Farney M, Elrod N, Henderson C, Weiss E. Exercise as an Adjunctive Treatment for Substance Use Disorders: Rationale and Intervention Description. J Subst Abuse Treat 2017 Jan;72:40-47 [FREE Full text] [doi: 10.1016/j.jsat.2016.09.002] [Medline: 27666958]
15. Tiffany S, Wray J. The clinical significance of drug craving. Ann N Y Acad Sci 2012 Feb;1248:1-17 [FREE Full text] [doi: 10.1111/j.1749-6632.2011.06298.x] [Medline: 22172057]
16. Cheetham A, Allen NB, Yücel M, Lubman DI. The role of affective dysregulation in drug addiction. Clin Psychol Rev 2010 Aug;30(6):621-634. [doi: 10.1016/j.cpr.2010.04.005] [Medline: 20546986]
17. Bernstein EE, McNally RJ. Acute aerobic exercise helps overcome emotion regulation deficits. Cogn Emot 2017 Jun;31(4):834-843. [doi: 10.1080/02699931.2016.1168284] [Medline: 27043051]
18. Chau JY, Grunseit AC, Chey T, Stamatakis E, Brown WJ, Matthews CE, et al. Daily sitting time and all-cause mortality: a meta-analysis. PLoS One 2013;8(11):e80000 [FREE Full text] [doi: 10.1371/journal.pone.0080000] [Medline: 24236168]
19. Haskell WL, Lee I, Pate RR, Powell KE, Blair SN, Franklin BA, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Med Sci Sports Exerc 2007 Aug;39(8):1423-1434. [doi: 10.1249/mss.0b013e3180616b27] [Medline: 17762377]
20. Martinsen EW. Physical activity in the prevention and treatment of anxiety and depression. Nord J Psychiatry 2008;62 Suppl 47:25-29. [doi: 10.1080/08039480802315640] [Medline: 18752115]
21. Hallgren M, Stubbs B, Vancampfort D, Lundin A, Jääkallio P, Forsell Y. Treatment guidelines for depression: Greater emphasis on physical activity is needed. Eur Psychiatry 2017 Feb;40:1-3. [doi: 10.1016/j.eurpsy.2016.08.011] [Medline: 27837666]
22. Ashdown-Franks G, Firth J, Carney R, Carvalho AF, Hallgren M, Koyanagi A, et al. Exercise as Medicine for Mental and Substance Use Disorders: A Meta-review of the Benefits for Neuropsychiatric and Cognitive Outcomes. Sports Med 2020 Jan;50(1):151-170. [doi: 10.1007/s40279-019-01187-6] [Medline: 31541410]
23. Stubbs B, Vancampfort D, Hallgren M, Firth J, Veronese N, Solmi M, et al. EPA guidance on physical activity as a treatment for severe mental illness: a meta-review of the evidence and Position Statement from the European Psychiatric Association (EPA), supported by the International Organization of Physical Therapists in Mental Health (IOPTMH). Eur Psychiatry 2018 Oct;54:124-144. [doi: 10.1016/j.eurpsy.2018.07.004] [Medline: 30257806]
24. Basso JC, Suzuki WA. The Effects of Acute Exercise on Mood, Cognition, Neurophysiology, and Neurochemical Pathways: A Review. BPL 2017 Mar 28;2(2):127-152. [doi: 10.3233/bpl-160040]
25. Bodin T, Martinsen E. Mood and Self-Efficacy During Acute Exercise in Clinical Depression. A Randomized, Controlled Study. Journal of Sport and Exercise Psychology 2004;26(4):623-633. [doi: 10.1123/jsep.26.4.623]
26. Ussher MH, Taylor AH, Faulkner GEJ. Exercise interventions for smoking cessation. Cochrane Database Syst Rev 2014 Aug 29(8):CD002295. [doi: 10.1002/14651858.CD002295.pub5] [Medline: 25170798]
27. Roberts V, Maddison R, Simpson C, Bullen C, Prapavessis H. The acute effects of exercise on cigarette cravings, withdrawal symptoms, affect, and smoking behaviour: systematic review update and meta-analysis. Psychopharmacology (Berl) 2012 Jul;222(1):1-15. [doi: 10.1007/s00213-012-2731-z] [Medline: 22585034]
28. Hallgren M, Vancampfort D, Giesen ES, Lundin A, Stubbs B. Exercise as treatment for alcohol use disorders: systematic review and meta-analysis. Br J Sports Med 2017 Jul;51(14):1058-1064. [doi: 10.1136/bjsports-2016-096814] [Medline: 28087569]
29. Wang D, Wang Y, Wang Y, Li R, Zhou C. Impact of physical exercise on substance use disorders: a meta-analysis. PLoS One 2014 Oct;9(10):e110728 [FREE Full text] [doi: 10.1371/journal.pone.0110728] [Medline: 25330437]
30. Colledge F, Gerber M, Pühse U, Ludyga S. Anaerobic Exercise Training in the Therapy of Substance Use Disorders: A Systematic Review. Front Psychiatry 2018;9:644 [FREE Full text] [doi: 10.3389/fpsyt.2018.00644] [Medline: 30564150]

31. Everson ES, Daley AJ, Ussher M. The effects of moderate and vigorous exercise on desire to smoke, withdrawal symptoms and mood in abstaining young adult smokers. Mental Health and Physical Activity 2008 Jun;1(1):26-31. [doi: 10.1016/j.mhpa.2008.06.001]
32. Ussher M, Sampuran A, Doshi R, West R, Drummond D. Acute effect of a brief bout of exercise on alcohol urges. Addiction 2004 Dec;99(12):1542-1547. [doi: 10.1111/j.1360-0443.2004.00919.x] [Medline: 15585045]
33. Wang D, Zhou C, Chang Y. Acute exercise ameliorates craving and inhibitory deficits in methamphetamine: An ERP study. Physiol Behav 2015 Aug 01;147:38-46. [doi: 10.1016/j.physbeh.2015.04.008] [Medline: 25846839]
34. Wang D, Zhou C, Zhao M, Wu X, Chang Y. Dose-response relationships between exercise intensity, cravings, and inhibitory control in methamphetamine dependence: An ERPs study. Drug Alcohol Depend 2016 Apr 01;161:331-339. [doi: 10.1016/j.drugalcdep.2016.02.023] [Medline: 26946990]
35. Liu Y, Williamson V, Setlow B, Cottler L, Knackstedt L. The importance of considering polysubstance use: lessons from cocaine research. Drug Alcohol Depend 2018 Nov 01;192:16-28 [FREE Full text] [doi: 10.1016/j.drugalcdep.2018.07.025] [Medline: 30195242]
36. Ellingsen M, Johannesen S, Martinsen E, Hallgren M. Effects of acute exercise on drug craving, self-esteem, mood and affect in adults with poly-substance dependence: Feasibility and preliminary findings. Drug Alcohol Rev 2018 Sep;37(6):789-793. [doi: 10.1111/dar.12818] [Medline: 29869351]
37. Legrand FD, Thatcher J. Acute mood responses to a 15-minute long walking session at self-selected intensity: effects of an experimentally-induced telic or paratelic state. Emotion 2011 Oct;11(5):1040-1045. [doi: 10.1037/a0022944] [Medline: 21517170]
38. Hallgren M, Moss ND, Gastin P. Regular exercise participation mediates the affective response to acute bouts of vigorous exercise. J Sports Sci Med 2010;9(4):629-637 [FREE Full text] [Medline: 24149790]
39. Hardy CJ, Rekeski WJ. Not what, but how one feels: The measurement of affect during exercise. J Sport Exerc Psycol 1989;11(3):304-317. [doi: 10.1123/jsep.11.3.304]
40. Rejeski WJ, Gauvin L, Hobson ML, Norris JL. Effects of baseline responses, in-task feelings, and duration of activity on exercise-induced feeling states in women. Health Psychology 1995;14(4):350-359. [doi: 10.1037/0278-6133.14.4.350]
41. Prapavessis H, De Jesus S, Harper T, Cramp A, Fitzgeorge L, Mottola MF, et al. The effects of acute exercise on tobacco cravings and withdrawal symptoms in temporary abstinent pregnant smokers. Addict Behav 2014 Mar;39(3):703-708 [FREE Full text] [doi: 10.1016/j.addbeh.2013.10.034] [Medline: 24290209]
42. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: The PANAS scales. Journal of Personality and Social Psychology 1988;54(6):1063-1070. [doi: 10.1037/0022-3514.54.6.1063]
43. Rosenberg M. Society and the Adolescent Self-Image. In: Science. Princeton, NJ: Princeton University Press; May 07, 1965.
44. Borg G, Ljunggren G, Ceci R. The increase of perceived exertion, aches and pain in the legs, heart rate and blood lactate during exercise on a bicycle ergometer. Europ J Appl Physiol 1985 Oct;54(4):343-349. [doi: 10.1007/bf02337176]
45. Herring MP, Monroe DC, Gordon BR, Hallgren M, Campbell MJ. Acute Exercise Effects among Young Adults with Analogue Generalized Anxiety Disorder. 2019;51(5):962-969. [doi: 10.1249/mss.0000000000001860]
46. Sayette MA, Shiffman S, Tiffany ST, Niaura RS, Martin CS, Shadel WG. The measurement of drug craving. Addiction 2000 Aug;95 Suppl 2:S189-S210 [FREE Full text] [doi: 10.1080/09652140050111762] [Medline: 11002914]
47. Sayette M. The Role of Craving in Substance Use Disorders: Theoretical and Methodological Issues. Annu Rev Clin Psychol 2016;12:407-433. [doi: 10.1146/annurev-clinpsy-021815-093351] [Medline: 26565121]
48. Sinha R, Fox HC, Hong KA, Bergquist K, Bhagwagar Z, Siedlarz KM. Enhanced negative emotion and alcohol craving, and altered physiological responses following stress and cue exposure in alcohol dependent individuals. Neuropsychopharmacology 2009 Apr;34(5):1198-1208 [FREE Full text] [doi: 10.1038/npp.2008.78] [Medline: 18563062]
49. Miranda R, Ray L, Blanchard A, Reynolds EK, Monti PM, Chun T, et al. Effects of naltrexone on adolescent alcohol cue reactivity and sensitivity: an initial randomized trial. Addict Biol 2014 Sep;19(5):941-954 [FREE Full text] [doi: 10.1111/adb.12050] [Medline: 23489253]
50. Golden SH, Wand GS, Malhotra S, Kamel I, Horton K. Reliability of hypothalamic-pituitary-adrenal axis assessment methods for use in population-based studies. Eur J Epidemiol 2011 Jul;26(7):511-525 [FREE Full text] [doi: 10.1007/s10654-011-9585-2] [Medline: 21533585]

Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
ICD-10: International Classification of Disease, Tenth Revision
PANAS: Positive and Negative Affect Schedule
RPE: Rating of Perceived Exertion
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SUD: substance use disorder
VAS: visual analog scale

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Protocol

High-Intensity Interval Aerobic Resistance Training to Counteract Low Relative Appendicular Lean Soft Tissue Mass in Middle Age: Study Protocol for a Randomized Controlled Trial

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Abstract

Background: Sarcopenia is the age-related loss of skeletal muscle mass and function and may exist in early middle age. Previous research in this area has focused on resistance training in older individuals; however, there is a lack of intervention trials in middle-aged adults with low relative appendicular lean soft tissue mass who may be at risk for sarcopenia in older age.

Objective: This randomized controlled trial aims to determine the effects of a high-intensity interval aerobic resistance training intervention on appendicular lean soft tissue mass in middle-aged adults with low relative appendicular lean soft tissue mass.

Methods: We will conduct a 40-week, single-blinded randomized controlled trial in 84 middle-aged adults with low appendicular lean soft tissue mass in the wider Dunedin area, New Zealand. We will randomly allocate participants to receive either a group-based, 20-week high-intensity interval aerobic resistance training intervention program or a single, 60-minute education session on current exercise recommendations. After the first 20 weeks, both groups will be given a 20-week home program. The study will assess primary and secondary outcome measures, including body composition (regional and whole-body lean soft tissue mass, fat mass, percentage body fat, measured by dual x-ray absorptiometry), blood biomarkers (cortisol, creatinine, C-reactive protein, lipid profile, hemoglobin), physical fitness (maximum oxygen consumption, blood pressure), physical activity (accelerometry), physical function (handgrip strength, sit-to-stand, gait speed, quadriceps strength), and self-reported questionnaires (health outcomes, self-efficacy, perceived enjoyment of physical activity, and multifactorial lifestyle), at baseline, 20 weeks, and 40 weeks. Physical function and self-reported questionnaires will also be measured at 10 weeks. We will assess the primary outcome measure, total body lean soft tissue mass, at baseline, 20 weeks, and 40 weeks. Analyses will be performed using intention-to-treat principles, comparing the outcomes resulting from the intervention, using linear mixed models.

Results: We obtained ethical approval for this study from The University of Otago Human Ethics Committee on December 10, 2018. Participant recruitment started on February 11, 2019 and was completed on May 14, 2019. Data collection started on February 25, 2019 and was completed on February 28, 2020. We expect to publish the results in January 2021.

Conclusions: High-intensity interval aerobic resistance training is a time-efficient form of exercise, enabling busy middle-aged adults to meet physical activity recommendations while maximizing training results. The findings can inform the development of future prevention-focused interventions aimed at counteracting the high prevalence of sarcopenia in the aging population.

Trial Registration: Australian New Zealand Clinical Trials Registry (ACTRN12618001778279); https://tinyurl.com/y555z6fz.

International Registered Report Identifier (IRRID): DERR1-10.2196/22989

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KEYWORDS

sarcopenia; high-intensity interval training; randomized controlled trial

Introduction

Background

Sarcopenia is the age-related loss of skeletal muscle mass and function [1]. Due to the gradual decline in muscle mass with age, the focus of research into this disease thus far has mainly been in those over 60 years of age [1]. However, the progressive loss of skeletal muscle mass and strength begins in middle age, and evidence demonstrates that abnormal body composition is apparent before the age of 50 years [2,3]. If abnormal body composition is already present in early middle age, then implementing lifestyle interventions in younger age groups may mitigate the trajectory to low physical function, frailty, and premature death in later life. This could have important public health implications, as older people with sarcopenia are consistently reported to have lower physical function, overall health, and survival than people with normal body composition [4]. Also, low physical activity is common as people grow older [5], increasing the risk for sarcopenia [6].

Two recently published systematic reviews concluded that exercise therapy, with or without combined dietary interventions or supplementation, can be an effective treatment for older adults with sarcopenia [7,8]. However, Yoshimura et al concluded that more high-quality randomized controlled trials (RCTs) are required to confirm these results [7]. To the best of our knowledge, only 3 trials have been conducted in older adults with low muscle mass. A 10-week resistance training program was effective for maintaining functional strength and increasing muscle mass in men and women aged 70 years with low muscle mass [9]. This intervention included moderate- to high-intensity resistance training, where intensity was measured using the Borg CR10 scale, with participants rating their perceived exertion between 6 and 7 out of 10 [9]. Participants performed 8 exercises with the aim of engaging muscle groups in the whole body [9]. In another study, a 12-week multicomponent exercise program improved physical function in sarcopenic or presarcopenic individuals (≥60 years of age) [10]. The intervention consisted of resistance training, balance, flexibility, and aerobic exercises and participants determined their individual resistance load as 12 to 14 on the Borg scale [10]. Finally, a 6-month home exercise program improved physical function in 52 community-dwelling individuals (≥60 years of age) with low muscle mass or sarcopenia [11]. The home program consisted of a combination of walking (20-30 minutes per day) and lower limb resistance exercises (6× squats, 1-minute single-leg standing and 20× heel raises) [11]. To date, to our knowledge, no interventions have been conducted in middle-aged adults with low relative appendicular lean soft tissue mass.

High-intensity interval training (HIIT) was within the top 3 fitness trends for 2016 and is reported to be safe and well tolerated, with adherence that exceeds steady state training [12]. In addition to better adherence, different forms of HIIT are time efficient and provide aerobic fitness and health benefits similar to or better than traditional steady state training [12]. HIIT workouts are usually short and involve aerobic high-intensity exercises, accumulated through short bursts of activity [13]. These short bouts of activity often last between 1 and 4 minutes with a recovery phase between the bouts [13]. A metareview of 33 systematic reviews, including studies across the lifespan, showed that HIIT improved cardiorespiratory fitness, anthropometric measures, blood glucose and glycemic control, arterial compliance and vascular function, cardiac function, some inflammatory markers, and exercise capacity, and decreased heart rate (HR) and increased muscle mass compared with nonactive controls [14]. Different forms of HIIT have been proven safe in different patient populations, including cardiac rehabilitation patients [15,16] and patients with type 2 diabetes [17], rheumatoid arthritis [18], and cancer [19].

To date, to our knowledge, only a few studies have investigated the effects of HIIT on sarcopenia. A recent study in older sedentary adults demonstrated that a combination of HIIT and increased protein intake resulted in a greater increase in mitochondrial content compared with a nonexercise control group, helping to preserve oxidative capacity and slow the process of sarcopenia [20]. The protocol consisted of 5 intervals of 1 minute of stationary cycling at 85% of maximal load reached during maximum oxygen consumption (O_2max) [20]. Another study demonstrated that HIIT can improve skeletal muscle vascularization in older men [21]. The protocol as proposed by Leuchtmann et al consisted of 12 weeks of HIIT followed by 12 weeks of progressive resistance training [21]. The HIIT protocol consisted of seven 1-minute intervals of stationary cycling at 85% of the participants' peak power [21]. The resistance training consisted of 3 sets of leg extensions, leg press, and squats with a 3-minute rest between sets [21]. After each HIIT and resistance training session, participants received a drink containing 30 g of whey protein [21]. In animal models, HIIT led to a greater muscle mass, larger muscle fiber size, and an increase in mitochondrial biomass in old, sarcopenic, and frail mice compared with nonexercise controls [22]. This research agrees with a study comparing moderate-intensity continuous training versus HIIT in middle-aged rats, showing that HIIT was better at mitigating age-related sarcopenic physiological processes such as oxidative stress and inflammation [23].

The majority of high-intensity training protocols conducted in sarcopenic individuals have been in older adults and are aerobic based. Thus, the opportunity for muscle mass development may be limited. A newer form of high-intensity training using circuit training has recently been proven effective in improving both body composition and strength measurements in middle-aged men and women (50-65 years of age) [12]. In the study by Greenlee et al, 3 center-based trainings a week with at least one day of rest between sessions for 16 weeks, improved muscle mass and muscle strength [12]. The program started with a warm-up and was followed by high-intensity cardioresistance training of 3 sets of 3 to 4 resistance training exercises followed

by a set of rope jumping, 4 minutes of high-intensity cardiorespiratory exercises, and 3 sets of 2 to 4 resistance exercises [12]. These exercises were followed by 5 to 15 minutes of whole-body training and 5 to 10 minutes of yoga-inspired flexibility training [12]. HR averaged more than 80% of maximum HR throughout the sessions, and participants spent 66% of the exercise sessions between vigorous and maximal training zones [12].

Objective

Despite the positive effects of the study by Greenlee et al, to our knowledge, no high-intensity aerobic resistance training (HIART) intervention studies have been conducted in middle-aged adults with low relative lean soft tissue mass. Therefore, the primary aims of this research are to determine whether HIART can increase lean soft tissue mass and whether these changes can be maintained in the long term. Secondary aims include investigating the effect of HIART on biomarkers of sarcopenia, physical fitness, physical activity, physical function, physical activity enjoyment, self-efficacy, and adherence.

Methods

Study Design and Setting

The HIIT Your Exercise Target is a single-blinded RCT testing the effectiveness of a 20-week high-intensity interval circuit training intervention on appendicular lean soft tissue mass. We obtained ethical approval for this study from The University of Otago Human Ethics Committee (H18/131) and registered it (ACTRN12618001778279). All participants will provide written informed consent in accordance with the Declaration of Helsinki. This community-based study will be conducted in the Department of Medicine, University of Otago, Dunedin, New Zealand, with training sessions carried out in the Southern District Health Board staff gymnasium, Dunedin.

Recruitment and Eligibility Criteria

We will recruit sedentary but otherwise healthy participants aged between 40 and 50 years through flyers, community webpage postings, electronic bulletin boards, and local newspapers. Interested people will be directed to complete an online screening questionnaire. Participants will be prescreened for exclusion criteria, exercise safety, and their weekly amount of physical activity. We will deem participants to be eligible to attend a screening appointment if their self-reported physical activity level is below the minimum weekly current exercise recommendations [24]; they do not take medications known to affect body composition or HR; they are not diagnosed with moderate or severe hypertension; they are not pregnant or breastfeeding, or planning on becoming pregnant during the intervention; they are not previously diagnosed with or have symptoms of cardiovascular disease or other serious medical condition; they do not weigh more than 159.9 kg (weight limit of the dual energy x-ray absorptiometry [DXA] scanner); they do not live outside of metropolitan Dunedin; and they are able to communicate in English or te Reo Māori. Further exclusion will occur for exercise safety (see the Exercise Safety Screening subsection below). Participants will receive the information sheet and will be given 2 days to decide if they are willing to participate.

Exercise Safety Screening

Participants will undergo medical screening, as part of the screening questionnaire, to allow identification of those at high risk of an adverse event during high-intensity exercise. We will do individual medical screening, following the guidelines as proposed by the American College of Sports Medicine/American Heart Association. High-risk participants will be excluded after the online screening questionnaire. All other participants, including medium-risk participants, will be monitored with a 12-lead electrocardiogram (ECG) during the O_2max test at their first screening appointment. All ECGs will be assessed by an experienced cardiologist and require approval before the participant can enter the study.

Screening Appointment

Potentially eligible participants will attend 2 appointments as part of the screening process. During the first appointment, a blood sample will be taken, the participant will undergo a total body DXA scan to measure body composition and they will undergo a O_2max test on a stationary bicycle (see outcome measures below for more detail). At the end of the first appointment participants will receive an accelerometer (ActiGraph) to wear for 7 days and nights to assess physical activity (see outcome measures for more detail). Participants will be emailed a weblink and will be asked to fill out several questionnaires on demographics, generic health outcomes, self-efficacy, physical activity enjoyment, and lifestyle (see outcome measures for more detail).

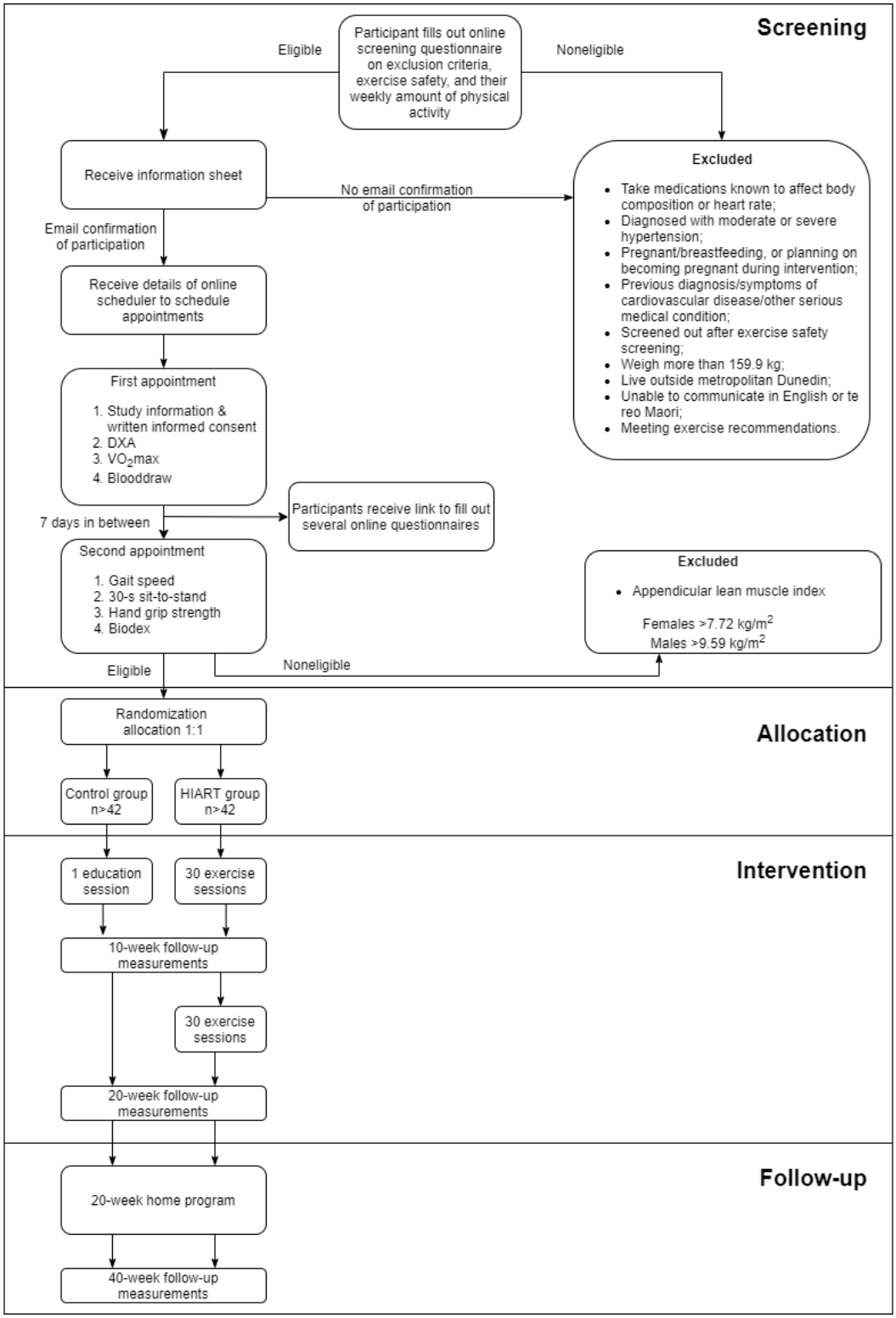
During the second appointment, 8 days after the first appointment, we will assess gait speed, 30-second sit-to-stand, hand grip strength, and maximal isokinetic and isometric strength of the quadriceps (see outcome measures for more detail). We will apply further exclusion criteria at this point. We will use sex-specific, height squared adjusted cutoff scores as proposed by Prado et al, to classify low appendicular lean soft tissue mass index (ALMI) measured by DXA [25]. Females with an ALMI greater than 7.72 kg/m^2 and males with an ALMI greater than 9.59 kg/m^2 will be excluded.

Blinding, Randomization Methods, and Allocation Concealment

Figure 1 shows the study flow. Following the screening assessments eligible participants will be randomly allocated to either a control group or HIART group at a 1:1 allocation ratio. Stratified block randomization allocation sequence will be generated in REDCap (REDCap Consortium) and will be used to automatically randomly allocate participants to groups of equal sample size, stratified by sex, age and BMI. The block sizes and allocation sequence will not be disclosed to ensure concealment. The investigator collecting the data will feed data into the computer in separate datasheets, which will be anonymized by a different investigator, to ensure that all other investigators, including lab technicians, cardiologist and the primary investigators remain blinded to the treatment allocation.

Statistical analysis will be performed using the anonymized datasets to ensure masking to treatment allocation.

Figure 1. Study design flow diagram. DXA: dual energy x-ray absorptiometry; HIART: high-intensity interval aerobic resistance training; <inline-graphic xlink:href="researchprotocols_v9i10e22989_fig3.png" mimetype="image" xlink:type="simple"/>O_2max: maximum oxygen consumption.



Intervention

Control Group

The control group will receive education on current exercise recommendations during a 60-minute group session, provided by a physiotherapist. We will define current exercise recommendations as proposed by the World Health Organization: adults aged 18 to 64 years should do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week, or at least 75 minutes of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity activity [24]. Following the

20-week intervention, the control group will be offered 3 weeks of supervised exercise, where they are taught how to perform HIART. After 3 weeks, they will be given access to the remainder of the 20-week home program. We will design the home program specifically for this study and it will be viewable with protected YouTube links.

High-Intensity Interval Training Group

The intervention includes a 40-week RCT of HIART. The 40-week intervention involves 20 weeks of training followed by a 20-week follow-up. Each training session will start with a warm-up, followed by HIART, and finishing with a cooldown. HIART involves 3 phases, as follows.

The first is a *power phase* consisting of 2 whole-body exercises, performed for 20 seconds each with maximum intensity, followed by 10 seconds of rest and repeated 8 times. Between each whole-body exercise will be a 1-minute rest. Exercises include jumping jacks, skaters, burpees, and numerous other calisthenics varied by session.

The second is a *cycling phase*, which will be based on the 3-minute all-out protocol as proposed by Gillen et al [26]. We will use stationary spin bikes for this phase (4000GT Spin Bike; AeroSpin). The cycling phase will begin with a 2-minute warm-up, followed by 2 times 4 sets of 20-second all-out sprints interspersed with a 1-minute recovery, followed by a 2-minute cooldown. Participants will be encouraged to increase wattage when appropriate.

Third is a *resistance phase* consisting of 2 resistance exercises with or without free weights. The resistance exercises will target major muscle groups. Exercises will be performed as supersets (antagonistic muscle groups), compound sets (same muscle group[s]), or staggered sets (noncompeting muscle groups; eg, upper and lower body). Participants will perform each exercise 8 times for 20 seconds, followed by a 10-second rest.

Participants will complete all exercises as a circuit with a 1-minute rest between exercises. Training load will be self-selected, but participants will be encouraged to choose a weight or resistance that will ensure that their HR reaches 85% of maximum HR during the high-intensity peaks and does not drop below 60% of maximum HR during the low-intensity periods in the power and cycling phases. All training sessions will be group based, with a maximum of 9 people in each group. Experienced staff with extensive background in group fitness will lead every exercise class. At the end of the 20-week exercise intervention, participants will be given access to the 20-week home program to complete sessions at home.

Outcome Assessments

We will conduct outcome assessments at T0 (baseline), T1 (midpoint of intervention, 10 weeks), T2 (end of intervention, 20 weeks), and T3 (end of follow-up, 40 weeks) (Figure 2).

Figure 2. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) diagram. HIART: high-intensity interval aerobic resistance training.

	Study period				
	Enrollment	Allocation	Postallocation		Follow-up
Time point	T0	0	T1	T2	T3
Enrollment:					
Eligibility screen	X				
Informed consent	X				
First screening appointment	X				
Second screening appointment	X				
Allocation		X			
Interventions:					
HIART group		←	—	—	→
Control group		←	—	—	→
Assessments:					
Body composition	X			X	X
Blood test	X			X	X
Physical fitness	X			X	X
Physical activity	X			X	X
Physical function	X		X	X	X
Self-reported questionnaires	X		X	X	X
Evaluation questionnaire				X	

Anthropometry and Body Composition

We will assess body composition by a Lunar Prodigy DXA (Lunar Prodigy; GE Medical Systems) and analyze the results with standard software (Lunar enCORE version 16). The regions of interest for regional body composition will be defined using the software provided by the manufacturer. The scanner will be calibrated daily with phantoms for quality assurance. The laboratory coefficients of variation for repeat in vivo scans in adults in our laboratory are 1.8% for total fat mass, 1.8% for percentage fat, and 1.0% for bone-free lean tissue mass. We will measure height with a fixed stadiometer (Harpenden stadiometer; Holtain, Ltd) and weight with an electronic scale (Seca electronic scale; Seca Corp), both with participants wearing light clothing and with no shoes. Waist circumference will be measured at the top of the iliac crest, upper arm circumference will be measured halfway up the upper arm, and thigh circumference will be measured halfway up the upper leg, with nonelastic tape.

Biomarkers

We will measure cortisol, creatinine, C-reactive protein, lipid profile, and hemoglobin by venous blood draw. Blood will be collected at baseline and postintervention. All blood tests will be analyzed by Southern Community Laboratories, Dunedin, New Zealand, using standard procedures. We chose these biomarkers based on previous literature suggesting they are involved in the physiological processes of sarcopenia. A relative increase in cortisol may increase muscle catabolism [27]. Creatinine is a breakdown product of creatine phosphate in muscle and its serum levels are therefore proportional to muscle mass [28]. The literature has demonstrated that inflammatory cytokines (such as C-reactive protein) activate many of the molecular pathways involved in sarcopenia, which could lead

to an imbalance between protein synthesis and catabolism [29]. Cholesterol is an essential component of biological membranes and signaling pathways involved in the adaptation of muscle mass to exercise training [30]. Hemoglobin affects the structure and quality of muscle connective tissue through collagen synthesis [31]. Hemoglobin is a marker of nutritional status and has been found to be low in older individuals with sarcopenia [31].

Physical Fitness

Participants will perform maximal incremental exercise tests on a cycle ergometer (Model E100 P; COSMED) while blood pressure and metabolic variables (Quark Cardiopulmonary exercise test; COSMED) are monitored and measured. During the first exercise tests we will also measure 12-lead ECG. Resting HR and resting blood pressure will be measured in seated position before the test. Metabolic measures refer to the volume and gas concentrations of inspired and expired air. The protocol will start at 50 W and will be increased at a magnitude of 25 or 50 W (individualized for each participant) every 2 minutes until volitional exhaustion. We will determine the O_2max, calculate maximum HR as the highest obtained HR, and calculate the HR reserve as the maximum HR minus resting HR.

Physical Activity

We will measure physical activity (counts per minute) over 7 days by using an accelerometer attached to a waist strap (GT3X+; ActiGraph). Participants will be asked to wear the accelerometer continuously for 24 hours and physical activity will be analyzed after sleep has been identified and removed.

Physical Function

We will measure hand grip strength, gait speed, 30-second sit-to-stand, and quadriceps strength to determine physical function. All physical function measurements will be conducted using standardized encouragement and explanation.

Hand Grip Strength

We will measure grip strength using a Saehan model hydraulic hand dynamometer (MSD Europe bvba). The participant will be asked to remove watches, rings, or bracelets and will be given the dynamometer in their dominant hand seated with their back supported by the backrest. Grip strength will be measured with elbows at their side and their elbows at a 90° angle with thumb placed vertically and their feet flat on the floor. Grip strength will be measured in triplicate for each hand, with a 1-minute rest between each test. We will record an average of the 3 trials to determine grip strength.

Gait Speed

The participant will be asked to walk down a hallway through a 1-m zone for acceleration, a central 5.5-m testing zone, and a 1-m zone for deceleration. The participant will be asked to walk down the testing zone at normal gait speed and as fast as possible without running, and not to slow down before the 5.5-m mark. Normal gait speed and maximal gait speed will be recorded once.

30-Second Sit-to-Stand Test

We will measure lower extremity strength and endurance with the 30-second sit-to-stand test. The participant will be asked to sit in a standardized chair (a 43-cm high chair, without arm rests, placed against the wall) and asked to sit in the middle, back straight, feet approximately hip width apart and placed flat on the floor, with knees 90° flexed. If needed, one foot can be placed slightly in front of the other to help maintain balance. The participant will be asked to stand and sit as many times as possible in 30 seconds keeping their arms crossed against the chest and instructed to fully sit down between each stand. We will record the number of correct sit-to-stands performed in 30 seconds.

Quadriceps Strength

We will measure isokinetic and isometric strength of the quadriceps muscle in both legs using an isokinetic dynamometer (Biodex Corporation). Participants will be seated on the dynamometer with a hip angle of 90° flexion stabilized with thigh and pelvic straps. The chair will be positioned so that the medial condyle of the knee is centered with the axis of the dynamometer with little or no gap behind the knee and the edge of the seat. The lower leg will be secured and the calf pad will be placed 5 cm proximal to the lateral malleolus. The range of motion will be set so as to obtain maximal speed during the isokinetic tests (from 90°of knee flexion to –5° of full knee extension) and at 60° for the isometric tests. Prior to each test, the participants will be given the opportunity to become familiar with the procedures and to warm up, by doing 10 submaximal contractions and 2 maximal contractions. For the test, 6 maximal concentric reciprocal contractions and 3 maximal muscle contractions held for 5 seconds will be completed with a 3-minute rest between.

Questionnaires

We will obtain demographic information (age, sex, education, ethnicity, employment, income) at baseline using the relevant New Zealand census questions. To measure generic health outcomes from the participant's perspective, we will use the 12-item Short-Form Health Survey (SF-12) [32]. To measure exercise self-efficacy, we will use the 18-item Exercise Self-Efficacy Scale (ESES) [33]. We will use the 18-item Physical Activity Enjoyment Scale (PACES) to measure perceived enjoyment of physical activity [34]. To assess lifestyle from a multifactorial perspective, we will use the Lifestyle Appraisal Questionnaire (LAQ) [35]. After the 20-week intervention period, we will measure satisfaction and obtain feedback information from the participants by asking the participants, anonymously, to fill out an evaluation questionnaire.

Termination Criteria

In the event of chest discomfort, failure of HR to increase normally with increased workload, light-headedness, severe fatigue, and shortness of breath, which are all abnormal responses to exercise, we will advise the participant to discontinue that exercise session. If symptoms continue for longer than 24 hours, the participant will be referred to their general practitioner. If symptoms are recurrent or take longer

than 24 hours to resolve, the participant will be withdrawn from the study.

Adherence

Strategies to improve adherence will include group-based participation [36], individualized exercise goals, flexibility in rescheduling to another session online, and the use of reminders. We will monitor participation adherence using attendance checklists. Adherence to the set HR goals will be monitored by recording the participants' HR throughout the exercise sessions using HR monitors (Polar RC3; Polar Electro Oy). Adherence to the home program will be monitored with a self-reported physical activity diary.

Sample Size

Based on a standard deviation of 1.9 kg and an effect size *f* of 0.39 (obtained from previous literature [37]), our study has 95% power using a 2-sided 5% level of significance to detect clinically meaningful differences in lean soft tissue mass of 1.5 kg between the intervention and the control group with 35 participants per group. We will aim to recruit 84 participants (42 per group), which allows for 15% dropout or unusable data.

Statistical Analysis

All analysis will be conducted in Stata version 15 (StataCorp LP) using the principles of intention-to-treat analysis. We will use descriptive statistics to characterize the groups at baseline. The intention-to-treat analysis for this study will include all participants, including those who are not fully compliant and those with missing outcome data. The primary outcome will be the change in total body lean soft tissue mass. Secondary outcomes include changes in physical fitness, muscle strength, physical function, and blood biomarkers. The primary analysis will compare the primary and secondary outcomes resulting from the intervention, using linear mixed models to model outcomes at T1, T2, and T3 adjusted for baseline values. Standard mixed-model diagnostics will be performed. Group differences will be presented in the form of mean differences for continuous outcomes and an odds ratio for binary outcomes, with their associated 95% confidence intervals.

Results

We obtained ethical approval for this study from The University of Otago Human Ethics Committee on December 10, 2018. The project is supported by a University of Otago Research Grant and a Dunedin School of Medicine Dean's Bequest Fund (January 2019 to March 2020). Patient recruitment started on February 11, 2019 and was completed on May 14, 2019. Data collection started on February 25, 2019 and was completed on February 28, 2020. We enrolled 82 participants. Data analysis is underway and we expect to publish results in January 2021.

Discussion

HIART may have substantial benefit, including improving body composition, strength, and fitness, in middle-aged adults with low lean soft tissue mass. HIART is a time-efficient form of exercise, enabling busy middle-aged adults to meet physical activity recommendations while maximizing training results.

This RCT is rigorously designed, allowing conclusions to be formed about the acceptability and effectiveness of a supervised, group-based HIART intervention in middle-aged adults with low lean soft tissue mass. The findings can inform the development of future prevention-focused interventions aimed at counteracting the high prevalence of sarcopenia in the aging population.

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Authors' Contributions

All authors (LV, DLW, LMJ, KMJ) were involved in developing the study design and methods. LV was responsible for writing the first draft of the manuscript. All authors read, critically revised, and approved the final manuscript and met the International Committee of Medical Journal Editors (ICMJE) criteria for authorship.

Conflicts of Interest

None declared.

References

1. Sayer AA, Stewart C, Patel H, Cooper C. The developmental origins of sarcopenia: from epidemiological evidence to underlying mechanisms. J Dev Orig Health Dis 2010 Jun;1(3):150-157. [doi: 10.1017/S2040174410000097] [Medline: 25141783]
2. Grimby G, Saltin B. The ageing muscle. Clin Physiol 1983 Jun;3(3):209-218. [doi: 10.1111/j.1475-097x.1983.tb00704.x] [Medline: 6347501]

3. Bijlsma AY, Meskers CGM, Ling CHY, Narici M, Kurrle SE, Cameron ID, et al. Defining sarcopenia: the impact of different diagnostic criteria on the prevalence of sarcopenia in a large middle aged cohort. Age (Dordr) 2013 Jun;35(3):871-881 [FREE Full text] [doi: 10.1007/s11357-012-9384-z] [Medline: 22314402]
4. Beaudart C, Zaaria M, Pasleau F, Reginster J, Bruyère O. Health outcomes of sarcopenia: a systematic review and meta-analysis. PLoS One 2017;12(1):e0169548 [FREE Full text] [doi: 10.1371/journal.pone.0169548] [Medline: 28095426]
5. Hallal PC, Andersen LB, Bull FC, Guthold R, Haskell W, Ekelund U, Lancet Physical Activity Series Working Group. Global physical activity levels: surveillance progress, pitfalls, and prospects. Lancet 2012 Jul 21;380(9838):247-257. [doi: 10.1016/S0140-6736(12)60646-1] [Medline: 22818937]
6. Marzetti E, Calvani R, Tosato M, Cesari M, Di Bari M, Cherubini A, SPRINTT Consortium. Physical activity and exercise as countermeasures to physical frailty and sarcopenia. Aging Clin Exp Res 2017 Feb;29(1):35-42. [doi: 10.1007/s40520-016-0705-4] [Medline: 28181204]
7. Yoshimura Y, Wakabayashi H, Yamada M, Kim H, Harada A, Arai H. Interventions for treating sarcopenia: a systematic review and meta-analysis of randomized controlled studies. J Am Med Dir Assoc 2017 Jun 01;18(6):553.e1-553.e16. [doi: 10.1016/j.jamda.2017.03.019] [Medline: 28549707]
8. Vlietstra L, Hendrickx W, Waters DL. Exercise interventions in healthy older adults with sarcopenia: a systematic review and meta-analysis. Australas J Ageing 2018 Sep;37(3):169-183. [doi: 10.1111/ajag.12521] [Medline: 29638028]
9. Vikberg S, Sörlén N, Brandén L, Johansson J, Nordström A, Hult A, et al. Effects of resistance training on functional strength and muscle mass in 70-year-old individuals with pre-sarcopenia: a randomized controlled trial. J Am Med Dir Assoc 2019 Jan;20(1):28-34 [FREE Full text] [doi: 10.1016/j.jamda.2018.09.011] [Medline: 30414822]
10. Makizako H, Nakai Y, Tomioka K, Taniguchi Y, Sato N, Wada A, et al. Effects of a multicomponent exercise program in physical function and muscle mass in sarcopenic/pre-sarcopenic adults. J Clin Med 2020 May 08;9(5) [FREE Full text] [doi: 10.3390/jcm9051386] [Medline: 32397192]
11. Maruya K, Asakawa Y, Ishibashi H, Fujita H, Arai T, Yamaguchi H. Effect of a simple and adherent home exercise program on the physical function of community dwelling adults sixty years of age and older with pre-sarcopenia or sarcopenia. J Phys Ther Sci 2016 Nov;28(11):3183-3188 [FREE Full text] [doi: 10.1589/jpts.28.3183] [Medline: 27942146]
12. Greenlee TA, Greene DR, Ward NJ, Reeser GE, Allen CM, Baumgartner NW, et al. Effectiveness of a 16-week high-intensity cardioresistance training program in adults. J Strength Cond Res 2017 Sep;31(9):2528-2541 [FREE Full text] [doi: 10.1519/JSC.0000000000001976] [Medline: 28820847]
13. Kilpatrick MW, Jung ME, Little JP. High-intensity interval training: a review of physiological and psychological responses. ACSM Health Fitn J 2014;18(5):11-16. [doi: 10.1249/fit.0000000000000067]
14. Martland R, Mondelli V, Gaughran F, Stubbs B. Can high-intensity interval training improve physical and mental health outcomes? A meta-review of 33 systematic reviews across the lifespan. J Sports Sci 2020 Feb;38(4):430-469. [doi: 10.1080/02640414.2019.1706829] [Medline: 31889469]
15. Wewege MA, Ahn D, Yu J, Liou K, Keech A. High-intensity interval training for patients with cardiovascular disease-is it safe? A systematic review. J Am Heart Assoc 2018 Nov 06;7(21):e009305. [doi: 10.1161/JAHA.118.009305] [Medline: 30376749]
16. Hannan AL, Hing W, Simas V, Climstein M, Coombes JS, Jayasinghe R, et al. High-intensity interval training versus moderate-intensity continuous training within cardiac rehabilitation: a systematic review and meta-analysis. Open Access J Sports Med 2018;9:1-17 [FREE Full text] [doi: 10.2147/OAJSM.S150596] [Medline: 29416382]
17. De Nardi AT, Tolves T, Lenzi TL, Signori LU, Silva AMVD. High-intensity interval training versus continuous training on physiological and metabolic variables in prediabetes and type 2 diabetes: a meta-analysis. Diabetes Res Clin Pract 2018 Mar;137:149-159. [doi: 10.1016/j.diabres.2017.12.017] [Medline: 29329778]
18. Bartlett DB, Willis LH, Slentz CA, Hoselton A, Kelly L, Huebner JL, et al. Ten weeks of high-intensity interval walk training is associated with reduced disease activity and improved innate immune function in older adults with rheumatoid arthritis: a pilot study. Arthritis Res Ther 2018 Jun 14;20(1):127 [FREE Full text] [doi: 10.1186/s13075-018-1624-x] [Medline: 29898765]
19. Mugele H, Freitag N, Wilhelmi J, Yang Y, Cheng S, Bloch W, et al. High-intensity interval training in the therapy and aftercare of cancer patients: a systematic review with meta-analysis. J Cancer Surviv 2019 Apr;13(2):205-223. [doi: 10.1007/s11764-019-00743-3] [Medline: 30806875]
20. Chrøis KM, Dohlmann TL, Søgaard D, Hansen CV, Dela F, Helge JW, et al. Mitochondrial adaptations to high intensity interval training in older females and males. Eur J Sport Sci 2020 Feb;20(1):135-145. [doi: 10.1080/17461391.2019.1615556] [Medline: 31145037]
21. Leuchtmann AB, Mueller SM, Aguayo D, Petersen JA, Ligon-Auer M, Flück M, et al. Resistance training preserves high-intensity interval training induced improvements in skeletal muscle capillarization of healthy old men: a randomized controlled trial. Sci Rep 2020 Apr 20;10(1):6578 [FREE Full text] [doi: 10.1038/s41598-020-63490-x] [Medline: 32313031]
22. Seldeen KL, Lasky G, Leiker MM, Pang M, Personius KE, Troen BR. High intensity interval training improves physical performance and frailty in aged mice. J Gerontol A Biol Sci Med Sci 2018 Mar 14;73(4):429-437. [doi: 10.1093/gerona/glx120] [Medline: 28633487]

23. Li F, Sun L, Zhu M, Li T, Gao H, Wu D, et al. Beneficial alterations in body composition, physical performance, oxidative stress, inflammatory markers, and adipocytokines induced by long-term high-intensity interval training in an aged rat model. Exp Gerontol 2018 Nov;113:150-162. [doi: 10.1016/j.exger.2018.10.006] [Medline: 30308288]
24. World Health Organization. Global Strategy on Diet, Physical Activity and Health. Physical activity and adults. URL: https://www.who.int/dietphysicalactivity/factsheet_adults/en/ [accessed 2020-08-04]
25. Prado CMM, Siervo M, Mire E, Heymsfield SB, Stephan BCM, Broyles S, et al. A population-based approach to define body-composition phenotypes. Am J Clin Nutr 2014 Jun;99(6):1369-1377. [doi: 10.3945/ajcn.113.078576] [Medline: 24760978]
26. Gillen JB, Percival ME, Skelly LE, Martin BJ, Tan RB, Tarnopolsky MA, et al. Three minutes of all-out intermittent exercise per week increases skeletal muscle oxidative capacity and improves cardiometabolic health. PLoS One 2014;9(11):e111489 [FREE Full text] [doi: 10.1371/journal.pone.0111489] [Medline: 25365337]
27. Yanagita I, Fujihara Y, Kitajima Y, Tajima M, Honda M, Kawajiri T, et al. A high serum cortisol/DHEA-S ratio is a risk factor for sarcopenia in elderly diabetic patients. J Endocr Soc 2019 Apr 01;3(4):801-813 [FREE Full text] [doi: 10.1210/js.2018-00271] [Medline: 30963138]
28. Tosato M, Marzetti E, Cesari M, Savera G, Miller RR, Bernabei R, et al. Measurement of muscle mass in sarcopenia: from imaging to biochemical markers. Aging Clin Exp Res 2017 Feb;29(1):19-27. [doi: 10.1007/s40520-016-0717-0] [Medline: 28176249]
29. Bano G, Trevisan C, Carraro S, Solmi M, Luchini C, Stubbs B, et al. Inflammation and sarcopenia: a systematic review and meta-analysis. Maturitas 2017 Feb;96:10-15. [doi: 10.1016/j.maturitas.2016.11.006] [Medline: 28041587]
30. Riechman SE, Andrews RD, Maclean DA, Sheather S. Statins and dietary and serum cholesterol are associated with increased lean mass following resistance training. J Gerontol A Biol Sci Med Sci 2007 Oct;62(10):1164-1171. [doi: 10.1093/gerona/62.10.1164] [Medline: 17921432]
31. Bani Hassan E, Vogrin S, Hernandez Viña I, Boersma D, Suriyaarachchi P, Duque G. Hemoglobin levels are low in sarcopenic and osteosarcopenic older persons. Calcif Tissue Int 2020 Aug;107(2):135-142. [doi: 10.1007/s00223-020-00706-2] [Medline: 32440760]
32. Ware J, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996 Mar;34(3):220-233. [Medline: 8628042]
33. Bandura A. Self-Efficacy: The Exercise of Control. New York, NY: Freeman & Co; 1997.
34. Mullen SP, Olson EA, Phillips SM, Szabo AN, Wójcicki TR, Mailey EL, et al. Measuring enjoyment of physical activity in older adults: invariance of the physical activity enjoyment scale (paces) across groups and time. Int J Behav Nutr Phys Act 2011 Sep 27;8:103 [FREE Full text] [doi: 10.1186/1479-5868-8-103] [Medline: 21951520]
35. Craig A, Hancock K, Craig M. The lifestyle appraisal questionnaire: a comprehensive assessment of health and stress. Psychol Health 1996 Mar;11(3):331-343. [doi: 10.1080/08870449608400262]
36. Farrance C, Tsofliou F, Clark C. Adherence to community based group exercise interventions for older people: a mixed-methods systematic review. Prev Med 2016 Jun;87:155-166 [FREE Full text] [doi: 10.1016/j.ypmed.2016.02.037] [Medline: 26921655]
37. Peterson MD, Sen A, Gordon PM. Influence of resistance exercise on lean body mass in aging adults: a meta-analysis. Med Sci Sports Exerc 2011 Feb;43(2):249-258 [FREE Full text] [doi: 10.1249/MSS.0b013e3181eb6265] [Medline: 20543750]

Abbreviations

ALMI: appendicular lean soft tissue mass index
DXA: dual energy X-ray absorptiometry
ECG: electrocardiogram
ESES: Exercise Self-Efficacy Scale
HIART: high-intensity interval aerobic resistance training
HIIT: high-intensity interval training
HR: heart rate
LAQ: Lifestyle Appraisal Questionnaire
PACES: Physical Activity Enjoyment Scale
RCT: randomized controlled trial
SF-12: 12-item Short Form Health Survey
O_2max : maximum oxygen consumption

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Protocol

Tobacco-Free Duo Adult-Child Contract for Prevention of Tobacco Use Among Adolescents and Parents: Protocol for a Mixed-Design Evaluation

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Abstract

Background: Universal tobacco-prevention programs targeting youths usually involve significant adults, who are assumed to be important social influences. Commitment not to use tobacco, or to quit use, as a formal contract between an adolescent and a significant adult is a preventive model that has not been widely practiced or explored and has been formally evaluated even less. In this paper, we present the rationale and protocol for the evaluation of the Swedish Tobacco-free Duo program, a multicomponent school-based program the core of which rests on a formal agreement between an adolescent and an adult. The adolescent's commitment mainly concerns avoiding the onset of any tobacco use while the adult commits to support the adolescent in staying tobacco free, being a role model by not using tobacco themselves.

Objective: To assess (1) whether Tobacco-free Duo is superior to an education-only program in preventing smoking onset among adolescents and promoting cessation among their parents, (2) whether exposure to core components (adult-child agreement) entails more positive effects than exposure to other components, (3) the impact of the program on whole school tobacco use, (4) potential negative side effects, and (5) school-level factors related to fidelity of the program's implementation.

Methods: A mixed-design approach was developed. First, a cluster randomized controlled trial was designed with schools randomly assigned to either the comprehensive multicomponent program or its educational component only. Primary outcome at the adolescent level was identified as not having tried tobacco during the 3-year junior high school compulsory grades (12-15 years of age). An intention-to-treat cohort-wise approach and an as-treated approach complemented with a whole school repeated cross-sectional approach was devised as analytical methods of the trial data. Second, an observational study was added in order to compare smoking incidence in the schools participating in the experiment with that of a convenience sample of schools that were not part of the experimental study. Diverse secondary outcomes at both adolescent and adult levels were also included.

Results: The study was approved by the Umeå Regional Ethics Review Board (registration number 2017/255-31) in 2017. Recruitment of schools started in fall 2017 and continued until June 2018. In total, 43 schools were recruited to the experimental study, and 16 schools were recruited to the observational study. Data collection started in the fall 2018, is ongoing, and is planned to be finished in spring 2021.

Conclusions: Methodological, ethical, and practical implications of the evaluation protocol were discussed, especially the advantage of combining several sources of data, to triangulate the study questions. The results of these studies will help revise the agenda of this program as well as those of similar programs.

Trial Registration: International Standard Randomized Controlled Trial Number (ISRCTN) 52858080; https://doi.org/10.1186/ISRCTN52858080

International Registered Report Identifier (IRRID): DERR1-10.2196/21100

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KEYWORDS

tobacco use; prevention; school; social influence; public commitment; cluster randomized trial; observational study

Introduction

Social influences, such as smoking parents, siblings, or friends, are the strongest determinants of smoking initiation in adolescence [1,2]. In practice, one may conceptualize smoking initiation as a socially learned behavior, while the subsequent trajectories leading to escalation or to extinction of smoking behavior are determined by a more complex mixture of reinforcing or weaning factors, including genetics, psychosocial circumstances, and availability of tobacco products [3].

According to Bronfenbrenner's theoretical frame [4], people in close microenvironments are likely to exert the strongest health-related influences (in this case pro or antismoking), at least in early adolescence and during initial episodes. Peers normally exert a direct and proximal influence by creating the context for smoking to occur; in fact, the association of friends or siblings smoking is in many cases stronger than that of parents smoking [5]. Adult influences, on the other end, are conveyed on a broader frame. First, adults may shape opinions and attitudes over developmental years by simply tolerating or not explicitly disapproving of smoking [6]. Smoking behavior among significant adults may further encourage the onset of smoking in adolescence by creating an implicitly favorable norm [7]. Availability of cigarettes with or without permission is high in environments where adults smoke [8], which is an important facilitating factor when purchase is not affordable as it is the case among adolescents, a price sensitive group [9]. Also, the possibility that early exposure to environmental smoking primes the child's brain to the rewarding properties of nicotine has been presented [10].

Importantly, social influence seems to extend to tobacco uses other than smoking, at least in countries where other established forms of tobacco use exist, as is the case in Sweden, where the use of the oral moist tobacco snus is widespread among men [11].

For these reasons. adult influences (and parents' influences, in particular) are usually regarded as an important cue in universal prevention of tobacco use.

Consistent with these observations, youth smoking prevention programs in different settings have often included some degree of parental involvement [12]. Despite promising indications that adding a family component increases the effectiveness of school-based programs, the findings of studies have not been consistent [13]. Some encouraging evidence exists on using public commitment as a strategy for prevention. In a systematic review [14] of school-based smoking prevention programs, there was a significant effect of programs including commitments to not smoke. A community-wide school-based intervention program aimed at preventing adolescent tobacco use, incorporating public commitment activities as one of several components, led to a reduced smoking in those who initiated smoking [15].

A component of public commitment has been successfully included in a variety of public health programs and target groups. For instance, in programs using life skills training to prevent drug use, some positive results have been found when including this component [16]. In a school-based diabetes prevention project, there was a suggestion that a public commitment to a healthy lifestyle was associated with a lower prevalence of obesity at follow-up [17]. Some support has also been found for interventions using public commitment as a strategy in adult smoking cessation, including the use of contracts in general practitioner-led interventions [18].

Concerning smoking prevention in youths, a comprehensive social influence program including a decision-making component was found to be effective in a randomized trial [19] for students aged 13-15 years. An evaluation of a prevention program against substance use and other problem behaviors among adolescents in grade 9 using a contract as a component reported small to moderate differences in substance use between groups based on length of participation in the prevention program; however, limitations in the study design made it difficult to draw firm conclusions [20]. A school-based smoking prevention program called the Smoke Free Class competition was introduced in more than 20 European countries during the years 1997-2009. The program included a commitment to not smoke and prize draws. The program was evaluated by randomized controlled trials in several countries, and a meta-analysis [21] reported that the program seemed to be effective in preventing smoking.

The Swedish program *Tobacco-free Duo* is an example of this category of programs, addressing all forms of tobacco use. Details on the intervention and on its preliminary evaluation have been published [22-24]; however, firm conclusions on favorable effects of the intervention could not be reached due to weak study design or to methodologic shortcomings in these earlier evaluations. The Public Health Agency of Sweden commissioned this evaluation in order to strengthen the evidence base to be incorporated in possible future recommendations.

This commission was translated into the following specific objectives: (1) to assess whether the comprehensive Tobacco-free Duo program is superior to an education-only program in preventing onset of use of cigarettes or other tobacco among adolescents or in fostering smoking cessation among smoking parents, (2) to assess whether the adolescents or parents exposed to the core component of the program (adult-child agreement) refrained from using tobacco to a higher extent than those who were only exposed to other components of the program, (3) to explore the impact of the program on the whole school tobacco use prevalence over time, (4) to understand whether receipt of the program entailed negative side effects on the participating adolescents, and (5) to analyze school-level factors related to fidelity of the program implementation.

A health economic evaluation (cost-effectiveness study) will be conducted alongside the randomized controlled trial, and its corresponding protocol will be the object of a separate publication.

Methods

Intervention

Overview

The Tobacco-free Duo is a complex intervention for the universal prevention of tobacco use developed in Sweden and in use since 1993, starting from the County of Västerbotten in the North of Sweden. From 2007, the intervention has also been adopted in other counties, by request of the regional government or by request of the individual municipalities or schools, therein. About 80 municipalities are known to have implemented the Tobacco-free Duo program [25].

Components

In brief, the program aims to mobilize antitobacco practices and attitudes in adolescents' near environments, with schools as main promoters and arenas for the activities. The recommended starting point is in the sixth or seventh grade of compulsory school (between 12 and 13 years of age), and it encompasses 6 central components that were manualized in this study.

1. The tobacco-free pair (Duo) core component that is the origin of the program's name consists of an agreement between an adolescent and a significant adult (at least 18 years old) elected as partner by the adolescents. The pair agrees to remain tobacco free during the following 3 years, at least, until the index adolescent leaves the compulsory school (about 15 years of age). The written agreement is signed by both partners, possibly during a public event in school, strengthening the mutual commitment. However, a pair can be formed anytime during the school year.
2. Student information is given by a member of the school staff who informs the student in the sixth or seventh grade about the school choice to adopt the program, briefly discusses tobacco control issues, and actively encourages participation of the adolescents.
3. Parent information is given during an ordinary parent meeting at school where they are given access to information and materials explaining their role in tobacco prevention and how they can actively support their children in their commitment.
4. As an incentive to participate, all adolescents signing a contract will receive a membership card that entitles them to some fringe benefits in local shops or leisure-time activities.
5. At the end of each school year, the pairs disclose and confirm their tobacco-free status. The disclosure entitles the index adolescent to participate in a lottery taking place just before the summer break.
6. Interactive classroom education is conducted by trained school personnel in all classes during grades 6 (or 7) to 9. This education consists of age-specific information and practical exercises (eg, how to identify and resist social influences). For the purpose of this evaluation, the educational part was further structured and manualized before training personnel.

Effectiveness Evaluation

The evaluation protocol has been developed in order to address the objectives of the study through the following primary and secondary questions, formulated according to a PICO (population, intervention, comparator, outcome) framework [26]. It should be observed that, for feasibility purposes (due to educational block organizations in Swedish schools where many children change school between sixth and seventh grade), in this evaluation, the start of the intervention was set in the seventh grade (12- to 13-year old adolescents).

Study Design

The evaluation questions will be addressed through a mixed-design approach, where experimental and nonexperimental designs will be combined.

Experimental Design

A parallel cluster randomized controlled experiment will be conducted with schools as units of randomization and individual students as unit of analysis. A superiority approach will be employed for hypothesis testing (ie, the null hypothesis to be rejected will be that the Tobacco-free Duo comprehensive intervention is either inferior or equivalent to the education-only component). Through this design, questions 1 to 5 will be addressed (Tables 1 and 2). The trial was registered (ISRCTN 52858080) on January 4, 2019 (ie, after enrollment of the first participant but prior to baseline assessments being completed).

Table 1. Evaluation questions.

Objective–question	Formal question definition
Objective 1	
Questions 1 and 3	Is the probability of having never smoked (question 1) or used any tobacco product[a] (question 3) at the end of follow-up in the ninth grade higher for seventh-grade adolescents in schools assigned to the full program (Tobacco-free Duo components 1-6) compared to that of adolescents in schools assigned to conduct only the educational component (component 6)?
Questions 2 and 4	Is the probability of never having progressed to regular (weekly during at least 3 consecutive months) use (question 2: smoking cigarettes; question 4: any tobacco product) by grade 9 higher for adolescents in Tobacco-free Duo schools than for those in education-only schools?
Objective 2	
Question 5	Is the probability of having refrained from using cigarettes or any tobacco by the end of follow-up higher among adolescents and parents who smoke who signed the formal agreement to become a tobacco-free pair (core component) compared to those who only received other components?
Question 6	Is the proportion of sustained quitters (no smoking in the past 30 days) among parents who smoke before the program's start higher when the index child attended a Tobacco-free Duo school compared to an education-only school, at the end of the compulsory grades?
Objective 3	
Question 7	Is the total prevalence of never smokers among students in the grades 7 to 9 declining more slowly over 3 years in Tobacco-free Duo schools compared to education-only schools or schools delivering their usual antismoking programs (external reference group schools)?
Objective 4	
Question 8	Are there undesirable side effects of the full-component intervention, such as: exclusion or frequent dropout from child-adult contracts of adolescents in families of low socioeconomic status; or worsening of perceived mental or general health among participants receiving the Tobacco-free Duo intervention compared to those only receiving the educational component?

[a]The term *any tobacco product* encompasses the use of Swedish smokeless tobacco snus and of e-cigarettes.

Table 2. PICO questions addressed in the experimental (cluster randomized trial) and nonexperimental (observational) studies for the effectiveness evaluation of Tobacco-free Duo.

Question	PICO[a] description
Experimental	
Superiority of Tobacco-free Duo comprehensive intervention vs education only in preventing smoking/tobacco onset	
Population	Adolescents 13 years old at baseline with valid parental consent—average follow-up 38 months
Intervention	Tobacco-free Duo 6 components
Comparator	Educational component of Tobacco-free Duo
Outcome 1	Never smoked (negative answer to the question: Did you ever try smoking, even a few puffs?)
Outcome 2	Never smoked regularly (negative answer to the question: Did you ever smoke weekly for 3 or more months in a row?)
Outcome 3	Never used any tobacco (negative answer to both questions: Did you ever try smoking, even a few puffs? Did you try smokeless tobacco?)
Outcome 4	Never used any tobacco regularly (negative answer to both questions: Did you ever smoke weekly for 3 or more months in a row? Did you ever use snus weekly for 3 or more months in a row?)
Superiority of Tobacco-free Duo comprehensive intervention vs education only in determining smoking cessation among participants' parents	
Population	Parents of adolescents participating in the trial who reported smoking at baseline
Intervention	Signing an adult-child contract
Comparator	Receiving other intervention components, no contract
Outcome	No past 30-day smoking at follow-up
Nonexperimental	
Effect of adhering to the core component *child-adult contract*	
Population 1	Adolescents participating the longitudinal assessment of the cluster randomized trial
Intervention	Signing an adult-child contract (as treated)
Comparator	Receiving other intervention components, no contract (as treated)
Outcome	Never smoked or used tobacco at follow-up in ninth grade
Population 2	Parents of adolescents participating the longitudinal assessment of the cluster randomized trial, baseline smokers
Intervention	Signing an adult-child contract
Comparator	Receiving other intervention components, no contract
Outcome	No past 30-day smoking at follow-up
Decline in school prevalence of never smokers	
Population	Students registered in the grades 7-9 of the schools participating in the experimental study and in the schools serving as external reference during three consecutive years
Intervention 1	Tobacco-free Duo 6 components (as treated)
Intervention 2	Educational component of Tobacco-free Duo only (as treated)
Comparator	Usual education or health promotion
Outcome	Average point prevalence of never smoking in spring term of each school year

[a]PICO: population, intervention, comparator, outcome.

Nonexperimental (Observational) Design

Two different comparisons will be established. In the first comparison (addressing objective 2 question 6) an as-treated analysis of the trial data will be conducted where individual students assigned to the Tobacco-free Duo intervention and signing a child-adult contract will be contrasted to students receiving other Tobacco-free Duo components but not signing the contract. In the second comparison (addressing objective 3 question 7), all students attending schools in grades 7 to 9 in both experimental groups will be contrasted to students in a convenience sample of schools in the same broad catchment areas where the experiment takes place (an external reference group). Schools in this external reference group will be those willing to participate in the survey data collection but not in the experimental study. Therefore, they will represent the subset of

schools in the target areas that will probably not be willing to adopt the program once released for dissemination. In Table 2, a summary is presented of the relevant comparisons established with an observational design.

Intervention Implementation and Fidelity (Objective 5)

As a complement to the evaluation of effectiveness, we plan to monitor and describe the implementation of the Tobacco-free Duo intervention, in particular the average proportion of schools and classes delivering the intervention components as intended; the observed versus expected frequency of delivery of each of the 6 components and their range; and the characteristics of the schools not conducting or completing the program as intended and alleged reasons for this failure.

Adolescents' Experiences and Reported Side Effects of the Intervention (Objective 4)

We plan to identify negative outcomes of the intervention, particularly those connected with the administration of the core component agreement between an adult and a child. We will use the conceptual framework proposed by Lorenc and collaborators [27] to identify adverse effects in 2 domains: psychological side effects and equity side effects. Specifically, we will use adolescent questionnaire data to explore unequal distribution of application of the core components across socioeconomic status and composition of the index families (equity aspect). Reasons for not signing a contract or changing contract partner, satisfaction with the partnership, and perception of the partner's support will also be explored (psychological aspects), both through questionnaire data and through in-depth interviews with adolescents. To this end, a convenience sample of both contract holders and nonholders will be enrolled.

Study Procedures

Invitation and Selection of Schools

All schools located in 11 regions of central and south Sweden encompassing the higher block grades (7 to 9) will be invited to participate in the study through a letter addressed to the school's headmaster at the end of the school year preceding the conduction of the intervention. We estimate this underlying source sample as about 600 schools. Schools will be eligible if they have at least 2 classes in the target grades and if they did not or do not plan to adopt the Tobacco-free Duo program until the evaluation is completed. The eligibility criteria will be assessed among respondents willing to participate through a questionnaire on school organization and characteristics sent concurrently with the invitation.

The final selection will rest on a formal agreement issued by the school headmaster to be randomly assigned to the intervention or comparator condition, to engage the school personnel in the training for and in the delivery of the intervention, and to facilitate the data collection. We estimate that at least 40 schools will be recruited into the experimental study.

Schools not willing to be randomized will be asked if they are willing to participate as part of the external reference group (ie, to deliver and report on the usual antismoking program if any and to collect data from students in repeated anonymous cross-sectional surveys).

Randomization

After recruitment, the consenting schools will be simultaneously randomly assigned to either the full program (Tobacco-free Duo) or to the education-only component of the same program. The random assignment will be performed by a statistician based at the steering group through a computer-generated series of random numbers, paired to each school, after stratification into publicly and privately run schools.

The results of the randomization will not be disclosed to the participating schools until the beginning of the school year during which the intervention will be delivered. Because of the nature of the interventions, blinding of participants will not be possible.

Identification and Enrollment in the Trial of Individual Students

Based on the school rosters, all students attending the seventh grade in the beginning of the school year will potentially be eligible for participation in the study. Besides the information delivered in class and school (see components 2 and 3), an individual invitation letter is sent to students' home addresses, and individual parental consent will be sought with an opt-in procedure. In the invitation, it will be underlined that it will be possible to withdraw the assumed consent any time, both from the parents' side and from the student's side. Also, it will be clarified that the consent to participation concerns the baseline and follow-up collection of information to be entered in a register with personal identifiers but not the receipt of the intervention. The latter is decided at the school level, therefore not submitted to any individual consent, similar to any school-based activity.

Based on previous experience, we foresee that we will be able to enroll approximately 85% of the eligible students in the seventh grade. All recruitment procedures will be conducted by an executive team composed of research officers under the guidance of the principal investigators.

Training of School Personnel

School staff involved in the study are offered an annual meeting with education, training, and networking in their respective experimental group (Tobacco-free Duo school or education-only school). The content of the meeting is diversified according to the assigned intervention, with a common part regarding instructions for data collection and the educational intervention component. The aim is to gradually increase the personnel's knowledge, to give an opportunity for exchange of experiences during the project period, and assure quality of data collection over time. The meetings are scheduled to be held annually before the fall term start, separately for education-only and Tobacco-free Duo schools.

Delivery of the Interventions

The school leadership at each participating school nominates a contact person and constitutes an operative team responsible for the implementation of the assigned intervention. The contact person will be responsible for contacts with the research group

and for convening the school's operative team. This includes the contact person, one or more persons from the student health care team, and one or more teachers in grades 7-9. Together they are responsible for the implementation of the assigned intervention components.

Data Collection and Management

At both baseline and follow-up, information on outcome and predictor variables will be collected at 2 levels.

School-level information will encompass compositional and organization measures such as number of registered students and staff, staff average qualification, proportion of students with parents with lower than high school education, proportion of students with parents born outside Sweden, public or private management, and prior and current health promotion initiatives or preventive programs. Structured checklists and questionnaire forms will be developed.

In schools participating in the experimental part of the study, information will be continuously collected about the actual implementation of the intervention components and staff effort dedicated to them. To this end, a structured web-based form will be used.

Individual-level information will be gathered from individual students in Tobacco-free Duo schools, education-only schools, and reference group schools; from parents of students in Tobacco-free Duo and education-only schools; and adults in Tobacco-free Duo schools signing the contract with individual students, when not coinciding with one parent. All information will be collected with self-completed structured questionnaires with different content and administered with different procedures as shown in Table 3. All questionnaires will be based on sets of questions that have been previously used in Swedish surveys or longitudinal studies of tobacco use in youths. Individual participants in the experimental study will be traced through school records, even in cases of change of school or residence address. In fact, during compulsory education, changes of schools are registered at both ends of the transition (former and new school). Those absent during data collection days will be reached at their latest registered residence addresses.

Table 3. Data collection instruments, information, and procedures.

Population	Instrument and main domains	Administration	Identifier	Time-points
Participating students in schools randomized to Tobacco-free Duo or education only	Paper questionnaire, with information on: Cigarette and snus use (any, current, frequency, quitting) Tobacco use among friends and family members Received education, knowledge and attitudes toward tobacco Recent and current use of alcohol Ever use of illicit drugs General health, physical activity, and sedentary time Perceptions about the contract (if appropriate)	Self-administered in the classroom	Unique study code matched to identity information	Baseline: fall term of school year 1- grade 7 Follow-up 1: end of school year, grade 7 Follow-up 2: end of school year 2, grade 8 Follow-up 3: end of school year 3. grade 9
Guardians of the participating students above	Paper questionnaire, with information on: Sociodemographics Relation with the index child and perception of risks with tobacco use Own tobacco and alcohol use	Self-administered at home	Same code as the index child above	Same time points as above
Adults in Tobacco-free Duo pairs	Paper questionnaire, with information on: Own use of cigarette and snus Perception of own role in the intervention	Self-administered at home	Same code as the index child above	Anytime a contract is signed
All students registered in Tobacco-free Duo schools, education-only schools and reference group schools in grades 7-9	Paper questionnaire, with information on: Ever, regular and recent use of cigarette and snus	Self-administered in the classroom	No identifier (anonymous survey)	Cross-sectional surveys at the end of school year 1, 2 and 3

Figure 1 displays a scheme of the participants' enrollment and assessments time-points for the experimental part of the study.

Individual data from questionnaires will be optically scanned, and the corresponding electronic files will be stored in a password-protected section of the server at the Department of Global Public Health, Karolinska Institutet. In order to preserve strict confidentiality, this data will be stored without personal identifiers, substituted by a study code unique to each participant. Personal identifiers will be kept in a separate section of the same server, only accessible to 2 members of the study team, responsible for data linkage and follow-up procedures, respectively. Ten years after the study start the personal

identifiers will be removed and all information will be kept identified only through the study code.

Figure 1. Schedule of enrollment, interventions, and assessments related to the experimental study (cluster randomized trial).

	Enrolment (schools)	Allocation (schools)	Enrolment (students and families)	Post-allocation			
TIMEPOINT	*February-May 2018*	*September 2018*	*September-October 2018*	*October 2018-April 2019*	*May 2019 (f1)*	*May 2020 (f2)*	*May 2021 (f3)*
ENROLMENT:							
Eligibility screen	X		X				
Informed consent	X		X				
Allocation		X	NR				
INTERVENTIONS:							
T-Duo 6 components				←	—	→	
Reference: teaching only				←	—	→	
ASSESSMENTS (see also table 2):							
Socio-demographic/structural	X		X				
Outcome variables: ever and current tobacco use			X		X	X	X
Other individual variables			X		X	X	X
Intervention monitoring				X	X	X	X

Statistical Methods

Estimation of Sample Size for the Experimental Study

We estimated that an optimal sample of 3000 students (about 40 schools) should be recruited in order to detect as statistically significant at the 5% level a risk ratio intervention to control of 1.10 based on the primary outcome (never smoker in the ninth grade). The estimation is based on the following assumptions: desired power 80% or higher; design effect due to the cluster design 1.98, an average cluster size of 50, and an intraclass correlation coefficient of 0.02; prevalence of the outcome in the minimal intervention (control) group 0.70; eligible students at baseline (never smoke) 92%; attrition between seventh and ninth grade 20%; and ratio intervention to control 1:1.

Data Analysis

Data from the trial will be analyzed primarily according to an intention-to-treat approach, preserving the random assignment [28]. Missing outcome information because of attrition at follow-up will be addressed by means of sensitivity analyses including last observation carried forward; best- and worst-case scenario, assuming missing answers as representing either the best or the worst outcome; and multiple imputation if a missing at random assumption for the missing data will not be dismissed [29].

Secondary analyses will be conducted per protocol, thus including only students in schools that adhered to at least 80% of the whole assigned intervention. Furthermore, an as-treated analysis will be conducted, comparing the outcome among students exposed to different components and intensities of the intervention, in particular the adoption of the core component *child-adult agreement* (research question 6). These approaches disregard randomization, therefore they are prone to producing biased estimates of the effect unless adjusted for most of the potential confounders [30]. However, they may be useful in order to assess the consistency between an expected effect and the intervention's theoretical rationale [30] and in order to gain insights on the reasons for not detecting the estimated effect [31].

Finally, we will be able to compare the prevalence trends across 3 school years as well as the final prevalence at the end of follow-up between schools participating in the experimental study and schools in the external reference group, carrying on usual health education. This will enable us to estimate the potential impact of the intervention when released.

Ethics and Dissemination

Ethics Approval and Consent to Participate

The study was approved by the Regional Ethics Review Board, Umeå (registration number 2017/255-31). Participant schools and individuals were required to give explicit informed consent to data collection, analysis, and reporting prior to inclusion in the study. Written and verbal operator-recorded consent has been obtained from parents or guardians of participating minors. The procedure approved by the Ethic Review Board included verbal and even opt-out consent.

Coordination of the Study, Roles, and Responsibilities

The several study components described in this protocol will be jointly coordinated by Umeå University (principal

investigator: MN) and Karolinska Institutet (principal investigator: MRG). A steering group based at Umeå University will be responsible of all decisions concerning the scientific integrity of the protocol, amendments to the protocol, and the consequent operative procedures, including data monitoring and the decision to terminate the study. Besides the principal investigators, the group will include a researcher in charge of the economic evaluation, a statistician and data manager, and a senior research officer coordinating the field activities.

Twice a year, the steering group will report on the conduct of the trial to the funder (Public Health Agency of Sweden), and will agree on a plan for the dissemination of the results of the study besides the freedom of scientific publication in peer-reviewed journals. The dissemination plan will include interim news on the funder's website, newsletters to participant schools and students, public lectures and educational occasions, and press-releases in relevant cases.

A data share policy will be also developed and maintained by the steering committee. This usually entails a formal written agreement with the requesting investigators and agencies to commit themselves to the same confidentiality levels as the leader institution.

Results

Recruitment of schools started in the fall of 2017 and continued until June 2018. In total, 43 schools were recruited to the experimental study, and 16 schools were recruited to the observational study. Data collection started in the fall 2018 and is ongoing. The last round of data collection is planned for the spring 2021. Data analysis of baseline characteristics is due to commence, and first results are expected at the end of 2020.

Discussion

This study protocol, for the evaluation of a complex intervention for the universal prevention of tobacco use initiation among early adolescents, proposes a mixed methods approach, combining the reciprocal strengths of a randomized experiment and of observational studies, as well as primary and secondary analyses of both study designs.

The protocol has several strengths, compared to similar studies. First, it aligns with the current increasing consensus on the importance of mixed methods [32] and of triangulation approaches in accruing robust evidence in the evaluation of interventions [33-35]. Two aspects of community trials call for triangulation approaches. On the one side, experiments establish the effect of being randomized to specific conditions, which in pragmatic trials do not coincide necessarily with the receipt of the intervention [31]. By conducting an as-treated analysis [30] according to the actual implementation of and adherence to the intervention, we aim to triangulate the question of effectiveness of Tobacco-free Duo program. By comparing groups no longer randomly assigned to the levels of the intervention, this analysis will have to take bias from confounding into account.

On the other side, participants in an experiment (be they organizations or individuals) constitute an imperfect representation of the underlying populations on which the inference should be drawn, because of the numerous selection steps involved in the conduction of an experiment [36]. In this study, we plan to include a comparison group that comprises schools that agreed to participate in annual surveys among all students in the 3 final compulsory grades but did not agree to be randomized to either experimental group. These schools are likely to well-represent the majority of Swedish schools (ie, the subgroup consisting of those that would not adopt the intervention if offered it at the scaling-up stage). By comparing the development over time of tobacco use in these schools with that of schools randomized to the minimal or comprehensive intervention (across a set of school-level characteristics), we aim to infer the added effect of the intervention on decline in tobacco uptake. For instance, if the prevalence of lifetime smoking or tobacco use similarly declines in reference group schools as in the randomized ones, we may project that the impact of a large and intensive dissemination of the intervention (even if effective in the randomized comparison) would be minimal.

Furthermore, we propose the use of qualitative methods and of process data in order to achieve 2 additional objectives. The first objective to be pursued is a deeper understanding of how the conduction of the intervention may differ between school organization characteristics. This knowledge is important in order to judge cluster-level confounding in nonrandomized studies [37]. An additional advantage of such a piece of knowledge would be the possibility to make projections of the potential benefits deriving from the application of the method to large communities with a known distribution of the studied characteristics.

The second objective is to study the occurrence and the nature of undesirable side effects connected with the intervention when delivered as intended. While it is recognized that such effects are of importance in the study of medical or psychological treatments, much less attention has been devoted to methods for studying them in the domain of preventive interventions. One of the reasons behind this failure is the need to carefully conceptualize expected adverse outcomes in a logic framework (one cannot study all kind of potential outcomes). According to the framework presented by Lorenc and collaborators [27], we will focus on potential adverse effects connected with the core component of the intervention (ie, the adult-child agreement) in terms of psychological and equity adverse effects. Children not able to be supported by an adult may be particularly vulnerable for reasons that may or may not be connected to the target behavior. The publicity around the contract among peers and the presence of fringe benefits for those complying may increase the segregation of these psychosocial risks. Also, children whose adult partners "infringe" the agreement by starting or relapsing into smoking may experience a profound disappointment and loss of trust that undermines the relation with a significant other.

The third strength of this study protocol rests in the choice of a standardized comparison group in the randomized controlled trial design. Several community trials employ comparator conditions that are largely opportunistic (ie, rely upon the concept of usual conditions). While undoubtedly pragmatic,

this approach may be misleading at the stage of judging on causal effects deriving from the application of an intervention that is the explicit scope of a randomized controlled trial. In fact, while the alternative intervention under investigation is often quite standardized, usual conditions are not, even if in a certain context (for instance, in a given school system), there may be some recurrent features. To clump together different conditions without any knowledge of their potential effects or even of their content may lead to biased results in any direction [38]. It is purported that the advantage of usual conditions would be to represent the background reality of which the actual participants would be a valid representation [37]. Anyone who has conducted experimental studies is aware that this is far from being true, rather the opposite. Participants in studies (be they experimental or not) are usually a nonrepresentative sample of the background populations (individuals or organizations), both because of the application of explicit inclusion and exclusion criteria and because of self-selection.

When the Tobacco-free Duo program started in the early 1990s, there was a limited amount of research on decision support and public commitments as components of public health interventions; the latter was mainly investigated among adults [18]. Since then, there have been some advancements in knowledge regarding intervention models including decision support and public commitment among young people, but this knowledge must still be regarded as insufficient. The proposed study will, therefore, add substantially to the empirical evidence in this regard.

Acknowledgments

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Authors' Contributions

MRG and MN designed the study. MN was responsible for the standardization of the intervention, acquired the Ethic Board’s permission, and was responsible for the trial protocol’s registration. All authors developed the study instruments and procedures. MRG drafted the article and MN and A-MP-B gave important intellectual contribution to the rationale and discussion of the study. All authors have read and approved the manuscript.

Conflicts of Interest

None declared.

References

1. McNeill AD, Jarvis MJ, Stapleton JA, Russell MA, Eiser JR, Gammage P, et al. Prospective study of factors predicting uptake of smoking in adolescents. J Epidemiol Community Health 1989 Mar 01;43(1):72-78. [doi: 10.1136/jech.43.1.72] [Medline: 2592895]
2. Leonardi-Bee J, Jere ML, Britton J. Exposure to parental and sibling smoking and the risk of smoking uptake in childhood and adolescence: a systematic review and meta-analysis. Thorax 2011 Oct 15;66(10):847-855. [doi: 10.1136/thx.2010.153379] [Medline: 21325144]
3. Brynin M. Smoking behaviour: predisposition or adaptation? J Adolesc 1999 Oct;22(5):635-646. [doi: 10.1006/jado.1999.0259] [Medline: 10527535]
4. Bronfenbrenner U. Ecological models of human development. In: Husten T, Postlethwaite TN, editors. International Encyclopedia of Education 2nd ed. New York: Elsevier Science; 1994:E-7.
5. Sargent JD, DiFranza JR. Tobacco control for clinicians who treat adolescents. CA Cancer J Clin 2003 Mar 01;53(2):102-123. [doi: 10.3322/canjclin.53.2.102] [Medline: 12691267]
6. Vitória PD, Salgueiro M, Silva S, De Vries H. The impact of social influence on adolescent intention to smoke: combining types and referents of influence. Br J Health Psychol 2009 Nov;14(Pt 4):681-699. [doi: 10.1348/135910709X421341] [Medline: 19288976]
7. Scalici F, Schulz PJ. Parents' and peers' normative influence on adolescents' smoking: results from a Swiss-Italian sample of middle schools students. Subst Abuse Treat Prev Policy 2017 Jan 21;12(1):5 [FREE Full text] [doi: 10.1186/s13011-017-0089-2] [Medline: 28109189]
8. Doubeni CA, Li W, Fouayzi H, DiFranza JR. Perceived accessibility of cigarettes among youth: a prospective cohort study. Am J Prev Med 2009 Mar;36(3):239-242. [doi: 10.1016/j.amepre.2008.11.006] [Medline: 19162433]
9. Preventing tobacco use among youth and young adults. a report of the surgeon general. In: Centers for Disease Control and Prevention. Atlanta, GA: U.S. Department of Health and Human Services; 2012.

10. Anthonisen N. A new childhood pathway for transmission of an increased likelihood of smoking? Canadian Medical Association Journal 2005 Aug 16;173(4):382-383. [doi: 10.1503/cmaj.050704]
11. Rosendahl K, Galanti M, Gilljam H, Ahlbom A. Smoking mothers and snuffing fathers: behavioural influences on youth tobacco use in a Swedish cohort. Tob Control 2003 Mar;12(1):74-78. [doi: 10.1136/tc.12.1.74] [Medline: 12612366]
12. Sowden A, Arblaster L, Stead L. Community interventions for preventing smoking in young people. Cochrane Database Syst Rev 2003(1):CD001291. [doi: 10.1002/14651858.CD001291] [Medline: 12535406]
13. Thomas R, Baker P, Thomas B, Lorenzetti D. Family-based programmes for preventing smoking by children and adolescents. Cochrane Database Syst Rev 2015 Feb 27(2):CD004493 [FREE Full text] [doi: 10.1002/14651858.CD004493.pub3] [Medline: 25720328]
14. Flay BR. School-based smoking prevention programs with the promise of long-term effects. Tob Induc Dis 2009 Mar 26;5(1):6 [FREE Full text] [doi: 10.1186/1617-9625-5-6] [Medline: 19323826]
15. Biglan A, Ary D, Smolkowski K, Duncan T, Black C. A randomised controlled trial of a community intervention to prevent adolescent tobacco use. Tob Control 2000 Mar;9(1):24-32. [doi: 10.1136/tc.9.1.24] [Medline: 10691755]
16. Huang C, Chien L, Cheng C, Guo J. Integrating life skills into a theory-based drug-use prevention program: effectiveness among junior high students in Taiwan. J Sch Health 2012 Jul;82(7):328-335. [doi: 10.1111/j.1746-1561.2012.00706.x] [Medline: 22671949]
17. DeBar LL, Schneider M, Drews KL, Ford EG, Stadler DD, Moe EL, HEALTHY study group. Student public commitment in a school-based diabetes prevention project: impact on physical health and health behavior. BMC Public Health 2011 Sep 20;11:711 [FREE Full text] [doi: 10.1186/1471-2458-11-711] [Medline: 21933431]
18. Slama K, Redman S, Perkins J, Reid AL, Sanson-Fisher RW. The effectiveness of two smoking cessation programmes for use in general practice: a randomised clinical trial. BMJ 1990 Jun 30;300(6741):1707-1709 [FREE Full text] [doi: 10.1136/bmj.300.6741.1707] [Medline: 2202445]
19. Dijkstra M, Mesters I, De Vries H, van Breukelen G, Parcel G. Effectiveness of a social influence approach and boosters to smoking prevention. Health Educ Res 1999 Dec;14(6):791-802. [doi: 10.1093/her/14.6.791] [Medline: 10585386]
20. Bortes C, Geidne S, Eriksson C. Evaluating the effectiveness of the SMART contract-signing strategy in reducing the growth of Swedish Adolescents' substance use and problem behaviors. BMC Public Health 2016 Jun 22;16:519 [FREE Full text] [doi: 10.1186/s12889-016-3131-9] [Medline: 27333865]
21. Isensee B, Hanewinkel R. Meta-analysis on the effects of the smoke-free class competition on smoking prevention in adolescents. Eur Addict Res 2012;18(3):110-115. [doi: 10.1159/000335085] [Medline: 22285973]
22. Nilsson M, Stenlund H, Bergström E, Weinehall L, Janlert U. It takes two: reducing adolescent smoking uptake through sustainable adolescent-adult partnership. J Adolesc Health 2006 Dec;39(6):880-886. [doi: 10.1016/j.jadohealth.2006.07.004] [Medline: 17116519]
23. Nilsson M, Stenlund H, Weinehall L, Bergström E, Janlert U. "I would do anything for my child, even quit tobacco": bonus effects from an intervention that targets adolescent tobacco use. Scand J Psychol 2009 Aug;50(4):341-345. [doi: 10.1111/j.1467-9450.2009.00716.x] [Medline: 19364395]
24. Hedman L, Andersson M, Stridsman C, Rönmark E. Evaluation of a tobacco prevention programme among teenagers in Sweden. BMJ Open 2015 May 14;5(5):e007673. [doi: 10.1136/bmjopen-2015-007673] [Medline: 25976765]
25. Tobacco Free Duo. Tobacco Free. URL: https://tobaksfri.se/ [accessed 2020-10-11]
26. Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. J Clin Epidemiol 2011 Apr;64(4):395-400. [doi: 10.1016/j.jclinepi.2010.09.012] [Medline: 21194891]
27. Lorenc T, Oliver K. Adverse effects of public health interventions: a conceptual framework. J Epidemiol Community Health 2014 Mar;68(3):288-290. [doi: 10.1136/jech-2013-203118] [Medline: 24336237]
28. Lee YJ, Ellenberg JH, Hirtz DG, Nelson KB. Analysis of clinical trials by treatment actually received: is it really an option? Stat Med 1991 Oct;10(10):1595-1605. [doi: 10.1002/sim.4780101011] [Medline: 1947515]
29. Molenberghs G. Editorial: What to do with missing data? J Royal Statistical Soc A 2007 Oct;170(4):861-863. [doi: 10.1111/j.1467-985x.2007.00504.x]
30. Hernán MA, Hernández-Díaz S. Beyond the intention-to-treat in comparative effectiveness research. Clin Trials 2012 Feb;9(1):48-55 [FREE Full text] [doi: 10.1177/1740774511420743] [Medline: 21948059]
31. Agbla SC, DiazOrdaz K. Reporting non-adherence in cluster randomised trials: A systematic review. Clin Trials 2018 Jun;15(3):294-304 [FREE Full text] [doi: 10.1177/1740774518761666] [Medline: 29608096]
32. de Jong MAJG, Wagemakers A, Koelen MA. Study protocol: evaluation of a community health promotion program in a socioeconomically deprived city district in the Netherlands using mixed methods and guided by action research. BMC Public Health 2019 Jan 16;19(1):72 [FREE Full text] [doi: 10.1186/s12889-019-6389-x] [Medline: 30651093]
33. Lawlor DA, Tilling K, Davey Smith G. Triangulation in aetiological epidemiology. Int J Epidemiol 2016 Dec 01;45(6):1866-1886 [FREE Full text] [doi: 10.1093/ije/dyw314] [Medline: 28108528]
34. Munafò MR, Davey Smith G. Robust research needs many lines of evidence. Nature 2018 Jan 25;553(7689):399-401. [doi: 10.1038/d41586-018-01023-3] [Medline: 29368721]

35. Benn CS, Fisker AB, Rieckmann A, Jensen AKG, Aaby P. How to evaluate potential non-specific effects of vaccines: the quest for randomized trials or time for triangulation? Expert Rev Vaccines 2018 May;17(5):411-420. [doi: 10.1080/14760584.2018.1471987] [Medline: 29715057]
36. Dahabreh IJ, Hernán MA. Extending inferences from a randomized trial to a target population. Eur J Epidemiol 2019 Aug;34(8):719-722. [doi: 10.1007/s10654-019-00533-2] [Medline: 31218483]
37. Brumback BA, Dailey AB, He Z, Brumback LC, Livingston MD. Efforts to adjust for confounding by neighborhood using complex survey data. Stat Med 2010 Aug 15;29(18):1890-1899. [doi: 10.1002/sim.3946] [Medline: 20680982]
38. Developing a Protocol for Observational Comparative Effectiveness Research: A User's Guide. In: Agency for Health Care Research and Quality Publication No. 12(13)-EHC099. Rockville, MD: Government Printing Office; 2013.

Abbreviations

PICO: population, intervention, comparator, outcome

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Protocol

Coping Skills Mobile App to Support the Emotional Well-Being of Young People During the COVID-19 Pandemic: Protocol for a Mixed Methods Study

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Abstract

Background: The COVID-19 pandemic is likely to increase anxiety and distress in young people worldwide. It is important to prioritize mental health during crisis events to mitigate the negative and often long-term effects of the crises on young people, families, and society. Mental health and well-being apps represent a scalable approach for improving psychological outcomes in young people and have potential to improve the equity of service access.

Objective: The Whitu: 7 Ways in 7 Days well-being app was recently developed by our group to address the urgent need for innovative approaches to reach young New Zealanders who are struggling to cope with the COVID-19 pandemic. The aim of this study is twofold: to evaluate the acceptability of the prototype app and to examine the effectiveness of the refined app at improving mental and emotional well-being and reducing depression, anxiety, and stress in young people in New Zealand.

Methods: A two-phase mixed methods study will be undertaken to achieve these aims. During the first phase, 20 young people aged 16-30 years (including those of Māori and Pacific ethnicity) will participate in a qualitative study to help refine the prototype app. During the second phase, 90 young people aged 16-30 years will participate in a randomized waitlist-controlled trial (RCT) to evaluate the efficacy of the refined Whitu app at 4 weeks and 3 months after baseline. Outcomes will be evaluated using validated web-based questionnaires at baseline, 4 weeks, and 3 months.

Results: The study received ethics approval in May 2020, and recruitment for the focus groups commenced in June 2020. Recruitment for the RCT is expected to commence in October 2020. Participants for both study phases will be recruited via social media and web-based communities. Data collection for the RCT is expected to be completed by January 2021, and analyses are expected to be completed by March 2021. Linear mixed modelling will be used to determine between-group differences in psychological outcomes.

Conclusions: There is an urgent need to develop culturally appropriate, scalable mental health interventions to address the psychological consequences of the COVID-19 pandemic. In this study, we will develop and test an evidence-based well-being app that, if effective, can be made available to all young people in New Zealand and internationally.

Trial Registration: Australian New Zealand Clinical Trials Registry (ACTRN12620000516987); https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=379597.

International Registered Report Identifier (IRRID): PRR1-10.2196/23716

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KEYWORDS

COVID-19; pandemic; mental health; mobile applications; apps; mHealth; coping skills; wellbeing; adolescent; young adult; coping

Introduction

Background and Rationale

Prior to the COVID-19 pandemic, New Zealand young people, especially Māori (indigenous New Zealanders) and those of Pacific ethnicity, were already experiencing high rates of psychological distress and mental illness [1-4]. Crisis events, including pandemics, can result in significant mental health consequences both during and after the crisis, including increases in depression, anxiety, posttraumatic stress disorder, and suicide [5-8]. In the longer term, these problems can leave a damaging societal footprint, with markers such as increased exclusion or disengagement from education, academic underachievement, and unemployment [9]. It is likely that recent local stressors related to rapid lockdown, physical isolation, disrupted academic routines, and families' financial insecurity will exacerbate pre-existing mental health issues and generate new ones, especially anxiety and depression in young people [10-12]. To minimize the immediate and future adverse psychological and social consequences of the pandemic, young people urgently need support to develop skills to maintain their well-being, address mental health issues early, and continue to build resilience during the coming months.

Over the past 20 years, rapidly evolving mobile technology has fostered the development of a range of eHealth interventions, including those designed to improve mental health, such as mental health apps [13]. Evidence has suggested that eHealth interventions for mental health conditions, such as depressive disorders, can be as effective as face-to-face therapies [14,15]. Acknowledging the effectiveness of eHealth interventions for people of all ages and the relatively good smartphone access in most developed countries, international organizations such as the Lancet Global Mental Health Group have highlighted the role of eHealth interventions in preventing and addressing common mental health issues in adults, young people, and children [16]. Key purported advantages of eHealth interventions include their flexibility of use, cost-effectiveness, and potential to increase equity of service access and reduce stigma [17]. These advantages are reflected by the willingness of people, especially "digital natives," to use eHealth interventions [18].

Alongside these technological developments, evidence has been increasing that specific therapeutic modalities enhance mental health and well-being in children and young people and that these can effectively be delivered as eHealth interventions, such as cognitive behavioral therapy (CBT) [13,19] and psychoeducation [20]. Awareness is also growing that self-empowerment of well-being can improve the quality of care and outcomes for people experiencing mental health problems [21,22], and it has been suggested that interventions should equally aim to enhance well-being and attempt to reduce distress [23]. Digital interventions such as apps must be user-centered to produce the best outcomes for people [24,25]. Well-designed interventions can cost less to produce and lead to greater user satisfaction and content completion [25]. There are currently no evidence-based well-being apps specifically tailored for young people living in New Zealand to help them manage their psychological well-being during the COVID-19 pandemic.

This project has been designed to address the psychological needs of New Zealand young people aged 16-30 years, especially those of Māori and Pacific ethnicity, during the COVID-19 pandemic. At the start of the pandemic (in March 2020), a preliminary prototype app called Whitu: 7 Ways in 7 Days was rapidly developed by our group in response to our clinical concern for this cohort. *Whitu* is the Māori word for "seven," and as its name suggests, the app includes seven modules that can be completed within a week to learn evidence-based coping skills based on our previous work using CBT, psychoeducation, and positive psychology techniques [26-28]. The seven modules and skills included in the app have all previously demonstrated efficacy for young people and as individual eHealth interventions: (1) identifying and rating emotions [20], (2) relaxation [19], (3) self-compassion [29,30], (4) gratitude [31,32], (5) staying connected [33,34], (6) physical care [35,36], and (7) goal setting [37,38].

The specific objectives of the current project are to refine the prototype evidence-based app for improving the well-being and mental health of New Zealand young people aged 16-30 years; ensure broad end-user and cultural acceptability of the app, particularly to Māori and Pacific young people; and demonstrate the preliminary clinical effectiveness of the app via objective outcome measurement during a randomized waitlist-controlled trial (RCT).

Methods

Study Design

A two-phase, mixed-methods design will be employed. During the first phase, a qualitative study will be conducted with users of the prototype app, and the app will be refined on the basis of their feedback. During the second phase, an RCT will be conducted according to CONSORT (Consolidated Standards of Reporting Trials) guidelines [39].

Phase 1: Qualitative Study

Participants

Approximately 20 young people from New Zealand aged between 16 and 30 years will be recruited during June to August 2020 from web-based communities and groups (eg, Facebook, Instagram, Tuakana-teina/Māori student mentorship programs)

to help refine the prototype app design and content. A series of five focus groups will be conducted to collect feedback, with three to six people per group. We will recruit at least ten Māori and Pacific young people to ensure the app appeals to these audiences and is culturally appropriate.

Procedures

Recruitment will be conducted and informed consent will be obtained on the internet over a secure website, Research Electronic Data Capture (REDCap) [40,41]. Prior to attending the focus groups, participants will be asked to provide demographic variables, including age, sex, ethnicity, pre-existing mental health conditions, and experience of using well-being and mental health apps, via self-report questionnaires on REDCap. Participants will also be asked to download and use the prototype app for approximately one week prior to attending the focus groups.

The focus groups will last between 1.5 and 2 hours and will be conducted via Zoom, with two focus groups including only Māori and Pacific young people. To ensure culturally appropriate processes and participant comfort, these focus groups will be facilitated by our Māori and Pacific researchers (EM and NC). Ideas for integrating wider Māori and Pacific views of mental well-being will be explored, and the cultural appropriateness of Māori and Pacific design motifs will be assessed.

During the focus groups, participants will provide audio-recorded feedback on their experiences of using all seven modules. All participants will receive a voucher for NZ$40 (US $26.36) for attending the focus groups.

Data Analysis

Participants' qualitative data will be audio-recorded and transcribed. The transcribed data will be analyzed using directed content analysis [42], a qualitative approach that is well suited for focus groups or interviews where predetermined concepts or categories are examined (eg, usability and acceptability of the different functions and content of the app). The coding scheme will be partly based on the user version of the Mobile Application Rating Scale (uMARS) [43] domains (Engagement, Functionality, Aesthetics, and Information), and the cultural acceptability of the scheme will also be explored by EM and NC. The data will be coded and analyzed independently by at least two members of the research team. Any discrepancies in coding will be resolved by consulting the wider research team.

Phase 2: Randomized Waitlist-Controlled Trial

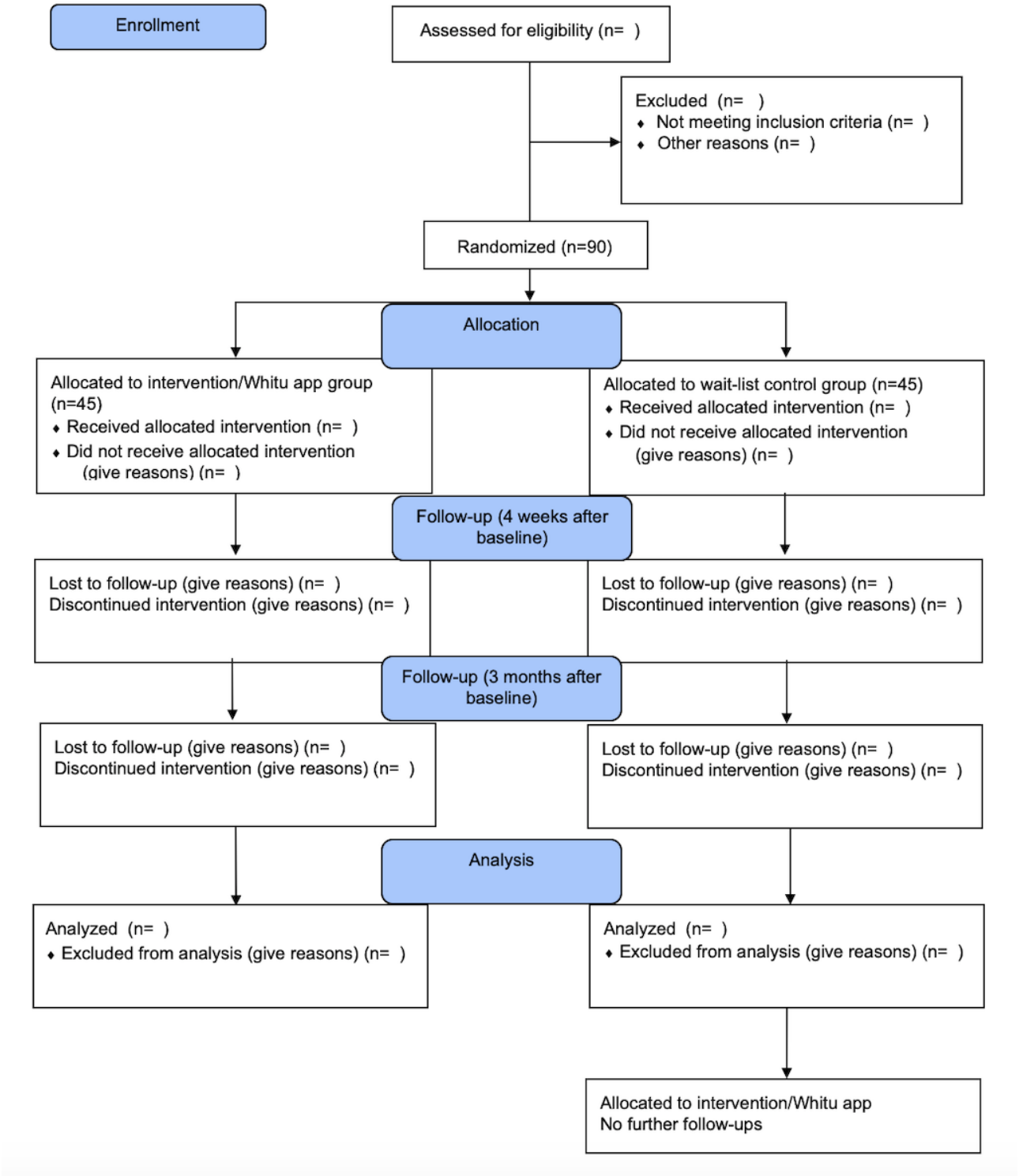
Participants

Participants will be New Zealand residents between the ages of 16 and 30 years. Recruitment is expected to commence in October 2020 via social media (Facebook, Instagram) as well as on other New Zealand–based web-based communities. Young people who participated in phase 1 (qualitative study) will not be eligible to participate in the RCT. Participants will receive a NZ$40 voucher (US $26.36) for taking part in the RCT. Participants who are currently receiving mental health treatment (including using a mental health app) are not eligible to participate.

Procedures

Participants will be recruited from web-based communities (eg, social media) by an advertisement or flyer with a link to the REDCap site. On REDCap, interested participants will be screened for eligibility. If eligible, they can read and download the Participant Information Sheet, provide web-based consent, and complete the baseline questionnaires once they have consented. Once participants have consented and completed the baseline questionnaires, they will be randomized into either the intervention group (Whitu app) or wait-list control group. Randomization will occur using REDCap's randomization module. Participants and research staff will not be blinded to treatment allocation. The wait-list control group will receive the app 3 months after the initial app group. Figure 1 shows the CONSORT flow diagram.

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram of participant recruitment, randomization, and attrition.



After randomization, the wait-list group will be informed that they are in the wait-list control group on REDCap. The intervention group will be shown a link and instructions on how to download the Whitu app on REDCap. During the first four weeks, participants in the intervention group will receive 2 emails reminding them to complete the app modules and an SMS text message asking them to confirm whether they have been able to download the app. Four weeks after completing the baseline questionnaires, participants in both groups will receive an email with a link to the first follow-up questionnaire on REDCap. Three months after baseline, both groups will receive an email with the link to the final follow-up assessment. After the wait-list control group completes the 3-month assessment, REDCap will send each group member an automated email with instructions on how to download the Whitu app. We will not follow up with the wait-list control group after they receive the app at the 3-month time-point.

All participant outcome data (eg, demographic data and psychological outcomes) will be collected via REDCap. We will not collect any information via the app, and any user input

(eg, first name, responses to exercises) will only be stored locally on the user's device. Only the Principal Investigators and research assistants (AS, HT, AB, and DL) will have access to the participant data collected over REDCap. When the data are exported from REDCap, all data will be deidentified and stored separately from the participants' information.

Power Calculation

A previous study of a web-based positive psychology intervention for mildly depressed adults [44] found a between-group improvement in well-being (effect size of f=0.155) using the World Health Organization-Five Well-Being Index (WHO-5) [45]. Using G*Power [46], we calculated that the minimum required sample size to detect an effect size of f=0.155 using a mixed analysis of variance (ANOVA) including within-subject (3 time points) and between-subject (2 groups) effects with 90% power and at a 2-sided 5% significance level was 90 participants (45 per treatment arm). To ensure cultural acceptability, we will aim to recruit at least 40% Māori and Pacific young people (n=36).

Ethical Approval and Trial Registration

The study received ethics approval from the University of Auckland Human Participant Ethics Committee on June 18, 2020 (Ethics Committee reference: 024542). The protocol for the RCT was prospectively registered with the Australian New Zealand Clinical Trials Registry on April 17, 2020 (ACTRN12620000516987).

Intervention: Whitu: 7 Ways in 7 Days

The intervention has been developed as a cross-platform app; therefore, it will function on both Android and iOS operating systems. Data or internet connectivity is required to stream the informational videos contained in each module. The app is free to download. No user information or app analytics data are collected or stored over the internet. Any data input by the user are stored locally on the user's device in an unencrypted SQLite database. These data can be safely deleted at any time by the user via the system settings on the device or by deleting the app.

Evidence shows that young people often do not use health apps for long periods; for example, one review of 93 health apps found that only 3.9% of people who downloaded these apps used them for a median of 15 days [47], and another review of 10 self-help interventions for anxiety and depression found that only 0.5% to 28.7% of users completed the interventions [48]. Therefore, the Whitu app has been purposely designed to be completed over the course of one week. The user receives daily push notifications reminding them to complete at least one module per day and to practice preferred exercises from previous modules. Many CBT-based, psychoeducational, and positive psychology interventions focus on teaching a repertoire of coping strategies and techniques to allow users to choose from a broad range of strategies and discover which ones work best for them individually. In a similar fashion, our aim in offering seven modules is to ask participants to try all the modules over the course of one week and keep practicing the strategies that work best for them. The seven modules are described in detail in Table 1.

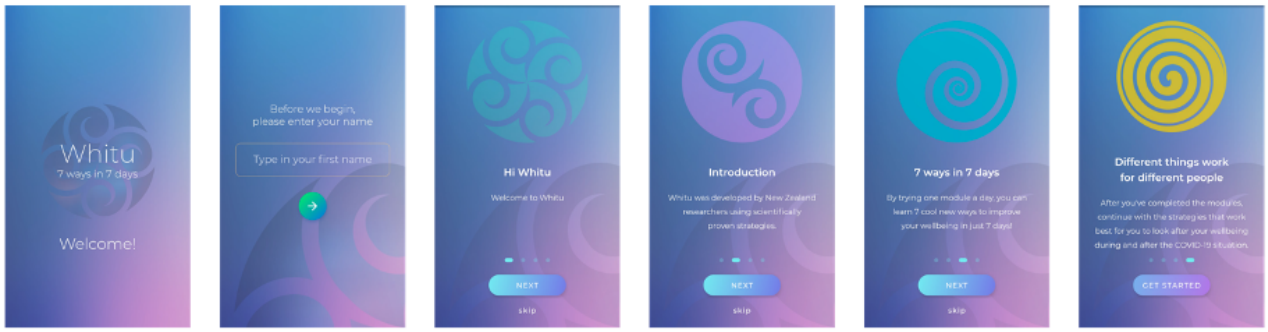
Table 1. The seven modules included in the Whitu: 7 Ways in 7 Days app.

Module	Description
Module 1: Feel	The first module acknowledges that young people may be feeling low and struggling with negative emotions due to COVID-19. The module introduces the concept of identifying and monitoring emotions and recognizing adaptive and maladaptive coping skills. Exercises include recognizing and rating recent emotions as well as grouping coping skills into adaptive and maladaptive categories.
Module 2: Relax	The second module recognizes the uncertainty and stress that young people may be feeling due to the COVID-19 pandemic. The module introduces common relaxation techniques to manage stressful situations. Exercises including deep breathing, progressive muscle relaxation, and visualization.
Module 3: Be kind to yourself	The third module introduces the concept self-compassion and includes a short check-in meditation. The module then asks participants to be mindful of a hard feeling they have had in the past week, reflect on whether friends and family have felt the same, and write self-kindness statements.
Module 4: Be thankful	The fourth module introduces the concept of gratitude and how it is linked to positive well-being. This module encourages grateful contemplation and action by asking users to list things they are thankful for daily and in different situations and to keep a written or photographic record of things they are thankful for.
Module 5: Connect	The fifth module recognizes the negative impact that lockdowns as well as physical distancing can have on relationships. The module introduces the importance of social connection for well-being. It encourages participants to identify important people in their lives and to practice ways of staying connected with them.
Module 6: Look after your body	The sixth module discusses how the COVID-19 situation makes it more difficult to stay active and look after our bodies. This module introduces how eating well, moving regularly, and getting rest support psychological well-being. Information is provided about the key food groups, benefits of physical activity, and sleep. Participants are encouraged to plan how to improve their diet, increase their physical activity, and get more sleep.
Module 7: Set goals	The seventh module acknowledges that the COVID-19 pandemic has likely interrupted users' routines and made it harder to set healthy goals. This module introduces goal setting and guides the user to set their own specific, measurable, achievable, realistic, and time-based (SMART) goals. Explores benefits and barriers to setting different goals and helps the user build confidence by identifying various factors that impact the process of achieving their particular goal.

Onboarding

When the user first opens the app, they are presented with a splash screen containing the app logo, the app title, and a welcome message. This is followed by a screen where the user can input their name. This name is used to personalize messages and exercises throughout the app. The user is then presented with four Onboarding screens, including a welcome message and a brief explanation of the features of the app (see Figure 2).

Figure 2. Screenshots of the onboarding process of the Whitu: 7 Ways in 7 Days app.



Badges

Users earn badges as they complete modules and revision exercises. The aesthetics of the badges are inspired by Māori and Pacific design motifs. Earned badges will appear in color on the Badges screen, while unearned badges appear greyed out. Users can collect a total of 20 badges.

Videos

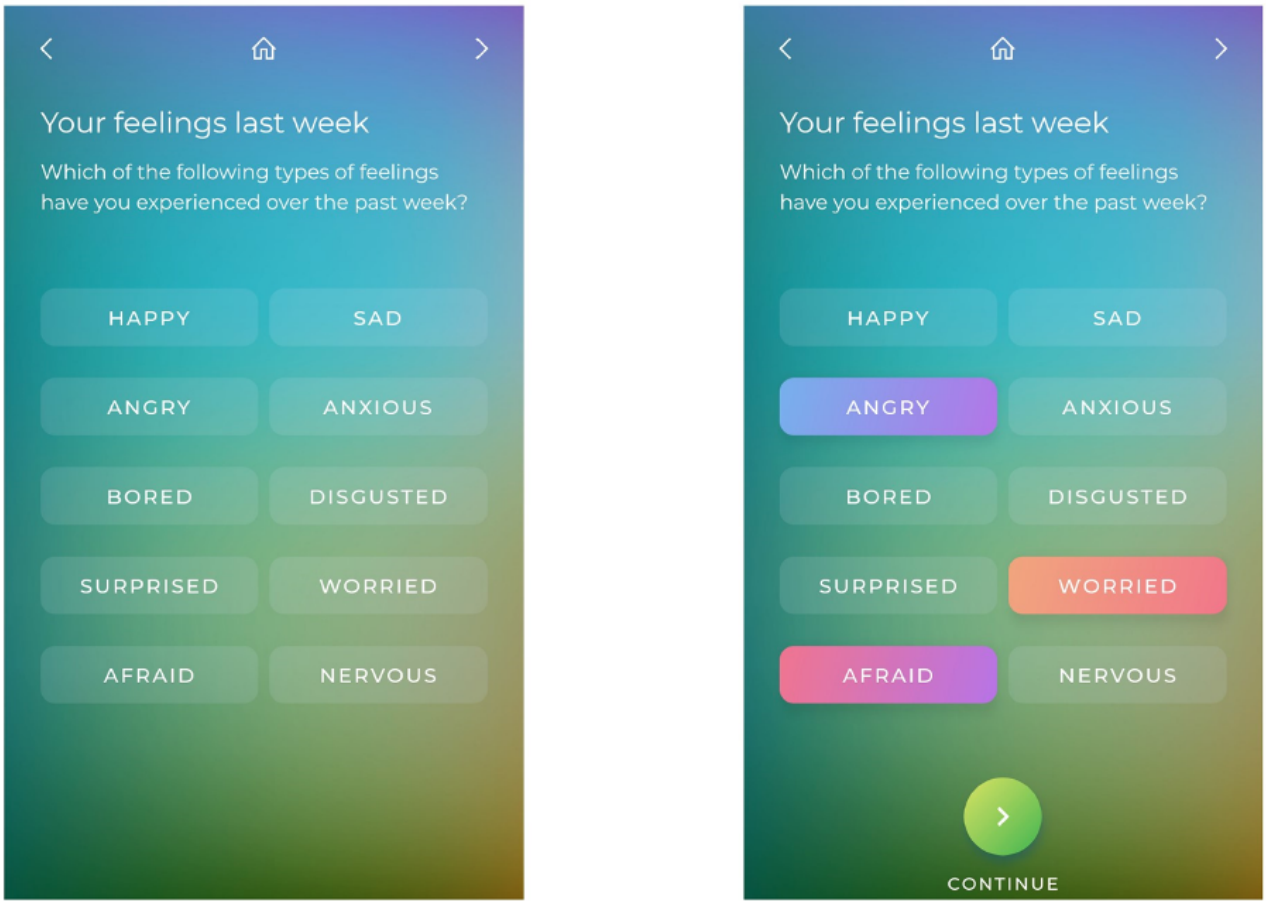
Each module contains at least one informative video that provides a graphical and audio description of its content. The videos are narrated by two characters, Ana and Ben.

Exercises

Each module contains one or more exercises that demonstrate the well-being concepts and techniques described in the videos.

For example, in Exercise 1 of Module 1, users are asked to identify and select various emotions they may have experienced over the past week (Figure 3).

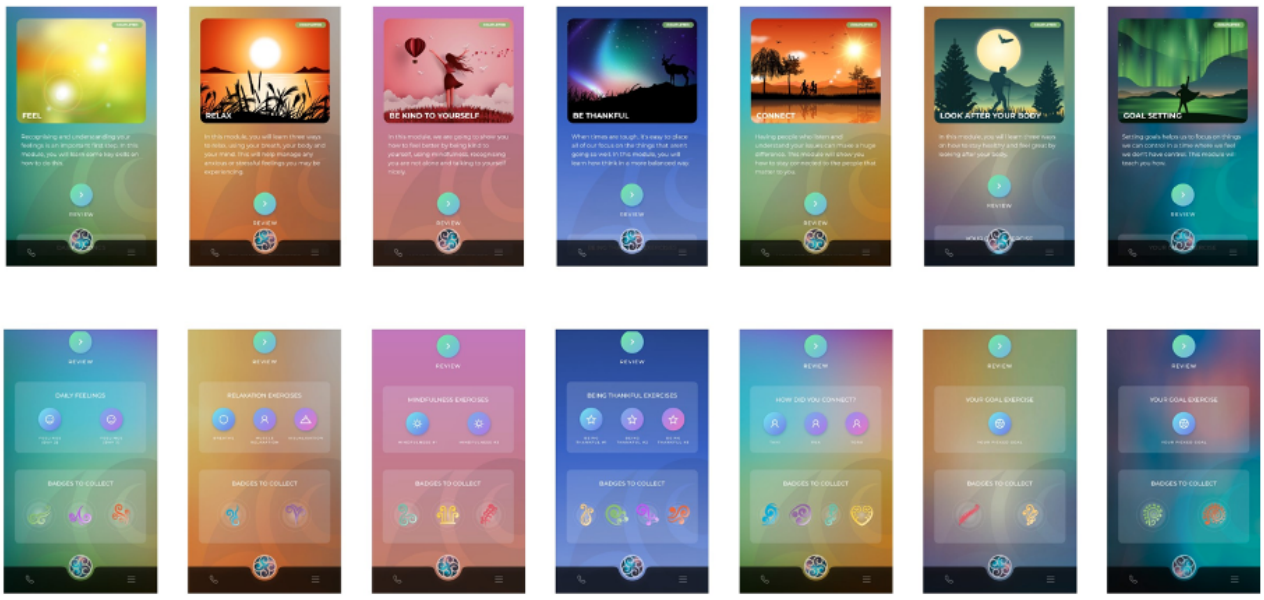
Figure 3. Screenshots of the Identifying Emotions exercise from Module 1 of the Whitu: 7 Ways in 7 Days app.



Completed Modules

When users have viewed all videos and completed all exercises in a module, they are able to review the content of the module or carry out revision exercises intended to refresh and reinforce the message of each module. Users earn badges for each revision exercise they complete (see Figure 4).

Figure 4. Screenshots of the seven modules and associated badges of the Whitu: 7 Ways in 7 Days app.



Revision Exercises

Each module has one or more associated revision exercises that only become available after the module is completed. For some modules, the same revision exercise can be repeated across multiple days. For example, the revision exercise for Module 1 is a condensed version of the main module content that users can use to track their feelings over two days.

Outcome Measures

Outcome measures will be assessed at baseline, 4 weeks after baseline, and 3 months after baseline. Demographic data, including sex, age, ethnicity, and pre-existing mental health conditions, will be collected at baseline via self-report on REDCap. All the outcome measures listed below are brief and have acceptable reliability and validity. Completing the questionnaires at each time point will take approximately 20-30 minutes.

Primary Outcomes

1. Emotional Well-Being

This outcome will be assessed via the WHO-5 [45]. The WHO-5 is a 5-item scale that assesses positive emotional well-being (eg, "I have felt cheerful and in good spirits"). Participants are asked to indicate the extent to which each item matches how they have been feeling over the past two weeks on a 6-point Likert scale ranging from 0 ("at no time") to 5 ("all of the time"). The final score is calculated by summing the five responses and multiplying the total by four. This gives a percentage score ranging from 0-100, with 0 representing the worst possible well-being and 100 representing the best possible well-being. The internal consistency of the WHO-5 demonstrates good reliability (α=.84) in children and adolescents [49].

2. Mental Well-Being

This outcome will be assessed by the Short Warwick-Edinburgh Mental Well-being Scale (SWEMWBS) [50,51]. The SWEMWBS is a short version of the 14-item Warwick-Edinburgh Mental Well-Being Scale (WEMWBS), which is comprised of positively worded items measuring different aspects of positive mental health [41]. The SWEMWBS is a 7-item scale that asks participants to rate their experience of a range of thoughts and feelings (eg, "I've been dealing with problems well") over the last two weeks on a 5-point Likert scale ranging from 1 ("none of the time") to 5 ("all of the time"). The score is calculated by summing individual ratings and transforming the total into a metric score using a transformation provided by the scale authors. Scores range from 7 to 35, with higher scores indicating greater positive mental well-being. The original scale has demonstrated good content validity and is correlated with other mental health and well-being measures [50]. The short version has demonstrated similar reliability and validity to the full version (α=.84) and is suitable to be used by adolescents [52,53].

Secondary Outcomes

1. Depression

This outcome will be assessed by the short version of the Centre for Epidemiological Studies Depression Scale (CES-D) [54]. The CES-D is a 20-item scale designed to measure depressive symptoms in the general population. Participants are asked to rate on a 4-point Likert scale how often they have experienced a variety of different feelings or behaviors (eg, "My sleep was restless"), ranging from 0, rarely or none of the time (less than 1 day) to 3, most or all of the time (5-7 days). Scores are calculated by reverse scoring positive items and summing item totals, yielding a total score between 0 and 60. Higher scores indicate more depressive symptoms. The scale has demonstrated excellent internal consistency (α=.85) and demonstrates high correlations with other depression measures [54].

2. Anxiety

This outcome will be assessed by the Generalized Anxiety Disorder seven item scale (GAD-7) [55]. The GAD-7 is a 7-item self-report scale assessing how often participants experience different symptoms of anxiety (eg, "feeling nervous, anxious, or on edge"). Items are rated on a 4-point Likert scale including 0, not at all; 1, several days; 2, more than half the days; and 3, nearly every day, yielding one total score. Scores of 5, 10, and 15 represent cutoffs for mild, moderate, and severe anxiety, respectively. This scale has been demonstrated to be capable of identifying probable cases of generalized anxiety disorder. It demonstrates excellent reliability (α=.92) and validity [55] in a general population [56] and in adolescents [57].

3. Stress

This outcome will be assessed by the 10-item Perceived Stress Scale (PSS-10) [58,59]. The PSS-10 is a 10-item scale that assesses the extent to which individuals have felt a range of stressors over the last month. Participants are asked to rate how often they experienced different stressful thoughts and feelings (eg, "In the last month, how often have you felt that you were unable to control the important things in your life?") on a 5-point Likert scale ranging from 0, never, to 4, very often. A total score is calculated by reverse scoring items 4, 5, 7, and 8 and summing all ten of the responses. Scores below 13 are considered to indicate low stress, scores between 14 and 26 are considered to indicate moderate stress, and scores between 27 and 40 are considered to indicate high stress. The PSS-10 scale has superior psychometric properties relative to other existing perceived stress scales and has demonstrated good reliability and validity [60].

4. Self-Compassion

This outcome will be assessed using the Self-Compassion Scale–Short Form (SCS-SF) [61].The SCS-SF is an alternative to the long form Self-Compassion Scale [62]. The SCS-SF comprises 12 items that ask participants to rate how they typically act toward themselves in different situations (eg, "When I'm going through a very hard time, I give myself the caring and tenderness I need") on a 5-point Likert scale ranging from 1, almost never, to 5, almost always. The SCS-SF has six subscales (overidentification, self-kindness, mindfulness, isolation, common humanity, and self-judgement) comprising two questions each. Scores are calculated by reverse scoring the negative subscale items, calculating the mean for each subscale, and computing a total mean. Higher scores indicate greater levels of self-compassion. The SCS-SF demonstrates good reliability (α>.86), is highly correlated with the long form

scale [49], and has shown adequate reliability in an adolescent sample [63].

5. Sleep

This outcome will be assessed using a single-item Sleep Quality Scale (SQS) [64]. This single-item questionnaire ("During the past 7 days, how would you rate your sleep quality overall?") is assessed on an 11-point visual analog scale (VAS) from 0-10. The VAS scores are anchored with 0, terrible; 1-3, poor; 4-6, fair; 7-9, good; and 10, excellent. The SQS has demonstrated excellent concurrent and convergent validity with other lengthier sleep scales and has been deemed to be effective in determining clinically meaningful changes in sleep quality [64].

6. User Engagement

This outcome will be assessed via two subscales (App Subjective Quality, Perceived Impact) of the end-user version of the uMARS [65]. The uMARS is a self-report scale designed to assess the quality of health apps. The Subjective Quality score for the app is derived from four items that determine user experience (eg, "Would you recommend this app to people who might benefit from it?"). These items are scored on a 5-point Likert scale ranging from 1 to 5; however, each has different anchors. Scores from this subscale can be reported individually or as a mean total. The Perceived Impact score consists of six items that measure the impact of using the app on knowledge, attitudes, and intentions. The six items are reported as individual items and measured on a Likert scale ranging from 1 to 5 (1, strongly disagree; 5, strongly agree). The uMARS demonstrates good internal reliability overall (α=.90), and the two subscales demonstrate good to moderate reliability (α=.71 and .80) [43]. The scale also contains an open-ended question that asks: "Do you have any further comments about the app?"

In addition to the uMARS, participants will also be asked the following questions about their use of the Whitu app: (1) How many modules did you complete? (2) On how many days did you use the app? (3) What module was the most useful? Why? (4) What did you like about the app? (5) How can we make the app better for young people in the future? and (7) Did you experience any technical difficulties with the app? If yes, what happened?

Hypotheses and Statistical Analyses

It is predicted that the Whitu app group will demonstrate improved well-being (increased emotional and mental well-being), increased self-compassion, and improved sleep at 4-week and 3-month follow-up compared to the wait-list control group. We also hypothesize that the Whitu app group will demonstrate decreased stress, depression, and anxiety at 4-week and 3-month follow-up compared to the wait-list control group.

Data will be analyzed in SPSS (IBM Corporation) or SAS (SAS Institute). Prior to any data analysis, the data will be tested for violations of statistical assumptions and screened for errors and outliers. If parametric assumptions are not met due to nonnormality, transformations or nonparametric tests will be used. Pearson correlations (or Spearman ρ if nonnormal) will be used to explore the relationships between the outcome measures and demographic characteristics and other psychosocial factors. ANOVAs or Kruskal-Wallis tests (if nonnormal) will be used to explore associations between categorical variables and outcome measures. Linear mixed models will be used to determine whether changes in psychological outcomes are the result of the interaction between the intervention group and time, with post-hoc tests to assess pairwise comparisons of groups at each time point and within-group changes over time. Linear mixed models also allow for missing data, as they enable all participants with baseline data to be included in the analysis. We will also examine possible 3-way interactions with age, sex, or ethnicity (eg, age*group*time). Means, SDs, and CIs will be presented with the analysis. Data will be subjected to both intention-to-treat and per-protocol analyses. Per-protocol analyses will include participants who report completing all seven modules. Study results will be disseminated through peer-reviewed journals and conferences.

Discussion

General Considerations

Through this mixed-methods study, we hope to develop a coping skills app for young people in New Zealand aged 16-30 years to use during and immediately following the COVID-19 pandemic and to provide preliminary evidence of its acceptability and effectiveness at improving well-being and other mental health outcomes. As young people of Māori and Pacific ethnicity are already at greater risk of developing psychological problems such as anxiety and depression, we hope the app is particularly appealing and useful for young people in these groups. As the app is based on proven strategies and techniques for improving psychological well-being, we hope it will also be of longer-term value to its users.

Limitations of this study may include low adherence and attrition, which we have attempted to minimize by framing the intervention as a resource that can be completed within seven days. Another possible limitation is that we are only assessing self-reported user engagement. In future prototypes, we hope to also include app analytics to explore more objective measures of user engagement. Lastly, as the app is tailored to New Zealand youth aged 16-30 years, we will not be able to generalize our findings to people younger than 16 years or those outside New Zealand. However, if the app is effective in improving well-being, we hope to conduct a larger and more definitive study in the future that includes younger participants and those outside New Zealand.

Conclusions

There is a pressing need for mental health professionals to create appropriate resources and interventions to improve well-being and help prevent mental health deterioration due to the COVID-19 pandemic. Our study builds on our previous research and addresses the clear needs to develop a mental health toolkit to help New Zealanders cope with the COVID-19 pandemic [66] and to develop a resource that is cost-effective and scalable and that reduces mental health inequities.

We predict that use of the app will lead to maintenance of well-being and reduced rates of anxiety and depression throughout and immediately following the COVID-19 pandemic.

In the longer-term, we hope that the skills learned via the app will also result in reduced need to access mental health services for COVID-19–related issues. Economically, improved well-being, reduced mental health problems, and maintenance of usual activities are likely to result in less societal workforce disruption and loss of productivity. This project also provides opportunities for future research collaboration to evaluate this scalable and evidence-based app with an international audience.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report.
[PDF File (Adobe PDF File), 151 KB - resprot_v9i10e23716_app1.pdf]

References

1. Crengle S, Clark T, Robinson E, Bullen P, Dyson B, Denny S, The Adolescent Health Research Group. The health and wellbeing of Māori New Zealand secondary school students in 2012. Te Ara Whakapiki Taitamariki: Youth'12. Auckland, New Zealand: The University of Auckland; 2013.
2. Clark T, Robinson E, Crengle S, Herd R, Grant S, Denny S. Te Ara Whakapiki Taitamariki. Youth'07: The Health and Wellbeing Survey of Secondary School Students in New Zealand. Results for Māori Young People. Auckland, New Zealand: The University of Auckland; 2008.
3. Rasanathan K, Ameratunga S, Chen J, Robinson E, Young W, Wong G, et al. A health profile of young Asian New Zealanders who attend secondary school: findings from Youth2000. Auckland, New Zealand: The University of Auckland; 2006.
4. Ministry OH. Understanding suicide in New Zealand. New Zealand Ministry of Health. 2016. URL: http://www.health.govt.nz/our-work/mental-health-and-addictions/working-prevent-suicide/understanding-suicide-new-zealand [accessed 2020-04-03]
5. Norris FH. Range, Magnitude, and Duration of the Effects of Disasters on Mental Health: Review Update 2005. ResearchGate. 2005 Jan. URL: https://www.researchgate.net/publication/228776235_Range_Magnitude_and_Duration_of_the_Effects_of_Disasters_on_Mental_Health_Review_Update_2005 [accessed 2020-09-30]
6. Douglas PK, Douglas DB, Harrigan DC, Douglas KM. Preparing for pandemic influenza and its aftermath: mental health issues considered. Int J Emerg Ment Health 2009;11(3):137-144. [Medline: 20437844]
7. North CS, Pfefferbaum B. Mental health response to community disasters: a systematic review. JAMA 2013 Aug 07;310(5):507-518. [doi: 10.1001/jama.2013.107799] [Medline: 23925621]
8. Wheaton MG, Abramowitz JS, Berman NC, Fabricant LE, Olatunji BO. Psychological Predictors of Anxiety in Response to the H1N1 (Swine Flu) Pandemic. Cogn Ther Res 2011 Feb 22;36(3):210-218. [doi: 10.1007/s10608-011-9353-3]
9. Khan L. Missed opportunities: A review of recent evidence into children and young people's mental health. Centre for Mental Health.: . Centre for Mental Health; 2016. URL: https://www.centreformentalhealth.org.uk/publications/missed-opportunities [accessed 2020-09-30]
10. Coronavirus: Impact on Young People with Mental Health Needs. YoungMinds. 2020. URL: https://youngminds.org.uk/about-us/reports/coronavirus-impact-on-young-people-with-mental-health-needs/ [accessed 2020-09-30]
11. Crawley E, Loades M, Feder G, Logan S, Redwood S, Macleod J. Wider collateral damage to children in the UK because of the social distancing measures designed to reduce the impact of COVID-19 in adults. BMJ Paediatr Open 2020 May 04;4(1):e000701 [FREE Full text] [doi: 10.1136/bmjpo-2020-000701] [Medline: 32420459]
12. Lee J. Mental health effects of school closures during COVID-19. Lancet Child Adolesc Health 2020 Jun;4(6):421. [doi: 10.1016/s2352-4642(20)30109-7]
13. Hollis C, Falconer CJ, Martin JL, Whittington C, Stockton S, Glazebrook C, et al. Annual Research Review: Digital health interventions for children and young people with mental health problems - a systematic and meta-review. J Child Psychol Psychiatry 2017 Apr 10;58(4):474-503. [doi: 10.1111/jcpp.12663] [Medline: 27943285]
14. Merry SN, Stasiak K, Shepherd M, Frampton C, Fleming T, Lucassen MFG. The effectiveness of SPARX, a computerised self help intervention for adolescents seeking help for depression: randomised controlled non-inferiority trial. BMJ 2012 Apr 18;344(apr18 3):e2598-e2598. [doi: 10.1136/bmj.e2598] [Medline: 22517917]

15. Luo C, Sanger N, Singhal N, Pattrick K, Shams I, Shahid H, et al. A comparison of electronically-delivered and face to face cognitive behavioural therapies in depressive disorders: A systematic review and meta-analysis. EClinicalMedicine 2020 Jul;24:100442 [FREE Full text] [doi: 10.1016/j.eclinm.2020.100442] [Medline: 32775969]
16. Lancet Global Mental Health Group. Scale up services for mental disorders: a call for action. Lancet 2007 Oct;370(9594):1241-1252. [doi: 10.1016/s0140-6736(07)61242-2]
17. Schröder J, Berger T, Westermann S, Klein JP, Moritz S. Internet interventions for depression: new developments. Dialogues Clin Neurosci 2016 Jun;18(2):203-212 [FREE Full text] [Medline: 27489460]
18. Torous J, Chan SR, Yee-Marie Tan S, Behrens J, Mathew I, Conrad EJ, et al. Patient Smartphone Ownership and Interest in Mobile Apps to Monitor Symptoms of Mental Health Conditions: A Survey in Four Geographically Distinct Psychiatric Clinics. JMIR Ment Health 2014 Dec 23;1(1):e5 [FREE Full text] [doi: 10.2196/mental.4004] [Medline: 26543905]
19. Spence SH, Donovan CL, March S, Gamble A, Anderson RE, Prosser S, et al. A randomized controlled trial of online versus clinic-based CBT for adolescent anxiety. J Consult Clin Psychol 2011 Oct;79(5):629-642. [doi: 10.1037/a0024512]
20. Taylor-Rodgers E, Batterham PJ. Evaluation of an online psychoeducation intervention to promote mental health help seeking attitudes and intentions among young adults: randomised controlled trial. J Affect Disord 2014 Oct;168:65-71. [doi: 10.1016/j.jad.2014.06.047] [Medline: 25038293]
21. Going digital to deliver wellbeing services to young people? Insights from e-tools supporting youth mental health and parenting. Superu. 2016 Jun. URL: https://thehub.sia.govt.nz/resources/what-works-going-digital-to-deliver-wellbeing-services-to-young-people-insights-from-e-tools-supporting-youth-mental-health-and-parenting/ [accessed 2020-04-09]
22. Sin NL, Lyubomirsky S. Enhancing well-being and alleviating depressive symptoms with positive psychology interventions: a practice-friendly meta-analysis. J Clin Psychol 2009 May;65(5):467-487. [doi: 10.1002/jclp.20593] [Medline: 19301241]
23. Keyes CLM. Promoting and protecting mental health as flourishing: A complementary strategy for improving national mental health. Am Psychol 2007;62(2):95-108. [doi: 10.1037/0003-066x.62.2.95]
24. Yardley L, Morrison L, Bradbury K, Muller I. The person-based approach to intervention development: application to digital health-related behavior change interventions. J Med Internet Res 2015 Jan 30;17(1):e30 [FREE Full text] [doi: 10.2196/jmir.4055] [Medline: 25639757]
25. Thabrew H, Fleming T, Hetrick S, Merry S. Co-design of eHealth Interventions With Children and Young People. Front Psychiatry 2018 Oct 18;9:481 [FREE Full text] [doi: 10.3389/fpsyt.2018.00481] [Medline: 30405450]
26. Serlachius AS, Scratch SE, Northam EA, Frydenberg E, Lee KJ, Cameron FJ. A randomized controlled trial of cognitive behaviour therapy to improve glycaemic control and psychosocial wellbeing in adolescents with type 1 diabetes. J Health Psychol 2016 Jun 10;21(6):1157-1169. [doi: 10.1177/1359105314547940] [Medline: 25213114]
27. Schache KR, Hofman PL, Serlachius AS. A pilot randomized controlled trial of a gratitude intervention for adolescents with Type 1 diabetes. Diabet Med 2020 Aug 04;37(8):1352-1356. [doi: 10.1111/dme.14078] [Medline: 31315150]
28. Boggiss AL, Consedine NS, Jefferies C, Bluth K, Hofman PL, Serlachius AS. Protocol for a feasibility study: a brief self-compassion intervention for adolescents with type 1 diabetes and disordered eating. BMJ Open 2020 Feb 09;10(2):e034452. [doi: 10.1136/bmjopen-2019-034452] [Medline: 32041861]
29. Neff KD, Germer CK. A pilot study and randomized controlled trial of the mindful self-compassion program. J Clin Psychol 2013 Jan 15;69(1):28-44. [doi: 10.1002/jclp.21923] [Medline: 23070875]
30. Finlay-Jones A, Kane R, Rees C. Self-Compassion Online: A Pilot Study of an Internet-Based Self-Compassion Cultivation Program for Psychology Trainees. J Clin Psychol 2017 Jul 27;73(7):797-816. [doi: 10.1002/jclp.22375] [Medline: 27787877]
31. Froh JJ, Yurkewicz C, Kashdan TB. Gratitude and subjective well-being in early adolescence: examining gender differences. J Adolesc 2009 Jun;32(3):633-650. [doi: 10.1016/j.adolescence.2008.06.006] [Medline: 18760465]
32. Baños RM, Etchemendy E, Mira A, Riva G, Gaggioli A, Botella C. Online Positive Interventions to Promote Well-being and Resilience in the Adolescent Population: A Narrative Review. Front Psychiatry 2017 Jan 30;8:10 [FREE Full text] [doi: 10.3389/fpsyt.2017.00010] [Medline: 28194117]
33. Barrera JM, Prelow H. Interventions to promote social support in children and adolescents. In: Cicchetti D, Rappaport J, Sandler I, Weissberg RP, editors. The promotion of wellness in children and adolescents. Washington, DC: Child Welfare League of America; 2000:309-339.
34. McLaughlin M, Nam Y, Gould J, Pade C, Meeske KA, Ruccione KS, et al. A videosharing social networking intervention for young adult cancer survivors. Comput Hum Behav 2012 Mar;28(2):631-641. [doi: 10.1016/j.chb.2011.11.009]
35. Oosterveen E, Tzelepis F, Ashton L, Hutchesson MJ. A systematic review of eHealth behavioral interventions targeting smoking, nutrition, alcohol, physical activity and/or obesity for young adults. Prev Med 2017 Jun;99:197-206. [doi: 10.1016/j.ypmed.2017.01.009] [Medline: 28130046]
36. Blake MJ, Blake LM, Schwartz O, Raniti M, Waloszek JM, Murray G, et al. Who benefits from adolescent sleep interventions? Moderators of treatment efficacy in a randomized controlled trial of a cognitive-behavioral and mindfulness-based group sleep intervention for at-risk adolescents. J Child Psychol Psychiatry 2018 Jun 22;59(6):637-649. [doi: 10.1111/jcpp.12842] [Medline: 29164609]
37. Shilts MK, Horowitz M, Townsend MS. An Innovative Approach to Goal Setting for Adolescents: Guided Goal Setting. Journal of Nutrition Education and Behavior 2004 May;36(3):155-156. [doi: 10.1016/s1499-4046(06)60153-x]

38. Cushing CC, Steele RG. A meta-analytic review of eHealth interventions for pediatric health promoting and maintaining behaviors. J Pediatr Psychol 2010 Oct 14;35(9):937-949. [doi: 10.1093/jpepsy/jsq023] [Medline: 20392790]
39. Schulz K, Altman D, Moher D, CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. Trials 2010 Mar 24;11:32 [FREE Full text] [doi: 10.1186/1745-6215-11-32] [Medline: 20334632]
40. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009 Apr;42(2):377-381 [FREE Full text] [doi: 10.1016/j.jbi.2008.08.010] [Medline: 18929686]
41. Harris P, Taylor R, Minor B, Elliott V, Fernandez M, O'Neal L, REDCap Consortium. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform 2019 Jul;95:103208 [FREE Full text] [doi: 10.1016/j.jbi.2019.103208] [Medline: 31078660]
42. Hsieh H, Shannon SE. Three approaches to qualitative content analysis. Qual Health Res 2005 Nov;15(9):1277-1288. [doi: 10.1177/1049732305276687] [Medline: 16204405]
43. Stoyanov SR, Hides L, Kavanagh DJ, Wilson H. Development and Validation of the User Version of the Mobile Application Rating Scale (uMARS). JMIR mHealth uHealth 2016 Jun 10;4(2):e72 [FREE Full text] [doi: 10.2196/mhealth.5849] [Medline: 27287964]
44. Bolier L, Haverman M, Kramer J, Westerhof GJ, Riper H, Walburg JA, et al. An Internet-based intervention to promote mental fitness for mildly depressed adults: randomized controlled trial. J Med Internet Res 2013 Sep 16;15(9):e200 [FREE Full text] [doi: 10.2196/jmir.2603] [Medline: 24041479]
45. Bech P, Olsen LR, Kjoller M, Rasmussen NK. Measuring well-being rather than the absence of distress symptoms: a comparison of the SF-36 Mental Health subscale and the WHO-Five Well-Being Scale. Int J Methods Psychiatr Res 2003;12(2):85-91 [FREE Full text] [doi: 10.1002/mpr.145] [Medline: 12830302]
46. Faul F, Erdfelder E, Lang A, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007 May;39(2):175-191. [doi: 10.3758/bf03193146] [Medline: 17695343]
47. Baumel A, Muench F, Edan S, Kane JM. Objective User Engagement With Mental Health Apps: Systematic Search and Panel-Based Usage Analysis. J Med Internet Res 2019 Sep 25;21(9):e14567 [FREE Full text] [doi: 10.2196/14567] [Medline: 31573916]
48. Fleming T, Bavin L, Lucassen M, Stasiak K, Hopkins S, Merry S. Beyond the Trial: Systematic Review of Real-World Uptake and Engagement With Digital Self-Help Interventions for Depression, Low Mood, or Anxiety. J Med Internet Res 2018 Jun 06;20(6):e199 [FREE Full text] [doi: 10.2196/jmir.9275] [Medline: 29875089]
49. Allgaier A, Pietsch K, Frühe B, Prast E, Sigl-Glöckner J, Schulte-Körne G. Depression in pediatric care: is the WHO-Five Well-Being Index a valid screening instrument for children and adolescents? Gen Hosp Psychiatry 2012;34(3):234-241. [doi: 10.1016/j.genhosppsych.2012.01.007] [Medline: 22325631]
50. Tennant R, Hiller L, Fishwick R, Platt S, Joseph S, Weich S, et al. The Warwick-Edinburgh Mental Well-being Scale (WEMWBS): development and UK validation. Health Qual Life Outcomes 2007 Nov 27;5(1):63 [FREE Full text] [doi: 10.1186/1477-7525-5-63] [Medline: 18042300]
51. Ng Fat L, Scholes S, Boniface S, Mindell J, Stewart-Brown S. Evaluating and establishing national norms for mental wellbeing using the short Warwick-Edinburgh Mental Well-being Scale (SWEMWBS): findings from the Health Survey for England. Qual Life Res 2017 May 16;26(5):1129-1144 [FREE Full text] [doi: 10.1007/s11136-016-1454-8] [Medline: 27853963]
52. McKay MT, Andretta JR. Evidence for the Psychometric Validity, Internal Consistency and Measurement Invariance of Warwick Edinburgh Mental Well-being Scale Scores in Scottish and Irish Adolescents. Psychiatry Res 2017 Sep;255:382-386. [doi: 10.1016/j.psychres.2017.06.071] [Medline: 28666244]
53. Ringdal R, Bradley Eilertsen M, Bjørnsen HN, Espnes GA, Moksnes UK. Validation of two versions of the Warwick-Edinburgh Mental Well-Being Scale among Norwegian adolescents. Scand J Public Health 2018 Nov 10;46(7):718-725. [doi: 10.1177/1403494817735391] [Medline: 29017402]
54. Radloff LS. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. Appl Psychol Meas 2016 Jul 26;1(3):385-401. [doi: 10.1177/014662167700100306]
55. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006 May 22;166(10):1092-1097. [doi: 10.1001/archinte.166.10.1092] [Medline: 16717171]
56. Löwe B, Decker O, Müller S, Brähler E, Schellberg D, Herzog W, et al. Validation and Standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the General Population. Med Care 2008;46(3):266-274. [doi: 10.1097/mlr.0b013e318160d093]
57. Mossman S, Luft M, Schroeder H, Varney S, Fleck D, Barzman D. The Generalized Anxiety Disorder 7-item (GAD-7) scale in adolescents with generalized anxiety disorderignal detection and validation. Ann Clin Psychiatry 2017;29(4):227. [doi: 10.1093/med:psych/9780192627254.003.0007]
58. Cohen S, Kamarck T, Mermelstein R. A Global Measure of Perceived Stress. Journal of Health and Social Behavior 1983 Dec;24(4):385. [doi: 10.2307/2136404]
59. Cohen S, Kamarck T, Mermelstein R. Perceived Stress Scale. APA PsycTests 1994;10. [doi: 10.1037/t02889-000]

60. Lee E. Review of the psychometric evidence of the perceived stress scale. Asian Nurs Res (Korean Soc Nurs Sci) 2012 Dec;6(4):121-127 [FREE Full text] [doi: 10.1016/j.anr.2012.08.004] [Medline: 25031113]
61. Raes F, Pommier E, Neff KD, Van Gucht D. Construction and factorial validation of a short form of the Self-Compassion Scale. Clin Psychol Psychother 2011;18(3):250-255. [doi: 10.1002/cpp.702] [Medline: 21584907]
62. NEFF KD. The Development and Validation of a Scale to Measure Self-Compassion. Self Identity 2003 Jul;2(3):223-250. [doi: 10.1080/15298860309027]
63. Bluth K, Gaylord SA, Campo RA, Mullarkey MC, Hobbs L. Making Friends With Yourself: A Mixed Methods Pilot Study of a Mindful Self-Compassion Program for Adolescents. Mindfulness 2016 Mar 01;7(2):479-492 [FREE Full text] [doi: 10.1007/s12671-015-0476-6] [Medline: 27110301]
64. Snyder E, Cai B, DeMuro C, Morrison MF, Ball W. A New Single-Item Sleep Quality Scale: Results of Psychometric Evaluation in Patients With Chronic Primary Insomnia and Depression. J Clin Sleep Med 2018 Nov 15;14(11):1849-1857 [FREE Full text] [doi: 10.5664/jcsm.7478] [Medline: 30373688]
65. Stoyanov SR, Hides L, Kavanagh DJ, Wilson H. Development and Validation of the User Version of the Mobile Application Rating Scale (uMARS). JMIR mHealth uHealth 2016 Jun 10;4(2):e72 [FREE Full text] [doi: 10.2196/mhealth.5849] [Medline: 27287964]
66. The S. Covid-19 live updates, April 7: Mental health resource Getting Through Together now available. The Spinoff. 2020 Apr 07. URL: https://thespinoff.co.nz/society/07-04-2020/covid-19-live-updates-april-7-public-database-shows-where-the-5-3bn-in-wage-subsidies-has-gone/ [accessed 2020-09-27]

Abbreviations

ANOVA: analysis of variance
CBT: cognitive behavior therapy
CES-D: Centre for Epidemiological Studies Depression Scale
CONSORT: Consolidated Standards of Reporting Trials
PSS-10: 10-item Perceived Stress Scale
RCT: randomized wait-list controlled trial
REDCap: Research Electronic Data Capture
SCS-SF: Self-Compassion Scale–Short Form
SMART: specific, measurable, achievable, realistic, time-based
SQS: Sleep Quality Scale
SWEMWBS: Short Warwick-Edinburgh Mental Well-being Scale
uMARS: user version of the Mobile Application Rating Scale
VAS: visual analog scale
WHO-5: World Health Organization-Five Well-Being Index

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Protocol

Improving Diabetes Management in Emerging Adulthood: An Intervention Development Study Using the Multiphase Optimization Strategy

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Abstract

Background: Poor diabetes self-management in emerging adulthood (age 18-25 years) is associated with poorer diabetes health and diabetes complications. Emerging adults' focus on individuation and independence underlies their poor diabetes outcomes, offering a lever for behavior change. Self-determination theory (SDT) suggests that interventions leveraging emerging adults' innate developmental need for autonomy may offer a route to improving diabetes outcomes by increasing feelings of responsibility for and control over diabetes self-management activities.

Objective: This research project will use the multiphase optimization strategy to test the efficacy of three autonomy-supportive intervention components to elicit a clinically significant improvement in metabolic control, assessed by a 0.5% improvement in hemoglobin A_{1c} (HbA_{1c}), among older adolescents and emerging adults (16-25 years) with poorly controlled type 1 diabetes (T1D; HbA_{1c}≥9.0%).

Methods: A question prompt list (QPL) is a tool to empower patients to assume a more active role during medical visits by asking questions and stating concerns. The motivation enhancement system (MES) is a brief counseling intervention that uses motivational interviewing communication strategies to build intrinsic motivation and self-efficacy for self-management. Text message reminders to complete diabetes care tasks may increase self-efficacy for diabetes self-management. After refining these intervention components for emerging adults, we will conduct a component selection experiment using an eight-arm full factorial design: 2 (QPL yes or no)×2 (MES yes or no)×2 (Text yes or no). Participants will complete 3 study visits: baseline, treatment end at 2 months, and a follow-up at 6 months. The primary outcome is metabolic control, which will be measured via HbA_{1c}. Secondary outcomes include diabetes management and diabetes clinic attendance. SDT constructs of intrinsic motivation, self-efficacy, and the quality of the patient-provider relationship (ie, relatedness) are hypothesized mediators. Depression symptoms and emerging adults' gender are hypothesized moderators. We will use the mixed-effects linear model for the analysis of variance of a factorial design to analyze continuous longitudinal experimental data; the generalized linear model will be used with categorical outcomes (eg, treatment attendance). The experiment was powered to detect the main effects of the intervention on the primary outcome.

Results: A total of 20 participants have enrolled and completed a qualitative interview after reviewing one or more intervention components. Analysis of interview data are underway, with a report of these results anticipated in the fall of 2020. The clinical

trial will be launched in the fall 2020, with participants enrolled through May 2023 and data collection continuing through November 2023.

Conclusions: At the end of this experiment, we will have empirical evidence to support a large-scale, multisite effectiveness trial of an intervention package that has been optimized for older adolescents and emerging adults with poorly controlled T1D.

Trial Registration: ClinicalTrials.gov NCT04066959; https://clinicaltrials.gov/ct2/show/NCT04066959

International Registered Report Identifier (IRRID): DERR1-10.2196/20191

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KEYWORDS

emerging adults; type 1 diabetes; self-determination theory; motivational interviewing

Introduction

Background

Diabetes management involves a regimen of daily blood glucose monitoring, insulin administration, and carbohydrate monitoring [1], a complex and demanding care routine that is primarily under the control of the patient [2]. Once considered a transient time of poor type 1 diabetes (T1D) management, the persistence of suboptimal diabetes management from adolescence into emerging adulthood (the unique developmental period between adolescence and adulthood, age 18-25 years [3]) is increasingly evident [4,5]. Studies of emerging adults suggest that rates of self-reported diabetes management are no different than those of adolescents [6]. Emerging adults complete fewer blood glucose checks per day and are more likely to miss insulin doses than older adults, a pattern of diabetes management associated with elevated hemoglobin A_{1c} (HbA_{1c}) levels, the standard measure of glycemic control, and diabetes disease control [7]. Poor diabetes management in emerging adulthood has been attributed to factors such as a continuation of the decline in parental involvement in diabetes care that begins in adolescence [6] and the characteristic developmental focus of this age group on identity exploration, increasing independence, developing social networks, including increased peer and romantic relationships, new opportunities and choices, and becoming less reliant on parental support and oversight [3].

Entering adulthood with inadequate diabetes management increases the risk for gaps in health care [8] and overreliance on the emergency department for primary health care needs [9,10]. Consequently, the HbA_{1c} levels of emerging adults are similar to those of adolescents, with mean levels in the range of 8.4%-9.3% (SD 1.2-2.4) [6,11] and an estimated 83% of emerging adults failing to meet glycemic control recommendations [11]. Further, poor metabolic control is not the only consequence of inadequate diabetes management [12,13]; it is also associated with short- and long-term diabetes complications, which can appear as early as 5 years post diagnosis [14]. Thus, emerging adulthood and the period immediately preceding it are critical times for intervention. Despite this, no intervention study specifically targeting older adolescents' and emerging adults' T1D self-management has demonstrated improvement in diabetes management or health outcomes [15].

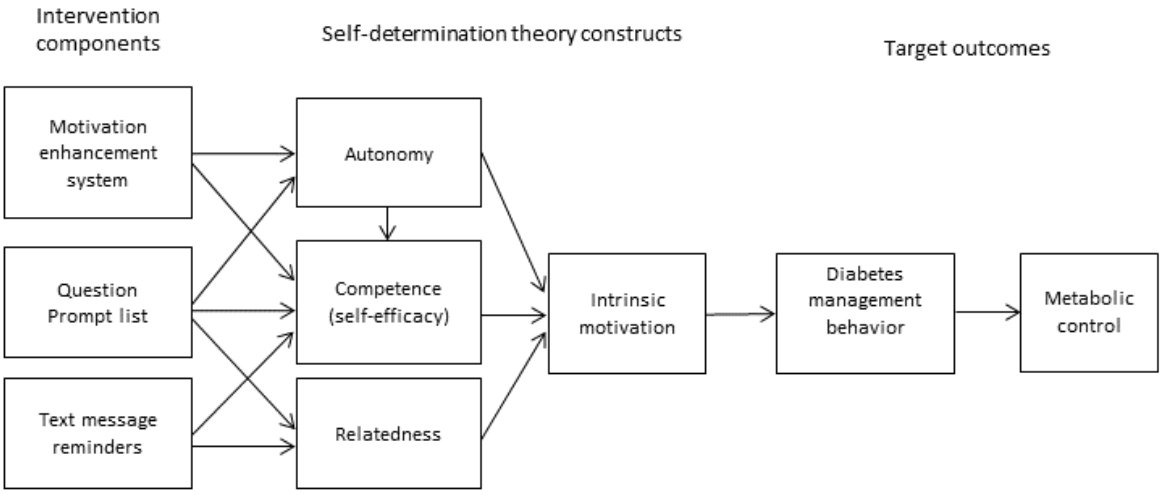
The developmental need for autonomy is particularly salient during late adolescence and early adulthood [3,5], making this an optimal time for interventions focused on improving capacity for independent self-management. The proposed study will test a new intervention designed to align with emerging adults' developmental need for autonomy based on *self-determination theory* (SDT), an empirically derived theory of human motivation. SDT posits that autonomous (ie, self-initiated, driven by intrinsic vs extrinsic motivation [16]) behavior depends upon the fulfillment of 3 innate psychological needs: autonomy, or the perception that one's behavior is self-directed; competence, or self-efficacy; and relatedness, or the existence of caring relationships supportive of the behavior [17,18]. Interventions grounded in SDT have been empirically linked to enhanced feelings of autonomy [19-21] and competence [21] as well as improvements in glycemic control [20-22] and related health outcomes [19] among adults with diabetes. Among adolescents and emerging adults with diabetes, interventions to improve self-management and glycemic control have been few. Husted et al [23] found that guided self-determination delivered by diabetes clinicians in a clinic setting increased adolescents' perceptions of autonomy and decreased amotivation for diabetes self-management but did not improve metabolic control. Autonomy-supportive T1D camps increased adolescents' sense of relatedness but did not change autonomy and competence; glycemic control was not examined [24]. Neither study examined the effect of autonomy-supportive interventions on diabetes self-management behavior. Most interventions targeting older adolescents and emerging adults have focused on strengthening family and peer support for diabetes management or on addressing psychological barriers (eg, mood) [25]. Few have targeted older adolescents' and emerging adults' own sense of responsibility for and control of their own health.

Aims

In this paper, we present the protocol for a research project (NIH R01DK116901; Multimedia Appendix 1). The goal of this project is to develop an optimized, guided eHealth autonomy-supportive intervention to improve metabolic control through improved diabetes self-management among older adolescents and emerging adults (16-25 years) with poorly controlled (HbA_{1c}≥9.0%) T1D. We have developed three self-management intervention components with theoretical and empirical links to SDT, each of which can function independently or in combination with the other components. The first is a question prompt list (QPL), a simple, inexpensive communication tool comprising a list of questions related to the physical and psychosocial aspects of illness and treatment

that patients may want to ask their physicians during a clinic visit [26,27]. Theoretically, participating actively during medical visits increases patients' feelings of control (autonomy) and competency (self-efficacy), which, in turn, empowers them to actively complete their medical care outside of medical visits. Adult cancer patients who arrive at their medical visit prepared with a QPL ask more questions and state more concerns assuming a more active role during medical visits [28-30]. There are no published studies using the QPL with older adolescents and emerging adults with T1D; however, a study of adolescents with asthma found that QPL increased confidence and helped adolescents think of and remember to ask their provider questions [31]. The second component is a brief counseling intervention, the motivation enhancement system (MES). MES uses communication strategies derived from motivational interviewing (MI) [32-34] to directly enhance intrinsic motivation and self-efficacy for self-management. Emerging adults living with HIV and asthma reported that the MES intervention increased their motivation to engage in health behaviors [35,36], adherence to medical regimens [37,38], and associated health outcomes [37,39]. MES improved parental monitoring of preadolescents' T1D care and glycemic control [40]. Preadolescents reported improved motivation (importance) for diabetes care, greater empowerment to complete diabetes care, and enhanced support from family [41]. The third component is automated text message reminders to complete diabetes care. Engaging patients between routine diabetes clinic visits via text may increase self-efficacy for diabetes self-management [42-46]. Doing so also generates feelings of social support [47] and a caring relationship (relatedness) even when patients know the text messages are automated [44]. Figure 1 illustrates the theoretical model guiding the intervention.

Figure 1. Theoretical model of the proposed intervention components.



The primary aim of this study is to test the efficacy of the QPL, MES, and text intervention components to improve older adolescents' and emerging adults' metabolic control (primary outcome) and diabetes management behavior (secondary outcome). We hypothesize that at the end of treatment (2 months) and at follow-up (6 months), older adolescents and emerging adults with poorly controlled T1D who receive one or more of the intervention components will demonstrate a clinically significant improvement in metabolic control (improvement in HbA_{1c}≥0.5%) and a statistically significant improvement in self-reported and objectively measured (frequency of blood glucose monitoring) diabetes management behavior. Secondary aims include examining whether changes in SDT constructs (self-reported autonomy, self-efficacy, and patient-provider relationship) mediate intervention effects on primary outcomes at the end of treatment (2 months) and at follow-up (6 months). We also aim to explore whether treatment participation improves diabetes clinic visit attendance and whether gender and depressed mood moderate intervention effects.

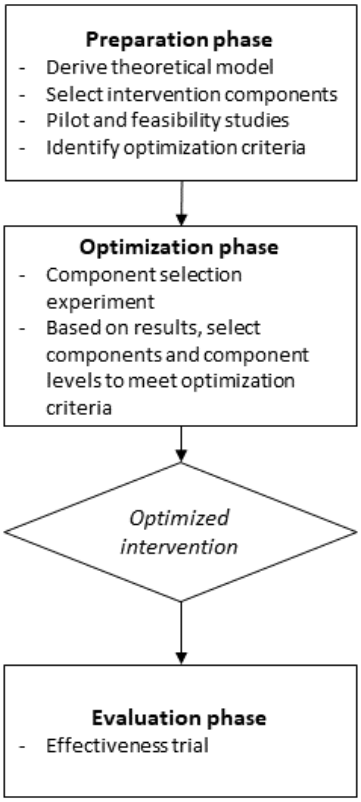
Methods

Design

This study will use a factorial trial model following the *multiphase optimization strategy* (MOST) [48,49]. The MOST design is an efficient approach to develop a multicomponent intervention in which the final intervention components are tested against an a priori defined optimization criteria. The MOST design involves 3 phases: preparation, optimization, and evaluation (Figure 2 [49]). In the *preparation phase*, a theoretical model for intervention is derived, intervention components are selected, the optimization criteria for intervention component selection are identified, and preclinical pilot and/or feasibility studies may be undertaken. In this study, we will invite members of the target population (ie, emerging adults with T1D) to review and provide feedback on three existing intervention components and then refine the components based on their feedback. In the *optimization phase*, we will conduct a component selection experiment using a randomized factorial research design to build an autonomy support

intervention that has been optimized for efficacy. We will use a clinically significant improvement in metabolic control (decrease in HbA_{1c}, HbA_{1c}≥0.5%) as the optimization criterion for determining which intervention components should be retained in the multicomponent intervention. We chose efficacy as the optimization criterion because the eHealth intervention components, once developed, are relatively low cost (a common optimization criterion) to implement and sustain making a clinically significant reduction in HbA_{1c} the most persuasive optimization criterion for clinicians and potential payers. The MOST approach offers distinct advantages over the traditional multiple pilot randomized clinical trial approach. Including all participants in the analysis will enable an efficient, simultaneous investigation of the efficacy of each intervention component as well as synergies resulting from combinations of intervention components. Thus, this component selection experiment is analogous to conducting multiple pilot randomized clinical trials to evaluate the efficacy of each of the three intervention components and the combination of intervention components using only a fraction of the sample size and resources. At the end of this study, we will have empirical evidence supporting the efficacy of each intervention component and estimates of the efficacy of the intervention package as a whole to improve metabolic control, diabetes self-management, and diabetes clinic attendance. Empirical evidence from this study will inform the design of a large-scale, multisite effectiveness trial of the optimized intervention package.

Figure 2. The multiphase optimization strategy study design.



As shown in Figure 3, the component selection experiment will use an eight-arm full factorial design: 2 (QPL yes or no)×2 (MES yes or no)×2 (text yes or no). In arms 1-3, participating youth will receive one of the three intervention components, in arms 4-6 two components; arm 7 will include all three components, and arm 8 will be the standard care control. This design will allow us to evaluate the main effect of each intervention component and explore whether combinations of components have synergy (interaction effects). The experiment, powered on the main effects, will require 320 (296 after attrition) older adolescent and young adult participants (16-25 years) with poorly controlled T1D (HbA_{1c}≥9.0%). Participants will complete 3 study visits: baseline and 2 and 6 months. The intervention period is 30 days with MES session 1, and text message reminders initiated 1 week after the baseline visit. MES session 2 occurs 30 days later with the text intervention occurring between the two MES sessions. The QPL is delivered 2 weeks before the participant's next diabetes clinic visit; hence, participants will be enrolled approximately 1 month before an upcoming diabetes clinic visit to ensure that the QPL occurs during the intervention period. The participant timeline is shown in Figure 4.

Figure 3. Full factorial 2×2×2 component selection experimental design in which 40 participants will be randomized to each study arm.

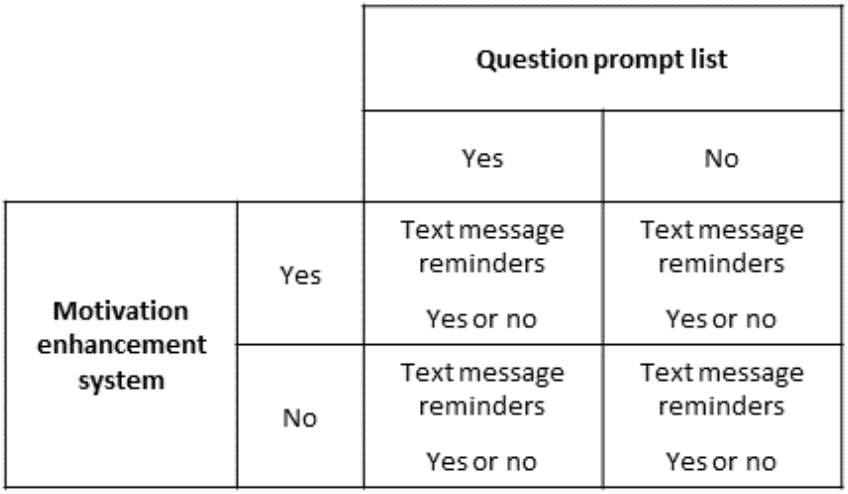
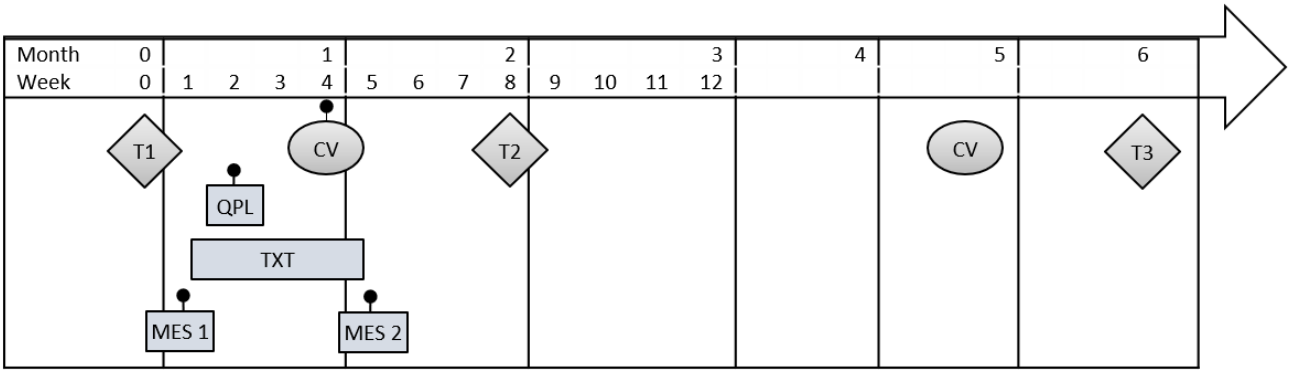


Figure 4. Participant timeline. CV: clinic visit; MES: motivation enhancement system; QPL: question prompt list; T: time; TXT: text message reminders.



Setting and Participants

Participants will be recruited from two Wayne State University School of Medicine sites, both located in Detroit, Michigan. We will invite eligible youth from the pediatric diabetes clinics at the Children's Hospital of Michigan (CHM) and the adult comprehensive diabetes clinics at the Detroit Medical Center's (DMC) University Health Center (UHC). We will target older adolescent and emerging adult patients aged 16 to 25 years, inclusive, who have been diagnosed with T1D for at least 6 months and have an elevated HbA_{1c} (HbA_{1c}≥9.0% currently and averaged over the previous 6 months). We select this age range based on expert recommendations for when autonomous diabetes management is appropriate [14]. We will not exclude youth based on comorbid mental health problems (eg, depression) with the exception of conditions (ie, thought disorders, psychosis, autism, developmental delay, and suicidality) or problems of a severity that compromise data integrity, intervention participation, or youths' ability to assume autonomous diabetes care. Nor will we exclude based on the presence of comorbid physical health problems unless the diagnosis of diabetes is secondary to another chronic medical illness (eg, cystic fibrosis) or results in atypical diabetes management. Due to the minority of non-English speaking youth at CHM and UHC, the ability to speak and read English will be required. Finally, youth will also be required to have access to a mobile device with texting capability on which they can receive the intervention components.

Procedures

Recruitment and Retention

Following procedures approved by the institutional review board, we will mail a letter, cosigned by our clinician collaborators, introducing the research study to all potentially eligible youth and the caregivers of minor youth. This strategy will ensure that all eligible youth are informed of the study with adequate time to enroll. It will also permit disinterested youth the opportunity to *opt out* of being contacted regarding the study. Research assistants (RAs) will follow-up with potentially eligible youth and the caregivers of eligible minors by telephone to present the details of the study and assess their interest in participating. If the recruitment letter is returned undeliverable or RAs are unable to establish contact by phone, clinicians will introduce the study at a diabetes clinic visit and obtain a release of information and updated contact information for follow-up. RAs will obtain informed consent or, in the case of participants <18 years old, parental consent and youth assent before data collection. We will use multiple techniques to minimize follow-up attrition, including collecting detailed contact information (including three contact persons), advanced scheduling, and multiple reminder mailings and phone calls.

Data Collection

Given this population's known propensity to miss clinic visits, we will conduct all study visits in youths' homes. One month before an upcoming diabetes clinic visit, participants will have their first study visit at which the RA will obtain informed consent, baseline measurements, and download the intervention software app to the participant's preferred device (eg, phone or tablet). The postintervention study visit will occur 2 months after baseline and is timed to occur immediately after the completion of the interventions. A second follow-up study visit will occur 6 months after baseline to assess the sustainability of intervention effects. RAs will collect self-report data using REDCap, a Health Insurance Portability and Accountability Act -compliant electronic data capture system. RAs will manually download glucose meters and extract medical chart data obtained as part of the routine medical care encounter onto paper-based forms for direct data entry. The results of HbA_{1c} tests will be similarly entered from laboratory test result forms. RAs will offer participants US $50 for completing each of the three data collections (US $150 total).

Randomization

Participants will be randomly assigned to one of the eight intervention conditions following their first study visit. We will stratify randomization by HbA_{1c} (high: >11.5% vs low: ≤11.5% based on the median HbA_{1c} in our prior T1D intervention studies with emerging adults). As HbA_{1c} is strongly associated with age [14], race [50], and insulin treatment [14], we effectively control for these other variables via this strategy. We will use a permuted block algorithm with blocks of eight within each HbA_{1c} stratum. Permuted blocks have the advantage of ensuring balance between treatment arms for important prognostic variables without unmasking the next treatment allocation [51]. To keep data collection staff blind to the youth's treatment status, one RA will have exclusive data collection responsibilities. A data analyst, under our biostatistician's supervision, will develop the randomization schedule and convey treatment assignments to the intervention coordinator who will deliver treatment assignments and initiate and monitor treatment protocols.

Interventions

During the first study visit, the RA will ensure that the participant can access the intervention via their preferred device (either as a mobile web app for Android devices or as a hybrid app on iOS devices) and will explain the different intervention conditions. Within 1 week of this visit, the intervention coordinator will contact youth by phone to notify them of their randomization assignment and initiate their intervention(s). Participants will be triggered to complete intervention components via text message–delivered hyperlinks. The intervention coordinator will monitor youths' treatment completion rates, providing support and technical assistance as needed. Conversations between the intervention coordinator and youth will be audio recorded. These audio recordings will be randomly selected on a biweekly basis for the assessment of protocol fidelity. Drift from the delivery protocol will be addressed with retraining.

All three intervention components will be delivered using communication strategies derived from MI, a method of talking with people about their behavior in a way that is simultaneously client-centered and directive [34,52]. The MI framework is an autonomy-supportive intervention with strong empirical support for eliciting behavior change through intrinsic motivation. MI is consistent with SDT [53,54], as the goal of MI is to increase intrinsic motivation and self-efficacy for engaging in health-promoting behaviors [55]. In addition, emphasis on patients' decision-making autonomy is a critical element of *MI spirit*, the relational component of MI [32-34]. The technical component of MI, that is, the use of communication techniques consistent with the MI framework [56], leads to behavior change through the elicitation of patients' statements of intrinsic motivation (ie, *change talk*, statements about patients' own desire, ability, reasons, and need for behavior change, and *commitment language*, patients' statements about their intentions and plans for change). The empirical link between change talk, commitment language, and behavior change is well established [57], and evidence is growing to support the role of providers' use of MI-consistent communication strategies in eliciting patient motivational statements [58-66]. We have previously demonstrated that clinician use of autonomy-supportive statements has been empirically linked to patient statements of intrinsic motivation [67,68]. This knowledge is integrated into the three intervention components for this study by including statements that explicitly emphasize decision-making autonomy.

Computerized Intervention Authoring Software

All three interventions will be developed and delivered via the Computerized Intervention Authoring Software (CIAS), version 2.0 (Interva, Inc) CIAS 2.0 is an e-intervention authoring tool that generates HTML5 mobile web apps with a responsive design capable of being deployed on any web browser and accessed via any device (eg, Apple or Android) of any size (ie, automatically reformats for optimal viewing on any size screen). As interventions built using CIAS 2.0 feature an animated narrator and a voice that reads content out loud for each screen and as iOS devices specifically disallow automatic triggering of sound files, participants with iOS devices access content via a hybrid app approach. The current mobile version of CIAS has an enhanced feature set including improved voice quality for narrated content and an updated appearance. Although mobile web and hybrid apps require internet access, 96% of Americans aged 18-29 years report consistent internet access [69]. Furthermore, technology-based interventions are ideal for youth who already have technology (cell phones and computers) integrated into their natural ecology [70-72]. Mobile web apps offer several advantages over native apps in that they do not require separate programming for different platforms, are less expensive to build and maintain, updates are centralized and automatic, they are more easily accessible and shared, and require negligible device storage space. Thus, mobile web apps exclude only a minority of youth and are consistent with trends toward ubiquitous device ownership and ready access to the internet.

Diabetes QPL

A QPL is a simple, inexpensive communication tool composed of questions related to the physical and psychosocial aspects of

illness and treatment that patients may want to ask their physicians during a clinic visit [26,27]. QPLs are grounded in social cognitive theory, which posits that behavioral performance is largely a function of confidence in one's ability to perform the behavior (self-efficacy) and the expectation that the behavior will result in the desired outcome [73]. Patients prepared with a QPL are more likely to ask questions and state their concerns, enabling shared decision-making and bolstering self-efficacy.

The diabetes QPL content development will be guided by the American Diabetes Association's guidelines for diabetes treatment [14] and the empirical literature on factors that influence diabetes management during emerging adulthood. The diabetes QPL will focus on common questions about the management of T1D, various treatment options, complications, psychosocial adjustment, and transitioning to adult medical care. A diabetologist and a certified diabetes nurse educator will review the diabetes QPL for clinical relevance. Ten members of the target population will provide feedback on its relevance and acceptability via a semistructured interview. The QPL will be further refined based on this feedback.

Within 1 week of the first study visit, the intervention coordinator (an unblinded research assistant) will contact the youth randomized to the QPL by phone to explain the QPL. Approximately 2 weeks before their diabetes clinic visit, the youth will receive a text message containing a link to complete the QPL. The youth will receive reminders to complete the QPL every 3 days, escalating to daily reminders for the 3 days before the clinic visit. Upon completion, the personalized QPL will be emailed to the youth with a message reminding them to bring their QPL to their upcoming diabetes clinic visit. Additional reminders to bring the QPL to the diabetes clinic visit will be sent 1 week before and the day before the scheduled clinic visit.

MES

MES is a brief, computer-delivered intervention to enhance intrinsic motivation for behavior change. MES is grounded in the MI framework [32-34] and the information-motivation-behavioral skills (IMB) model of health behavior change [74]. The IMB model posits that behavior change results from the joint function of 3 critical components: accurate information about risk behaviors (eg, risks of poor diabetes self-management) or replacement health behaviors (eg, benefits of effective diabetes self-management), motivation to change behavior, and having the behavioral skills necessary to perform the behavior (eg, self-efficacy) [75]. The MES system delivers therapeutic content with high fidelity to MI principles. An animated character (avatar) guides patients through the intervention, reflecting back their responses with affirmations to boost self-efficacy and making statements emphasizing personal choice. The avatar speaks, moves/points, and displays emotional responses such as surprise, sadness, or thoughtfulness, as appropriate. The inclusion of a lifelike, synchronously interactive avatar (ethopoeia) is related to better treatment outcomes [76].

The 3Ms MES is a brief (>15 min), two-session mobile health intervention originally developed to improve preadolescents' motivation for diabetes management behavior, that is, monitoring blood glucose, medication/insulin adherence, and meal/carbohydrate counting [41]. Session 1 begins with psychoeducation describing optimal diabetes self-management (ie, information). Youth's motivation (operationalized as the importance of diabetes self-management) and self-efficacy (operationalized as confidence for diabetes self-management) are assessed, followed by exercises designed to increase or reinforce his/her current motivational state (eg, decisional balance) and build self-efficacy (eg, building on strengths and past success). Session 1 concludes with goal setting to promote autonomous diabetes self-management and provides the participant with optional strategies for improving diabetes management. Session 2 begins with an assessment of progress toward the behavioral goal and proceeds to build motivation and self-efficacy with exercises consistent with the youth's current motivational state. Session 2 concludes with goal setting to promote autonomous diabetes self-management. The content of *the 3Ms* MES will be refined to be more consistent with the needs of older adolescents and emerging adults with T1D. Specifically, we will edit the avatar's language to more strongly emphasize youths' autonomy as it relates to diabetes self-management and edit the interactive components (ie, reasons to engage in self-management activities, potential past successes, and personal strengths/weaknesses) to be developmentally consistent with emerging adulthood. A diabetologist will review the MES for clinical relevance, and 10 members of the target population will provide feedback on its relevance and acceptability via a semistructured interview. The MES will be further refined based on this feedback.

Within 1 week of the baseline data collection, the intervention coordinator will contact youth randomized to MES by phone to explain the intervention and initiate session 1 via a link sent by a text message. Thirty days after the initial session, youth will receive a link to complete session 2. Youth will receive weekly reminders to complete the sessions until they complete the session or the intervention period has elapsed.

Text Message Reminders

Text message reminders (one-way) are a behavioral support strategy with theoretical support from social cognitive theory. Text message reminders promote adherence by increasing the likelihood that health-related tasks are completed, which leads to perceptions of control over health behavior and supports goal attainment [77]. We will refine a one-way text messaging protocol previously developed and evaluated with young adults with moderate to severe persistent asthma [39]. Youth will receive 30 days of one-way text message reminders. Messages will be tailored according to the youths' preferred behavioral target derived from *the 3Ms* MES intervention, that is, youth may choose to receive text messages to monitor their blood glucose, take their insulin, count carbohydrates, or all 3 behaviors. They will be given the ability to opt out of text message reminders (none did in the asthma study [39]). Youth that do not opt out will receive daily text messages but will choose at what time(s) of day to receive their reminders. A diabetologist will review the text message reminders for clinical relevance, and 10 members of the target population will provide feedback on its relevance and acceptability via a semistructured

interview. Text message reminders will be further refined based on this feedback.

Within 1 week of the baseline data collection, the intervention coordinator will contact youth randomized to text by phone to explain the intervention. The intervention coordinator will solicit a target behavior (ie, monitoring, medicine, meals, or all 3) using standardized language. The intervention coordinator will also finalize the reminder schedule and other logistics. Youth will then receive 30 days of one-way text message reminders consistent with their diabetes management goals and delivery preferences.

Standard Medical Care

All participants will continue to receive standard medical care at 1 of the 2 DMC clinical sites: CHM or the UHC comprehensive diabetes clinic. DMC's clinical practices are consistent with the standards of T1D care recommended by the American Diabetes Association. Established patients with T1D visit a DMC diabetes clinic every 3-4 months for routine diabetes medical care provided by an endocrinologist and/or nurse practitioner.

Measures

All measures have previously been used with adolescent populations; however, we will assess their psychometric performance before analysis.

Metabolic control is the primary outcome and will be measured using *HbA$_{1c}$*. HbA_{1c} is an indirect and retrospective measure of average blood glucose levels over the previous 2-3 months. The Accubase A_{1c} test kit manufactured by DTI Laboratories will be used to measure HbA_{1c}. This kit is United States Food and Drug Administration approved and uses a capillary tube blood collection method instead of venipuncture, making it suitable for home-based data collection by nonphlebotomists. DTI uses high-performance liquid chromatography to analyze the blood sample; the reagent solution contains 1 ml of ethylenediaminetetraacetic acid and 0.025 mom/l potassium cyanide, a blood preservative. A custom lot of test kits will be ordered to minimize variability across test kits. The Accubase test kit is comparable with HbA_{1c} obtained from venous whole blood (r^2=0.987) [78].

Diabetes management is a secondary outcome and will be assessed via self-report and objective measures. The *diabetes management scale (DMS)* [79] is a self-report measure of daily diabetes care that assesses a broad range of management behaviors, including insulin management, dietary management, blood glucose monitoring, and symptom response. Questions ask "What percent of the time do you [eg, take all your insulin doses every day]?", with a 0%-100% response scale. The DMS has been adapted for intensive insulin regimens with good internal consistency (α=.74 to .84) [80]. RAs will download *glucose monitors* to obtain objective data on the frequency of blood glucose monitoring. Data for participants using a blood glucose meter will be reported as the mean daily frequency of blood glucose testing during the 14 days before assessment. Continuous glucose monitoring data will be reported as the proportion of days the monitor was worn out of 14.

SDT constructs are mediators and will be assessed via self-report. The *treatment self-regulation questionnaire (TSRQ)* assesses the extent to which youth perceive their behavior as intrinsically (autonomous) or extrinsically (controlled externally) motivated [81]. The diabetes version of the TSRQ is valid and reliable (α=.80 to .86) [20]. Items (N=19, 7-point Likert) form 2 subscales, autonomous and controlled regulation, and an overall scale, the relative autonomy index [82]. Two versions of *Rollnick's readiness ruler* [83] will be used to assess adolescents' motivation to change their diabetes self-management routines. The *importance ruler* assesses individuals' perceptions of the importance of changing their blood glucose testing frequency, taking prescribed doses of insulin, and adhering to dietary recommendations. The *confidence ruler* assesses an individual's confidence (self-efficacy) in their ability to implement changes in self-management [33]. Both rulers use a 1 (not ready to change) to 10 (already trying to change) rating scale. Items are summed to obtain the total motivation for change score. Behavior-specific rulers have been widely used and are related to adolescent medication adherence [84], treatment dose [85], and treatment outcomes [86]. Cronbach α=.71 in previous research with the study population [87]. Self-efficacy for diabetes self-management will also be assessed using the *diabetes empowerment scale (DES)* [88] and the *perceived health competence scale (PHCS)* [89]. DES has 28 items assessing 3 domains of diabetes self-efficacy: managing the psychosocial aspects of diabetes, assessing dissatisfaction and readiness to change, and setting and achieving diabetes goals. DES is a widely used measure with demonstrated reliability (α=.96), validity [88], and sensitivity to change with improvements in HbA_{1c} [90]. PHCS (8 items, 5-point Likert) will be modified to assess perceptions of diabetes (vs health) competence. PHCS is reliable (α=.82 to .90) and valid (associated with health intentions and behavior) [89]. The patient-provider relationship will be assessed with the *health care climate questionnaire (HCCQ)* [91]. Participants use a 7-point Likert scale to rate 18 items in 2 domains: communicative support and practical support. The HCCQ is reliable (α=.87) and valid. The *patient activation scale (PAS)* was derived from the observation scale of the same name developed by Street et al [92]. The PAS consists of 19 items rated on a 5-point Likert scale comprising 2 scales, patient-centered communication and patient active participation.

Due to the comorbidity of depression and diabetes [93,94] and the moderating role of depression on self-efficacy in chronic illness self-management [95], symptoms of depression will be measured with the *Center for Epidemiologic Studies Depression Scale (CES-D)* [96]. The CES-D is a widely used, 20-item self-report scale that has been validated for use with adolescents [97].

The investigator-developed *family information form* will be used to collect demographic information, such as age, gender, race/ethnicity, family structure, and income level. Clinical data, including type of diabetes regimen (ie, traditional injections, intensive injections, and insulin pump), duration of diabetes, and other relevant clinical variables, will be extracted from the participants' medical records. Diabetes clinic attendance will

also be extracted for the 6-month periods before and after study initiation.

The *client evaluation of treatment (CET)*, an investigator-developed measure to assess participants' perceptions of the usability, comprehensibility, comfort with, and usefulness of the intervention components, will be completed at the first follow-up data collection visits. Sample questions include "Do you feel this question list/computer session/text messaging program will be useful for you?" and "How easy was it for you to use the question list/computer session/text messaging program?", with a 4-point Likert response scale.

Data Analysis Plan

The data analysis plan is twofold. Qualitative interview data collected during the intervention refinement phase will be analyzed using thematic analysis. Quantitative experimental data will be analyzed using the mixed-effects linear model for the analysis of variance (ANOVA) of a factorial design to identify the intervention components that significantly contribute to a clinically significant improvement in HbA_{1c} (ie, a ≥0.5% decrease from baseline).

Framework matrix analysis (FMA) is an efficient, systematic approach to conducting thematic analysis [98]. An FMA analysis begins with the construction of a matrix in which the rows are based on content areas derived from the interview guide and the columns represent respondents. Two coders will first familiarize themselves with the data by reviewing the interview data. They then independently code the interviews by *charting* a summary of participant feedback into the matrix. Coders will meet after every interview to review and compare their matrices. Discrepancies will be resolved through a review of the audio and discussion, resulting in the construction of a final consensus-coded matrix. Together, the coders will identify emergent themes summarizing youths' feedback. Data analysis will be ongoing during the data collection process. We will solicit feedback from up to 10 youth, stopping interviews if there is evidence of data saturation [99], that is, interviews are no longer generating new feedback.

Analysis of experimental data will begin with descriptive statistical analyses. The biostatistician will first characterize data heterogeneity and document the distributions of HbA_{1c}, the primary outcome, and all secondary and exploratory outcomes (ie, diabetes management and clinic attendance). The data will be examined for out-of-range values, outliers, and abnormal values using graphical methods (eg, boxplots and histograms) and descriptive statistics. Unexpected findings will prompt the checking of raw data for accuracy of data entry and recording. The effect of the intervention components on the longitudinal measures of HbA_{1c} will be examined using the mixed-effects linear model for the ANOVA of a factorial design. This model will include a fixed effects indicator for each intervention component (QPL, MES, and text), time, and all interactions with time. Random intercepts will be used to account for the longitudinal nature of the data. Each model will include a random intercept and slope and fixed effects for treatment combinations ($=2^3$) and time as well as the stratification variable (eg, high/low HbA_{1c}). Before evaluating which components contribute to a potential reduction in HbA_{1c}, models comparing the treatment with all three components and the control treatment will be examined to determine whether the complete intervention was efficacious. If this statistical test is significant, components resulting in a significant reduction in HbA_{1c} will be identified by examining the interactions between the main effects and time using the strategy advocated by Collins et al [100], which begins with the simplest effects and only adding higher-order interactions if needed. Significance thresholds will be set at α=.05 for the test of total effect (difference between the treatment with all three components and the control treatment) and α=.1 to identify which components contribute to the total effect. A higher alpha value will be used for the component selection test because it reduces the likelihood of not selecting a component that contributes to the total effect. Secondary and exploratory outcomes (diabetes management and treatment attendance) will be analyzed using a similar approach but are not powered. As treatment attendance is not a continuous outcome, a generalized linear model will be employed.

The power analyses examined the sample size required to detect clinically meaningful group differences using a mixed effect model. The proposed experiment quantifies the effects of the three experimental treatment components. Factorial trials are most often powered to detect the main effects of interventions, as adequate power to detect plausible interactions requires a greatly increased sample size [101]. As two primary hypotheses have been proposed, the Hochberg alpha adjustment will be used in hypothesis testing. The smaller of those sequential alpha levels of .025 was used in our estimates of the multiplicity-adjusted sample sizes [102]. On the basis of the simulation, the protocol proposes recruitment of 296 participants (37/condition) for a standardized medium effect size (Cohen d≥0.47). After adjusting for 10% attrition, our final projected sample size is 320 (40/condition), which is sufficient to preserve >80% power. The power analysis was completed in SAS (SAS Institute Inc) 9.3 software using the mixed linear model procedure. Strong preliminary support for each intervention component's efficacy suggests that each intervention component will uniquely contribute to the overall intervention's efficacy. Thus, the study has sufficient power to determine whether any combination of the intervention components is efficacious in improving older adolescents' and emerging adults' metabolic control (HbA_{1c}, H1) or self-reported diabetes management behaviors (H2).

The role of sex and baseline depression status (high vs low) as moderators will be explored. These results will not be used for treatment decision-making but instead could guide the design of subsequent confirmatory trials (eg, inclusion/exclusion criteria). The focus will be on the magnitude of the effect, as recommended by Kraemer et al [103], not on significance. Fixed effects linear regression models will be used for the exploratory analyses of moderators. The dependent variable (HbA_{1c}) will be expressed as a change from baseline to treatment endpoint. Independent variables include treatment and one hypothesized moderating effect per model. To demonstrate evidence of the

effect of each hypothesized moderator, there must be a treatment by moderator interaction with $R^2 \geq .05$. Treatment effect sizes will be estimated for each level of the moderator.

The hypothesis that SDT constructs (autonomy, self-efficacy, and the patient-provider relationship) will mediate intervention effects on primary outcomes at the end of treatment (2 months) and at follow-up (6 months) will also be assessed using fixed effects linear regression models. The dependent variable will be change in the primary outcome from baseline to months 2 and 6. Independent variables will include treatment and one hypothesized mediating effect (specified as change from baseline to months 2 and 6). Initially, the main effects will be tested with subsequent models examining the incremental contribution of the treatment by mediator interaction. Either a main effect of the mediator or treatment by mediator interaction would provide evidence of a mediator effect [103].

Attrition introduces bias and reduces power, precision, and generalizability [104]. To offset these threats and in keeping with the intention-to-treat principle, intervention termination and study termination will be distinguished, and all efforts to continue study assessments for the entire course of the study, even among those who do not continue with randomized treatment, will be undertaken [105]. The proposed mixed-effects models will incorporate all available data, even from subjects who do not complete the trial. Mixed-effects models yield valid inferences assuming ignorable attrition [106]. Two approaches will be used to examine the sensitivity of the assumption of ignorable attrition. First, we will use a pattern mixture model [107] to examine response to treatment among participants with various dropout patterns and implemented using a longitudinal strategy [108]. Second, we will ask subjects at each assessment session to rate their *intent-to-attend* the next assessment session on a Likert scale and, at baseline, to rate their intent to complete the study [109]. This variable will be used in sensitivity analyses as a baseline covariate. Estimates of the treatment effect from the models described above will be compared with models that also include the main effects of either dropout pattern or intent-to-attend.

Results

At the writing of this report, intervention refinement activities are underway. As of July 2020, 20 participants have been enrolled and have completed a qualitative interview after reviewing one or more intervention components. The interventions are being further refined in response to this feedback. Analysis of interview data are underway, with a report of these results anticipated in the fall of 2020. The clinical trial phase is contingent on the intervention refinement activities and, thus, will be launched in the fall 2020. Participant enrollment is scheduled through May 2023, with intervention delivery wrapping up about 1 month later, in June 2023. Data collection activities will continue through November 2023, at which point study activities will focus on data analysis, dissemination, and preparing the next phase of the research, for example, developing an effectiveness trial proposal.

Discussion

This research addresses the problem of poor diabetes management among adolescents that persists into early adulthood. We leverage the developmental needs of older adolescents/emerging adults for independence and autonomy in the construction of a multicomponent intervention that translates a basic social science theory, SDT, into three autonomy-supportive intervention components with demonstrated efficacy in similar populations and/or problems: a QPL, a MES (an eHealth intervention), and text message reminders. These intervention components will be vetted by the target population of emerging adults and then efficacy tested using the MOST, an efficient method of intervention development resulting in a potent, efficacious multicomponent intervention.

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Conflicts of Interest

SO is a part owner of Interva, Inc. All other authors have no conflicts of interest to report.

Multimedia Appendix 1
National Institute of Diabetes, Digestive, and Kidney Diseases peer reviews.
[PDF File (Adobe PDF File), 177 KB - resprot_v9i10e20191_app1.pdf]

References

1. American Diabetes Association. Standards of medical care in diabetes-2014. Diabetes Care 2014 Jan;37 Suppl 1:S14-S80. [doi: 10.2337/dc14-S014] [Medline: 24357209]
2. Gonder-Frederick LA, Cox DJ, Ritterband LM. Diabetes and behavioral medicine: the second decade. J Consult Clin Psychol 2002 Jun;70(3):611-625. [doi: 10.1037//0022-006x.70.3.611] [Medline: 12090372]
3. Arnett JJ. Emerging adulthood a theory of development from the late teens through the twenties. Am Psychol 2000 May;55(5):469-480. [Medline: 10842426]

4. Wiebe DJ, Helgeson V, Berg CA. The social context of managing diabetes across the life span. Am Psychol 2016 Oct;71(7):526-538 [FREE Full text] [doi: 10.1037/a0040355] [Medline: 27690482]
5. Weissberg-Benchell J, Wolpert H, Anderson BJ. Transitioning from pediatric to adult care: a new approach to the post-adolescent young person with type 1 diabetes. Diabetes Care 2007 Oct;30(10):2441-2446. [doi: 10.2337/dc07-1249] [Medline: 17666466]
6. Keough L, Sullivan-Bolyai S, Crawford S, Schilling L, Dixon J. Self-management of type 1 diabetes across adolescence. Diabetes Educ 2011;37(4):486-500. [doi: 10.1177/0145721711406140] [Medline: 21602489]
7. McCarthy MM, Grey M. Type 1 diabetes self-management from emerging adulthood through older adulthood. Diabetes Care 2018 Aug;41(8):1608-1614. [doi: 10.2337/dc17-2597] [Medline: 29802144]
8. van Walleghem N, Macdonald CA, Dean HJ. Evaluation of a systems navigator model for transition from pediatric to adult care for young adults with type 1 diabetes. Diabetes Care 2008 Aug;31(8):1529-1530 [FREE Full text] [doi: 10.2337/dc07-2247] [Medline: 18458141]
9. Callahan ST, Cooper WO. Changes in ambulatory health care use during the transition to young adulthood. J Adolesc Health 2010 May;46(5):407-413. [doi: 10.1016/j.jadohealth.2009.09.010] [Medline: 20413075]
10. Fortuna RJ, Robbins BW, Mani N, Halterman JS. Dependence on emergency care among young adults in the United States. J Gen Intern Med 2010 Jul;25(7):663-669 [FREE Full text] [doi: 10.1007/s11606-010-1313-1] [Medline: 20306149]
11. Bryden KS, Dunger DB, Mayou RA, Peveler RC, W Neil HA. Poor prognosis of young adults with type 1 diabetes: a longitudinal study. Diabetes Care 2003 Apr;26(4):1052-1057. [doi: 10.2337/diacare.26.4.1052] [Medline: 12663572]
12. Helgeson VS, Siminerio L, Escobar O, Becker D. Predictors of metabolic control among adolescents with diabetes: a 4-year longitudinal study. J Pediatr Psychol 2009 Apr;34(3):254-270 [FREE Full text] [doi: 10.1093/jpepsy/jsn079] [Medline: 18667479]
13. Haller MJ, Stalvey MS, Silverstein JH. Predictors of control of diabetes: monitoring may be the key. J Pediatr 2004 May;144(5):660-661. [doi: 10.1016/j.jpeds.2003.12.042] [Medline: 15127007]
14. Silverstein J, Klingensmith G, Copeland K, Plotnick L, Kaufman F, Laffel L, American Diabetes Association. Care of children and adolescents with type 1 diabetes: a statement of the american diabetes association. Diabetes Care 2005 Jan;28(1):186-212. [doi: 10.2337/diacare.28.1.186] [Medline: 15616254]
15. Hilliard ME, Powell PW, Anderson BJ. Evidence-based behavioral interventions to promote diabetes management in children, adolescents, and families. Am Psychol 2016 Oct;71(7):590-601 [FREE Full text] [doi: 10.1037/a0040359] [Medline: 27690487]
16. Williams GC, Deci EL, Ryan RM. Building healthcare partnerships by supporting autonomy: promoting maintained behavior change and positive health outcomes. In: Suchman AL, Botelho RJ, Hinton–Walker P, editors. Partnerships in Healthcare: Transforming Relational Process. Rochester, NY: University of Rochester Press; 1998:67-87.
17. Deci EL, Ryan RM. Intrinsic Motivation and Self-Determination in Human Behavior. New York, USA: Springer US; 1985:372.
18. Ryan RM, Deci EL. Self-determination theory and the facilitation of intrinsic motivation, social development, and well-being. Am Psychol 2000 Jan;55(1):68-78. [doi: 10.1037//0003-066x.55.1.68] [Medline: 11392867]
19. Williams GC, Lynch M, Glasgow RE. Computer-assisted intervention improves patient-centered diabetes care by increasing autonomy support. Health Psychol 2007 Nov;26(6):728-734. [doi: 10.1037/0278-6133.26.6.728] [Medline: 18020845]
20. Williams GC, Freedman ZR, Deci EL. Supporting autonomy to motivate patients with diabetes for glucose control. Diabetes Care 1998 Oct;21(10):1644-1651. [doi: 10.2337/diacare.21.10.1644] [Medline: 9773724]
21. Williams GC, McGregor HA, Zeldman A, Freedman ZR, Deci EL. Testing a self-determination theory process model for promoting glycemic control through diabetes self-management. Health Psychol 2004 Jan;23(1):58-66. [doi: 10.1037/0278-6133.23.1.58] [Medline: 14756604]
22. Williams GC, McGregor H, Zeldman A, Freedman ZR, Deci EL, Elder D. Promoting glycemic control through diabetes self-management: evaluating a patient activation intervention. Patient Educ Couns 2005 Jan;56(1):28-34. [doi: 10.1016/j.pec.2003.11.008] [Medline: 15590220]
23. Husted GR, Thorsteinsson B, Esbensen BA, Gluud C, Winkel P, Hommel E, et al. Effect of guided self-determination youth intervention integrated into outpatient visits versus treatment as usual on glycemic control and life skills: a randomized clinical trial in adolescents with type 1 diabetes. Trials 2014 Aug 12;15:321 [FREE Full text] [doi: 10.1186/1745-6215-15-321] [Medline: 25118146]
24. Hill E, Sibthorp J. Autonomy support at diabetes camp: a self determination theory approach to therapeutic recreation. Ther Recreation J 2006;40(2):107-125 [FREE Full text]
25. Datye KA, Moore DJ, Russell WE, Jaser SS. A review of adolescent adherence in type 1 diabetes and the untapped potential of diabetes providers to improve outcomes. Curr Diab Rep 2015 Aug;15(8):51 [FREE Full text] [doi: 10.1007/s11892-015-0621-6] [Medline: 26084580]
26. Sansoni JE, Grootemaat P, Duncan C. Question prompt lists in health consultations: a review. Patient Educ Couns 2015 Jun 03 ePub ahead of print. [doi: 10.1016/j.pec.2015.05.015] [Medline: 26104993]

27. Brandes K, Linn AJ, Butow PN, van Weert JC. The characteristics and effectiveness of question prompt list interventions in oncology: a systematic review of the literature. Psychooncology 2015 Mar;24(3):245-252. [doi: 10.1002/pon.3637] [Medline: 25082386]
28. Brandes K, Butow PN, Tattersall MH, Clayton JM, Davidson PM, Young J, et al. Advanced cancer patients' and caregivers' use of a question prompt List. Patient Educ Couns 2014 Oct;97(1):30-37. [doi: 10.1016/j.pec.2014.06.010] [Medline: 25023487]
29. Rodenbach RA, Brandes K, Fiscella K, Kravitz RL, Butow PN, Walczak A, et al. Promoting end-of-life discussions in advanced cancer: effects of patient coaching and question prompt lists. J Clin Oncol 2017 Mar 10;35(8):842-851 [FREE Full text] [doi: 10.1200/JCO.2016.68.5651] [Medline: 28135140]
30. Dimoska A, Butow PN, Lynch J, Hovey E, Agar M, Beale P, et al. Implementing patient question-prompt lists into routine cancer care. Patient Educ Couns 2012 Feb;86(2):252-258. [doi: 10.1016/j.pec.2011.04.020] [Medline: 21741195]
31. Sleath B, Carpenter DM, Davis SA, Watson CH, Lee C, Loughlin CE, et al. Acceptance of a pre-visit intervention to engage teens in pediatric asthma visits. Patient Educ Couns 2017 Nov;100(11):2005-2011 [FREE Full text] [doi: 10.1016/j.pec.2017.05.013] [Medline: 28550963]
32. Rollnick S, Miller WR. Motivational Interviewing: Preparing People to Change Addictive Behavior. New York, USA: The Guilford Press; 1992.
33. Miller W, Rollnick S. Motivational Interviewing: Preparing People for Change. Second Edition. New York, USA: The Guilford Press; 2002.
34. Miller WR, Rollnick S. Motivational Interviewing: Helping People Change. Third Edition. New York, USA: The Guilford Press; 2012.
35. Outlaw AY, Naar-King S, Tanney M, Belzer ME, Aagenes A, Parsons JT, Adolescent Medicine Trials Network for HIV/AIDS Interventions. The initial feasibility of a computer-based motivational intervention for adherence for youth newly recommended to start antiretroviral treatment. AIDS Care 2014 Jan;26(1):130-135 [FREE Full text] [doi: 10.1080/09540121.2013.813624] [Medline: 23869650]
36. Kolmodin MacDonell K, Naar S, Gibson-Scipio W, Lam P, Secord E. The Detroit Young Adult Asthma Project: Pilot of a Technology-Based Medication Adherence Intervention for African-American Emerging Adults. J Adolesc Health 2016 Oct;59(4):465-471 [FREE Full text] [doi: 10.1016/j.jadohealth.2016.05.016] [Medline: 27475032]
37. Naar-King S, Outlaw AY, Sarr M, Parsons JT, Belzer M, Macdonell K, Adolescent Medicine Network for HIV/AIDS Interventions. Motivational enhancement system for adherence (MESA): pilot randomized trial of a brief computer-delivered prevention intervention for youth initiating antiretroviral treatment. J Pediatr Psychol 2013 Jul;38(6):638-648 [FREE Full text] [doi: 10.1093/jpepsy/jss132] [Medline: 23359664]
38. Kolmodin MacDonell K, Naar S, Gibson-Scipio W, Lam P, Secord E. The Detroit Young Adult Asthma Project: Pilot of a Technology-Based Medication Adherence Intervention for African-American Emerging Adults. J Adolesc Health 2016 Oct;59(4):465-471 [FREE Full text] [doi: 10.1016/j.jadohealth.2016.05.016] [Medline: 27475032]
39. Kolmodin MacDonell K, Naar S, Gibson-Scipio W, Lam P, Secord E. The Detroit Young Adult Asthma Project: Pilot of a Technology-Based Medication Adherence Intervention for African-American Emerging Adults. J Adolesc Health 2016 Oct;59(4):465-471 [FREE Full text] [doi: 10.1016/j.jadohealth.2016.05.016] [Medline: 27475032]
40. Ellis DA, Carcone AI, Ondersma SJ, Naar-King S, Dekelbab B, Moltz K. Brief computer-delivered intervention to increase parental monitoring in families of african american adolescents with type 1 diabetes: a randomized controlled trial. Telemed J E Health 2017 Jun;23(6):493-502 [FREE Full text] [doi: 10.1089/tmj.2016.0182] [Medline: 28061319]
41. Rajkumar D, Ellis DA, May DK, Carcone A, Naar-King S, Ondersma S, et al. Computerized intervention to increase motivation for diabetes self-management in adolescents with type 1 diabetes. Health Psychol Behav Med 2015;3(1):236-250 [FREE Full text] [doi: 10.1080/21642850.2015.1079716] [Medline: 26973800]
42. Arora S, Peters AL, Agy C, Menchine M. A mobile health intervention for inner city patients with poorly controlled diabetes: proof-of-concept of the TExT-MED program. Diabetes Technol Ther 2012 Jun;14(6):492-496. [doi: 10.1089/dia.2011.0252] [Medline: 22524591]
43. Dick JJ, Nundy S, Solomon MC, Bishop KN, Chin MH, Peek ME. Feasibility and usability of a text message-based program for diabetes self-management in an urban African-American population. J Diabetes Sci Technol 2011 Sep 1;5(5):1246-1254 [FREE Full text] [doi: 10.1177/193229681100500534] [Medline: 22027326]
44. Nundy S, Dick JJ, Solomon MC, Peek ME. Developing a behavioral model for mobile phone-based diabetes interventions. Patient Educ Couns 2013 Jan;90(1):125-132 [FREE Full text] [doi: 10.1016/j.pec.2012.09.008] [Medline: 23063349]
45. Nundy S, Mishra A, Hogan P, Lee SM, Solomon MC, Peek ME. How do mobile phone diabetes programs drive behavior change? evidence from a mixed methods observational cohort study. Diabetes Educ 2014;40(6):806-819 [FREE Full text] [doi: 10.1177/0145721714551992] [Medline: 25278512]
46. Franklin VL, Waller A, Pagliari C, Greene SA. A randomized controlled trial of sweet talk, a text-messaging system to support young people with diabetes. Diabet Med 2006 Dec;23(12):1332-1338. [doi: 10.1111/j.1464-5491.2006.01989.x] [Medline: 17116184]
47. Fischer HH, Moore SL, Ginosar D, Davidson AJ, Rice-Peterson CM, Durfee MJ, et al. Care by cell phone: text messaging for chronic disease management. Am J Manag Care 2012 Feb 1;18(2):e42-e47 [FREE Full text] [Medline: 22435883]

48. Collins L, Murphy S, Nair V, Strecher V. A strategy for optimizing and evaluating behavioral interventions. Ann Behav Med 2005 Aug;30(1):65-73. [doi: 10.1207/s15324796abm3001_8] [Medline: 16097907]
49. Collins LM, Kugler KC, Gwadz MV. Optimization of multicomponent behavioral and biobehavioral interventions for the prevention and treatment of HIV/AIDS. AIDS Behav 2016 Jan;20 Suppl 1:S197-S214 [FREE Full text] [doi: 10.1007/s10461-015-1145-4] [Medline: 26238037]
50. Auslander WF, Thompson S, Dreitzer D, White NH, Santiago JV. Disparity in glycemic control and adherence between African-American and caucasian youths with diabetes. Family and community contexts. Diabetes Care 1997 Oct;20(10):1569-1575. [doi: 10.2337/diacare.20.10.1569] [Medline: 9314637]
51. Matts JP, Lachin JM. Properties of permuted-block randomization in clinical trials. Control Clin Trials 1988 Dec;9(4):327-344. [doi: 10.1016/0197-2456(88)90047-5] [Medline: 3203524]
52. Rollnick S, Miller WR, Butler CC. Motivational Interviewing in Health Care: Helping Patients Change Behavior. New York, USA: Guilford Press; 2007.
53. Markland D, Ryan R, Tobin V, Rollnick S. Motivational Interviewing and Self–Determination Theory. Journal of Social and Clinical Psychology 2005 Sep;24(6):811-831 [FREE Full text] [doi: 10.1521/jscp.2005.24.6.811]
54. Ryan RM, Lynch MF, Vansteenkiste M, Deci EL. Motivation and Autonomy in Counseling, Psychotherapy, and Behavior Change: A Look at Theory and Practice 1ψ7. The Counseling Psychologist 2010 Feb 10;39(2):193-260. [doi: 10.1177/0011000009359313]
55. Miller WR, Rollnick S. Ten things that motivational interviewing is not. Behav Cogn Psychother 2009 Mar;37(2):129-140. [doi: 10.1017/S1352465809005128] [Medline: 19364414]
56. Miller WR, Rose GS. Toward a theory of motivational interviewing. Am Psychol 2009 Sep;64(6):527-537 [FREE Full text] [doi: 10.1037/a0016830] [Medline: 19739882]
57. Apodaca TR, Longabaugh R. Mechanisms of change in motivational interviewing: a review and preliminary evaluation of the evidence. Addiction 2009 May;104(5):705-715 [FREE Full text] [doi: 10.1111/j.1360-0443.2009.02527.x] [Medline: 19413785]
58. Moyers TB, Martin T. Therapist influence on client language during motivational interviewing sessions. J Subst Abuse Treat 2006 Apr;30(3):245-251. [doi: 10.1016/j.jsat.2005.12.003] [Medline: 16616169]
59. Moyers TB, Martin T, Christopher PJ, Houck JM, Tonigan JS, Amrhein PC. Client language as a mediator of motivational interviewing efficacy: where is the evidence? Alcohol Clin Exp Res 2007 Oct;31(10 Suppl):40s-47s. [doi: 10.1111/j.1530-0277.2007.00492.x] [Medline: 17880345]
60. Moyers TB, Martin T, Houck JM, Christopher PJ, Tonigan JS. From in-session behaviors to drinking outcomes: a causal chain for motivational interviewing. J Consult Clin Psychol 2009 Dec;77(6):1113-1124 [FREE Full text] [doi: 10.1037/a0017189] [Medline: 19968387]
61. Gaume J, Bertholet N, Faouzi M, Gmel G, Daeppen J. Counselor motivational interviewing skills and young adult change talk articulation during brief motivational interventions. J Subst Abuse Treat 2010 Oct;39(3):272-281. [doi: 10.1016/j.jsat.2010.06.010] [Medline: 20708900]
62. Gaume J, Gmel G, Faouzi M, Daeppen J. Counsellor behaviours and patient language during brief motivational interventions: a sequential analysis of speech. Addiction 2008 Nov;103(11):1793-1800. [doi: 10.1111/j.1360-0443.2008.02337.x] [Medline: 19032529]
63. Glynn LH, Moyers TB. Chasing change talk: the clinician's role in evoking client language about change. J Subst Abuse Treat 2010 Jul;39(1):65-70. [doi: 10.1016/j.jsat.2010.03.012] [Medline: 20418049]
64. McCambridge J, Day M, Thomas BA, Strang J. Fidelity to Motivational Interviewing and subsequent cannabis cessation among adolescents. Addict Behav 2011 Jul;36(7):749-754. [doi: 10.1016/j.addbeh.2011.03.002] [Medline: 21440994]
65. Glynn L, Houck J, Moyers T, Bryan A, Montanaro E. Are Change Talk And Sustain Talk Contagious in Groups? Sequential Probabilities and Safer-Sex Outcomes in Alcohol-and Marijuana-Using Adolescents. Alcoholism-Clinical and Experimental Research 2014: Wiley-Blackwell. Alcoholism: Clinical and Experimental Research 2014;38(s1).
66. Gaume J, Bertholet N, Faouzi M, Gmel G, Daeppen J. Counselor motivational interviewing skills and young adult change talk articulation during brief motivational interventions. J Subst Abuse Treat 2010 Oct;39(3):272-281. [doi: 10.1016/j.jsat.2010.06.010] [Medline: 20708900]
67. Carcone AI, Naar-King S, Brogan KE, Albrecht T, Barton E, Foster T, et al. Provider communication behaviors that predict motivation to change in black adolescents with obesity. J Dev Behav Pediatr 2013 Oct;34(8):599-608 [FREE Full text] [doi: 10.1097/DBP.0b013e3182a67daf] [Medline: 24131883]
68. Jacques-Tiura AJ, Carcone AI, Naar S, Brogan Hartlieb K, Albrecht TL, Barton E. Building motivation in african american caregivers of adolescents with obesity: application of sequential analysis. J Pediatr Psychol 2017 Mar 1;42(2):131-141 [FREE Full text] [doi: 10.1093/jpepsy/jsw044] [Medline: 27246865]
69. Perrin A, Duggan M. Americans' internet access 2000-2015. Pew Research Center. 2015. URL: https://www.pewresearch.org/internet/2015/06/26/americans-internet-access-2000-2015/ [accessed 2020-09-30]
70. Aoki K, Downes EJ. An analysis of young people's use of and attitudes toward cell phones. Telematics and Informatics 2003 Nov;20(4):349-364. [doi: 10.1016/s0736-5853(03)00018-2]

71. Auter PJ. Portable social groups: willingness to communicate, interpersonal communication gratifications, and cell phone use among young adults. IJMC 2007;5(2):139. [doi: 10.1504/ijmc.2007.011813]
72. Fotheringham MJ, Wonnacott RL, Owen N. Computer use and physical inactivity in young adults: public health perils and potentials of new information technologies. Ann Behav Med 2000;22(4):269-275. [doi: 10.1007/BF02895662] [Medline: 11253437]
73. Street RL, Slee C, Kalauokalani DK, Dean DE, Tancredi DJ, Kravitz RL. Improving physician-patient communication about cancer pain with a tailored education-coaching intervention. Patient Educ Couns 2010 Jul;80(1):42-47 [FREE Full text] [doi: 10.1016/j.pec.2009.10.009] [Medline: 19962845]
74. Fisher JD, Fisher WA. Changing AIDS-risk behavior. Psychol Bull 1992 May;111(3):455-474. [doi: 10.1037/0033-2909.111.3.455] [Medline: 1594721]
75. Fisher W, Fisher J, Harman J. The Information-Motivation-Behavioral Skills Model: A general social psychological approach to understandingpromoting health behavior. Jerry Suls KAW. editor2003. 82-106 p 2020:A. [doi: 10.1002/9780470753552.ch4]
76. Appel J, von der Pütten A, Krämer NC, Gratch J. Does Humanity Matter? Analyzing the Importance of Social Cues and Perceived Agency of a Computer System for the Emergence of Social Reactions during Human-Computer Interaction. Advances in Human-Computer Interaction 2012;2012:1-10. [doi: 10.1155/2012/324694]
77. Herbert L, Owen V, Pascarella L, Streisand R. Text message interventions for children and adolescents with type 1 diabetes: a systematic review. Diabetes Technol Ther 2013 May;15(5):362-370. [doi: 10.1089/dia.2012.0291] [Medline: 23550554]
78. A1c Home Test Kit. DTI Laboratories Inc. 2004. URL: https://www.dtilaboratories.com/accubase-a1c-test-kit.html [accessed 2020-09-30]
79. Ellis DA, Naar-King S, Frey M, Templin T, Rowland M, Greger N. Use of Multisystemic Therapy to Improve Regimen Adherence Among Adolescents with Type 1 Diabetes in Poor Metabolic Control: A Pilot Investigation. Journal of Clinical Psychology in Medical Settings 2004 Dec;11(4):315-324. [doi: 10.1023/b:jocs.0000045351.98563.4d] [Medline: 15983308]
80. Ellis DA, Naar-King S, Chen X, Moltz K, Cunningham PB, Idalski-Carcone A. Multisystemic therapy compared to telephone support for youth with poorly controlled diabetes: findings from a randomized controlled trial. Ann Behav Med 2012 Oct;44(2):207-215 [FREE Full text] [doi: 10.1007/s12160-012-9378-1] [Medline: 22644587]
81. Levesque CS, Williams GC, Elliot D, Pickering MA, Bodenhamer B, Finley PJ. Validating the theoretical structure of the treatment self-regulation questionnaire (TSRQ) across three different health behaviors. Health Educ Res 2007 Oct;22(5):691-702. [doi: 10.1093/her/cyl148] [Medline: 17138613]
82. Grolnick WS, Ryan RM. Parent styles associated with children's self-regulation and competence in school. Journal of Educational Psychology 1989;81(2):143-154. [doi: 10.1037/0022-0663.81.2.143]
83. Stott N, Rollnick S, Rees M, Pill R. Innovation in clinical method: diabetes care and negotiating skills. Fam Pract 1995 Dec;12(4):413-418. [doi: 10.1093/fampra/12.4.413] [Medline: 8826057]
84. MacDonell KE, Naar-King S, Murphy DA, Parsons JT, Harper GW. Predictors of Medication Adherence in High Risk Youth of Color Living with HIV. Journal of Pediatric Psychology 2009 Sep 15;35(6):593-601. [doi: 10.1093/jpepsy/jsp080] [Medline: 19755495]
85. MacDonell K, Ellis D, Naar-King S, Cunningham P. Predictors of Home-Based Obesity Treatment Efficacy for African American Youth. Children's Health Care 2010 Jan 21;39(1):1-14. [doi: 10.1080/02739610903455087]
86. Gunnarsdottir T, Njardvik U, Olafsdottir AS, Craighead LW, Bjarnason R. The Role of Parental Motivation in Family-Based Treatment for Childhood Obesity. Obesity 2011 Mar 31;19(8):1654-1662. [doi: 10.1038/oby.2011.59] [Medline: 25181608]
87. Ellis D, Berio H, Carcone A, Naar-King S. Adolescent and Parent Motivation for Change Affects Psychotherapy Outcomes Among Youth With Poorly Controlled Diabetes. Journal of pediatric psychology 2012;37(1):75-84. [doi: 10.1093/jpepsy/jsr072] [Medline: 21933812]
88. Anderson RM, Funnell MM, Fitzgerald JT, Marrero DG. The Diabetes Empowerment Scale: a measure of psychosocial self-efficacy. Diabetes Care 2000 Jun 01;23(6):739-743. [doi: 10.2337/diacare.23.6.739]
89. Smith MS, Wallston KA, Smith CA. The development and validation of the perceived health competence scale. Health Educ Res 1995 Mar;10(1):51-64. [doi: 10.1093/her/10.1.51] [Medline: 10150421]
90. Anderson RM, Fitzgerald JT, Gruppen LD, Funnell MM, Oh MS. The diabetes empowerment scale-short form (DES-SF). Diabetes Care 2003 May;26(5):1641-1642. [doi: 10.2337/diacare.26.5.1641-a] [Medline: 12716841]
91. Gensichen J, von Korff M, Rutter CM, Seelig MD, Ludman EJ, Lin EH, et al. Physician support for diabetes patients and clinical outcomes. BMC Public Health 2009 Sep 29;9:367 [FREE Full text] [doi: 10.1186/1471-2458-9-367] [Medline: 19788726]
92. Street RL, Gordon H, Haidet P. Physicians' communication and perceptions of patients: is it how they look, how they talk, or is it just the doctor? Soc Sci Med 2007 Aug;65(3):586-598 [FREE Full text] [doi: 10.1016/j.socscimed.2007.03.036] [Medline: 17462801]
93. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. Diabetes Care 2001 Jun;24(6):1069-1078. [doi: 10.2337/diacare.24.6.1069] [Medline: 11375373]
94. Grey M, Whittemore R, Tamborlane W. Depression in type 1 diabetes in children: natural history and correlates. J Psychosom Res 2002 Oct;53(4):907-911. [doi: 10.1016/s0022-3999(02)00312-4] [Medline: 12377302]

95. Jerant A, Kravitz R, Moore-Hill M, Franks P. Depressive symptoms moderated the effect of chronic illness self-management training on self-efficacy. Med Care 2008 May;46(5):523-531. [doi: 10.1097/MLR.0b013e31815f53a4] [Medline: 18438201]
96. Radloff LS. The CES-D scale: A self-report depression scale for research in the general population. Applied Psychological Measurement 1977;1(3):385-401 [FREE Full text]
97. Radloff LS. The use of the center for epidemiologic studies depression scale in adolescents and young adults. J Youth Adolesc 1991 Apr;20(2):149-166. [doi: 10.1007/BF01537606] [Medline: 24265004]
98. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC Med Res Methodol 2013 Sep 18;13:117 [FREE Full text] [doi: 10.1186/1471-2288-13-117] [Medline: 24047204]
99. Francis JJ, Johnston M, Robertson C, Glidewell L, Entwistle V, Eccles MP, et al. What is an adequate sample size? operationalising data saturation for theory-based interview studies. Psychol Health 2010 Dec;25(10):1229-1245. [doi: 10.1080/08870440903194015] [Medline: 20204937]
100. Collins LM, Trail JB, Kugler KC, Baker TB, Piper ME, Mermelstein RJ. Evaluating individual intervention components: making decisions based on the results of a factorial screening experiment. Transl Behav Med 2014 Sep;4(3):238-251 [FREE Full text] [doi: 10.1007/s13142-013-0239-7] [Medline: 25264464]
101. Chakraborty B, Collins LM, Strecher VJ, Murphy SA. Developing multicomponent interventions using fractional factorial designs. Stat Med 2009 Sep 20;28(21):2687-2708 [FREE Full text] [doi: 10.1002/sim.3643] [Medline: 19575485]
102. Leon AC. Multiplicity-adjusted sample size requirements: a strategy to maintain statistical power with bonferroni adjustments. J Clin Psychiatry 2004 Nov;65(11):1511-1514. [Medline: 15554764]
103. Kraemer HC, Mintz J, Noda A, Tinklenberg J, Yesavage JA. Caution regarding the use of pilot studies to guide power calculations for study proposals. Arch Gen Psychiatry 2006 May;63(5):484-489. [doi: 10.1001/archpsyc.63.5.484] [Medline: 16651505]
104. Leon AC, Mallinckrodt CH, Chuang-Stein C, Archibald DG, Archer GE, Chartier K. Attrition in randomized controlled clinical trials: methodological issues in psychopharmacology. Biol Psychiatry 2006 Jun 1;59(11):1001-1005. [doi: 10.1016/j.biopsych.2005.10.020] [Medline: 16503329]
105. Lavori PW. Clinical trials in psychiatry: should protocol deviation censor patient data? Neuropsychopharmacology 1992 Jan;6(1):39-48; discussion 49. [Medline: 1571068]
106. Laird NM. Missing data in longitudinal studies. Stat Med 1988;7(1-2):305-315. [doi: 10.1002/sim.4780070131] [Medline: 3353609]
107. Little RJ, Wang Y. Pattern-mixture models for multivariate incomplete data with covariates. Biometrics 1996 Mar;52(1):98-111. [Medline: 8934587]
108. Hedeker D, Gibbons R. Application of random-effects pattern-mixture models for missing data in longitudinal studies. Psychological Methods 1997;2(1):64-78. [doi: 10.1037/1082-989X.2.1.64]
109. Leon AC, Demirtas H, Hedeker D. Bias reduction with an adjustment for participants' intent to dropout of a randomized controlled clinical trial. Clin Trials 2007;4(5):540-547. [doi: 10.1177/1740774507083871] [Medline: 17942469]

Abbreviations

ANOVA: analysis of variance
CES-D: Center for Epidemiologic Studies Depression Scale
CHM: Children's Hospital of Michigan
CIAS: Computerized Intervention Authoring Software
DES: diabetes empowerment scale
DMC: Detroit Medical Center
DMS: diabetes management scale
FMA: framework matrix analysis
HbA_{1c}: hemoglobin A_{1c}
HCCQ: health care climate questionnaire
HPLC: high-performance liquid chromatography
IMB: information-motivation-behavioral skills
MES: motivation enhancement system
MI: motivational interviewing
MOST: multiphase optimization strategy
PAS: patient activation scale
PHCS: perceived health competence scale
QPL: question prompt list
RA: research assistant
SDT: self-determination theory
T1D: type 1 diabetes

TSRQ: treatment self-regulation questionnaire
UHC: University Health Center

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Protocol

A Telemonitoring and Hybrid Virtual Coaching Solution "CAir" for Patients with Chronic Obstructive Pulmonary Disease: Protocol for a Randomized Controlled Trial

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is one of the most common disorders in the world. COPD is characterized by airflow obstruction, which is not fully reversible. Patients usually experience breathing-related symptoms with periods of acute worsening and a substantial decrease in the health-related quality-of-life. Active and comprehensive disease management can slow down the progressive course of the disease and improve patients' disabilities. Technological progress and digitalization of medicine have the potential to make elaborate interventions easily accessible and applicable to a broad spectrum of patients with COPD without increasing the costs of the intervention.

Objective: This study aims to develop a comprehensive telemonitoring and hybrid virtual coaching solution and to investigate its effects on the health-related quality of life of patients with COPD.

Methods: A monocentric, assessor-blind, two-arm (intervention/control) randomized controlled trial will be performed. Participants randomized to the control group will receive usual care and a CAir Desk (custom-built home disease-monitoring device to telemonitor disease-relevant parameters) for 12 weeks, without feedback or scores of the telemonitoring efforts and virtual coaching. Participants randomized to the intervention group will receive a CAir Desk and a hybrid digital coaching intervention for 12 weeks. As a primary outcome, we will measure the delta in the health-related quality of life, which we will assess with the St. George Respiratory Questionnaire, from baseline to week 12 (the end of the intervention).

Results: The development of the CAir Desk and virtual coach has been completed. Recruitment to the trial started in September 2020. We expect to start data collection by December 2020 and expect it to last for approximately 18 months, as we follow a multiwave approach. We expect to complete data collection by mid-2022 and plan the dissemination of the results subsequently.

Conclusions: To our knowledge, this is the first study investigating a combination of telemonitoring and hybrid virtual coaching in patients with COPD. We will investigate the effectiveness, efficacy, and usability of the proposed intervention and provide evidence to further develop app-based and chatbot-based disease monitoring and interventions in COPD.

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KEYWORDS

protocol; randomized controlled trial; chronic obstructive pulmonary disease; telemonitoring; virtual coaching; disease management; chatbot; conversational agents

Introduction

Background

Chronic obstructive pulmonary disease (COPD) is a chronic lung disease commonly caused by exposure to noxious particles (primarily from smoking) and characterized by respiratory symptoms (ie, dyspnea, cough, and sputum) and airflow obstruction [1]. Patients experience persistent respiratory symptoms with periods of acute worsening (exacerbations) and a substantial decrease in health-related quality of life (HRQOL). In 2016, about 251 million people worldwide were affected by COPD [2]. COPD is projected to become the third-leading global cause of death by 2030 [3]. In addition to the health implications, COPD causes a substantial economic burden on the individual and the health care systems [4]. There is no cure for COPD. However, effective treatment such as medication, smoking cessation, and physical exercise helps to relieve symptoms and prevent exacerbations [5]. Active disease management to reduce the burden of COPD and improve HRQOL therefore plays a crucial role in the therapeutic strategy.

Effective COPD management plans follow a patient-centered approach and aim to (1) prevent disease progression through the reduction of risk factors, (2) improve exercise tolerance, (3) improve health status, and (4) relieve symptoms [5]. Best practice treatment of COPD should be multidimensional and include medical care, self-management strategies, physical activity coaching, and behavioral change approaches [6-8]. One of these evidence-based disease management programs is *Living well with COPD* [9,10]. The program was developed by a Canadian consortium and is based on a disease self-management approach that covers educational topics as well as lifestyle coaching and physical activity advice supervised by health care professionals [9]. A randomized clinical trial showed that compared to usual care in a multicenter setup, the *Living well with COPD* intervention program reduced hospital admissions due to COPD exacerbations, emergency department visits, and unscheduled physician visits and improved HRQOL significantly [9]. A recent clinical trial conducted in Switzerland confirmed these results [8]. The implementation of the program, however, is both time and cost intensive.

Technological progress and the digitalization of medicine have the potential to make comprehensive interventions such as the *Living well with COPD* program easily accessible and applicable to a broad spectrum of patients with COPD without increasing the costs of the intervention. Prior research has proven the effectivity and efficiency of novel treatment solutions that incorporate telemonitoring and virtual coaching [11]. To our knowledge, however, no clinical trial has been conducted with a multimodal intervention based on the concept of *Living well with COPD* that is delivered remotely.

To fill this gap in research, we, a consortium between IBM Research, docdok.health, the University Hospital Zurich, and the Swiss Federal Institute of Technology developed a comprehensive telemonitoring and hybrid virtual coaching solution called CAir, which is based on the *Living well with COPD* program, and will investigate its effects on the HRQOL in patients with COPD.

Hypotheses

The primary outcome of this study is the assessment of patients' change in HRQOL, which we will evaluate with the St. George Respiratory Questionnaire (SGRQ) [12], a survey specifically designed for patients with chronic airflow limitations. A minimal clinically important difference of an average SGRQ score decrease of 4 units is associated with a slightly effective intervention, 8 units with a moderately effective intervention, and 12 units with a very effective intervention in patients with COPD [13].

Against this backdrop and considering the comprehensiveness of CAir, the hypotheses of this study are as follows:

1. More than 80% of the intervention group will have a ≥4-point change in SGRQ.
2. More than 40% of the intervention group will have a ≥8-point change in SGRQ.
3. More than 20% of the intervention group will have a ≥12-point change in SGRQ.
4. Approximately 10% of the control group will have a ≥4-point change in SGRQ.

We formulated the fourth hypothesis based on the Hawthorne effect [14], which states that individuals change their behaviour when they know they are being observed. This assumption is further supported by several studies in which the mean HRQOL within the control group also increased in a clinically relevant manner without any intervention [15].

Methods

We will perform a monocentric, assessor-blind, two-arm (intervention/control) randomized controlled trial. The allocation ratio between the intervention and control group will be 2:1. Bias will be minimized through randomization, allocation concealment, assessor blinding, and statistical adjustment or subgrouping during the analysis. The study is expected to have an overall duration of 18 months (first patient in, last patient out). The length of study per patient will be 12 weeks. The recruitment period will last several months.

Participants

Eligibility Criteria

Participants will be recruited from the Swiss population affected by COPD. Inclusion and exclusion criteria are outlined in Textbox 1.

Textbox 1. Inclusion and exclusion criteria and re-screening for the CAir study.

Inclusion criteria:

- Provision of written informed consent
- Age≥40 years
- Ability to speak German fluently
- Diagnosis of chronic obstructive pulmonary disease according to the Global Initiative for Chronic Obstructive Lung Disease guidelines

Exclusion criteria:

- Physical or intellectual impairment precluding informed consent or protocol adherence
- Acute or recent (within the last 6 weeks) exacerbation of chronic obstructive pulmonary disease
- Attending a pulmonary rehabilitation program within the last 3 months
- Ongoing pregnancy

Re-screening

- In case of an exacerbation less than 6 weeks prior to the study or completing a pulmonary rehabilitation less than 3 months previous to the study, patients can be included with a delay to ensure eligibility

Recruitment, Screening, and Informed Consent Procedure

Participants will be recruited directly from the outpatient clinic of the Department of Pulmonology of the University Hospital Zurich by a physician or study coordinator involved in the care, and indirectly by screening the hospital's patient database for the eligibility and ineligibility criteria (Textbox 1). In case patients meet the criteria, they will be contacted by a letter of enquiry that contains a study information sheet and a prestamped reply envelope. Those indicating interest in taking part in the study will be contacted by phone. In addition, cooperating pulmonary clinics and primary care physicians will equally screen their databases for patients fulfilling the main inclusion criteria (ie, diagnosis of COPD and age ≥40 years) and will send them study participation requests. Interested patients will then independently contact the study team of the University Hospital Zurich, which will evaluate the remaining inclusion and exclusion criteria.

We will not offer any material compensation for participating in this study. Potential participants will be informed about the scientific benefit of their participation; however, no other incentives will be offered.

All patients will be required to provide written informed consent before starting the trial. In that context, investigators will educate each participant about the nature of the study, its purpose, procedures involved, expected duration, potential risks and benefits, and any possible discomfort. Patients will also be informed that their participation is strictly voluntary and that they can withdraw from the study at any time without stating any reason. They will also be informed that withdrawing from the study will not affect subsequent medical assistance and treatment. The participants will be further advised that their medical records may be examined by authorized individuals other than their treating physician. Participants will be given sufficient time to reflect extensively on their participation.

The consent form will be signed and dated by the investigator or designee immediately following the signature of the participant. The consent form will be retained as part of the study records. A signed copy will be provided to each study participant.

Sample Size

Sample size calculations used a power of 80% and a two-sided significance level of 0.05. To increase usability reporting and account for possible dropouts, we decided to use a 2:1 (intervention:randomization) ratio and doubled the result of the sample size calculation. The sample size calculation yielded a total of 42 patients (28 intervention, 14 control). This sample size will result in an effect size of 0.9 to detect a clinically relevant between-group difference in the SGRQ.

Technological Study Setup

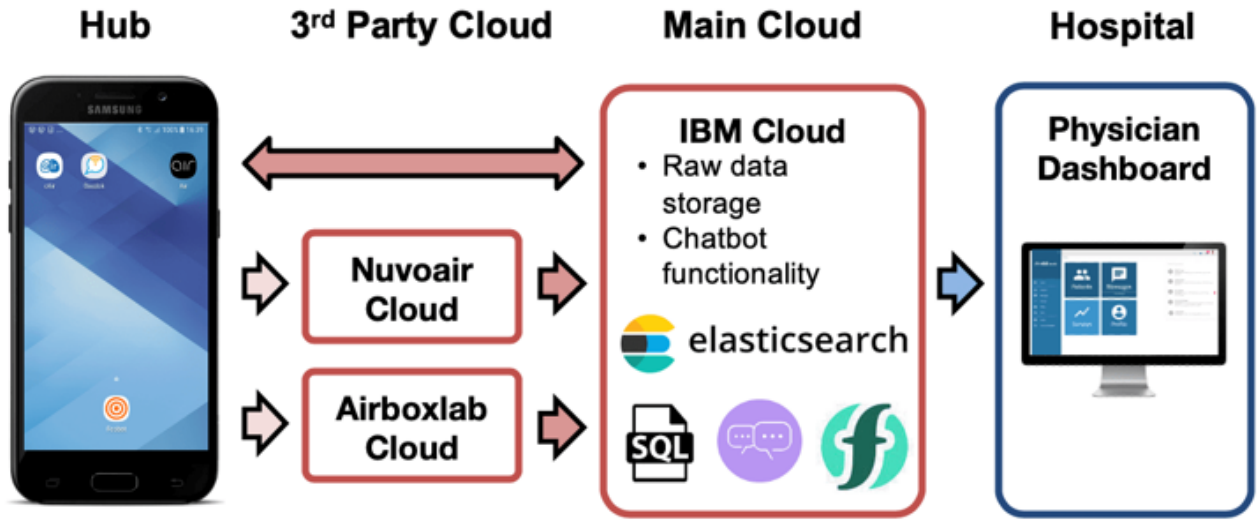
Considering proper charging and data transfer, the daily usage of multiple connected devices can be very demanding for some individuals. Thus, a selection of sensors was combined into the CAir Desk to improve usability and compliance. The CAir Desk can be placed next to the patient's bed and allows charging of all devices with a single power plug (Figure 1).

Figure 1. CAir Desk with sensors.

The smartphone serves as not only the user interface to enter questionnaires and access the symptom history through the docdok app, but also a data transfer hub from the devices to the CAir database in the IBM Cloud. Patient symptoms and the environment are tracked through a home spirometer (Air Next Spirometer, NuvoAir) to capture lung function (forced expiratory volume in 1 second/forced vital capacity), a wearable physical activty tracker (Charge 3, Fitbit Inc) to report vital signs as well as the number of daily steps as a proxy for physical activity, and the microphone and camera of the smartphone (A320, 2017, Samsung Group) to acquire nocturnal cough intensity and the color of patients' sputum as an indicator for bacterial content. Finally, the air quality and smoking behavior in the bedroom is monitored (Foobot, Airboxlab, Esch sur Alzette) through modalities like temperature and humidity, particulate matters, and volatile organic compounds in the air. This integrated approach allows the initialization, setup, and testing of all devices before the handover to the patient and thus mitigates any installations and related technical issues from the patient. To assure the on-state of the Bluetooth and WiFi hotspot channel of the smartphone, a macro app (MacroDroid, developed by ArloSoft) was enabled, triggering switch-on events after a system restart or power connection events. All unnecessary apps on the phone are suppressed by an app-blocking app (Confidant, developed by Confidant Inc.).

The CAir backend performs data collection and storage management by microservices running in the cloud (Figure 2). Patient information, device allocations, and interactions are stored in a relational database, compared to a schema-free JavaScript Object Notation object store (ElasticSearch, Lucene library) for the raw sensor data. Data are collected from the sensors in one of two ways: (1) through the third party cloud of the sensor providers and then downloaded to the CAir cloud or (2) directly from the CAir app to the CAir cloud. Patient details and daily summaries can be accessed by the study team through a web-based docdok.health physician dashboard.

Figure 2. CAir data management architecture and data flow.



Further, a CAir chatbot backend was implemented using IBM cloud functions and the IBM Watson Assistant for just-in-time interactions with the patients through a chatbot frontend provided by docdok.health. Timed triggers initiate daily conversations, such as informative sessions, physical exercises, or patient feedback through the docdok app. Further, these functions scan the databases for daily activities, degrading scores of the COPD assessment test, or nonadherence to the study protocol, notifying the study team through the docdok dashboard for health care professionals to intervene. The content and logic of the chatbot conversations are implemented using the IBM Watson Assistant, which is queried by the cloud functions to manage the conversation flow between the patient docdok app and the backend.

Intervention

Control Group

Participants randomized to the control group will receive usual care (ie, physician visits every 3-6 months and therapy according to respective treatment guidelines) and a CAir Desk for 12 weeks. The CAir Desk will assess daily symptom burden, physical activity, and spirometry data. Patients will receive daily COPD assessment questionnaires through the smartphone and will be required to wear the physical activity monitor during the day and night. The threshold for sufficient physical activity and spirometry data requires measurements on at least 3 days per week. In contrast to the intervention group, participants will not receive any feedback or scores of the telemonitoring efforts, such as the daily reported COPD assessment test and daily physical activity, nor will they receive any virtual coaching.

In case of any worsening symptoms, no alert message will be generated. Patients will have to contact their general physician or pulmonologist individually and independently. No modification of any treatment will be made by the study team during the study.

Intervention Group

Participants randomized to the intervention group will receive a CAir Desk and a hybrid digital coaching intervention for 12 weeks.

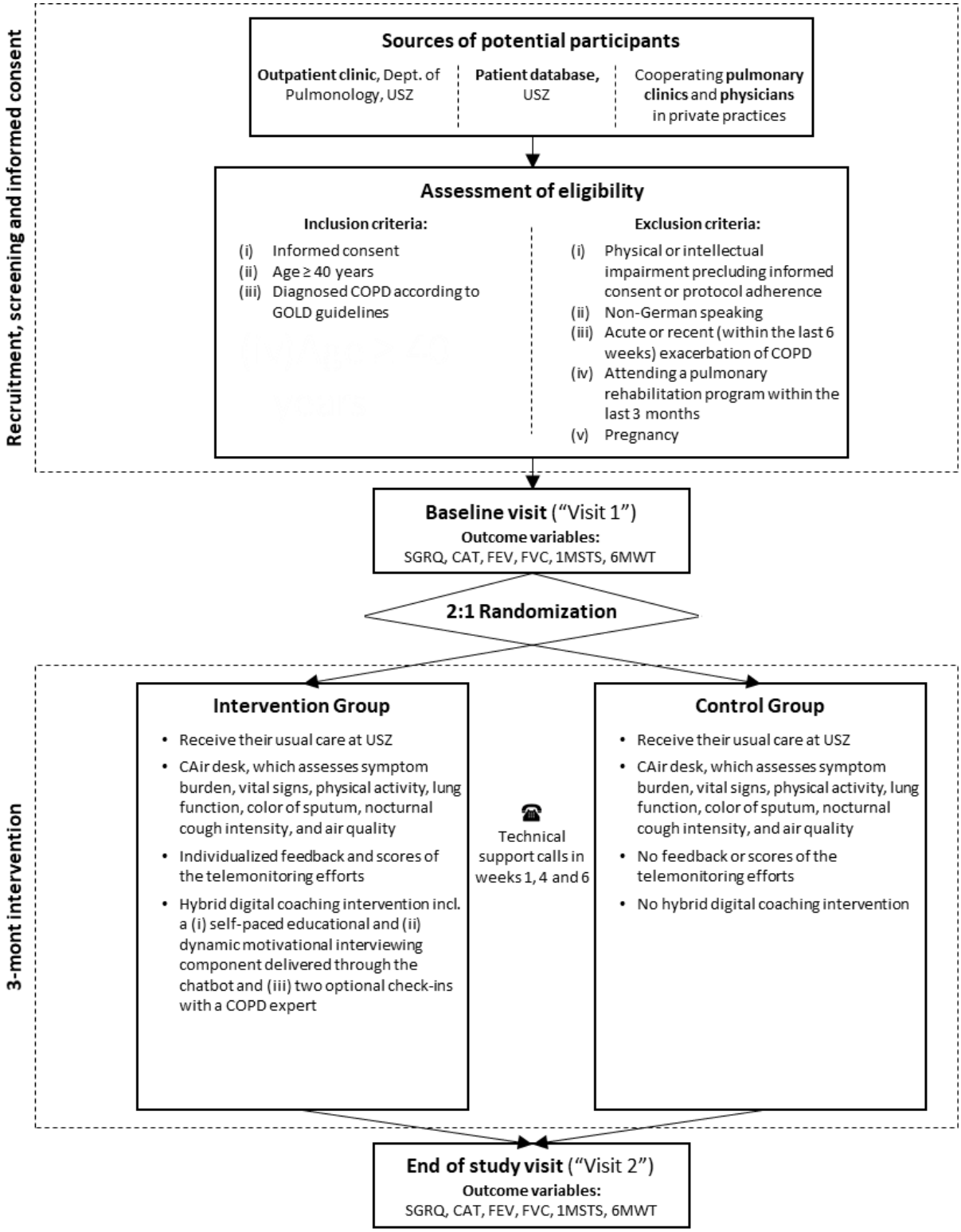
The first week will serve to measure baseline levels of daily physical activity. Starting in the second week of the study, participants will receive individualized feedback on their daily physical activity through the CAir chatbot app. We calibrated the daily target step count to be 15% above the patient's baseline value. The telemonitoring solution will send alerts to the study team in case the patient's daily COPD assessment test score drops by 2 or more points in 2 consecutive days. A 2-point drop is considered the minimum clinically relevant difference [16]. In those cases, a physician will contact patients by phone to discuss if any further actions have to be taken to treat or prevent a possible exacerbation (ie, taking medication or planning a physician visit).

In addition, the CAir chatbot will provide virtual coaching to the patients of the intervention group: (1) a self-paced educational component about living with COPD based on the *Living well with COPD* program [9] that aims to foster patient empowerment through engagement and awareness and (2) a dynamic motivational interviewing component to increase physical activity, one of the most critical behaviours that are of prognostic relevance. The chatbot is rule-based with predefined answer options only and does not have any anthropomorphic visual cues. We used IBM Watson as a development tool. Data gathered via the CAir Desk autonomously feeds into the chatbot interaction without time lag as a digital trigger, that is, the script of the chatbot automatically adapts if the patient has not achieved the required target step count.

During 2 time periods of the intervention, a COPD expert will grant optional additional support via chat, making the entire intervention a hybrid solution (involving the chatbot and human health care provider), which has been described in other studies [17].

The overall study is depicted in Figure 3.

Figure 3. CAir Study overview.



Outcomes

Primary Outcome

As a primary outcome, we will measure the delta in HRQOL, which we will assess with the SGRQ [12] from baseline to week 12 (the end of the intervention). The SGRQ is a well-established self-administered questionnaire that is valid, reliable, and responsive for the population affected by COPD. Participants will not have access to their completed questionnaires and scoring to reduce potential bias.

Secondary Outcomes

To evaluate the effectiveness of CAir holistically, we will include a set of secondary endpoints. Changes in the functional exercise capacity will be analyzed using the 1-minute sit-to-stand test and the 6-minute walk test, which have been

demonstrated to be reliable, valid, and responsive in assessing functional exercise capacity in patients with COPD [18,19].

The 1-minute sit-to-stand test is performed using a standardized protocol [18,20]. A conventional chair without armrest and a seat height of 46 cm will be used. The patient will be instructed to stand up and sit down as often as possible at a self-chosen speed over 1 minute. The number of sit-stand repetitions will be counted by the assessor. Verbal encouragement will not be provided during the test, but the patient will be told after 45 seconds that another 15 seconds are left until the test is over. Patients will be allowed to stop at any time during the test. When standing up, the patient's legs have to be completely straight, and when sitting down, the bottom has to have clear contact with the chair. The patients will be told to place their hands at the hips and will not be allowed to use their hands or arms to assist movement. Measurements of heart rate, peripheral capillary oxygen saturation, and modified Borg scale of perceived exertion [21] will be performed before and after the 1-minute sit-to-stand test using the same assessment tools as for the 6-minute walk test.

The 6-minute walk test will be performed according to technical standards of the American Thoracic Society/European Respiratory Society [22]. The test will be carried out on a marked circular 75-m hallway and patients will be told to walk as far as possible within the 6 minutes. The walking distance (in meters) will be registered at the end of the test. Patients will be allowed to take breaks during the test if necessary; time recording, however, will not be interrupted. Standardized instructions and phrases of encouragement will be given each minute. Oxygen supplementation will be installed if required, and the patients will carry their oxygen device during the test. Before and after the test, heart rate and oxygen saturation will be measured with a pulse oximeter (Masimo Rad-5v, Masimo Corp) connected to the index finger. Ratings of perceived exertion and dyspnea will be evaluated using a 0-10 modified Borg scale.

The COPD Assessment Test [23], a validated patient-completed questionnaire, will be provided daily on the smartphone to capture the gradual change in symptom burden.

Changes in spirometry will be measured daily with the forced expiratory volume in 1 second and forced vital capacity. Lung function testing will be performed according to the guidelines of the European Respiratory Association and the American Thoracic Society [24].

Total change in daily physical activity will be expressed as the number of steps per day. This will be assessed using a physical activity tracker. The device will be worn as a wrist band. Wearing times will be throughout day and night. During times of lower activity (eg, while having dinner, reading, or watching TV), the device may be placed on the CAir Desk, recharging its battery and synchronizing the data.

The number of recorded coughs per night will be used as a proxy for the total change in nightly cough. Compliance with the COPD medication will be captured daily and compared within and between the intervention and control group.

Exploratory Endpoints

Exploratory endpoints to support the analysis will also be considered. We will investigate the usability and limitations of CAir through specifically designed questionnaires (eg, usability questionnaire) and structured focus group interviews at the end of the study. In the case of an exacerbation, we will compare the data assessed by CAir before and after the event. We will also analyze air quality by continuously measuring volatile organic compounds, which are harmful organic chemicals found in products such as cleaners and in cigarette smoke. Serious adverse events related to the intervention, such as medical occurrences that require in-patient hospitalization or prolongation of existing hospitalization, will be captured as safety endpoint variables.

A detailed overview of primary, secondary, and exploratory endpoints, including their measurement frequency, is depicted in Table 1.

Table 1. Overview of the information collected during screening, at baseline, during the intervention and at the end of the study.

Outcome	Assessment	Cadence			
		Screening	Baseline visit	Within the intervention	End of study visit
Primary outcome					
Health-related quality of life	St George Respiratory Questionnaire		✓		✓
Secondary outcome					
Symptom burden	COPD[a] assessment test		✓	Daily	✓
Spirometry	Forced expiratory volume in one second		✓	Daily	✓
	Forced vital capacity		✓	Daily	✓
Functional exercise capacity	1-minute sit-to-stand test		✓		✓
	6-minute walk test		✓		✓
Compliance with COPD[a] medication	Self-reported			Daily	
Physical activity	Step count			Daily	
Cough	Night-time cough count			Daily	
Explanatory endpoints					
System usability					
	Questionnaires			Weekly	
	Focus group interviews				✓
Exacerbation and air quality					
	Ex ante data		In case of event		
	Ex post data		In case of event		
	Volatile organic compounds			Continuously	

[a]COPD: chronic obstructive pulmonary disease.

Statistical Analysis

Statistical analysis will be carried out after completing the data collection period, which will last around 18 months. We will not perform any interim analysis. We will use descriptive statistics to describe group characteristics and perform independent samples *t* tests to explore and identify potential differences at the primary endpoint (HRQOL) between the intervention and control group. We will compare the differences in the percentages of SGRQ (≥4 points) improvement between the control and intervention groups. The statistical analysis will be performed using the latest version of R (R Core Team 2019) for Windows. Missing data at the baseline and end of study visits will be handled through multiple imputation at the analysis stage. Factors prone to influence endpoints, such as gender, age, and the Global Initiative for Chronic Obstructive Lung Disease classification, will be assessed and accounted for in the analysis and interpretation of the data.

Ethics and Dissemination

The study has received approval by the Ethics Committee of the Canton of Zurich and was registered in ClinicalTrials.gov (identifier: NCT04373070).

After the statistical analysis of this study, overall and subordinate findings will be submitted for publication in peer-reviewed journals. Dissemination of the results will be independent of negative or positive findings. The principles of the American Psychological Association guidelines for authorship eligibility will be followed.

Results

The development of the CAir Desk and virtual coach is completed. Recruitment to the trial started in September 2020. We expect to start data collection by December 2020. This is 5 months behind schedule, which is due to the outbreak of COVID-19 that heavily impairs patients with COPD. Data collection is expected to last for approximately 18 months (first patient in, last patient out), as we follow a multiwave approach. The length of study per patient will be 12 weeks. The limited amount of available CAir Desks prevents us from executing a larger number of interventions simultaneously. We expect to complete data collection by mid-2022 and plan the dissemination of results subsequently.

Discussion

Study Contributions

To our knowledge, this is the first study investigating a combination of telemonitoring and hybrid virtual coaching in

patients with COPD. We will investigate the effectiveness, efficacy, and usability of the proposed intervention and thus provide evidence to further develop app-based and chatbot-based disease monitoring and interventions in COPD. The study may also be extended to other respiratory diseases (eg, cystic fibrosis and COVID-19) and with an adapted technical setup to other chronic diseases requiring long-term treatment (eg, diabetes mellitus type 2 and chronic kidney disease).

Strengths and Limitations

Randomized controlled trials are considered the "gold standard for evaluating efficacy in clinical research and constitute evidence for medical treatment" [25]. By adopting such a trial and ensuring internal as well as external validity, we maximize the robustness of our study. To make sure that the CAir Desk will function well with the study population, we extensively pretested the device in patients with COPD. The technology we used as part of the CAir Desk is well established and not likely to malfunction in daily use. A possible limitation is that the intervention is rather technology-heavy and the study population includes persons aged 45 years and older. Even though we pretested the system usability extensively in patients with COPD from the same population, some participants might feel overwhelmed and therefore discontinue the study. In addition, patients may feel overloaded by the daily measurements and questionnaires to be answered, which could also lead to dropouts. Another possible limitation is the limited size of the sample, given the heterogeneity in the population affected by COPD.

Acknowledgments

The project has received funding from Innosuisse (project number: 29844.1), a Swiss federal entity that promotes domestic science-based innovation. The funding body supervises the conduct of the overall project but is not involved in any operations.

Conflicts of Interest

YN is cofounder and Chief Medical Officer of docdok.health with a financial interest in commercialization of the docdok platform, used as part of the CAir desk. All other authors have no conflicts to declare.

Multimedia Appendix 1
Grant letter from Innosuisse.
[PDF File (Adobe PDF File), 388 KB - resprot_v9i10e20412_app1.pdf]

References

1. Agusti A, Edwards LD, Celli B, Macnee W, Calverley PMA, Müllerova H, ECLIPSE Investigators. Characteristics, stability and outcomes of the 2011 GOLD COPD groups in the ECLIPSE cohort. Eur Respir J 2013 Sep;42(3):636-646. [doi: 10.1183/09031936.00195212] [Medline: 23766334]
2. World Health Organization. Chronic obstructive pulmonary disease (COPD).: WHO; 2017. URL: https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd) [accessed 2020-09-28]
3. World Health Organization. World health statistics 2008.: WHO; 2008. URL: https://www.who.int/gho/publications/world_health_statistics/EN_WHS08_Full.pdf [accessed 2020-09-26]
4. Ehteshami-Afshar S, FitzGerald JM, Doyle-Waters MM, Sadatsafavi M. The global economic burden of asthma and chronic obstructive pulmonary disease. Int J Tuberc Lung Dis 2016 Jan;20(1):11-23. [doi: 10.5588/ijtld.15.0472] [Medline: 26688525]
5. Bellamy D, Bouchard J, Henrichsen S, Johansson G, Langhammer A, Reid J, et al. International primary care respiratory group (IPCRG) guidelines: management of chronic obstructive pulmonary disease (COPD). Prim Care Respir J 2006 Feb;15(1):48-57 [FREE Full text] [doi: 10.1016/j.pcrj.2005.11.003] [Medline: 16701758]
6. Bott J, Blumenthal S, Buxton M, Ellum S, Falconer C, Garrod R, et al. Guidelines for the physiotherapy management of the adult, medical, spontaneously breathing patient. Thorax 2009 May;64 Suppl 1:i1-51. [doi: 10.1136/thx.2008.110726] [Medline: 19406863]
7. Langer D, Hendriks E, Burtin C, Probst V, van der Schans C, Paterson W, et al. A clinical practice guideline for physiotherapists treating patients with chronic obstructive pulmonary disease based on a systematic review of available evidence. Clin Rehabil 2009 May;23(5):445-462. [doi: 10.1177/0269215509103507] [Medline: 19389745]
8. Steurer-Stey C, Dalla Lana K, Braun J, Ter Riet G, Puhan MA. Effects of the "Living well with COPD" intervention in primary care: a comparative study. Eur Respir J 2018 Jan;51(1). [doi: 10.1183/13993003.01375-2017] [Medline: 29301921]
9. Bourbeau J, Julien M, Maltais F, Rouleau M, Beaupré A, Bégin R, Chronic Obstructive Pulmonary Disease axis of the Respiratory Network Fonds de la Recherche en Santé du Québec. Reduction of hospital utilization in patients with chronic obstructive pulmonary disease: a disease-specific self-management intervention. Arch Intern Med 2003 Mar 10;163(5):585-591. [doi: 10.1001/archinte.163.5.585] [Medline: 12622605]
10. Living well with COPD. URL: https://www.livingwellwithcopd.com [accessed 2020-10-07]

11. Burkow TM, Vognild LK, Johnsen E, Bratvold A, Risberg MJ. Promoting exercise training and physical activity in daily life: a feasibility study of a virtual group intervention for behaviour change in COPD. BMC Med Inform Decis Mak 2018 Dec 18;18(1):136 [FREE Full text] [doi: 10.1186/s12911-018-0721-8] [Medline: 30563507]
12. Jones P, Quirk F, Baveystock C. The St George's Respiratory Questionnaire. Respir Med 1991 Sep;85:25-31. [doi: 10.1016/s0954-6111(06)80166-6]
13. Jones PW. St. George's Respiratory Questionnaire: MCID. COPD 2005 Mar;2(1):75-79. [doi: 10.1081/copd-200050513] [Medline: 17136966]
14. McCarney R, Warner J, Iliffe S, van Haselen R, Griffin M, Fisher P. The Hawthorne Effect: a randomised, controlled trial. BMC Med Res Methodol 2007 Jul 03;7:30 [FREE Full text] [doi: 10.1186/1471-2288-7-30] [Medline: 17608932]
15. Buffart LM, Kalter J, Sweegers MG, Courneya KS, Newton RU, Aaronson NK, et al. Effects and moderators of exercise on quality of life and physical function in patients with cancer: An individual patient data meta-analysis of 34 RCTs. Cancer Treat Rev 2017 Jan;52:91-104 [FREE Full text] [doi: 10.1016/j.ctrv.2016.11.010] [Medline: 28006694]
16. Kon SSC, Canavan JL, Jones SE, Nolan CM, Clark AL, Dickson MJ, et al. Minimum clinically important difference for the COPD Assessment Test: a prospective analysis. Lancet Respir Med 2014 Mar;2(3):195-203 [FREE Full text] [doi: 10.1016/S2213-2600(14)70001-3] [Medline: 24621681]
17. Fadhil A, Wang Y, Reiterer H. Assistive conversational agent for health coaching: A validation study. Methods Inf Med 2019 Jun;58(1):9-23. [doi: 10.1055/s-0039-1688757] [Medline: 31117129]
18. Crook S, Büsching G, Schultz K, Lehbert N, Jelusic D, Keusch S, et al. A multicentre validation of the 1-min sit-to-stand test in patients with COPD. Eur Respir J 2017 Mar;49(3). [doi: 10.1183/13993003.01871-2016] [Medline: 28254766]
19. Enright PL. The six-minute walk test. Respir Care 2003 Aug;48(8):783-785 [FREE Full text] [Medline: 12890299]
20. Puhan MA, Siebeling L, Zoller M, Muggensturm P, ter Riet G. Simple functional performance tests and mortality in COPD. Eur Respir J 2013 Oct;42(4):956-963. [doi: 10.1183/09031936.00131612] [Medline: 23520321]
21. Burdon JG, Juniper EF, Killian KJ, Hargreave FE, Campbell EJ. The perception of breathlessness in asthma. Am Rev Respir Dis 1982 Nov;126(5):825-828. [doi: 10.1164/arrd.1982.126.5.825] [Medline: 7149447]
22. Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J 2014 Dec;44(6):1428-1446. [doi: 10.1183/09031936.00150314] [Medline: 25359355]
23. Jones PW, Harding G, Berry P, Wiklund I, Chen W, Kline Leidy N. Development and first validation of the COPD Assessment Test. Eur Respir J 2009 Sep;34(3):648-654. [doi: 10.1183/09031936.00102509] [Medline: 19720809]
24. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, ATS/ERS Task Force. Standardisation of spirometry. Eur Respir J 2005 Aug;26(2):319-338. [doi: 10.1183/09031936.05.00034805] [Medline: 16055882]
25. Spieth PM, Kubasch AS, Penzlin AI, Illigens BM, Barlinn K, Siepmann T. Randomized controlled trials - a matter of design. Neuropsychiatr Dis Treat 2016;12:1341-1349 [FREE Full text] [doi: 10.2147/NDT.S101938] [Medline: 27354804]

Abbreviations

COPD: chronic obstructive pulmonary disease
HRQOL: health-related quality-of-life
SGRQ: St. George Respiratory Questionnaire

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Protocol

A Mobile Health Intervention (LifeBuoy App) to Help Young People Manage Suicidal Thoughts: Protocol for a Mixed-Methods Randomized Controlled Trial

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Abstract

Background: Self-help smartphone apps offer a new opportunity to address youth suicide prevention by improving access to support and by providing potentially high fidelity and cost-effective treatment. However, there have been very few smartphone apps providing evidence-based support for suicide prevention in this population. To address this gap, we developed the LifeBuoy app, a self-help smartphone app informed by dialectical behavior therapy (DBT), to help young people manage suicidal thoughts in their daily life.

Objective: This study describes the protocol for a randomized controlled trial to evaluate the efficacy of the LifeBuoy app for reducing suicidal thoughts and behaviors, depression, anxiety, and psychological distress, and improving general mental well-being in young adults aged 18 to 25 years.

Methods: This is a randomized controlled trial recruiting 378 young adults aged between 18 and 25 years and comparing the LifeBuoy app with a matched attention control (a placebo app with the same display but no DBT components). The primary outcome is suicidal thoughts measured by the Suicidal Ideation Attributes Scale (SIDAS). The secondary outcomes are suicidal behavior, depression, anxiety, psychological distress, and general mental well-being. The changes in the levels of insomnia, rumination, suicide cognitions, distress tolerance, loneliness, and help seeking before and after using the app are evaluated in this study. The study also addresses risk factors and responses to the intervention. A series of items assessing COVID-19 experiences is included in the trial to capture the potential impact of the pandemic on this study. Assessments will occur on the following three occasions: baseline, postintervention, and follow-up at 3 months postintervention. A qualitative interview about user experience with the LifeBuoy app will take place within 4 weeks of the final assessment. Using linear mixed models, the primary analysis will compare the changes in suicidal thoughts in the intervention condition relative to the control condition. To minimize risks, participants will receive a call from the team clinical psychologist by clicking a help button in the app or responding to an automated email sent by the system when they are assessed with elevated suicide risks at the baseline, postintervention, and 3-month follow-up surveys.

Results: The trial recruitment started in May 2020. Data collection is currently ongoing.

Conclusions: This is the first trial examining the efficacy of a DBT-informed smartphone app delivered to community-living young adults reporting suicidal thoughts. This trial will extend knowledge about the efficacy and acceptability of app-based support for suicidal thoughts in young people.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12619001671156; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=378366.

International Registered Report Identifier (IRRID): PRR1-10.2196/23655

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KEYWORDS

suicide prevention; mental health; eHealth; mHealth; mobile health; digital health; smartphone app; dialectical behavior therapy

Introduction

Suicidal thoughts and behaviors are a global public health concern for adolescents and young adults owing to their life-threatening nature and high prevalence [1]. Globally, it is estimated that over 200,000 people aged between 10 and 29 years died by suicide in 2016 [2]. Suicide remains the second leading cause of death for this age group despite numerous prevention initiatives over the last decade [3]. Rates have increased across multiple countries and regions in recent years [4-6], and the increased rates are likely to be a lasting concern owing to the coronavirus pandemic and economic recession [7]. One possible approach to prevent youth suicide is to provide accessible and engaging interventions that can effectively reduce suicidal thoughts and behaviors in this age group.

Dialectical behavior therapy (DBT) is one therapeutic approach that has been shown to reduce suicide-related outcomes, including nonsuicidal self-injurious behavior and suicide attempts [8,9]. DBT combines principles from behaviorism, Zen, and dialectics [10] that aim to help clients improve their emotional and cognitive regulation to overcome problems, including intense mood change [11,12], impulsivity [13,14], and loneliness [15]. DBT was initially developed for persons diagnosed with borderline personality disorder [16], and there is increasing evidence to suggest that DBT is also effective in reducing suicidal thoughts, nonsuicidal self-injurious behavior, and suicide attempts in both adults [17] and adolescents [18,19].

Traditional face-to-face psychotherapies, including DBT, usually carry high economic costs and personal barriers that may prevent youth from accessing them [20]. Literature suggests that only 28% of adolescents and young adults with current, past year, or lifetime suicidal thoughts, plans, and/or attempts have accessed mental health services [21]. Potential barriers to mental health services include lack of time, preference for self-reliance, stigma, and service unavailability [21,22]. Digitally delivered interventions offer a new opportunity to improve access to support and to provide high fidelity and cost-effective treatment [23] at scale. Self-help smartphone apps that are designed to be used without professional guidance can help address these gaps by allowing people to seek help anonymously at a relatively low cost and at a time that suits them [24]. There is emerging evidence that adults readily access and benefit from suicide prevention interventions delivered via smartphone-based apps [25]. However, there have been very few empirical studies examining the efficacy of mental health apps for young people, and there are even fewer studies for apps that specifically target suicidal thoughts in this population. To our best knowledge, no studies have investigated the possibility of using a DBT-informed app to reduce suicidal thoughts in young adults.

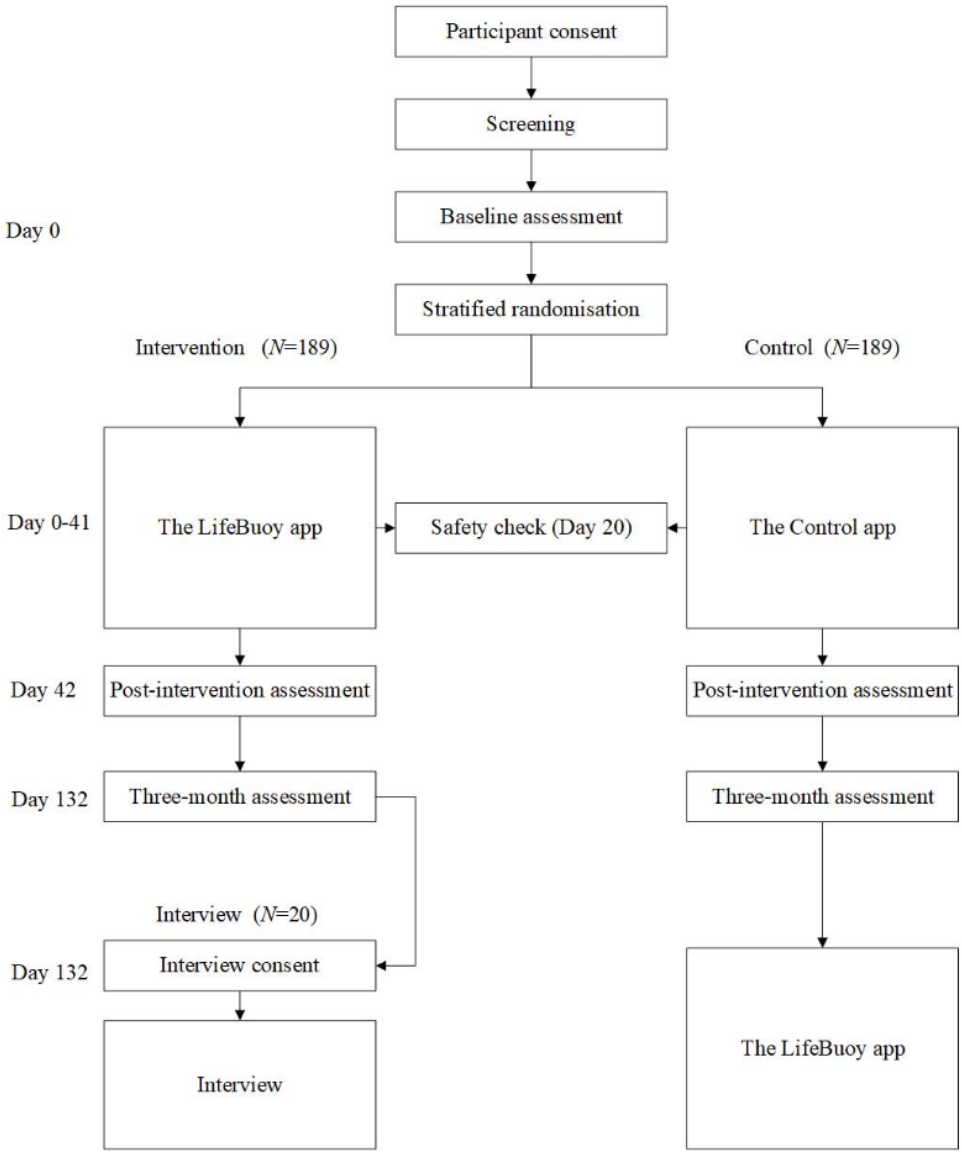
To address this gap, we developed the LifeBuoy app, a self-help smartphone app designed to help young adults manage suicidal thoughts and negative feelings in daily life. It includes seven structured therapeutic sessions derived from DBT and incorporates the principles of positive psychology. The primary objective of the trial is to investigate the efficacy of the LifeBuoy app compared with a matched attention control condition in reducing suicidal thoughts in young adults at postintervention and a 3-month follow-up compared with baseline. The second objective is to assess the impact of the app on secondary outcomes, including suicidal behaviors, depression, anxiety, psychological distress, and general mental well-being. We are also interested in examining the changes in tertiary outcomes, including insomnia, rumination, suicide cognitions, distress tolerance, loneliness, and help-seeking intentions and behaviors at postintervention and a 3-month follow-up compared with baseline, and assessing the potential impacts of demographics, perseverance, negative events, such as COVID-19, and expectation of treatment success on participants. The final objective of this trial is to investigate adherence, satisfaction, and acceptability of the LifeBuoy app via survey questions, app usage data, and qualitative interviews.

Methods

Trial Design

This study is a randomized controlled superiority trial with a matched attention control condition. Individuals are randomly allocated to either the intervention or attention control condition with a 2:2 allocation using a block design (four participants per block), stratified by gender and age group using an automated web-based platform tailored for this trial. Participants within each block (N=4) are randomly assigned to either of the two groups based on the six sequences, given a block size of four [26]. The trial has the following three measurement occasions: baseline, postintervention, and follow-up at 3 months postintervention. A qualitative interview about user experience with the LifeBuoy app will take place within 4 weeks of the final assessment (Figure 1).

Figure 1. Study flow.



Blinding

In the trial, participants are not notified about whether they are assigned to an intervention or control group. Participants may still discern their condition assignment owing to the nature of the intervention content. All the investigators will be blinded to intervention assignment throughout the study period.

Participants

Young adults aged between 18 and 25 years are eligible to participate in the trial if they (1) have experienced suicidal thoughts in the past 12 months, (2) have not made a suicide attempt in the past month, (3) do not have a diagnosis of psychosis or bipolar disorder, (4) currently live in Australia, and (5) are fluent in English. The inclusion criteria will be determined by an online self-report screening survey. They are not prohibited from receiving other treatments or interventions during the trial.

Sample Size

Based on a systematic review and meta-analysis on online and mobile apps for suicidal thoughts and self-harm [27], an effect size of 0.30 (Cohen *d*) is expected between the intervention condition and the control condition at posttest for the primary outcome suicidal thoughts. Based on an attrition rate of 30% [28,29] and a 0.50 correlation between pre- and posttest scores of the primary outcome, a sample size of 189 for each condition (total N=378) will be required to detect the expected effect size with a power of 0.80 and alpha of .05. For the qualitative interviews, we will recruit a 10% subsample of individuals who participate in the intervention condition to assess their experience with the app (N=20), which is likely to reach data saturation according to prior studies [30,31].

Recruitment

From May 2020, a community-based sample of participants is being recruited into the trial through targeted Facebook advertising hosted on the Black Dog Institute's social media pages. The recruitment is still ongoing. A subgroup of the

participants in the intervention group will be recruited for the qualitative interview via an expression of interest form provided before the final assessment.

Intervention

The LifeBuoy app includes seven structured therapeutic sessions derived from DBT and incorporates the principles of positive psychology. It includes sessions on value identification, goal setting, psychoeducation, emotion regulation, and distress tolerance. These sessions are self-paced and delivered sequentially in the app. Each module takes approximately 3 to 7 minutes to complete. A mood tracker is included in the app to allow participants to rate their feelings multiple times per day. The app also contains a toolbox, which includes two distraction activities (popping bubbles and funny quiz) and additional tips for reducing distress (self-soothing tips and the Temperature, Intense exercise, Paced breathing, Paired muscle relaxation [TIPP] technique). Finally, there is a "help" button embedded in the app with direct links to Australian crisis lines. The LifeBuoy app was developed using a person-centered approach, involving young people with lived experience of suicidal thoughts, to understand and accommodate the perspectives of young people who will use the intervention. The design process of the app will be reported in a separate paper, which is currently in preparation.

Matched Attention Control

Similar to the intervention app, the control app contains seven brief nontherapeutic education-based sessions. The topics are peripherally related to mental health and well-being, including confidence, performance stress, the importance of having goals, and the value of being present. Each session takes 2 to 3 minutes to read through. The control does not contain a mood tracker or toolbox but includes the "help" button for safety management. Participants in the control group will be granted access to the intervention app after they complete the 3-month follow-up assessment.

Assessments

There are three data collection points as follows: baseline (day 0), postintervention (day 42), and 3-month postintervention follow-up (day 132) (Table 1). Data collection will be fully automated and online, with participants accessing the study website to register for the trial, download the app, and complete assessments.

Table 1. Summary of the primary, secondary, and tertiary outcome measures, risk factors, other measures, and data collection time points.

Outcomes measures	Scale	Baseline	Postintervention	Three-month follow-up
Primary outcome				
Suicidal thoughts	Suicidal Ideation Attributes Scale (SIDAS)	Yes	Yes	Yes
Secondary outcomes				
Suicide behaviors	Suicide attempt and self-harm	Yes	Yes	Yes
Depression	Patient Health Questionnaire-9 (PHQ-9)	Yes	Yes	Yes
Anxiety	Generalized Anxiety Disorder-7 (GAD-7)	Yes	Yes	Yes
Psychological distress	Distress Questionnaire-5 (DQ-5)	Yes	Yes	Yes
General mental well-being	Short Warwick-Edinburgh Mental Wellbeing Scale (SWEMWBS)	Yes	Yes	Yes
Tertiary outcomes				
Insomnia	Insomnia Severity Index (ISI)	Yes	Yes	Yes
Rumination	Repetitive Thinking Questionnaire (RTQ)	Yes	Yes	Yes
Suicide cognitions	Suicide Cognitions Scale (SCS)	Yes	Yes	Yes
Distress intolerance	Distress Tolerance Scale (DTS)	Yes	Yes	Yes
Loneliness	Three-Item Loneliness Scale (TILS)	Yes	Yes	Yes
Help-seeking intentions	General Help-Seeking Questionnaire (GHSQ)	Yes	Yes	Yes
Help-seeking behaviors	Client Service Receipt Inventory (CSRI)	Yes	No	Yes
Risk factors and other measures				
Demographics	Questions	Yes	No	No
Perseverance	Short Grit Scale (SGS)	Yes	No	No
COVID-19–related worry	Questions	Yes	No	No
Negative events	Negative Life Events Scale for Students (NLESS)	Yes	No	No
Expectations of treatment success	Questions	Yes	No	No
Satisfaction with the app	Questions	No	Yes	No

Outcomes

Primary Outcome Measure

Suicidal Ideation Attributes Scale

The primary outcome measure is the severity of suicidal thoughts assessed by the Suicidal Ideation Attributes Scale (SIDAS [32]). It consists of five questions pertaining to frequency of suicidal thoughts in the past month, controllability of suicidal thoughts, closeness to suicide attempt, level of distress associated with the thoughts, and impact on daily functioning. Each item is assessed on a 11-point scale (0-10). Item two (controllability) is reverse scored. Total scale scores on the SIDAS range from 0 to 50, with higher scores indicating more severe suicidal thoughts.

Secondary Outcome Measures

Suicide Behaviors

Participants' previous suicide attempts and self-injury are assessed by eight questions developed for a previous suicide prevention trial [29]. Participants are invited to indicate whether they have attempted suicide in their lifetime and in the past 30 days on a three-point Likert scale, with responses of "No, never (0)," "Yes, once (1)," and "Yes, more than once (2)." They are also asked to report the number of suicide attempts over their lifetime and the number of months that they have been thinking about suicide. Apart from that, participants are asked to indicate whether they have experienced intentional self-injury in their lifetime on the aforementioned three-point Likert scale. If yes, they are asked to provide the number of times of their intentional self-injury and rate the severity of the worst injury in the past month on a three-point Likert scale, with responses of "No care was needed (1)," "Some care was needed (2)," and "Required medical care (3)."

Patient Health Questionnaire-9

The Patient Health Questionnaire-9 (PHQ-9 [33]) is a nine-item self-report questionnaire measuring the severity of depression. The scale assesses the frequency of occurrence of depression symptoms in the previous 2 weeks, with items rated on a four-point scale ranging from "Not at all (0)" to "Nearly every day (3)." Total scores on the PHQ-9 depression scale can range from 0 to 27, with higher scores reflecting more severe depression.

Generalized Anxiety Disorder-7

The Generalized Anxiety Disorder-7 (GAD-7 [34]) is a seven-item self-report measure designed to assess the severity of generalized anxiety symptoms over the previous 2-week period. Items are rated on a four-point scale, ranging from "Not at all sure (0)" to "Nearly every day (3)." Total scores on the GAD-7 can range from 0 to 21. Higher scores indicate higher levels of GAD symptoms.

Distress Questionnaire-5

The Distress Questionnaire-5 (DQ-5 [35]) is a five-item brief screening tool for identifying general psychological distress. Participants are asked to endorse the frequency of each item in the past 30 days on a five-point scale ranging from "Never (1)" to "Always (5)." Total scores range from 5 to 25, with higher scores indicating greater psychological distress.

Short Warwick-Edinburgh Mental Well-Being Scale

The Short Warwick-Edinburgh Mental Well-Being Scale (SWEMWBS [36,37]) is a shortened seven-item version of the 14-item Warwick-Edinburgh Mental Well-Being Scale (WEMWBS) [37], which was developed to assess mental well-being in the general population. It assesses mental well-being by asking about participants' feelings and experiences over the previous 2 weeks. Responses range from "None of the time (1)" to "All of the time (5)," and raw item scores are summed and converted to a metric total score using the SWEMWBS conversion table [38]. Total scores can range from 7 to 35, with higher scores indicating higher levels of mental well-being.

Tertiary Outcome Measures

Insomnia Severity Index

The Insomnia Severity Index (ISI [39]) is a psychometrically sound, seven-item, self-report measure assessing the perceived severity of insomnia symptoms, the degree of satisfaction with sleep, interference with daytime functioning, noticeability of impairment, and concern caused by the sleep problems in the previous 2 weeks. Responses are reported on a five-point scale yielding total scores of 0 to 28. Higher scores indicate greater insomnia severity.

Repetitive Thinking Questionnaire

The Repetitive Thinking Questionnaire-10 (RTQ-10 [40]) is a transdiagnostic measure of engagement in repetitive negative thinking following distressing situations. The RTQ was developed to capture the underlying construct of recurrent negative thinking underlying mental health disorders such as depression and anxiety. Participants are requested to respond to the RTQ-10 on a five-point Likert scale, with responses ranging from "Not true at all (1)" to "Very true (5)." Total scores fall between 10 and 50, with higher scores indicating greater rumination.

Shortened Version of the Suicide Cognition Scale

The shortened version of the Suicide Cognition Scale (SCS [41]) is a self-report instrument consisting of nine items that are designed to measure suicide-specific cognition. The items contain statements consistent with the suicidal schemas of unbearability (eg, "I can't cope with my problems any longer"), unlovability (eg, "I am completely unworthy of love"), and unsolvability (eg, "Nothing can help me solve my problems"). Items in the SCS are rated on a five-point Likert scale, with responses ranging from "Strongly disagree (1)" to "Strongly agree (5)." The instrument is scored by summing ratings across items, resulting in scores ranging from 9 to 45.

Distress Tolerance Scale

The Distress Tolerance Scale (DTS [42]) is a 15-item self-report measure designed to assess respondents' perceived capacity to experience and endure negative emotional states. The DTS encompasses four subscales, including tolerance, appraisal, absorption, and regulation. Items are rated on a five-point Likert scale, with responses ranging from "Strongly disagree (1)" to

"Strongly agree (5)." Higher mean scores indicate a greater tendency to withstand emotional distress.

Three-Item Loneliness Scale

The Three-Item Loneliness Scale (TILS [43]) is a brief self-report measure of loneliness. The three items that compose this scale were selected from the R-UCLA Loneliness Scale [44] and include the following: "How often do you feel that you lack companionship?" (relational connectedness); "How often do you feel left out?" (collective connectedness); and "How often do you feel isolated from others?" (general isolation). Response categories for the TILS are as follows: "Hardly ever (1)," "Some of the time (2)," and "Often (3)." Total scores are calculated by summing item scores, with higher scores indicating greater loneliness.

General Help-Seeking Questionnaire

The General Help-Seeking Questionnaire (GHSQ [45]) is used in the current trial to assess participants' intentions to seek help for suicidal thoughts from a variety of sources. Respondents are invited to rate on a six-point scale, ranging from "Not applicable (0)" and "Extremely unlikely (1)" to "Extremely likely (5)," the likelihood of seeking help from three professional sources (school or university counsellor, mental health professional, and doctor/general practitioner), four informal sources (boyfriend/girlfriend, friends, parents, and other relative/family members), three telephone/online sources (phone helpline, internet website, and mobile app), or no one. An optional item "I would seek help from another source not listed above" is also provided. Higher scores represent stronger intentions to seek help.

Modified Client Service Receipt Inventory

The adapted version of the Client Service Receipt Inventory (CSRI [46]) is designed to collect information about use of health care and social care services over a retrospective period of the past 6 months. Respondents are asked to indicate whether they have used any services in the past 6 months owing to mental health problems, including suicidal thoughts, on a binary scale ("Yes"/"No"). Services include hospital services, mental health helplines, crisis support team, police/ambulance, contact with a range of mental health professionals (eg, social worker and counsellor), self-help groups, and other medically qualified doctors.

Risk Factors and Other Measures

Demographic Information and Baseline Variables

At the baseline assessment, participants are asked to provide their age, gender identity, gender assigned at birth, sexual orientation, contact information (email and mobile number), state and area they live in (ie, metropolitan or rural/remote), language spoken at home, who they live with at home, current relationship status, highest level of education completed, employment status, and whether they have ever experienced or been diagnosed with mental illness. Information related to their service use is also collected, such as whether they have ever seen a mental health professional for a mental health problem and used health or well-being apps.

Short Grit Scale

The Short Grit Scale (SGS [47]) is an eight-item measure assessing perseverance and passion for pursuing long-term goals. Half of the items are worded positively (eg, "I am diligent"), while the other half are worded negatively (eg, "New ideas and projects sometimes distract me from previous ones") and are thus reverse scored. Items are rated on a five-point scale, with responses ranging from "Not like me at all (1)" to "Very much like me (5)" and the total scale score ranging from 8 to 40.

COVID-19–Related Worry

Ten items are used to assess the extent to which the coronavirus (COVID-19) pandemic influences participants' perception of their symptoms (anxiety, depression, and suicidal ideation) and coping strategies. Items 1 to 3 relate to perceptions of symptoms and are rated on a five-point scale, with responses ranging from "Not at all (1)" to "All of the time (5)" (eg, "Do you think the COVID-19 pandemic has increased your anxiety levels more than usual?"). Items 4 to 6 relate to anticipated, experienced, and current worry and have been modified from a previous study of pandemic-related worry [48], with item 7 asking participants to indicate what aspects of COVID-19 are worrying them from a list of responses (eg, "not knowing when the pandemic will end"). Items 8 to 9 relate to the frequency and effectiveness of coping strategies used from a list of 14 equally balanced healthy (eg, "using social support" and "relaxation techniques") and unhealthy (eg, "overeating/comfort food" and "avoidance/procrastination") strategies. Participants are asked to rate their use of the strategies on a four-point scale (do not use, use less, use the same, and use more) and rate on a five-point scale whether they think each strategy used has been less effective during the pandemic, with responses ranging from "Not at all (1)" to "All of the time (5)." Item 10 asks participants to indicate if they have noticed any symptom improvement during or following the pandemic (none; yes, anxiety; yes, depression; yes, suicidal thoughts; and yes, other).

Modified Negative Life Events Scale for Students

The Negative Life Events Scale for Students (NLESS [49]) is designed to assess the experience of stressful life events among students. Respondents are asked to indicate whether they have experienced 25 negative life events (eg, death of a family member and being arrested) in the past year, and if yes, how stressful that event has been for them. In the adapted version of this measure, items are rated on a five-point scale, with responses ranging from "Not stressful (1)" to "Extremely stressful (5)." Higher mean scores indicate higher negative impact on life.

Expectation of Treatment Success

Four items were created to measure participants' confidence and readiness in using an app to reduce suicidal thoughts, as well as the perceived importance of reducing suicidal thoughts and participating in research to reduce suicide risk. Items on this scale include "I am confident that people could reduce their suicidal thoughts using an app" and "I think that participating in a study that aims to reduce suicidal thoughts is an important thing to do." These items are rated on a five-point scale, with responses ranging from "Strongly disagree (1)" to "Strongly

agree (5).” Other items include “Please rate the importance of reducing your suicidal thoughts over the next 6 months,” with responses ranging from “Not important (0)” to “Very important (5),” and “Please rate your readiness to reduce your suicidal thoughts by using an app,” with responses ranging from “Not ready (1)” to “Completely ready (5).” Owing to the nature of these questions, this measure is administered only once during baseline assessment. Total scores indicate higher expectation of treatment success.

Satisfaction With the LifeBuoy App

Eighteen items were adapted from a previous study to assess participants’ satisfaction with the LifeBuoy app [50]. This measure consists of three parts. The first part contains seven statements related to the usability, readability, and helpfulness of the app, and the respondent’s intention to continue to use and recommend the app. Participants are asked to indicate whether they agree or disagree with each item. The second part of this measure comprises 10 questions pertaining to potential difficulties in using the app (eg, forgetting to use it and feeling worse after using it). Participants are asked to indicate whether they agree or disagree with each item. In the last part of this measure, they are asked to rate the overall helpfulness of the app on a five-point scale, with responses ranging from “Extremely unhelpful (1)” to “Extremely helpful (5).” Higher scores on each item indicate higher satisfaction with the app.

Treatment Adherence

Adherence to both the LifeBuoy app and control app is measured by the number of modules accessed and completed by participants, and the time spent on each module. The data are automatically collected via the app.

Statistical Analysis

Mixed model repeated measures analyses with maximum likelihood estimation and an appropriate covariance structure will be used to evaluate the efficacy of the LifeBuoy app relative to the control condition. Within-person variation will be modelled by using an unstructured covariance matrix, and degrees of freedom will be estimated using Satterthwaite correction [51]. The primary outcome is the change in severity of suicidal thoughts across time (baseline to postintervention and postintervention to the 3-month follow-up). The mixed model approach incorporates all available data, including participants with missing follow-up data points, under the missing-at-random assumption, in accordance with the intention-to-treat principle. The same analytic approach will be used to examine temporal changes in secondary and tertiary outcomes, including depression, anxiety, psychological distress, general mental well-being, insomnia, rumination, suicide cognition, distress tolerance, loneliness, help-seeking intentions, and behaviors. The difference between the two groups on potential risk factors, including demographics, perseverance, COVID-19–related worry, negative events, and expectation of treatment success will be assessed by descriptive statistics.

In the interview, participants will be asked about their general feelings about the app and the design, their favorite and unfavorite features, the scenarios where they find the app useful, and other feedback about the app. The interview data will be analyzed using Braun & Clarke thematic analysis [52]. An inductive approach will be used to identify group themes. Two researchers will independently refine the themes and determine the final coding framework. Discrepancies will be resolved by a third researcher to ensure reliability of the process.

Risk Management

In both the intervention and control versions of the LifeBuoy app, there is a help button that contains a list of 24-hour crisis support contacts that are publicly accessible nationwide. This button also contains a clinical psychologist contact button that allows participants to request a call from the team clinical psychologist.

Calls by the team clinical psychologist to participants will focus on ensuring the participants are safe and supported by their family and/or community if this is possible, and identifying how they can access the services they need. If participants express distress in relation to using the app or answering the assessment questionnaires, they will be reminded of their right to withdraw from the trial without penalty or explanation. In the event that a participant does not respond to the initial contact attempt, an email stating that contact was attempted and requesting for their availability will be sent. The psychologist will attempt to call the participants up to two times in the requested time. If the participant is still unavailable, another email stating that contact was attempted and containing referral sources will be sent.

At each survey timepoint (baseline, postintervention, and 3-month follow-up) and in the middle of the trial (3 weeks after commencing use of the LifeBuoy app), risk of suicide will be assessed using a standardized scale (SIDAS). If the SIDAS score is above 20 [32], indicating an elevated level of suicidal thoughts, an automated alert system will be triggered, in which a notification will be sent to the research inbox to notify the team clinical psychologist. An automated email will also be sent to the participants asking if they would like to receive a phone call from the team clinical psychologist as above. This email will also include a list of 24-hour crisis support contacts.

There are two levels of risk management in this project. The first is the trial steering committee, which consists of the research team, and the second is an independent Data Monitoring Safety Board (DSMB). The DSMB has three members who are experts in clinical trial conduct, statistics, and youth mental health. The trial manager will record the number of notifications at each assessment in a report for the DSMB and will notify the DSMB after each assessment period about how many alerts have been triggered and whether follow-ups have been carried out. Any serious adverse event will be reported to the DSMB. The DSMB will provide recommendations to the research team to continue the trial, temporarily pause the trial, or discontinue the trial owing to heightened risk or adverse events.

Privacy, Confidentiality, and Data Management

The sensitive data that are collected in this study include participants’ responses to the surveys, usage data collected by the LifeBuoy app, and the audio records of the interviews.

The survey and usage data are collected by the Black Dog Institute eHealth research platform, a bespoke trial management system. Each participant will be assigned a unique identification code automatically at the time of registration on the Black Dog Institute research platform. When online survey data are exported for analysis, the research team will remove the identifiable information from the initial data set (ie, first name, mobile phone number, and email address will be removed). A deidentified extract of the data will be downloaded for analysis on a shared drive, which is password protected and approved by the university for storing highly sensitive data. The file used for analysis will only include the unique ID code and raw research data. Only named study personnel will have access to any identifiable information. For participant withdrawal, only named study personnel will access the register to identify the personal details of participants using their ID code.

Transcription of the interviews will be undertaken by a professional transcription service, and only deidentified audio will be provided to the agency. The agency will need to sign a confidentiality agreement before being provided with the recordings. Participants will be informed that deidentified audio will be provided to an agency for transcription service only. Upon completion of this project, all deidentified data will be stored in an archive on the server hard drive for a period of a minimum of 7 years, in accordance with University of New South Wales guidelines and the Australian Code for the Responsible Conduct of Research.

Results

The current trial has ethical approval from the University of New South Wales Human Research Ethics Committee (HC190764). It has been registered in The Australian New Zealand Clinical Trials Registry (ACTRN12619001671156) and with the Therapeutic Goods Administration through the Clinical Trial Notification (CTN) scheme (CT-2020-CTN-00256-1-v1). Recruitment started on May 11, 2020. Data collection of the trial is expected to be complete by December 2020.

Discussion

Preventing suicide in young people is a pressing global imperative [1]. The current mental health system addresses less than half of the need of support [21], leaving most young people to manage their symptoms alone. Self-help smartphone apps offer an opportunity to improve access to support for this population.

To our knowledge, the LifeBuoy study is the first trial to examine the efficacy of a DBT-informed smartphone app in reducing suicidal thoughts and related mental health symptoms in young adults. The app is innovative by integrating structured therapeutic sessions derived from DBT with distraction activities and mood assessments. If the LifeBuoy app is found to be effective, it may prove to be useful as a way to support young adults who do not usually seek help from mental health services or as an adjunct for those who do seek help. Because we have asked about current health service use, we will be able to determine for whom it is effective. We will also determine whether the app is useful for those in underdeveloped areas, where professional health sources are usually scarce. Through our qualitative interviews, we will find information on who our participants think it could be used.

There are few limitations we would like to acknowledge in the current trial design. First, the participants may not be blinded in terms of intervention allocation owing to the nature of the content of the app. All the researchers involved in this study will be blinded to the allocation at the time of analysis, thus maintaining the integrity of study results reporting. Second, the trial sample is being recruited from targeted Facebook advertising rather than by mail or phone. Samples recruited by Facebook have been found to present similar representativeness to convention methods in achieving age and gender distribution and are usually less costly [53]. Finally, the sample is being recruited during the COVID-19 period, which is likely to elevate participants' levels of psychological distress and mental health symptoms [54]. We intend to examine this by measuring the relevant symptoms and the impact of COVID-19 in the surveys.

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Conflicts of Interest

None declared.

References

1. Preventing Suicide: A Global Imperative. Geneva, Switzerland: World Health Organization; 2014.
2. Mental health: Suicide data. World Health Organization. URL: https://www.who.int/mental_health/prevention/suicide/suicideprevent/en/ [accessed 2020-09-25]

3. Arensman E, Scott V, De Leo D, Pirkis J. Suicide and Suicide Prevention From a Global Perspective. Crisis 2020 Mar 01;41(Suppl 1):S3-S7. [doi: 10.1027/0227-5910/a000664] [Medline: 32208759]
4. Leckning BA, Li SQ, Cunningham T, Guthridge S, Robinson G, Nagel T, et al. Trends in hospital admissions involving suicidal behaviour in the Northern Territory, 2001-2013. Australas Psychiatry 2016 Jun;24(3):300-304. [doi: 10.1177/1039856216629838] [Medline: 26858241]
5. Han B, Compton WM, Blanco C, Colpe L, Huang L, McKeon R. National Trends in the Prevalence of Suicidal Ideation and Behavior Among Young Adults and Receipt of Mental Health Care Among Suicidal Young Adults. J Am Acad Child Adolesc Psychiatry 2018 Jan;57(1):20-27.e2. [doi: 10.1016/j.jaac.2017.10.013] [Medline: 29301664]
6. Griffin E, McMahon E, McNicholas F, Corcoran P, Perry IJ, Arensman E. Increasing rates of self-harm among children, adolescents and young adults: a 10-year national registry study 2007-2016. Soc Psychiatry Psychiatr Epidemiol 2018 Jul;53(7):663-671. [doi: 10.1007/s00127-018-1522-1] [Medline: 29721594]
7. Gunnell D, Appleby L, Arensman E, Hawton K, John A, Kapur N, et al. Suicide risk and prevention during the COVID-19 pandemic. The Lancet Psychiatry 2020 Jun;7(6):468-471. [doi: 10.1016/s2215-0366(20)30171-1] [Medline: 32330430]
8. DeCou CR, Comtois KA, Landes SJ. Dialectical Behavior Therapy Is Effective for the Treatment of Suicidal Behavior: A Meta-Analysis. Behav Ther 2019 Jan;50(1):60-72. [doi: 10.1016/j.beth.2018.03.009] [Medline: 30661567]
9. Ougrin D, Tranah T, Stahl D, Moran P, Asarnow JR. Therapeutic interventions for suicide attempts and self-harm in adolescents: systematic review and meta-analysis. J Am Acad Child Adolesc Psychiatry 2015 Feb;54(2):97-107.e2. [doi: 10.1016/j.jaac.2014.10.009] [Medline: 25617250]
10. Swales M, Heard H. Dialectical Behaviour Therapy: Distinctive Features. New York, USA: Taylor & Francis; 2016.
11. Palmier-Claus JE, Taylor PJ, Varese F, Pratt D. Does unstable mood increase risk of suicide? Theory, research and practice. J Affect Disord 2012 Dec 20;143(1-3):5-15. [doi: 10.1016/j.jad.2012.05.030] [Medline: 22842024]
12. Bowen R, Balbuena L, Peters EM, Leuschen-Mewis C, Baetz M. The Relationship between Mood Instability and Suicidal Thoughts. Arch Suicide Res 2015;19(2):161-171. [doi: 10.1080/13811118.2015.1004474] [Medline: 25774548]
13. Klonsky ED, May A. Rethinking impulsivity in suicide. Suicide Life Threat Behav 2010 Dec;40(6):612-619. [doi: 10.1521/suli.2010.40.6.612] [Medline: 21198330]
14. Liu RT, Trout ZM, Hernandez EM, Cheek SM, Gerlus N. A behavioral and cognitive neuroscience perspective on impulsivity, suicide, and non-suicidal self-injury: Meta-analysis and recommendations for future research. Neurosci Biobehav Rev 2017 Dec;83:440-450 [FREE Full text] [doi: 10.1016/j.neubiorev.2017.09.019] [Medline: 28928071]
15. Stravynski A, Boyer R. Loneliness in relation to suicide ideation and parasuicide: a population-wide study. Suicide Life Threat Behav 2001;31(1):32-40. [doi: 10.1521/suli.31.1.32.21312] [Medline: 11326767]
16. Linehan MM, Armstrong HE, Suarez A, Allmon D, Heard HL. Cognitive-behavioral treatment of chronically parasuicidal borderline patients. Arch Gen Psychiatry 1991 Dec;48(12):1060-1064. [doi: 10.1001/archpsyc.1991.01810360024003] [Medline: 1845222]
17. Linehan MM, Korslund KE, Harned MS, Gallop RJ, Lungu A, Neacsiu AD, et al. Dialectical behavior therapy for high suicide risk in individuals with borderline personality disorder: a randomized clinical trial and component analysis. JAMA Psychiatry 2015 May;72(5):475-482. [doi: 10.1001/jamapsychiatry.2014.3039] [Medline: 25806661]
18. McCauley E, Berk MS, Asarnow JR, Adrian M, Cohen J, Korslund K, et al. Efficacy of Dialectical Behavior Therapy for Adolescents at High Risk for Suicide: A Randomized Clinical Trial. JAMA Psychiatry 2018 Aug 01;75(8):777-785 [FREE Full text] [doi: 10.1001/jamapsychiatry.2018.1109] [Medline: 29926087]
19. Mehlum L, Tørmoen AJ, Ramberg M, Haga E, Diep LM, Laberg S, et al. Dialectical behavior therapy for adolescents with repeated suicidal and self-harming behavior: a randomized trial. J Am Acad Child Adolesc Psychiatry 2014 Oct;53(10):1082-1091. [doi: 10.1016/j.jaac.2014.07.003] [Medline: 25245352]
20. Andrade LH, Alonso J, Mneimneh Z, Wells JE, Al-Hamzawi A, Borges G, et al. Barriers to mental health treatment: results from the WHO World Mental Health surveys. Psychol Med 2014 Apr;44(6):1303-1317 [FREE Full text] [doi: 10.1017/S0033291713001943] [Medline: 23931656]
21. Hom MA, Stanley IH, Joiner TE. Evaluating factors and interventions that influence help-seeking and mental health service utilization among suicidal individuals: A review of the literature. Clin Psychol Rev 2015 Aug;40:28-39. [doi: 10.1016/j.cpr.2015.05.006] [Medline: 26048165]
22. Han J, Batterham PJ, Calear AL, Randall R. Factors Influencing Professional Help-Seeking for Suicidality. Crisis 2018 May;39(3):175-196. [doi: 10.1027/0227-5910/a000485] [Medline: 29052431]
23. WHO Guideline: recommendations on digital interventions for health system strengthening. Geneva, Switzerland: World Health Organization; 2019.
24. Torous J, Larsen ME, Depp C, Cosco TD, Barnett I, Nock MK, et al. Smartphones, Sensors, and Machine Learning to Advance Real-Time Prediction and Interventions for Suicide Prevention: a Review of Current Progress and Next Steps. Curr Psychiatry Rep 2018 Jun 28;20(7):51. [doi: 10.1007/s11920-018-0914-y] [Medline: 29956120]
25. Torok M, Han J, Baker S, Werner-Seidler A, Wong I, Larsen ME, et al. Suicide prevention using self-guided digital interventions: a systematic review and meta-analysis of randomised controlled trials. The Lancet Digital Health 2020 Jan;2(1):e25-e36. [doi: 10.1016/S2589-7500(19)30199-2] [Medline: 31803491]
26. Efron B. Forcing a Sequential Experiment to be Balanced. Biometrika 1971 Dec;58(3):403-417. [doi: 10.2307/2334377]

27. Witt K, Spittal MJ, Carter G, Pirkis J, Hetrick S, Currier D, et al. Effectiveness of online and mobile telephone applications ('apps') for the self-management of suicidal ideation and self-harm: a systematic review and meta-analysis. BMC Psychiatry 2017 Aug 15;17(1):297 [FREE Full text] [doi: 10.1186/s12888-017-1458-0] [Medline: 28810841]
28. Han J, Batterham PJ, Calear AL, Wu Y, Xue J, van Spijker BA. Development and pilot evaluation of an online psychoeducational program for suicide prevention among university students: A randomised controlled trial. Internet Interv 2018 Jun;12:111-120 [FREE Full text] [doi: 10.1016/j.invent.2017.11.002] [Medline: 30135775]
29. van Spijker BA, Werner-Seidler A, Batterham PJ, Mackinnon A, Calear AL, Gosling JA, et al. Effectiveness of a Web-Based Self-Help Program for Suicidal Thinking in an Australian Community Sample: Randomized Controlled Trial. J Med Internet Res 2018 Feb 14;20(2):e15 [FREE Full text] [doi: 10.2196/jmir.8595] [Medline: 29444769]
30. Werner-Seidler A, O'Dea B, Shand F, Johnston L, Frayne A, Fogarty AS, et al. A Smartphone App for Adolescents With Sleep Disturbance: Development of the Sleep Ninja. JMIR Ment Health 2017 Jul 28;4(3):e28 [FREE Full text] [doi: 10.2196/mental.7614] [Medline: 28754651]
31. Deady M, Johnston D, Milne D, Glozier N, Peters D, Calvo R, et al. Preliminary Effectiveness of a Smartphone App to Reduce Depressive Symptoms in the Workplace: Feasibility and Acceptability Study. JMIR Mhealth Uhealth 2018 Dec 04;6(12):e11661 [FREE Full text] [doi: 10.2196/11661] [Medline: 30514694]
32. van Spijker BA, Batterham PJ, Calear AL, Farrer L, Christensen H, Reynolds J, et al. The suicidal ideation attributes scale (SIDAS): Community-based validation study of a new scale for the measurement of suicidal ideation. Suicide Life Threat Behav 2014 Aug;44(4):408-419. [doi: 10.1111/sltb.12084] [Medline: 24612048]
33. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001 Sep;16(9):606-613. [doi: 10.1046/j.1525-1497.2001.016009606.x] [Medline: 11556941]
34. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006 May 22;166(10):1092-1097. [doi: 10.1001/archinte.166.10.1092] [Medline: 16717171]
35. Batterham PJ, Sunderland M, Carragher N, Calear AL, Mackinnon AJ, Slade T. The Distress Questionnaire-5: Population screener for psychological distress was more accurate than the K6/K10. J Clin Epidemiol 2016 Mar;71:35-42. [doi: 10.1016/j.jclinepi.2015.10.005] [Medline: 26464194]
36. Ng Fat L, Scholes S, Boniface S, Mindell J, Stewart-Brown S. Evaluating and establishing national norms for mental wellbeing using the short Warwick-Edinburgh Mental Well-being Scale (SWEMWBS): findings from the Health Survey for England. Qual Life Res 2017 May;26(5):1129-1144 [FREE Full text] [doi: 10.1007/s11136-016-1454-8] [Medline: 27853963]
37. Tennant R, Hiller L, Fishwick R, Platt S, Joseph S, Weich S, et al. The Warwick-Edinburgh Mental Well-being Scale (WEMWBS): development and UK validation. Health Qual Life Outcomes 2007 Nov 27;5:63 [FREE Full text] [doi: 10.1186/1477-7525-5-63] [Medline: 18042300]
38. Stewart-Brown S, Tennant A, Tennant R, Platt S, Parkinson J, Weich S. Internal construct validity of the Warwick-Edinburgh Mental Well-being Scale (WEMWBS): a Rasch analysis using data from the Scottish Health Education Population Survey. Health Qual Life Outcomes 2009 Feb 19;7:15 [FREE Full text] [doi: 10.1186/1477-7525-7-15] [Medline: 19228398]
39. Morin CM, Belleville G, Bélanger L, Ivers H. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. Sleep 2011 May 01;34(5):601-608 [FREE Full text] [doi: 10.1093/sleep/34.5.601] [Medline: 21532953]
40. McEvoy PM, Mahoney AE, Moulds ML. Are worry, rumination, and post-event processing one and the same? Development of the repetitive thinking questionnaire. J Anxiety Disord 2010 Jun;24(5):509-519. [doi: 10.1016/j.janxdis.2010.03.008] [Medline: 20409676]
41. Bryan CJ, Kanzler KE, Grieser E, Martinez A, Allison S, McGeary D. A Shortened Version of the Suicide Cognitions Scale for Identifying Chronic Pain Patients at Risk for Suicide. Pain Pract 2017 Mar;17(3):371-381. [doi: 10.1111/papr.12464] [Medline: 27317370]
42. Simons JS, Gaher RM. The Distress Tolerance Scale: Development and Validation of a Self-Report Measure. Motiv Emot 2005 Jun;29(2):83-102. [doi: 10.1007/s11031-005-7955-3]
43. Hughes ME, Waite LJ, Hawkley LC, Cacioppo JT. A Short Scale for Measuring Loneliness in Large Surveys: Results From Two Population-Based Studies. Res Aging 2004;26(6):655-672 [FREE Full text] [doi: 10.1177/0164027504268574] [Medline: 18504506]
44. Russell D, Peplau LA, Cutrona CE. The revised UCLA Loneliness Scale: Concurrent and discriminant validity evidence. Journal of Personality and Social Psychology 1980;39(3):472-480. [doi: 10.1037//0022-3514.39.3.472]
45. Wilson C, Deane F, Ciarrochi J, Rickwood D. Measuring help seeking intentions: Properties of the General Help seeking Questionnaire. Can J Couns 2005;39(1):15-28 [FREE Full text]
46. Beecham J, Knapp M. Costing psychiatric interventions. In: Measuring Mental Health Needs (Second Edition). London, UK: Cambridge University Press; 2001:200-224.
47. Duckworth AL, Peterson C, Matthews MD, Kelly DR. Grit: perseverance and passion for long-term goals. J Pers Soc Psychol 2007 Jun;92(6):1087-1101. [doi: 10.1037/0022-3514.92.6.1087] [Medline: 17547490]

48. Liao Q, Cowling BJ, Lam WW, Ng DM, Fielding R. Anxiety, worry and cognitive risk estimate in relation to protective behaviors during the 2009 influenza A/H1N1 pandemic in Hong Kong: ten cross-sectional surveys. BMC Infect Dis 2014 Mar 27;14:169 [FREE Full text] [doi: 10.1186/1471-2334-14-169] [Medline: 24674239]
49. Buri J, Cromett C, Post M, Landis A, Alliegro M. Negative Life Events Scale for Students (NLESS). 2015 Presented at: 123rd annual convention of the American Psychological Association; August 2015; Toronto.
50. O'Dea B, Han J, Batterham PJ, Achilles MR, Calear AL, Werner-Seidler A, et al. A randomised controlled trial of a relationship-focussed mobile phone application for improving adolescents' mental health. J Child Psychol Psychiatry 2020 Aug;61(8):899-913. [doi: 10.1111/jcpp.13294] [Medline: 32683737]
51. Verbeke G, Molenberghs G. Linear Mixed Models for Longitudinal Data. New York, USA: Springer; 2013.
52. Clarke V, Braun V, Hayfield N. Thematic analysis. In: Qualitative psychology: A practical guide to research methods. London: Sage; 2015:222-248.
53. Thornton L, Batterham PJ, Fassnacht DB, Kay-Lambkin F, Calear AL, Hunt S. Recruiting for health, medical or psychosocial research using Facebook: Systematic review. Internet Interv 2016 May;4:72-81 [FREE Full text] [doi: 10.1016/j.invent.2016.02.001] [Medline: 30135792]
54. Newby JM, O'Moore K, Tang S, Christensen H, Faasse K. Acute mental health responses during the COVID-19 pandemic in Australia. PLoS One 2020;15(7):e0236562 [FREE Full text] [doi: 10.1371/journal.pone.0236562] [Medline: 32722711]

Abbreviations

CSRI: Client Service Receipt Inventory
DBT: dialectical behavior therapy
DQ-5: Distress Questionnaire-5
DSMB: Data Monitoring Safety Board
DTS: Distress Tolerance Scale
GAD-7: Generalized Anxiety Disorder-7
GHSQ: General Help-Seeking Questionnaire
ISI: Insomnia Severity Index
NLESS: Negative Life Events Scale for Students
PHQ-9: Patient Health Questionnaire-9
RTQ-10: Repetitive Thinking Questionnaire-10
SCS: Suicide Cognitions Scale
SGS: Short Grit Scale
SIDAS: Suicidal Ideation Attributes Scale
SWEMWBS: Short Warwick-Edinburgh Mental Well-Being Scale
TILS: Three-Item Loneliness Scale
WEMWBS: Warwick-Edinburgh Mental Well-Being Scale

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Protocol

Web-Based Training for Nurses on Shared Decision Making and Prenatal Screening for Down Syndrome: Protocol for a Randomized Controlled Trial

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Abstract

Background: Pregnant women often find it difficult to choose from among the wide variety of available prenatal screening options. To help pregnant women and their partners make informed decisions based on their values, needs, and preferences, a decision aid and a web-based shared decision making (SDM) training program for health professionals have been developed. In Canada, nurses provide maternity care and thus can train as decision coaches for prenatal screening. However, there is a knowledge gap about the effectiveness of SDM interventions in maternity care in nursing practice.

Objective: This study aims to assess the impact of an SDM training program on nurses' intentions to use a decision aid for prenatal screening and on their knowledge and to assess their overall impressions of the training.

Methods: This is a 2-arm parallel randomized trial. French-speaking nurses working with pregnant women in the province of Quebec were recruited online by a private survey firm. They were randomly allocated (1:1 ratio) to either an experimental group, which completed a web-based SDM training program that included prenatal screening, or a control group, which completed a web-based training program focusing on prenatal screening alone. The experimental intervention consisted of a 3-hour web-based training hosted on the Université Laval platform with 4 modules: (1) SDM; (2) Down syndrome prenatal screening; (3) decision aids; and (4) communication between health care professionals and the patient. For the control group, the topic of SDM in Module 1 was replaced with "Context and history of prenatal screening," and the topic of decision aids in Module 3 was replaced with "Consent in prenatal screening." Participants completed a self-administered sociodemographic questionnaire with close-ended questions. We also assessed the participants' (1) intention to use a decision aid in prenatal screening clinical practice, (2) knowledge, (3) satisfaction with the training, (4) acceptability, and (5) perceived usefulness of the training. The randomization was done using a predetermined sequence and included 40 nurses. Participants and researchers were blinded. Intention to use a decision aid will be assessed by a t test. Bivariate and multivariate analysis will be performed to assess knowledge and overall impressions of the training.

Results: This study was funded in 2017 and approved by Genome Canada. Data were collected from September 2019 to late January 2020. This paper was initially submitted before data analysis began. Results are expected to be published in winter 2020.

Conclusions: Study results will inform us on the impact of an SDM training program on nurses' intention to use and knowledge of decision aids for prenatal screening and their overall impressions of the training. Participant feedback will also inform an upgrade of the program, if needed.

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KEYWORDS

shared decision making; prenatal screening; training; nurses; behavioral intention; Down syndrome; continuing professional development

Introduction

Choosing whether to undergo prenatal screening is a difficult decision for pregnant women, and they are rarely prepared for or supported in that decision [1]. Shared decision making (SDM) fosters decisions that reflect the best available evidence and what matters most to patients [2]. Evidence suggests that SDM is the best practice for informed consent [3]. SDM is now part of policy and legislation in many countries for ethical, social, and economic reasons [4]. According to the literature, SDM appears to improve patients' and clinicians' health care experiences, health care processes, patient outcomes, and health costs [5]. SDM also seems to reduce the overuse of ineffective tests and treatments and increase the uptake of effective ones [6]. It could thus play an important role in reducing harms and increasing patient safety [7]. Patient decision aids (DAs) are SDM tools that foster the involvement of patients in decisions by specifying a decision point, informing them of options and outcomes, and helping them clarify what matters most to them [8,9].

Nevertheless, SDM is rarely implemented in prenatal care [10]. Pregnant women are rarely given a chance to weigh the advantages and disadvantages of undergoing prenatal screening or to identify what matters most to them [1]. This can translate into discomfort with decisions (decisional conflict), decision regret, and potential complaints [11-13]. Results of systematic reviews indicate that SDM would be implemented if clinicians and patients had access to DAs, if providers were trained in SDM, and if public awareness campaigns about SDM were carried out [8,14]. However, despite an increase of 174% in SDM training programs in 4 years (2011-2015), only about 29% of these programs were evaluated [15]. Thus, there is little known about their overall effectiveness [15].

The province of Quebec, in Canada, offers each pregnant woman the opportunity to screen for Down syndrome with the serum-integrated prenatal screening test (which includes nuchal translucency) [16]. Currently, noninvasive prenatal testing is only offered in private institutions. Since several prenatal screening tests are available, health care professionals must be well-informed about the risks and probabilities surrounding screening results and must be able to communicate these to pregnant women in their care. Thus, effective informational resources, tools, and training are urgently required.

The members of the Canada Research Chair in Shared Decision Making and Knowledge developed a training program to support health care professionals in practicing SDM in the context of prenatal screening. The program was developed with the help of 5 professionals (family medicine doctors, biochemical doctors, ethicists, and scientists) who provided expertise on SDM, prenatal screening, and ethics. Their expertise is conveyed through videos in which experts respond to questions related to each module. Although the Research Chair has developed some SDM training programs [17,18], this program for prenatal screening is new; and no training evaluation, such as focus groups or usability testing, have been undertaken.

Nurses can play a larger role with pregnant women in prenatal screening. Those not already doing so can provide information and counseling about prenatal screening [19] and implement and evaluate it [20]. Patients themselves have suggested that nurses could provide significant help in SDM. Nurses already explain relevant medical notions, support the patients, and communicate with other clinicians [21]. However, to engage in SDM with future parents, nurses must be aware of evidence-based information on the kinds of screening available and must take the future parents' preferences into consideration. SDM training could be a way to implement this approach in nursing practice. While most SDM implementation studies focus on physicians [13], health care reforms are resulting in nurses taking more responsibilities [22], and their role in SDM will likely increase. It is therefore timely to address the gap in the literature on the effectiveness of SDM training, especially for nurses and for prenatal screening.

The primary objective of this study is to assess the impact of an SDM training program on the intention of nurses to use a DA to support prenatal screening decisions among pregnant women. The secondary objectives are to assess the impact of the training on knowledge related to SDM and prenatal screening as well as to assess nurses' overall impressions (satisfaction, acceptability of the training, and perceived usefulness) regarding the training. It is expected that this web-based training program will significantly increase nurses' intention to use a DA and will increase their knowledge about SDM and prenatal screening. It is also hypothesized that nurses will perceive this training as relevant and useful.

Methods

Study Design

This study is a 2-arm randomized controlled trial. Participants were randomly allocated to 2 parallel groups: (1) an experimental group exposed to a 3-hour web-based training program on SDM, including SDM for prenatal screening (n=18), or (2) a control group exposed to a 3-hour web-based training program on prenatal screening alone (n=18). The CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) checklist (V.1.6.1) will be used as a reporting guideline [23].

Research Approval

This project was approved by the ethics committee of the Centre Hospitalier Universitaire de Québec-Université Laval (MP-20-2019-4571). All stages of this research project will be carried out in accordance with the rules of ethics. If any amendment to the protocol is required, it will be submitted to the ethics committee and stated in the final paper. All participants consented to their participation in the research project before starting the study. The consent form stated that the participants had the right to refuse to participate and the right to withdraw at any time without providing any justification and without prejudice to preexisting entitlements.

Study Population

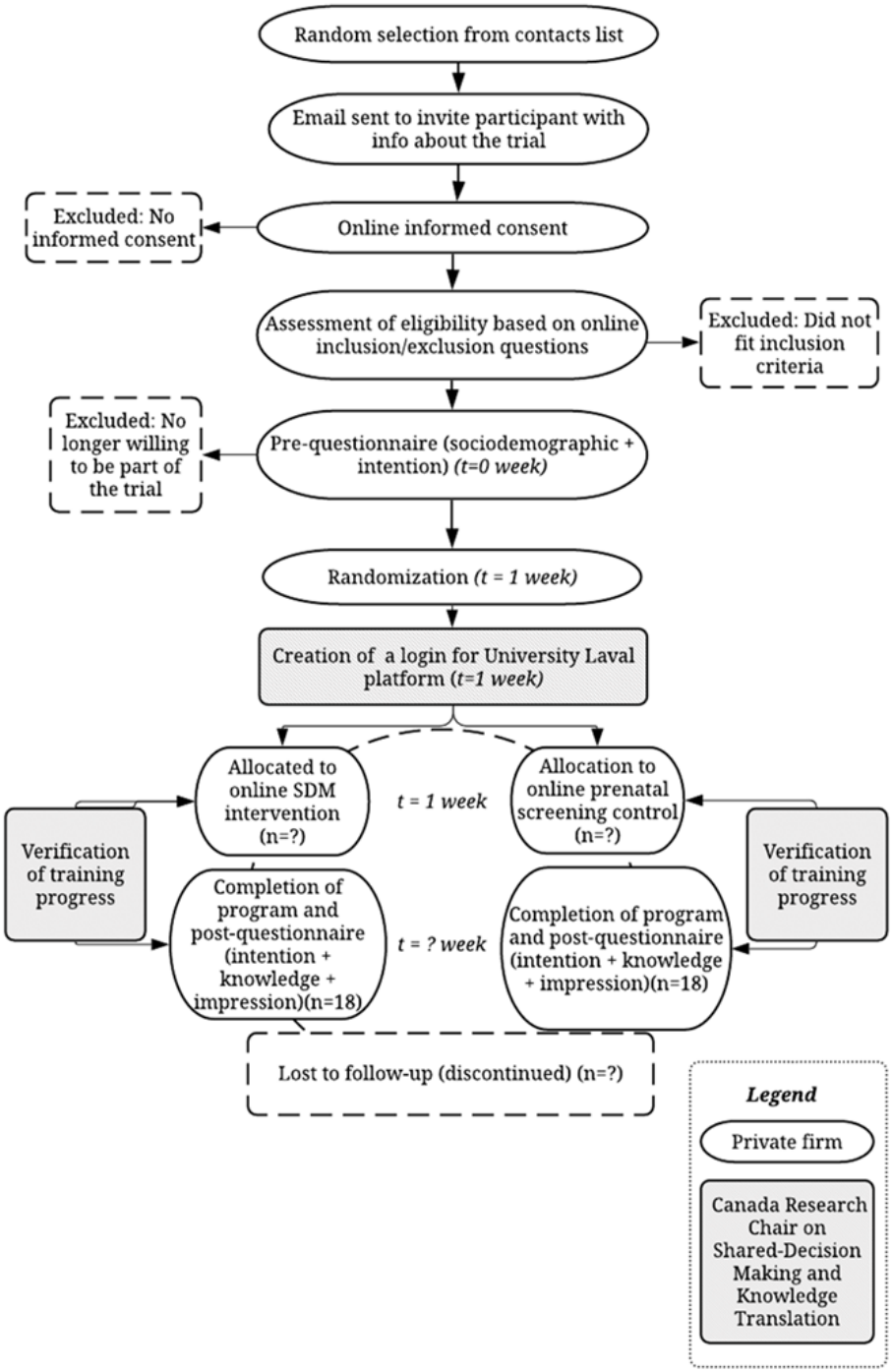
Inclusion criteria for nurses included those who (1) supported prenatal screening decision making or were involved in prenatal screening processes in the province of Quebec, (2) spoke and wrote French, (3) were active in professional practice during the year of data collection (eg, hospitals, community clinics), and (4) had enough internet skills (all procedures except recruitment were web-based, requiring a minimum of ability and equipment to enter and navigate through the web-based training program). There were no exclusion criteria.

Procedures and Recruitment

Participants were recruited online by a private polling firm that operates an internet panel. Members of this panel are nurses working in different areas and specialties, and they were invited by email to participate in the study. The polling firm also posted advertisements on social media to attract a larger number of nurses and sent emails to the human resources departments of 2 regional health authorities, the CIUSSS (Centre intégré universitaire de santé et services sociaux) of Chaudière-Appalaches and the CIUSSS of the Capitale-Nationale, asking them to share the study details with their employees. All 3 recruiting methods informed potential participants of how to contact the polling firm recruitment team.

If a participant contacted the firm to express interest in participating in the study, a member of the firm's recruitment team verified the participant's eligibility by asking some questions. Once the participant's eligibility was confirmed, the polling firm sent the participant the consent form in a first email. After receiving the consent forms, the private polling firm then sent a second email with a link to the preintervention questionnaire. The preintervention and postintervention questionnaires were programmed on the polling firm's platform, and a hyperlink to access them was inserted in the emails to be sent to the participants. Completion of the preintervention questionnaire was a prerequisite for accessing the training. Once the preintervention questionnaire was completed, the participant was randomly assigned to the intervention or control group. A login name and password for accessing the Université Laval training platform were then generated for each participant (unless they already had one). All information required to access the training and the link to the postintervention questionnaire (with instructions to complete once the training was completed) was emailed to participants. Participants were allowed a month to complete the training. After receiving access to the training, participants were asked to work through the modules and answer the quizzes at the end of each module. When the participants completed the training, they could answer the postintervention questionnaire. Weekly follow-ups and reminders to complete the training were sent to the participants if needed. The polling firm maintained a contact with participants via their personal emails. If assistance was needed by participants from either randomized group, they could either email the principal investigator or contact computer services at Université Laval. Figure 1 shows the participant timeline according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [24].

Figure 1. Participant timeline. SDM: shared decision making.



Randomization

The allocation of participants to trial groups was performed after collecting the sociodemographic data. These data were needed for the creation of the login name on the Université Laval platform, and were therefore, mandatory for accessing the training. For simple randomization, before the study started, the polling firm generated a random allocation sequence by computer, enrolled participants, and assigned them to one or the other of the study groups. Participants were blinded throughout the study. However, participants could find out which intervention was the experimental one and which one was the comparator by reading the informed consent procedures (where the desired training effect was indirectly stated). The videos of experts were recorded beforehand and were delivered asynchronously so that the experts/trainers were blinded to participants. The data analysts will also be blinded with respect to allocation groups until they have completed the analysis. One

of the members of the research team was not blinded, as she needed to follow the completion of the training program by participants.

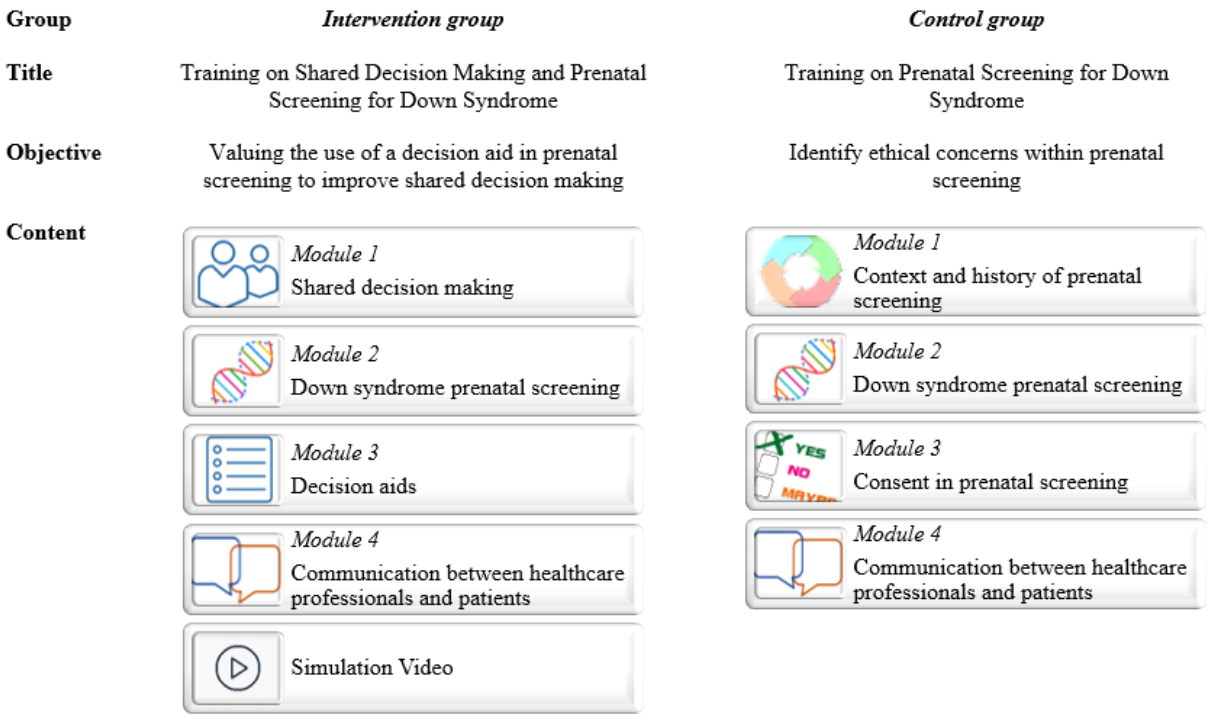
Study Interventions

Participants had to complete a web-based training program, but the content differed according to the group (control or experimental) to which the participant was randomized. The major differences were the SDM component and SDM-specific materials, which were missing in the training for the control group. In other words, in both arms the participants were exposed to a web-based training program, but only the intervention arm exposed the participants to the SDM component and SDM-specific materials. The training program was designed to adapt to the learning pace of users, who could leave the training and return later. For the purposes of this study, no major changes were made to the program during the evaluation process. Moreover, participants could consult other information sources during their training.

Intervention Group: Web-Based Training Program on SDM and Down Syndrome Prenatal Screening

The intervention consisted of a web-based self-study training program entitled *Formation en ligne – La prise de décision partagée pour le test de dépistage prénatal de la trisomie 21* (Shared Decision Making About Prenatal Screening for Down Syndrome). This program lasted 3 hours and aimed to integrate SDM into prenatal care. The training program was divided into 4 main modules: (1) shared decision making, (2) Down syndrome prenatal screening, (3) decision aids, and (4) communication between health care professionals and patients (Figure 2). This sequence was chosen to provide an overview of how SDM was defined, to highlight its benefits, to put the approach within the context of prenatal screening, and to provide concrete ways to implement SDM in clinical practice. In each module, the targeted learning objectives were presented along with the work to be carried out (eg, completing readings, watching a video, or filling in an evaluation form). A variety of teaching methods and media were used: videos, interviews, narrated capsules (explanatory videos with verbal explanations), readings, links to scientific articles, and complementary websites. At the end, a simulation video helped learners put the knowledge acquired during training into practice. It was strongly recommended that the users followed the order of presentation of the modules as their sequence was designed to promote progressive learning.

Figure 2. Description of interventions.



Control Group: Web-Based Training Program and Down Syndrome Prenatal Screening

The control group underwent a 3-hour web-based self-study training program but without the SDM component. It was entitled *Formation sur le dépistage prénatal de la trisomie 21* (Training on Prenatal Screening for Down Syndrome). In this program, the topic of SDM in Module 1 was replaced with "Context and history of prenatal screening," and the topic of DAs in Module 3 was replaced with "Consent in prenatal screening" (Figure 2). This consent module did not include key features of SDM, such as determining the decision points, providing science-based evidence for the pros and cons of options, clarification of patient values and preferences, or the use of a DA. As in the experimental group, each module had target learning objectives. The same teaching methods were used, except that in the 2 control modules, narrated capsules and reports replaced the videos of experts. The simulation at the end was removed because it focused exclusively on SDM and DAs.

Data Collection

For each study group, 2 data collection periods were planned, before and after the training programs. All outcomes were self-reported. No postintervention data were collected on participants who discontinued the intervention. The Kirkpatrick and Kirkpatrick model [25,26], a rigorous framework for evaluating training, was used as a guide. It divides effectiveness of a training program into 4 levels: (1) reaction to the training, (2) learning due to the training, (3) behavior following the training, and (4) results, such as a reduction in costs or better outcomes for the patient due to the training [25]. Although mid- and long-term outcomes are important for determining behavioral change, for the purposes of this study, these data were not collected.

Primary Outcome

The primary outcome was the intention to use a DA in clinical practice after completing the web-based training program on SDM in prenatal screening. The primary outcome was measured preintervention and postintervention (within 24-72 hours of completing the training, as duration is variable).

The intention to use a DA was chosen as an outcome because it facilitates the implementation of SDM in clinical practice [27]. Intentions have already been documented as a strong measure of predicting a behavior [28]. This outcome could predict nurses' mid- or long-term behavior in clinical practice after receiving the training, that is, it could match the third level of evaluation suggested by the Kirkpatrick and Kirkpatrick model [29].

Secondary Outcomes

The secondary objectives were to assess the impact of training on (1) knowledge related to SDM and prenatal screening, and (2) nurses' overall impression of the training, including satisfaction, acceptability, perceived usefulness, and reaction (to the pedagogical methods). All secondary outcomes were evaluated within 24-72 hours of completing the training.

Measures

The Continuing Professional Development Reaction (CPD Reaction) questionnaire [30] was used to measure behavioral intention. CPD Reaction is a validated questionnaire (Cronbach α ranging from .77 to .85) for evaluating continuing professional development, as the name suggests [29]. The 12-item questionnaire scores on 5 constructs: intention, social influence, beliefs about capabilities, moral norm, and beliefs about consequences. This study focuses on intention; however, the other constructs were also evaluated for their potential to predict the behavior of interest.

After receiving the intervention, participants were invited through the postintervention questionnaire to evaluate their knowledge. Knowledge was explored using 20 questions: 2 questions on Down syndrome, 7 on prenatal screening, 7 on SDM, and 4 on ethics. This questionnaire was created by the Canada Research Chair on Shared Decision Making and Knowledge Translation based on advice by an SDM expert (FL), numerous studies of SDM [2,9,31], and governmental information on prenatal screening [16]. Questions were also structured following Bloom's taxonomy of cognitive learning objectives [32].

Satisfaction was measured regarding the content, trainers, and overall satisfaction using a self-reported questionnaire created by Schmidt [33] and adapted for this study.

The measure of acceptability of the training program was based on a questionnaire by Kasper et al [34]; and questions addressed the comprehensibility, the amount of information, the quality of information, and the chosen format of the training.

The measures of perceived usefulness were based on a questionnaire by Giangreco et al [35]. It considered usefulness in terms of work responsibilities, relevance of topics to career development, relevance of topics in relation to individual learning needs, consistency with declared objectives of the training mentioned at the beginning of each module of both training programs, and balance between theory and practice.

Finally, the measure of nurses' reaction to the pedagogical aspects of the training used the Kirkpatrick and Kirkpatrick questionnaire, which assesses the general relevance and utility of the training for clinical practice [25].

Other Data to be Collected

Participants were invited to complete a sociodemographic questionnaire before accessing the training for two reasons: to have a broad picture of the participants and to extract the information required to create a personal username for the Université Laval web platform through which they were to access the training. At the end of the intervention, participants were asked an open qualitative question about their suggestions for improvement.

Data Management

All data collected will be kept on the secure server of the polling firm for 10 years. Following data collection, the firm sent a deidentified database of all data collected in an Excel file and a Statistical Analysis Software (SAS) file to the research team. An identification number was assigned to each participant to track them throughout the study. The research team saved these data on the secure server of the CIUSSS-CN (Centre intégré universitaire de santé et services sociaux de la Capitale-Nationale).

Sample Size

The sample size was determined in reference to a previous study in the field [27] that examined the intention to use a DA for Down syndrome screening among other prenatal care providers, namely gynecologists, general practitioners, and midwives. The mean intention score for midwives in this study was 5.78 (SD 0.84). Midwives' intention was selected as a point of reference because of their close affinities with nursing practice [36,37]. To detect an average difference between 2 independent groups, it was estimated that a sample size of 36 nurses (n=18 per group) would be enough to detect a difference in intention of using a DA with an error of 0.05, a size effect of 0.8, and power of 80%.

Data Analysis

Descriptive statistical analysis of sociodemographic characteristics will be performed to ensure the comparability

of groups (intervention and control). The *t* test will be performed on the mean of the intention to use the DA in both groups and on knowledge scores. Secondary outcomes (knowledge and overall impression) will be assessed by doing bivariate and multiple regression analyses. For each outcome analyzed, according to the type of variable (continuous or categorical), the degree of fit and the assumptions of each model will be assessed. The statistical significance threshold is a *P* value of <.05, and all statistical analyses will be performed using the SAS statistical package (SAS Institute). No subgroup analysis is planned as of yet.

Results

This study started in September 2019, and all data were collected by January 2020. Statistical analyses and submission of a paper for publication are anticipated by the end of 2020.

Discussion

It is expected that this study will provide information about the impact of training on the adoption of SDM skills, such as using a DA, among nurses in prenatal screening. It is expected that this web-based training program will significantly increase nurses' knowledge about SDM and prenatal screening and will strengthen their intention to use such a tool in their practice.

Regarding strengths of this study, the web-based training was created by a team that has 15 years of experience in the development of SDM tools, including DAs and continuing professional education programs, and has been specifically working on tools for prenatal screening decisions for more than 7 years. This training program was created in collaboration with Université Laval, an institution that can accredit continuing professional development. The randomized controlled trial is a strong study design for evaluating the effectiveness of interventions, as it reduces bias and is a rigorous tool for examining cause-effect relationships between interventions and their outcomes [38]. Participants come from different parts of the province of Quebec, and thus the study will be representative of different types of practice and demographic profiles (eg, rural and urban). Moreover, participants are active health care professionals, and their perspectives will reflect the realities of current practice and their SDM needs.

As for limitations, the first is that our results do not address the fourth level of the Kirkpatrick and Kirkpatrick model (2016). As the program is web-based and focuses exclusively on nurses, outcomes related to women and their partners, such as reduction of decisional regret, could not be examined. In addition, nurses are not the only health care professionals who discuss prenatal screening. The perspective of others should be integrated into the future implementation of this web-based program. Moreover, the sample size does not allow for an examination of the particularities within nursing practice, such as differences between registered nurses and nurse practitioners. Furthermore, the intention of using a DA was only measured once; therefore, it is not possible to know whether this program has a long-term effect on intention. Finally, participants could acquire parallel knowledge in their clinical practice or through curiosity while doing the training, and this knowledge may interfere with results.

Following analysis of the study results, the training program will be improved in line with participants' contributions. Health care providers' opinions, in this case the nurses' perspectives, provide critical input for upgrading training. A training program that nurses consider useful and acceptable is more likely to be adopted by nurses and the institutions in which they work with expecting parents. To date, evaluations of SDM interventions, especially in nursing, are rare. This study will be informative about the effectiveness of such training and can promote implementation of SDM in all health care practices.

Acknowledgments

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Conflicts of Interest

The authors of this paper are also the developers of the intervention. APH, TTA, MC, and FL participated in the creation of the training program.

Multimedia Appendix 1
Peer review report.
[PDF File (Adobe PDF File), 473 KB - resprot_v9i10e17878_app1.pdf]

Multimedia Appendix 2
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 1683 KB - resprot_v9i10e17878_app2.pdf]

References

1. St-Jacques S, Grenier S, Charland M, Forest J, Rousseau F, Légaré F. Decisional needs assessment regarding Down syndrome prenatal testing: a systematic review of the perceptions of women, their partners and health professionals. Prenat Diagn 2008 Dec;28(13):1183-1203. [doi: 10.1002/pd.2059] [Medline: 19097031]
2. Légaré F, Witteman H. Shared decision making: examining key elements and barriers to adoption into routine clinical practice. Health Aff (Millwood) 2013 Feb;32(2):276-284. [doi: 10.1377/hlthaff.2012.1078] [Medline: 23381520]
3. Moulton B, Collins PA, Burns-Cox N, Coulter A. From informed consent to informed request: do we need a new gold standard? J R Soc Med 2013 Oct;106(10):391-394 [FREE Full text] [doi: 10.1177/0141076813490686] [Medline: 23759895]
4. Gray M, Jani A. Promoting Triple Value Healthcare in Countries with Universal Healthcare. Healthc Pap 2016;15(3):42-48. [Medline: 27009586]
5. Shay LA, Lafata JE. Where is the evidence? A systematic review of shared decision making and patient outcomes. Med Decis Making 2015 Dec;35(1):114-131 [FREE Full text] [doi: 10.1177/0272989X14551638] [Medline: 25351843]
6. Stacey D, Légaré F, Lewis K, Barry MJ, Bennett CL, Eden KB, et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev 2017 Dec 12;4:CD001431. [doi: 10.1002/14651858.CD001431.pub5] [Medline: 28402085]
7. Hibbard JH, Greene J. What the evidence shows about patient activation: better health outcomes and care experiences; fewer data on costs. Health Aff (Millwood) 2013 Feb;32(2):207-214. [doi: 10.1377/hlthaff.2012.1061] [Medline: 23381511]
8. Légaré F, Stacey D, Turcotte S, Cossi M, Kryworuchko J, Graham ID, et al. Interventions for improving the adoption of shared decision making by healthcare professionals. Cochrane Database Syst Rev 2014;9:CD006732. [doi: 10.1002/14651858.CD006732.pub3] [Medline: 25222632]
9. Légaré F, Adekpedjou R, Stacey D, Turcotte S, Kryworuchko J, Graham ID, et al. Interventions for increasing the use of shared decision making by healthcare professionals. Cochrane Database Syst Rev 2018 Jul 19;7:CD006732 [FREE Full text] [doi: 10.1002/14651858.CD006732.pub4] [Medline: 30025154]
10. Légaré F, St-Jacques S, Gagnon S, Njoya M, Brisson M, Frémont P, et al. Prenatal screening for Down syndrome: a survey of willingness in women and family physicians to engage in shared decision-making. Prenat Diagn 2011 Apr;31(4):319-326. [doi: 10.1002/pd.2624] [Medline: 21268046]
11. Couët N, Desroches S, Robitaille H, Vaillancourt H, Leblanc A, Turcotte S, et al. Assessments of the extent to which health-care providers involve patients in decision making: a systematic review of studies using the OPTION instrument. Health Expect 2015 Aug;18(4):542-561. [doi: 10.1111/hex.12054] [Medline: 23451939]
12. Légaré F, O'Connor AC, Graham I, Saucier D, Côté L, Cauchon M, et al. Supporting patients facing difficult health care decisions: use of the Ottawa Decision Support Framework. Can Fam Physician 2006 Apr;52:476-477. [Medline: 17327891]
13. Légaré F, Ratté S, Gravel K, Graham ID. Barriers and facilitators to implementing shared decision-making in clinical practice: update of a systematic review of health professionals' perceptions. Patient Educ Couns 2008 Dec;73(3):526-535. [doi: 10.1016/j.pec.2008.07.018] [Medline: 18752915]
14. Stacey D, Hill S, McCaffery K, Boland L, Lewis KB, Horvat L. Shared Decision Making Interventions: Theoretical and Empirical Evidence with Implications for Health Literacy. Stud Health Technol Inform 2017;240:263-283. [Medline: 28972523]
15. Diouf NT, Menear M, Robitaille H, Painchaud GG, Légaré F. Training health professionals in shared decision making: Update of an international environmental scan. Patient Educ Couns 2016 Jun 14 [FREE Full text] [doi: 10.1016/j.pec.2016.06.008] [Medline: 27353259]
16. Gouvernement du Québec. Programme québécois de dépistage prénatal de la trisomie 21: cadre de référence. Québec: Direction des communications du ministère de la Santé et des Services sociaux; 2017.
17. Légaré F, Labrecque M, Cauchon M, Castel J, Turcotte S, Grimshaw J. Training family physicians in shared decision-making to reduce the overuse of antibiotics in acute respiratory infections: a cluster randomized trial. CMAJ 2012 Sep 18;184(13):E726-E734. [doi: 10.1503/cmaj.120568] [Medline: 22847969]
18. Dogba MJ, Menear M, Brière N, Freitas A, Emond J, Stacey D, et al. Enhancing interprofessionalism in shared decision-making training within homecare settings: a short report. J Interprof Care 2020;34(1):143-146. [doi: 10.1080/13561820.2019.1623764] [Medline: 31184540]
19. Rabiee M, Jouhari Z, Pirasteh A. Knowledge of Prenatal Screening, Down Syndrome, Amniocentesis, and Related Factors among Iranian Pregnant Women: A Cross-Sectional Study. Int J Community Based Nurs Midwifery 2019 Apr;7(2):150-160 [FREE Full text] [Medline: 31041325]
20. Grant SS. Prenatal genetic screening. Online J Issues Nurs 2000;5(3):2. [Medline: 11380268]
21. Joseph-Williams N, Elwyn G, Edwards A. Knowledge is not power for patients: a systematic review and thematic synthesis of patient-reported barriers and facilitators to shared decision making. Patient Educ Couns 2014 Mar;94(3):291-309. [doi: 10.1016/j.pec.2013.10.031] [Medline: 24305642]
22. Canadian Nurses Association. Registered Nurses: Stepping up to transform health care. Ottawa: Canadian Nurses Association; 2013.

23. Eysenbach G, CONSORT-EHEALTH Group. CONSORT-EHEALTH: improving and standardizing evaluation reports of Web-based and mobile health interventions. J Med Internet Res 2011;13(4):e126 [FREE Full text] [doi: 10.2196/jmir.1923] [Medline: 22209829]
24. Participant Timeline. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials). 2019. URL: https://www.spirit-statement.org/participant-timeline/ [accessed 2020-09-02]
25. Kirkpatrick J, Kirkpatrick W. Kirkpatrick's four levels of training evaluation. Alexandria, VA: ATD Press; 2016.
26. Gillan C, Lovrics E, Halpern E, Wiljer D, Harnett N. The evaluation of learner outcomes in interprofessional continuing education: a literature review and an analysis of survey instruments. Med Teach 2011;33(9):e461-e470. [doi: 10.3109/0142159X.2011.587915] [Medline: 21854139]
27. Abbasgholizadeh Rahimi S, Lépine J, Croteau J, Robitaille H, Giguere AM, Wilson BJ, et al. Psychosocial Factors of Health Professionals' Intention to Use a Decision Aid for Down Syndrome Screening: Cross-Sectional Quantitative Study. J Med Internet Res 2018 Apr 25;20(4):e114 [FREE Full text] [doi: 10.2196/jmir.9036] [Medline: 29695369]
28. Armitage CJ, Conner M. Efficacy of the Theory of Planned Behaviour: a meta-analytic review. Br J Soc Psychol 2001 Dec;40(Pt 4):471-499. [doi: 10.1348/014466601164939] [Medline: 11795063]
29. Légaré F, Borduas F, Freitas A, Jacques A, Godin G, Luconi F, et al. Development of a simple 12-item theory-based instrument to assess the impact of continuing professional development on clinical behavioral intentions. PLoS One 2014;9(3):e91013 [FREE Full text] [doi: 10.1371/journal.pone.0091013] [Medline: 24643173]
30. Légaré F, Freitas A, Turcotte S, Borduas F, Jacques A, Luconi F, et al. Responsiveness of a simple tool for assessing change in behavioral intention after continuing professional development activities. PLoS One 2017;12(5):e0176678 [FREE Full text] [doi: 10.1371/journal.pone.0176678] [Medline: 28459836]
31. Légaré F, Thompson-Leduc P. Twelve myths about shared decision making. Patient Educ Couns 2014 Sep;96(3):281-286 [FREE Full text] [doi: 10.1016/j.pec.2014.06.014] [Medline: 25034637]
32. Adams NE. Bloom's taxonomy of cognitive learning objectives. J Med Libr Assoc 2015 Jul;103(3):152-153 [FREE Full text] [doi: 10.3163/1536-5050.103.3.010] [Medline: 26213509]
33. Schmidt SW. The relationship between satisfaction with workplace training and overall job satisfaction. Human Resource Development Quarterly 2007;18(4):481-498. [doi: 10.1002/hrdq.1216]
34. Kasper J, Liethmann K, Heesen C, Reissmann DR, Geiger F. Training doctors briefly and in situ to involve their patients in making medical decisions-Preliminary testing of a newly developed module. Health Expect 2017 Dec;20(6):1254-1263 [FREE Full text] [doi: 10.1111/hex.12565] [Medline: 28521082]
35. Giangreco A, Sebastiano A, Peccei R. Trainees' reactions to training: an analysis of the factors affecting overall satisfaction with training. The International Journal of Human Resource Management 2009 Jan;20(1):96-111. [doi: 10.1080/09585190802528417]
36. Relyea MJ. The rebirth of midwifery in Canada: an historical perspective. Midwifery 1992 Dec;8(4):159-169. [doi: 10.1016/s0266-6138(05)80002-6] [Medline: 1291848]
37. Burst HV. The history of nurse-midwifery/midwifery education. J Midwifery Womens Health 2005;50(2):129-137. [doi: 10.1016/j.jmwh.2004.12.014] [Medline: 15749299]
38. Hariton E, Locascio JJ. Randomised controlled trials - the gold standard for effectiveness research: Study design: randomised controlled trials. BJOG 2018 Dec;125(13):1716 [FREE Full text] [doi: 10.1111/1471-0528.15199] [Medline: 29916205]

Abbreviations

CERSSPL-UL: Centre de recherche sur les soins et services de première ligne de l'Université Laval
CIUSSS: Centre intégré universitaire de santé et services sociaux
CIUSSS-CN: Centre intégré universitaire de santé et services sociaux de la Capitale-Nationale
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
CPD Reaction: Continuing Professional Development Reaction
DA: decision aid
PEGASUS: PErsonalized Genomics for prenatal Abnormalities Screening USing maternal blood
RRISIQ: Réseau de recherche en interventions en sciences infirmières du Québec
SDM: shared decision making
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Proposal

Community Gardening as a Way to Build Cross-Cultural Community Resilience in Intersectionally Diverse Gardeners: Community-Based Participatory Research and Campus-Community-Partnered Proposal

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Abstract

Background: Community-based agriculture has been found to decrease food insecurity and alleviate health inequities. Furthermore, it provides a sense of ownership, resources to help integrate new communities, and a space to nurture existing cultural identities for intersectionally diverse gardeners. This sense of belonging in connection with access to growing plots has been linked to psychological well-being and resilience. However, little is known about how the psychosocial benefits of plot ownership affect resilience and which aspects of this resilience are salient.

Objective: This community-based participatory research (CBPR) project will examine the role of community gardens in decreasing food insecurity and facilitating various forms of resilience in food-insecure groups in Rochester, Minnesota. Since participation in community gardens nurtures various forms of resilience along individual, group, and community dimensions, our research seeks to understand how dimensions of resilience vary along intersectional lines. In addition to mapping the psychosocial benefits linked to plot ownership, we find that examining which forms of resilience are fostered in community-based agricultural projects addresses an important gap in the academic literature. This can help us propose policy-level practices that reduce health inequities connected to food and nutrition at the local level.

Methods: Using a mixed methods approach, this ongoing community-campus partnership will examine the experiences of current and new plot owners. As a CBPR project, our data collection plan, from design to dissemination, incorporates the intellectual and creative labor of the individuals representing members of the campus community (ie, college students and faculty members engaged in other citizen science projects hosted by the garden), community growers, individuals involved in the community garden's board, and representatives of various organizational bodies. Data collection activities will consist of surveys, in-depth interviews, and photovoice.

Results: This project was funded in January 2020 and approved by the University of Minnesota's Institutional Review Board in March 2020. For the 2020 growing season, we will conduct evaluative interviews about the effect of COVID-19 on community gardeners, including their experiences during this growing season. For the 2021 growing season, data collection, via pre- and postsurveys, is projected to begin in March 2021 and end in November 2021. We will also conduct in-depth interviews from January to April 2021. Data analysis will commence in April 2021. Photovoice activities (ie, data collection, analysis, synthesis, and dissemination) are expected to take place during the spring and summer of 2021.

Conclusions: Findings emerging from this study will provide the preliminary data to foreground community gardening projects and initiatives to improve physical and mental health outcomes in food-insecure communities. Also, the data collected will highlight the role of CBPR methods in disseminating information about the organizational practices of the community garden; this will assist others in planning and implementing similar projects.

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KEYWORDS

community gardening; resilience; food insecurity; racial and ethnic minority populations; campus-community partnerships; CBPR

Introduction

Background

Food insecurity is a social condition where at least one member of a household unit has limited access to adequate amounts of nutritious and culturally adequate food or experiences hunger due to lack of economic and other social resources [1]. Food insecurity affected around 14.3 million people in the United States in 2018 [2]. The United States Department of Agriculture (USDA) indicated that half of the populations experiencing this deficit are those categorized as US communities of color [3]. Furthermore, households headed by a foreign-born adult tend to experience more food insecurity than other populations in the United States [4]. Differential access to sources of nutrition "leads to nutritional inequalities and diet-related health inequities in rich and poor cities alike" [5]. Participating in governmental and other community-based food supplementation and nutrition programs, such as food pantries; tapping into informal networks of friends and families for help; developing strategies to access lower-cost food items; regulating eating patterns; and using supplementary sources of income are in the range of strategies employed by food-insecure families in the United States [6].

Community gardening, defined as the use of "plots of land used for growing food by people from different families, typically urban dwellers with limited access to their land" [7], is one such strategy used by families facing food insecurity [8]. Community gardens provide spaces for people with little-to-no access to fresh and nutritious food [9], which may also have an impact on health inequities [10]. Research indicates that community garden access allows people to develop healthy behaviors, practices, and habits that could decrease health inequities in the long run [11], such as increased consumption of fruits and vegetables [12], aiding in obesity prevention [13,14], and engagement in sustained physical activities, such as walking [15].

In addition to a decrease in food insecurity and nutrition-based health inequities, community gardens provide additional related benefits to gardeners, especially those from diverse backgrounds of race, ethnicity, language, class, and other identity markers. Since these spaces are known to operate at different levels of "ownership, access, and degree of democratic control" [16], access to community garden plots nurtures ownership and belonging among refugees, immigrants, and other marginalized and minoritized groups in areas where they are socially devalued [17,18]. As in the case of US foreign-born groups, community gardens are also uniquely situated to both facilitate integration within new communities [18-20] and provide a context where these groups can continue to nurture existing cultural identities and practices [21,22]. This sense of belonging in connection with access to plots [18] has been linked to psychological well-being and resilience [7]. In addition to sustaining spaces for the exchange of knowledge and the creation of community bonds, these spaces might serve as "physical havens for safety and the development of social and spiritual support" [23] in areas where racial or ethnic and other minorities tend not to be welcomed by the majority population.

While there have been a few studies looking at the role of community gardens in fostering food security, well-being, and resilience in marginalized groups [7,24,25], especially during times of economic uncertainty [26], several questions remain unanswered. Despite gardens usually being located in neighborhoods populated by racial and ethnic minorities, community gardens tend to be most accessed by Anglo White gardeners [27]. Furthermore, community gardens have been conceptualized as "socio-ecological refuges" [23,28,29], since they increase social cohesion [30] and feelings of empowerment [31,32] in historically marginalized and socially devalued people by belonging to groups deemed mainstream in US society. However, there is little knowledge of how the various psychosocial benefits [33,34] of plot ownership that affect resilience in marginalized communities and which aspects of resilience are salient and possible by this process.

Objectives and Research Aims

Overview

The overall objective of this project is to understand the role of community gardens in decreasing food insecurity and facilitating psychosocial wellness and resilience among minoritized communities in Southeast Minnesota. The motivation for this inquiry is that the psychosocial benefits of community gardening include nurturing various forms of resilience in US gardeners belonging to racial and ethnic, refugee, and immigrant communities. In particular, our research will attempt to answer three interconnected issues: (1) the role of community gardens in *decreasing food insecurity* among community gardeners of refugee, immigrant, or racial and ethnic minority backgrounds, (2) the role of community gardening in *self-reported emotional health and well-being* in community gardeners from refugee, immigrant, or racial and ethnic minority backgrounds, and (3) the role of community gardening in *increasing resilience* at three levels—individual, group, and community dimensions—in community gardeners of refugee, immigrant, or racial and ethnic minority backgrounds. The rationale of this proposed research

is that, in addition to mapping the psychosocial benefits linked to community garden plot ownership, examining which forms of resilience are connected to community gardening addresses a gap in the academic literature, which can help us propose policy-level practices that reduce health inequities connected to food and nutrition at the local level.

Adhering to a community-based participatory research (CBPR) process, the specific aims outlined below will help us gather data for a larger examination of the role of community gardening in shaping health across minoritized communities in Minnesota. We will map and analyze these unique patterns through interviews and pre- and postsurveys of food-insecure populations in Rochester, Minnesota: current and new growers assigned community garden plots.

Aim 1

Our first aim is to examine food security in different, underserved communities in Rochester, Minnesota. Racial or ethnic, sociocultural, and demographic disparities in food security do not always align with data at the aggregate level or are masked when examined. Our pre- and postsurveys include measures on food insecurity, as detailed in our Methods section, and our qualitative interviews will also explore gardeners' experiences and perceptions of food insecurity and access in their community.

Aim 2

Our second aim is to identify the psychosocial benefits linked to community garden plot ownership. Access to community plots has been found to have psychological benefits for gardeners. Also, these are spaces that facilitate cross-cultural knowledge sharing [34-36]. We will examine these psychosocial benefits in both our pre- and postsurveys and qualitative interviews, as well as in our photovoice interviews with plot owners.

Aim 3

Our third aim is to establish the extent to which community garden plot ownership and support by *The Village Community Garden & Learning Center* (VCGLC) staff and volunteers facilitate resilience in food-insecure members of US racial or ethnic, immigrant, or refugee groups in Rochester, Minnesota. We will measure resilience by conducting interviews and pre- and postsurveys with plot owners. Our survey includes replication of an instrument developed by Kimhi and colleagues [37] to examine three different dimensions of resilience in majority-minority groups—individual, community, and ethnic origin–based resilience—taking into consideration protective and suppressing factors that shape a sense of resilience.

Methods

Target Community

Current research indicates that communities made up of refugees [4], immigrants [38], and racial or ethnic minorities [39] are at a higher risk of being food insecure than other population groups. Pilot data from conversations with VCGLC coordinators and board members collected at the end of the 2019 growing season suggest that a great need for the growers is being met. Most of these individuals are of Southeast Asian descent (ie, Hmong, Cambodian, and Indian), are Latino and Latina, are of African diaspora ancestry, or are individuals coming from economically fragile or working-class backgrounds. Racial and ethnic minorities and those claiming refugee status make up more than 90% of the current growers. At the moment, the health department is currently working with others in the community, including members of the VCGLC board, to conduct other assessment-related studies looking at food security in Rochester, Minnesota, to get a better understanding of the issue, specifically related to communities of color.

The Village Community Garden & Learning Center

As a community-campus initiative, the VCGLC maintains community garden spaces for diverse Rochester groups to feed themselves, reduce food costs, and foster connections across cultures and experiences. Since its inception, the VCGLC has served as a community partner and learning site for an upper-division course at the University of Minnesota Rochester. In a year and a half, the VCGLC has increased access to fresh, healthy, and culturally relevant foods for racial or ethnic minority, immigrant, and refugee community members who have limited access to such foods. In addition to supporting over 120 intersectionally diverse growers, the VCGLC currently donates excess vegetables and fruits to local food pantries. Stakeholders with a firm commitment to the VCGLC project, via funding and other forms of support, include higher education, the local public health office, the water and soil conservation district office, the local library, the mayor's office, various food cooperatives, nonprofit organizations, and the local farmers' market.

Community-Based Participatory Research

Our partnership's long-term goal is to improve the health of food-insecure groups in Rochester, Minnesota, via access to community garden spaces that nurture connections and community building among different groups by using equity-based approaches such as CBPR. By CBPR, we refer to the iterative and holistic process outlined by Israel and colleagues [40,41] that sees communities involved as unique units of identity, and centers the particular strengths and resources that these communities bring when defining, implementing, and engaging in research. Collaboration between community members and researchers is embedded throughout the research process, with the knowledge and practices gleaned being used to benefit all involved. As a process sensitive to the ebbs and flows of relationship building and trust, it also aims to disseminate knowledge and practices with language that is empowering and accessible to the communities involved, while being aware of the power dynamics inherent in research.

This project utilizes a community-participatory-based research oversight board—referred to throughout this article as the VCGLC board—composed of community members who are current growers in the garden, students, faculty researchers, and representatives from key local entities. Furthermore, many CBPR teams tend not to reflect the diversity of the community at the center of their inquiry; however, our board makeup not only reflects the membership of the garden but also features the collaboration of two research project supervisors with experience

in academic-community research partnerships and community health work with ethnic and racial minorities. Furthermore, both the community principal investigator and the academic principal investigator are first-generation Americans and native-language speakers of the two represented refugee and immigrant communities in the garden. Also, the research data will be collected by research assistants that speak the language, some of whom are members of the communities represented in the garden: Cambodian, Latino and Latina, Hmong, and Somalian. We will also train and compensate students and members of our board, many of whom are also community gardeners, in collecting, transcribing, and analyzing in-depth interviews and conducting some of the pre- and postsurveys.

Data Collection

COVID-19 has created and increased the severity of social issues that cause food insecurity, economic insecurity, and disconnection. Therefore, we believe that evaluating the outcomes of community-engaged gardening would not provide a usual, valid result. We have chosen to outline an evaluation plan for this COVID-19 growing season (2020) and a research plan for the next season (2021).

COVID-19 Growing Season (2020)

In the fall 2020 growing season, we plan to conduct a qualitative evaluation program and gather responses regarding COVID-19-related difficulties. Open-air interviews will be conducted in the community garden. Participants and moderators will be masked and will maintain adequate distancing. From September to November 2020, we will conduct 20 interviews, each 60 minutes in length, with the majority of the gardeners in English, Spanish, and Khmer. Participants will be recruited via telephone, an established means of communication for this project. We will sample participants to roughly match interviewees with the composition of our gardeners: approximately 10 Cambodian people, 5 Hispanic people, and 5 participants randomly sampled from other groups, the majority of whom are also of minority backgrounds. Each participant will be offered a US $20 gift card to a local grocery store for completing the interview.

These semistructured qualitative sessions will focus on evaluating the logistics of participating in the community garden, such as sign-up, plot allocation, provision of supplies, and support by the VCGLC staff throughout the growing season, as well as evaluating the community reaction (eg, we will ask if the community garden meets the participants' needs) and eliciting ideas to strengthen and expand the program. Finally, we will ask questions about how the community garden was accessed in relation to COVID-19. Some queries will involve perceptions of how the community garden helped participants navigate COVID-19-related economic difficulties, including food security, as well as other difficulties like the ability to grow food that may have been unavailable due to grocery store closures. We will also ask participants if the garden helped with other difficulties connected to the pandemic, such as social isolation and stress from stay-at-home orders.

At the time of writing, we are meeting as a board to develop the in-depth interview questions in light of COVID-19. Collected data will be transcribed; transcripts will then be coded inductively and deductively by at least two coders, using NVivo software (QSR International). Interrater reliability between coders will be checked.

Next Growing Season (2021)

We will measure food insecurity, emotional health, and resilience by employing a mixed methods approach, including pre- and postsurveys and semistructured interviews with plot owners.

Survey Data Collection

During the first months of the project, we engaged the VCGLC board to give us direction in refining data collection tools to measure the above outcomes. As of June 2020, the board discussed and approved the following measures to be used to survey gardeners at the start (ie, June 2021) and at the end of the growing season (ie, October 2021). We will conduct up to 130 preseason surveys and 130 postseason surveys of the same gardeners. Current enrollment is 130 plots, meaning that we plan to survey everyone involved. This number may increase next year, in which case we will use stratified random sampling so that the final sample reflects the ethnic makeup of the gardeners, which we learned from our community garden contract that we administered preseason. Participants will be recruited by telephone. Surveys will be administered via phone; non-English speakers will be given the survey in their native language. We anticipate high response rates due to the community's engagement with programmatic and community activities. Each participant will be compensated with a US $10 gift card for completing the pre- and postsurveys.

Measures

Food insecurity will be measured using the USDA's US Household Food Security Survey Module and the Food Insecurity Experience Scale Survey Module [42]. This scale not only measures severity levels of food insecurity arising from lack of resources, but it has also been cross-culturally validated using the language represented by the VCGLC's growers. We will include items regarding food behaviors from the US Centers for Disease Control and Prevention's Behavioral Risk Factor Surveillance System [43]. Psychosocial and resilience measures include the Kessler Psychological Distress Scale [44], the Connor-Davidson Resilience Scale [45], the Conjoint Community Resiliency Assessment Measure, and the short National Resilience Scale [46]. Many of these measures include validated translations in the languages of the growers and members of the VCGLC board. For those that do not, we will translate and back-translate de novo. So far, we have translated the instruments into Spanish and Khmer; we have plans for other languages as needed.

Qualitative Data Collection

Interviews

By conducting in-depth interviews with plot owners and people who attend our events, we will investigate the role of the VCGLC in facilitating opportunities and providing resources for cross-community connections, furthering a sense of collective well-being and increasing the sense of belonging and

empowerment. Conditions willing, we will conduct in-depth interviews from October to December 2021 with current and incoming gardeners. Interviews will be conducted in the participant's preferred language with one of the members of the VCGLC board interpreting or facilitating, some of whom are native speakers of Khmer, Spanish, and Somali. A telephone interpreter will be hired from one of our local community partners for other languages. Participants will be recruited via phone or on-site at the garden. Interviews will be 60 minutes long, semistructured, and conducted on-site or via phone. Each participant will be offered a US $20 gift card to a local grocery store for participating in the interview.

Photovoice

For the next growing season (2021), we will train a select group of the VCGLC's gardeners in photovoice, a visual participatory action research approach that gives voice to marginalized communities by using pictures to present their concerns to stakeholders [47,48]. Participants and facilitators will each be paid a stipend for participating in the photovoice meetings. This part of the research project will add a visual component that can be used during the community dissemination event at the end of 2021. An aspect of photovoice is the hosting of a photo exhibit to present findings to community stakeholders. This event will be open to growers and their families as well as to the wider community for input and support on the VCGLC's future steps.

Campus-Community Partnership

Community collaborations between educational institutions and community-based agricultural bodies strengthen community-campus relationships [49]. Using a model like CBPR, which puts equal weight on community and academic members' research interests, knowledge production, and opinions about how the research should be conducted, can promote healing and trust between the community and the University of Minnesota Rochester.

Data Analysis

We plan to use chi-square tests and paired *t* tests of the scales' scores to compare pre- and postresponses. This will give us an understanding of whether participants indicated that community gardening would improve food security, emotional health, and resilience. Qualitative interviews will be inductively and deductively coded by at least two coders; an interrater reliability score will be calculated.

A note on mixed methods: we propose an approach where data from the qualitative methods, including our photovoice findings, will be used to understand the experience of food insecurity, resilience, and psychosocial well-being as related to community gardening participation. The collection of quantitative data and in-depth interviews is happening almost simultaneously to allow both the previously collected 2020 evaluation data and the analytical insights from our 2021 surveys to inform the qualitative analysis of in-depth interviews and the photovoice process. Quantitative pre- and postsurvey data will allow us to track changes in our outcomes using validated scales across nearly all participants. Our qualitative data will allow us to better understand how and why gardeners felt that the process of gardening and community engagement affected them. While our quantitative data will allow us to compare outcomes effectively, the qualitative data will allow us to retain the ideas and voices of gardeners spoken in their own words.

Results

Overview

This project was funded in January 2020 and approved by the University of Minnesota's Institutional Review Board in March 2020. As of September 2, 2020, we have begun recruiting participants for the evaluation interviews. In addition, our original research design had to change due to pandemic conditions.

COVID-19 Safety Protocols

Our board met and approved a safety protocol and the creation of culturally relevant signage. These promote and inform how to socially distance while using the garden. We have also developed an approved calendar system to decrease contact between gardeners.

Increase in Participants

Initially, we sought to enroll all 30 of the active community gardeners. As of the time of writing, our total number of participants increased from 30 to 130, as noted in the Methods section, not including gardeners wait-listed to receive a plot. This was the result of two interconnected issues affecting the community at large: first, the closing of other community garden spaces once supported by a local social service agency; and second, the increase of people reaching out to the community garden's founder—a long-standing leader and member in the Southeast Asian community—for help finding places to grow food, citing fears that the pandemic would cause ethnic-based markets of culturally specific produce to close. The board sought areas for this sudden influx of participants by meeting with faith-based organizations, social services, and other agencies, one being the local museum, that could provide adequate space for garden plots. At the time of updating this proposal we have four sites to manage. We will survey all of the people currently assigned a garden plot in these four sites, but the board is currently meeting to decide how we will sample for the qualitative interviews.

Research Design

The board indicated the need to capture people's growing and food needs during a moment of crisis. We are currently meeting to discuss the way we will integrate COVID-19-specific questions during the in-depth interview phase of our research. We have also added to the pre- and postsurveys questions that ask participants how the current health pandemic has affected how they shop for produce.

Discussion

Overview

The three research aims detailed earlier in this proposal build toward a community-led design and implementation of a more extensive intervention to promote community-based agricultural

initiatives to improve physical and mental health in food-insecure communities of color in Rochester, Minnesota. Accomplishing these aims will shape and refine ongoing practices by the VCGLC that will assist others in planning and implementing similar community garden projects.

Limitations

There may be some limitations to our study, especially when taking into account the CBPR approach to the project, recruitment, and COVID-19. Firstly, our research plans may shift, not only because CBPR-based initiatives take more time, but because of input from community stakeholders. One example would be that additional time spent by research assistants requires additional compensation. Another shift may happen when members of the board seek to implement changes from one methodological approach, say photovoice, in response to already-collected data.

Due to our strategy of going through community leaders who have experience working in community gardens, owning and managing small farms, or designing urban green spaces, some of the people recruited might have more experience. Thus, results from this project may not be generalizable to all types of community garden projects, especially the few that serve growers from marginalized backgrounds.

Also, just like past research [6,50] and conversations with the VCGLC board suggest, COVID-19 worries may force people to strategize ways to minimize their food insecurity (eg, eating less, borrowing more money to buy food, and stretching food supplies to last longer). Since some of our participants were recruited with the help of a food pantry, some of the people agreeing to sign up might have experienced food insecurity in the past. Newly food-insecure families may deal with pandemic effects differently than those who have experienced bouts of food insecurity before COVID-19 [51], which could mean that we might not be capturing the experience of newly food-insecure community garden growers.

Strengths

Despite the limitations listed above, our project has several strengths: firstly, the makeup of the VCGLC board (ie, over 50% of the members represent not only growers but belong to communities found in the garden). Also, the processes outlined in our memorandum of understanding prevent us from replicating issues associated with some CBPR projects, such as "unintended consequences of re-colonizing the population" involved in the research [52]. Furthermore, both the academic investigator and the community coinvestigator identify as second-generation and first-generation immigrants to the United States, respectively, and belong to two of the largest ethnic and racial communities represented by the growers. Due to the time we spent carefully developing our CBPR processes and the sensitivity to the dynamics of power and privilege, our project might avoid issues that make it difficult for other CBPR projects to fulfill their goals of an equal research partnership that could "[e]nable fairness and equality at each step of the research" [53].

COVID-19 is intensifying inequities, especially concerning food and nutrition. For example, these social shifts and responses to the pandemic food issues increase chronic health conditions like those related to obesity [54], which makes our study timely. In the case of obesity, there is not only the link between obesity and food access; this is one of those chronic health conditions that increase the severity of COVID-19 symptoms [55].

Our study is focused on emotional health, which is also relevant to COVID-19 effects. As research suggests, there is a strong association between depression and anxiety and pandemic-related cases of food insecurity [56]. Also, there is what we call the urgency and agency of place during crisis, meaning that the garden may be giving growers a sense of empowerment at a moment of uncertainty, with the added caring support of our community garden volunteers and board members. Research has shown that gardens are considered safe spaces that facilitate positive mental health for those whose cultures are devalued by mainstream society. Our garden is providing this and more to growers from minoritized communities when they might bear the brunt of indignities and negative social effects.

Conclusions

Findings emerging from this study will provide us with preliminary data to implement a more extensive intervention for community gardening projects and initiatives to improve physical and mental health outcomes in food-insecure communities. Also, data collected will help us highlight the role of CBPR methods in disseminating information on the organizational community garden practices that can assist others in planning and implementing similar projects.

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Conflicts of Interest

None declared.

References

1. Gundersen C. Food insecurity is an ongoing national concern. Adv Nutr 2013 Jan 01;4(1):36-41 [FREE Full text] [doi: 10.3945/an.112.003244] [Medline: 23319121]
2. Coleman-Jensen A, Rabbit MP, Gregory CA, Singh A. Household Food Security in the United States in 2018. Washington, DC: US Department of Agriculture, Economic Research Service; 2019 Sep. URL: https://www.ers.usda.gov/webdocs/publications/94849/err-270.pdf?v=4948.5 [accessed 2020-09-22]
3. Coleman-Jensen A, Rabbitt MP, Gregory CA, Singh A. Statistical Supplement to Household Food Security in the United States in 2017. Washington, DC: US Department of Agriculture, Economic Research Service; 2018 Sep. URL: https://www.ers.usda.gov/webdocs/publications/90029/ap-079.pdf?v=5187.8 [accessed 2020-08-31]
4. Food insecurity among immigrants, refugees, and asylees. Food Insecurity and Hunger in the US: New Research. Washington, DC: Food Research and Action Center (FRAC) and Children's HealthWatch; 2016 Feb. URL: http://org2.salsalabs.com/o/5118/p/salsa/web/common/public/content?content_item_KEY=13089 [accessed 2020-09-26]
5. Dixon J, Omwega AM, Friel S, Burns C, Donati K, Carlisle R. The health equity dimensions of urban food systems. J Urban Health 2007 May;84(3 Suppl):i118-i129 [FREE Full text] [doi: 10.1007/s11524-007-9176-4] [Medline: 17401697]
6. Kempson K, Keenan DP, Sadani PS, Adler A. Maintaining food sufficiency: Coping strategies identified by limited-resource individuals versus nutrition educators. J Nutr Educ Behav 2003 Jul;35(4):179-188. [doi: 10.1016/s1499-4046(06)60332-1]
7. Okvat H, Zautra A. Community gardening: A parsimonious path to individual, community, and environmental resilience. Am J Community Psychol 2011 Jun;47(3-4):374-387. [doi: 10.1007/s10464-010-9404-z] [Medline: 21222153]
8. McCullum C, Desjardins E, Kraak VI, Ladipo P, Costello H. Evidence-based strategies to build community food security. J Am Diet Assoc 2005 Mar;105(2):278-283. [doi: 10.1016/j.jada.2004.12.015] [Medline: 15668689]
9. Corrigan MP. Growing what you eat: Developing community gardens in Baltimore, Maryland. Appl Geogr 2011 Oct;31(4):1232-1241. [doi: 10.1016/j.apgeog.2011.01.017]
10. Travers KD. The social organization of nutritional inequities. Soc Sci Med 1996 Aug;43(4):543-553. [doi: 10.1016/0277-9536(95)00436-x]
11. Stein, MJ. Community gardens for health promotion and disease prevention. Int J Hum Caring 2008 Apr 01;12(3):47-52. [doi: 10.20467/1091-5710.12.3.47]
12. Alaimo K, Packnett E, Miles RA, Kruger DJ. Fruit and vegetable intake among urban community gardeners. J Nutr Educ Behav 2008;40(2):94-101. [doi: 10.1016/j.jneb.2006.12.003] [Medline: 18314085]
13. Bice M, Ball J, Bickford N, Bickford S, Hollman AHE, Coughlin A, et al. Community gardens: Interactions between communities, schools, and impact on students. Health Educ 2018;50(1):2-10 [FREE Full text]
14. Zick C, Smith K, Kowaleski-Jones L, Uno C, Merrill B. Harvesting more than vegetables: The potential weight control benefits of community gardening. Am J Public Health 2013 Jun;103(6):1110-1115. [doi: 10.2105/AJPH.2012.301009] [Medline: 23597347]
15. Armstrong D. A survey of community gardens in upstate New York: Implications for health promotion and community development. Health Place 2000 Dec;6(4):319-327. [doi: 10.1016/S1353-8292(00)00013-7]
16. Ferris J, Norman C, Sempik J. People, land and sustainability: Community gardens and the social dimension of sustainable development. Soc Policy Adm 2001 Dec;35(5):559-568. [doi: 10.1111/1467-9515.t01-1-00253]
17. Eggert LK, Blood-Siegfried J, Champagne M, Al-Jumaily M, Biederman DJ. Coalition building for health: A community garden pilot project with apartment dwelling refugees. J Community Health Nurs 2015;32(3):141-150. [doi: 10.1080/07370016.2015.1057072] [Medline: 26212466]
18. Harris N, Minniss F, Somerset S. Refugees connecting with a new country through community food gardening. Int J Environ Res Public Health 2014 Sep 05;11(9):9202-9216 [FREE Full text] [doi: 10.3390/ijerph110909202] [Medline: 25198684]
19. Strunk C, Richardson M. Cultivating belonging: Refugees, urban gardens, and placemaking in the Midwest, USA. Soc Cult Geogr 2017 Oct 09;20(6):826-848. [doi: 10.1080/14649365.2017.1386323]
20. Sonti NF, Svendsen ES. Why garden? Personal and abiding motivations for community gardening in New York City. Soc Nat Resour 2018 Jul 24;31(10):1189-1205. [doi: 10.1080/08941920.2018.1484971]
21. Agustina I, Beilin R. Community gardens: Space for interactions and adaptations. Procedia Soc Behav Sci 2012;36:439-448. [doi: 10.1016/j.sbspro.2012.03.048]
22. Hartwig KA, Mason M. Community gardens for refugee and immigrant communities as a means of health promotion. J Community Health 2016 Dec;41(6):1153-1159. [doi: 10.1007/s10900-016-0195-5] [Medline: 27085720]
23. Chan J, DuBois B, Nemec K, Francis C, Hoagland K. Community gardens as urban social-ecological refuges in the global North. In: WinklerPrins AMGA, editor. Global Urban Agriculture. Boston, MA: CABI; 2017:229-241.
24. Shava S, O'Donoghue R, Krasny ME, Zazu C. Traditional food crops as a source of community resilience in Zimbabwe. Int J Afr Renaiss Stud Multi Inter Transdiscipl 2009 Jul;4(1):31-48. [doi: 10.1080/18186870903101982]

25. Shimpo N, Wesener A, McWilliam W. How community gardens may contribute to community resilience following an earthquake. Urban For Urban Green 2019 Feb;38:124-132. [doi: 10.1016/j.ufug.2018.12.002]
26. Metcalf K, Minnear J, Kleinert T, Tedder V. Community food growing and the role of women in the alternative economy in Tower Hamlets. Local Econ 2012 Aug 03;27(8):877-882. [doi: 10.1177/0269094212455290]
27. Meenar M, Hoover B. Community food security via urban agriculture: Understanding people, place, economy, and accessibility from a food justice perspective. J Agric Food Syst Community Dev 2012 Nov 28:143-160. [doi: 10.5304/jafscd.2012.031.013]
28. Chan J, Pennisi L, Francis CA. Social-ecological refuges: Reconnecting in community gardens in Lincoln, Nebraska. J Ethnobiol 2016 Dec 1;36(4):842. [doi: 10.2993/0278-0771-36.4.842]
29. Chan J, DuBois B, Tidball KG. Refuges of local resilience: Community gardens in post-Sandy New York City. Urban For Urban Green 2015;14(3):625-635. [doi: 10.1016/j.ufug.2015.06.005]
30. Kingsley JY, Townsend M. 'Dig in' to social capital: Community gardens as mechanisms for growing urban social connectedness. Urban Pol Res 2006 Dec;24(4):525-537. [doi: 10.1080/08111140601035200]
31. Camps-Calvet M, Langemeyer J, Calvet-Mir L, Gomez-Baggethun E, March H. Sowing resilience and contestation in times of crises: The case of urban gardening movements in Barcelona. Open J Sociopolitical Stud 2015;8(2):417-442 [FREE Full text] [doi: 10.1285/i20356609v8i2p417]
32. Certomà C. Critical urban gardening as a post-environmentalist practice. Local Environ 2011 Nov;16(10):977-987. [doi: 10.1080/13549839.2011.592181]
33. Shan H, Walter P. Growing everyday multiculturalism. Adult Educ Q 2014 Sep 05;65(1):19-34. [doi: 10.1177/0741713614549231]
34. Minkoff-Zern L. Pushing the boundaries of Indigeneity and agricultural knowledge: Oaxacan immigrant gardening in California. Agric Human Values 2012 Jan 8;29(3):381-392. [doi: 10.1007/s10460-011-9348-4]
35. Hallberg D. Community gardens as multipurpose, technological systems. J Sociol Soc Anthropol 2018;9(2):38-48 [FREE Full text] [doi: 10.31901/24566764.2018/09.02.286]
36. Shinew KJ, Glover TD, Parry DC. Leisure spaces as potential sites for interracial interaction: Community gardens in urban areas. J Leis Res 2017 Dec 13;36(3):336-355. [doi: 10.1080/00222216.2004.11950027]
37. Kimhi S, Dror G. Resilience among students from the majority and minority group: The Israeli case. J Psychol Behav Sci 2017;5(1):37-46. [doi: 10.15640/jpbs.v5n1a5]
38. Hadley C, Patil CL, Nahayo D. Difficulty in the food environment and the experience of food insecurity among refugees resettled in the United States. Ecol Food Nutr 2010;49(5):390-407. [doi: 10.1080/03670244.2010.507440] [Medline: 21888578]
39. Canales MK, Coffey N, Moore E. Exploring health implications of disparities associated with food insecurity among low-income populations. Nurs Clin North Am 2015 Sep;50(3):465-481. [doi: 10.1016/j.cnur.2015.05.003] [Medline: 26333604]
40. Israel BA, Eng E, Schulz AJ, Parker EA, editors. Methods for Community-Based Participatory Research for Health. 2nd edition. San Francisco, CA: Jossey-Bass; 2013.
41. Israel B, Schulz A, Parker E, Becker A, Community-Campus Partnerships for Health. Community-based participatory research: Policy recommendations for promoting a partnership approach in health research. Educ Health (Abingdon) 2001;14(2):182-197. [doi: 10.1080/13576280110051055] [Medline: 14742017]
42. Cafiero C, Viviani S, Nord M. Food security measurement in a global context: The food insecurity experience scale. Measurement 2018 Feb;116:146-152. [doi: 10.1016/j.measurement.2017.10.065]
43. Iachan R, Pierannunzi C, Healey K, Greenlund KJ, Town M. National weighting of data from the Behavioral Risk Factor Surveillance System (BRFSS). BMC Med Res Methodol 2016 Nov 15;16(1):155 [FREE Full text] [doi: 10.1186/s12874-016-0255-7] [Medline: 27842500]
44. Andrews G, Slade T. Interpreting scores on the Kessler Psychological Distress Scale (K10). Aust N Z J Public Health 2001 Dec;25(6):494-497. [doi: 10.1111/j.1467-842x.2001.tb00310.x] [Medline: 11824981]
45. Connor K, Davidson J. Development of a new resilience scale: The Connor-Davidson Resilience Scale (CD-RISC). Depress Anxiety 2003;18(2):76-82. [doi: 10.1002/da.10113] [Medline: 12964174]
46. Kimhi S, Eshel Y. Measuring national resilience: A new short version of the scale (NR-13). J Community Psychol 2019 Apr;47(3):517-528. [doi: 10.1002/jcop.22135] [Medline: 30295954]
47. Mejia AP. You better check your method before you wreck your method: Challenging and transforming photovoice. In: Bradbury H, editor. The SAGE Handbook of Action Research. 3rd edition. Thousand Oaks, CA: SAGE Publications; 2015:665-672.
48. Wang C, Burris MA. Photovoice: Concept, methodology, and use for participatory needs assessment. Health Educ Behav 1997 Jun;24(3):369-387. [doi: 10.1177/109019819702400309] [Medline: 9158980]
49. Aftandilian D, Dart L. Using garden-based service-learning to work toward food justice, better educate students, and strengthen campus-community ties. J Community Engagem Scholarsh 2013;6(1):55-69.
50. Kinsey EW, Kinsey D, Rundle AG. COVID-19 and food insecurity: An uneven patchwork of responses. J Urban Health 2020 Jun;97(3):332-335 [FREE Full text] [doi: 10.1007/s11524-020-00455-5] [Medline: 32504251]

51. Niles M, Bertmann F, Belarmino E, Wentworth T, Biehl E, Neff R. The early food insecurity impacts of COVID-19. Nutrients 2020 Jul 15;12(7):2096 [FREE Full text] [doi: 10.3390/nu12072096] [Medline: 32679788]
52. Muhammad M, Wallerstein N, Sussman AL, Avila M, Belone L, Duran B. Reflections on researcher identity and power: The impact of positionality on community-based participatory research (CBPR) processes and outcomes. Crit Sociol (Eugene) 2015 Nov;41(7-8):1045-1063 [FREE Full text] [doi: 10.1177/0896920513516025] [Medline: 27429512]
53. Burke JG, Hess S, Hoffmann K, Guizzetti L, Loy E, Gielen A, et al. Translating community-based participatory research principles into practice. Prog Community Health Partnersh 2013;7(2):115-122 [FREE Full text] [doi: 10.1353/cpr.2013.0025] [Medline: 23793242]
54. McLinden T, Stover S, Hogg R. HIV and food insecurity: A syndemic amid the COVID-19 pandemic. AIDS Behav 2020 Oct;24(10):2766-2769 [FREE Full text] [doi: 10.1007/s10461-020-02904-3] [Medline: 32385677]
55. Watanabe M, Risi R, Tuccinardi D, Baquero C, Manfrini S, Gnessi L. Obesity and SARS-CoV-2: A population to safeguard. Diabetes Metab Res Rev 2020 Apr 21:e3325. [doi: 10.1002/dmrr.3325] [Medline: 32314503]
56. Lauren B, Silver E, Faye A, Baidal J, Ozanne E, Hur C. Predictors of household food insecurity in the United States during the COVID-19 pandemic. medRxiv. 2020 Jun 12. URL: https://www.medrxiv.org/content/10.1101/2020.06.10.20122275v1.full.pdf [accessed 2020-09-29]

Abbreviations

CBPR: community-based participatory research
USDA: United States Department of Agriculture
VCGLC: The Village Community Garden & Learning Center

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Protocol

A Model of Intervention and Implementation of Quality Building and Quality Control in Childcare Centers to Strengthen the Mental Health and Development of 1-3–Year Olds: Protocol for a Randomized Controlled Trial of Thrive by Three

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Abstract

Background: Universal, high-quality childcare offers a unique opportunity to prevent developmental trajectories leading to mental health problems. Yet, growing evidence has shown that the process quality of Norwegian childcare centers varies considerably, and that research-based models for quality building are significantly lacking.

Objective: To examine whether a model for quality building in childcare centers, Thrive by Three, increases the quality of child–caregiver interactions, and promotes child development, well-being, and mental health.

Methods: The Thrive by Three study is a clustered randomized controlled trial involving 187 toddler groups in childcare centers across 7 municipalities within southern and central Norway. Each center is randomly allocated to the intervention or wait-list control group. Data are collected at 4 points: preintervention (T1), midway (T2), postintervention (T3), and 1-year postintervention (T4). Primary outcomes are changes in childcare quality measured by the Classroom Assessment Scoring System toddler version (CLASS), Student–Teacher Relationship Scale, Short Form (STRS-SF), and Life in Early Childhood Programs (LECP), as well as child development and mental health measured by The Brief Infant Toddler Social and Emotional Assessment (BITSEA, parent and teacher report), the Caregiver–Teacher Report Form (C-TRF), and Child Behavior Checklist (parent report) from the Achenbach System of Empirically Based Assessment (ASEBA) from 1.5 to 5 years, and child well-being measured by the Leiden Inventory for Child's Well-Being in Day Care (LICW-D). Secondary outcomes are child cortisol levels, assessed in a subsample of 372 children.

Results: As of August 2020, a total of 1531 children and 769 staff from 187 toddler groups were recruited. Because of turnover, the recruitment of staff will be ongoing until August 2020. As of January 2020, the intervention group has been working with Thrive by Three for 1.5 years. Data at T1, T2, and T3 from both the intervention and control groups have been completed and T4 will be completed in August 2020.

Conclusions: This study makes an important contribution to the field of quality building in childcare centers. The results will provide greater insight into how high quality can be obtained and the effects of high-quality early childcare on child mental health. This in turn will be significant for policymakers and to the Norwegian society at large.

Trial Registration: ClinicalTrials.gov NCT03879733; https://clinicaltrials.gov/ct2/show/NCT03879733 and Norwegian Research Council 260624/H10; https://prosjektbanken.forskningsradet.no/#/project/NFR/260624/Sprak=en

International Registered Report Identifier (IRRID): DERR1-10.2196/17726

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KEYWORDS

childcare quality; children's mental health; intervention; RCT; CLASS; well-being; pediatrics; mental health; toddler; children

Introduction

Background

Mounting evidence supports the notion that high-quality childcare centers promote children's mental health [1,2]. High-quality childcare protects and promotes the underpinnings of mental health in a phase of life when brain plasticity is most pronounced [3,4]; hence, it may prevent the onset of deviant developmental trajectories in toddlers and compensate for insufficient resources at home [5,6]. Evidence also suggests that centers of poor quality can have detrimental effects on children's development [7,8]. Because more than 80% of 1 and 2 year olds in Norway attend childcare, and stay there for long hours [9], interventions targeting caregiver–child interactions may prove an important avenue toward universal prevention of mental health problems.

Childcare quality includes elements of both structure (eg, number of staff, staff training and education, group size, child-to-caregiver ratio) and process (eg, caregiver–child relationship, parental involvement) [10]. *Process quality* in terms of warm, sensitive, and stimulating relationships between caregivers and young children [11] is arguably the most important ingredient of quality as it has long-term effects on children's mental health, well-being, and development [12]. Importantly, high process quality seems to be particularly important for children at risk [13].

New evidence shows that quality varies substantially between centers [14,15], and preliminary findings indicate that, by international comparison, quality in Norway is only moderately high [15]. Norway has failed to implement a minimum level of training for all childcare staff. As much as 60% of childcare staff have no formal qualifications on bachelor level for working with children [16]. Even some educated childcare teachers report lack of competence in taking care of children under the age of 3 [17]. This means that many toddlers spend most of their time interacting with staff with minimal or insufficient training. The need to enhance competence among childcare staff working with the youngest children is urgent. Moreover, a standardized and systematic procedure for measuring and monitoring process quality in childcare centers is lacking in Norway. This means that, unless a childcare center has participated in research, the level of quality that childcare centers provide to young children is largely unknown.

Few of the existing interventions for preventive quality improvement in childcare specifically focus on the youngest children. Furthermore, most interventions have been narrow in their scope, targeting only single topics such as conduct problems [18], anxiety [19], or language problems [20], thereby limiting their effect on children's mental health. We will therefore break new grounds by conducting a cluster randomized controlled trial (RCT) of a newly developed comprehensive intervention for promoting mental health among toddlers through quality-enhancement in childcare, the *Thrive by Three* [21-23].

Thrive by Three is grounded in transactional models for development [24,25] and research showing that interactions between young children and caregivers are primary mechanisms of mental health, child development, and learning [26-29]. Thrive by Three is culturally sensitive, and is universally preventive in the sense that it includes all 1-3 year olds attending childcare. The intervention consists of 3 core elements: (1) quality building through competence enhancement for all staff regardless of level of formal education, (2) a model for peer-driven quality control and tailored supervision at classroom level in the participating centers, and (3) supervision of supervisors and mentors. Thrive by Three is modeled after the *Thrive by Five*, *Seeds to Success*, and *Early Achievers* quality-building and quality control measures, broadly implemented in childcare centers in the state of Washington in the United States [21-23] and piloted in a large Norwegian community sample [30].

This study has 2 primary aims: to determine the extent to which Thrive by Three (1) improves the quality of caregiver–child interactions and (2) strengthens children's mental health, and social and cognitive development, after the intervention and at a 12-month follow-up. The secondary aims consist of determining the extent to which the intervention effects are moderated by (1) the implementation outcomes (fidelity and acceptability) and (2) child and family characteristics such as temperament, ethnicity, and socioeconomic background. In a subsample, we will also address (1) the characteristics of children with especially high cortisol levels during transition to childcare and (2) whether children in childcare units receiving the intervention have lower cortisol levels compared with controls. In another subsample we will qualitatively investigate parents' and caregivers' experience with the intervention.

Pilot Study

The Thrive by Three intervention was piloted in a large community sample in 2 cohorts of 25/49 public (51%) and 24/49 private (49%) childcare centers from August 2016 to June 2018. A total of 49 centers and 243 groups of children aged 1-5 participated. The design was a simple pre–post design. The childcare centers were observed with Classroom Assessment Scoring System (CLASS; toddler and Pre-K), before the intervention started (pre) and after 10 months (post). Childcare staff filled out electronic questionnaires on background factors of the centers, the childcare classrooms, and themselves (ethnicity, education, staff turnover, attitudes toward the intervention). The pilot intervention differed from the current version of Thrive by Three intervention in 2 ways:

1. The written material given to the staff was less comprehensive in the pilot and parents were not given any written material.
2. The staff supervisors did not receive supervision from mentors.

For toddler groups (ages 1-3) we found a small but significant increase in quality from pre to post in the Emotional and behavioral support domain (mean 5.97 [SD 0.41] vs mean 6.08 [SD 0.38]; t_{103}=–2.45; *P*=.02) but not in the Engaged support for learning domain (mean 3.24 [SD 0.76] vs mean 3.44 [0.77]; t_{103}=–1,86; *P*=.07). For the Pre-k groups (ages 3-5), there was a significant increase in quality from pre to post measures across all 3 domains: Emotional support (mean 6.06 [SD 0.56] vs mean 6.20 [SD 0.43]; t_{127}=–2.56; *P*=.01), Classroom organization (mean 5.27 [SD 0.76] vs mean 5.55 [SD 0.66]; t_{127}=–3.38; *P*=.001), and Instructional support (mean 2.67 [SD 0.84] vs mean 3.02 [SD 0.98]; t_{127}=–3.40; *P*=.001). Moreover, qualitative interviews with center leaders, head teachers, and staff from the first cohort (N=53) revealed great satisfaction with the quality-building framework and the holistic approach to quality building. Overall, they reported feeling more competent in their day-to-day interactions with the children and highlighted that the intervention had given all staff on different levels shared knowledge and a shared language to talk about quality with colleagues. There were, however, also several challenges. Most importantly, staff needed more time than predicted to fully comprehend the CLASS framework and content of the specific dimensions. The supervisors did not receive enough support and reported lacking a manual/written material to help structure the supervision throughout the intervention period.

Methods

Study Design

This study is a clustered RCT delivered in childcare centers with toddler groups in 2 regions in Norway: southern and central. We selected a random sample using SPSS (IBM). The stages of enrollment, intervention, and assessment are presented in Table 1. A more detailed display of the different assessment time points is presented in Table 2.

Table 1. The stages of enrollment, intervention, and assessment of Thrive by Three.

Research stage	Study period						
	Spring 2017	Fall 2017	Spring 2018	Fall 2018	Spring 2019	Fall 2019	Spring 2020
Enrollment							
Municipalities	x						
Informed consent							
Staff	x	x					
Children		x	x				
Allocation		x					
Intervention							
Intervention group				x	x		
Control group						x	x
Assessment							
Primary and secondary outcomes				Pre	Post		1-year follow up

Table 2. Overview of assessment and informants at different time points.

Assessment and informants	Time point			
	T1 (September 2018)	T2 (January 2019)	T3 (June 2019)	T4
Questionnaires				
Childcare staff about their job	x		x	x
Childcare staff about the child	x		x	x
Parents about themselves and child	x		x	x
CLASS[a] observations	x	x	x	x
Cortisol measurement (300 children)	x	x	x	

[a]CLASS: Classroom Assessment Scoring System.

Eligibility Criteria

Childcare settings with toddler groups in the Oslo region and Central Norway are eligible for participation. The participating children must be aged between 12 and 35 months. Childcare center eligibility is determined by region of the country and municipality. The primary study sites are in southeastern and central parts of Norway. The recruitment period started in February 2017 and lasted until August 2018. First, municipalities were recruited during the spring of 2017. Then, childcare centers within each municipality were recruited during spring and fall of 2017. Childcare staff consented during the fall of 2017. Children were recruited from fall of 2017 until August 2018. The long recruitment period of children is due to the fact that children under the age of 2 typically enter childcare centers for the first time in August, the year they turn 1. The lists of eligible children were therefore not complete until August 2018. Because of a high staff turnover, new staff members are invited to consent to participate throughout the year.

The intervention is offered during a complete year cycle in the participating centers. The control group is offered the intervention the following year cycle. Childcare quality is measured before, during, and after the intervention (3 time points). Parents and staff fill out questionnaires before and after the intervention. In addition, participating toddler groups and children will be measured 1 year after the intervention to identify possible long-term effects.

Children in the participating toddler groups are recruited via a written invitation to their parents given to them at the childcare center. Childcare staff keep in touch with the parents throughout the study period. The project team has no direct contact with parents. All information is given through the childcare center.

Inclusion Criteria

All childcare centers in the participating municipalities were allowed to participate as long as they had at least one toddler group, or groups with children aged 12–36 months. After the municipalities had consented to participate in the study, childcare centers within each municipality were recruited. Childcare centers volunteered to participate. All parents of children in the toddler groups of the participating childcare centers were invited to participate.

Exclusion Criteria

Childcare centers with no children under the age of 36 months were not eligible for the study.

Intervention Care and Comparison

Intervention

Thrive by Three is a 10-month intervention, aimed at increasing the quality of Norwegian childcare centers. It is grounded in transactional models for development [24,25] and research showing that interactions between young children and caregivers are a primary mechanism of mental health, child development, and learning [26-29].

Thrive by Three offers a standardized measurement of quality 3 times throughout the year through observations conducted by 25 certified observers (from the municipality) in classrooms with children between 1 and 3 years of age using a standardized observations method, CLASS toddler. Following observations, all staff in the intervention group receive feedback on a group level on their score based on the 8 quality dimensions of CLASS, showing strengths and weaknesses of interaction. Staff receive systematic guidance by their head teacher on a monthly basis based on the quality measure and an action plan for improvement. The head teachers, in turn, receive supervision from mentors. Staff in each toddler group meet together 10 times with their head teacher during the intervention period, focusing on 1 or 2 CLASS dimensions each time. Between meetings, all employees focus on the present CLASS dimension in their daily work with children.

All childcare employees in the 7 municipalities attend 3 full-day seminars, focusing on research-based knowledge on young children's mental health and its risk and protective factors, early signs of mental and developmental problems, and crucial aspects of childcare quality. Center leaders and head teachers participate in 2 extra sessions focusing on leadership, feedback, supervision, and how to address concerns about a child to his/her parents when necessary.

In addition, comprehensive written material is provided to parents, employees, head teachers, and mentors. There are 7 booklets for parents about children's early development and tips to help them support their own child's development, guidance manuals for mentors, and a 30-page resource booklet for all employees in the centers. Access to the project website is also available to parents and employees at tf3.no.

Control

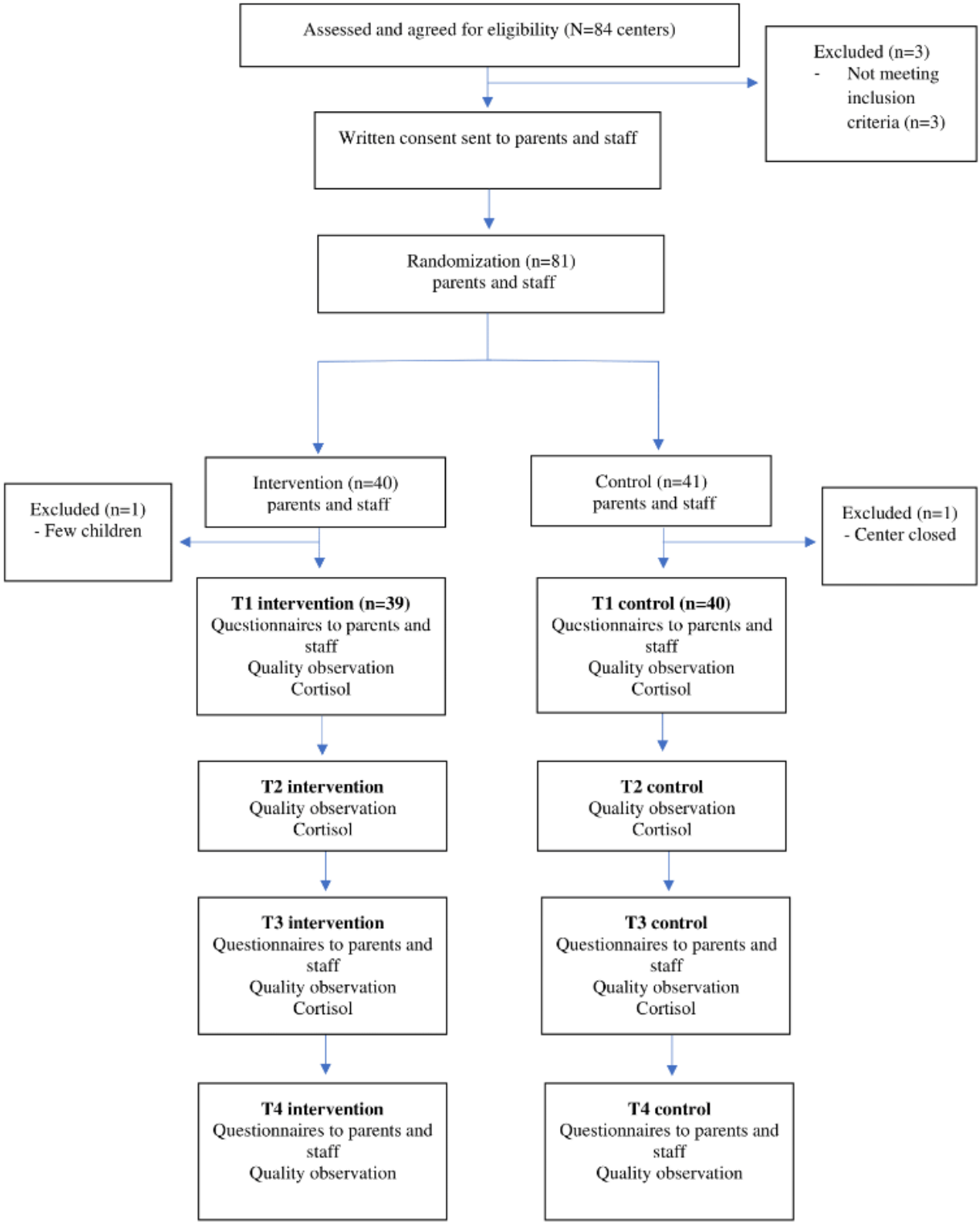
The wait-list control group is offered the intervention 1 year later but is observed at T1, T2, and T3 along with the intervention group. The control group does not receive feedback or guidance following the observations until they receive the intervention 1 year later.

Procedure

Overview

Figure 1 presents a graphic representation of the study procedures. Following recruitment, observers and mentors are trained in the childcare quality observation method, CLASS [31]. This is a 2-day training, led by a certified trainer. After training, the Teachstone reliability test is taken. Supervisors get extra training in the method, but do not go through the reliability test to become certified. Each childcare unit is observed by the CLASS-certified observers for 45 minutes, preintervention, midintervention, and postintervention and at 1-year follow-up. The preintervention CLASS observation is used as the basis for supervision and quality enhancement in each unit.

Figure 1. Flowchart of study procedures for Thrive by Three.



Randomization

Childcare centers within each municipality are randomly allocated to the intervention or wait-list control group. Because we could not randomize the units in the same center due to contamination, randomization occurred on the center level, but the intervention is on the unit level. The randomization was stratified based on center size to assure that larger and smaller centers were equally distributed across the control and intervention conditions.

Blinding

Because of the nature of the intervention, it is not possible for the participants to be unaware of the intervention condition they are assigned to.

Outcomes

Data Collection

Data are collected at four points: T1 (preintervention), T2 (midway assessment), T3 (postintervention), and T4 (1-year postintervention follow-up). Participants from the intervention and control centers (parents, childcare staff, and group leaders) are sent links to the questionnaire via SMS text message or email. Each child is given unique, confidential identifiers to log-in and answer questions about the child (by the parent/staff). Both parents and 1 selected staff member working with each participating child are asked to fill out the questionnaires about the child. In addition, parents and childcare staff answer questions about themselves, and the staff about aspects of the center they work in. Each unit in the participating centers (both intervention and control centers) is also observed by trained CLASS observers at the following periods: preintervention, midintervention, postintervention, and during a follow-up 1 year later (only the intervention group).

T1 took place in September and October 2018 with CLASS observations in 187 units (both the control and intervention groups, with only the intervention group receiving feedback) and questionnaires to all staff and parents. T2 took place in January 2019 with new CLASS observations but no questionnaires. T3 took place at the end of the intervention (1 childcare year) in May/June 2019 with CLASS observations and questionnaires to all staff and parents. In addition, qualitative interviews will be conducted at T3. At 1-year follow-up after the intervention (T4) the intervention group is observed with CLASS and questionnaires will be filed out by all staff and parents (Textbox 1).

Textbox 1. Study outcomes and measures used for Thrive by Three.

Primary outcomes

- Childcare quality:
  - Classroom Assessment Scoring System (CLASS) toddler version
  - The Student–Teacher Relationship Scale, Short Form (STRS-SF)
  - Life in Early Childhood Programs (LECP)
- Child outcomes:
  - The Brief Infant Toddler Social and Emotional Assessment (BITSEA, parent and teacher report)
  - Caregiver–Teacher Report Form (C-TRF, teacher report)
  - Child Behavior Checklist (CBCL, parent report)
  - Language Development Survey (LDS)
  - Leiden Inventory for Child's Well-Being in Day Care (LICW-D)
  - Secure Base Safe Haven Observation Unit (SBSHO)

Secondary outcomes

- Measurement of child cortisol levels

Primary Outcomes

Study Hypothesis

The primary outcome for this study is a comparison between centers randomly allocated to the Thrive by Three intervention and wait-list control centers receiving the intervention 12 months later. We hypothesize that Thrive by Three will prove superior to the wait-list control after the 10-month intervention period and at the 12-month follow-up with respect to childcare quality and children's mental health, development, and well-being.

Childcare Quality

The lead teacher in each classroom reports features of the childcare such as type of care, group size, staff-to-child ratio, and characteristics of the child group and staff.

CLASS toddler version [31,32] is used to evaluate process quality. CLASS provides relevant, valid, and reliable information about child–caregiver interactions [31]. Each unit is observed by the CLASS observers for three 15-minute periods (preintervention, midintervention, and postintervention) as well as during a follow-up 1 year later (only the intervention group).

The quality of teacher–child relationships (ie, children's relationship with teacher) as perceived by the teacher is assessed through 3 dimensions, namely, closeness, conflict, and dependency, using The Student–Teacher Relationship Scale, Short Form (STRS-SF) [33,34], which consists of 15 items.

Life in Early Childhood Programs (LECP) measures the atmosphere, routines, and rhythms of the group [35]. The LECP asks teachers about the degree of control and organization (degree of consistency or routines, if objects or toys are put in the same place), the use of space, contextual traffic (if many people are coming and going), and group density. A higher score on the LECP indicates a higher level of chaos in the group.

Child Outcomes

Children's development and mental health outcomes are determined by serval measures, gathered from both parents and 1 selected staff member working with each participating child.

The Brief Infant Toddler Social and Emotional Assessment (BITSEA, parent and teacher report) [36] is used to map children's social/emotional/behavior problems and delayed development across 4 domains: externalizing, internalizing, dysregulation, and competence.

Caregiver–Teacher Report Form (C-TRF, teacher report) and Child Behavior Checklist (CBCL, parent report) from the Achenbach System of Empirically Based Assessment (ASEBA) from 1.5 to 5 years [37] are checklists used for mapping emotional difficulties and behavior problems in children. The checklist measures symptoms of anxiety/depression, somatic disorder, withdrawnness, attention difficulties, and aggressive behavior, as well as overarching internalizing and externalizing behaviors. In addition, the Language Development Survey (LDS) is included as part of CBCL for parents to measure which words children use. LDS is answered by mother, father, and teacher for this study.

Leiden Inventory for Child's Well-Being in Day Care (LICW-D) [38] measures the child's socioemotional well-being in daycare with 12 items (eg, enjoys attending, feels at ease in the group, not difficult saying goodbye to parents). Mother, father, and teacher answer these questions in this study.

Secure Base Safe Haven Observation Unit (SBSHO) [39] measures children's secure attachment to their caregiver. Through 20 questions, parents and the child's key person in the group are asked to evaluate to which degree the child uses them as a secure base.

Secondary Outcome: Child Cortisol Levels

Child cortisol levels are assessed in a subsample of 300 children who enter childcare for the first time. The tests are done in the childcare center at 10 am and 3 pm and at home at 6 pm for 2 days at T1 (the average is calculated). At T2, cortisol levels are assessed at 10 am and 3 pm for 2 days in the center and 2 days at home during a weekend (the average for every point in time). At T3, measures are taken in the same way as T1. The collection, storage, and evaluation, including the placement of the material, are approved by Regional Committees for Medical and Health Research [40], reference number 2017/430 [40].

Implementation Outcomes

Fidelity

Fidelity to the intervention is measured through checklists and self-reporting [41]. Class attendance and attendance in monthly supervision sessions is registered. The supervisors rate their own fidelity of intervention on a 5-point Likert scale (from minimal to high) through questions such as "I helped use the CLASS dimensions and relational quality when the supervisor reflected on practice," "I focused on how the supervisor could develop as a mentor for their staff."

Acceptability

Acceptability (ie, the users' satisfaction with various aspects of the intervention) is measured by self-report and focus group interviews with parents and staff at the end of the intervention period.

Sustainability

Sustainability is to be measured through semistructured interviews and self-report at the end of the intervention period and at 1-year follow-up [41].

Background Variables

Child Factors

Serval measures and questions are used to gauge children's background, including the child's personal characteristics and aspects of their environment.

The Early Childhood Behaviour Questionnaire, Short Form (ECBQ) [42] measures children's temperament, including reactive processes that involve emotions, motor and sensory systems, and self-regulation processes that control reactivity.

The Emotionality, Activity, Sociability Temperament Survey for Children (EAS) [43] measures 4 dimensions of the child's temperament (emotionality, activity, sociability and shyness) on 5 items.

More general characteristics and childcare history are obtained through questionnaire data detailed by parents (eg, number of siblings, preterm, ethnicity, disabilities, when they started kindergarten, how many kindergartens they have attended).

Family Factors

Parents report on their own background such as their ethnicity, country of origin, marital status, education, and family socioeconomic status through information about parental income.

Childcare Factors

Leaders of the childcare centers report on the organization and size of the childcare center, as well as staff turnover and sick leave. Childcare staff report their gender, ethnicity, age, education, and experience working in childcare. Childcare staff also report on their level of occupational stress and well-being at work, their motivation, and receptiveness to changes in the workplace.

Recruitment and Participation

Recruitment and participation data will be reported for available data from baseline.

Participant Retention

Contact with childcare staff is maintained by the research group through meetings and emails. Contact with participating families (parents) is maintained mainly by childcare staff. Reminders to fill out questionnaires are sent via email or SMS text messages.

To reduce dropout in the control groups after randomization, childcare centers in the control group receive a gift certificate of 3000NOK (US $336.60) to buy material for their childcare center and are offered the intervention 1 year after the intervention group.

Data Management

Observational data are collected by CLASS toddler–certified observers. Questionnaire data are collected and managed by an independent data collection team at the primary sponsor site

(Centre for Child and Adolescent Mental Health [RBUP] East and South). The independent data collection team is responsible for monitoring the data as they are collected, as well as checking that the data are consistent and free from errors. Data analysis and cleaning will be performed by study investigators. Data are stored on a secure server at the primary sponsor site during the study and analysis of results. Project staff will have access to the final trial data set. Following the study, data will be anonymized and archived according to Norwegian law.

Data Analysis

The study is carried out in toddler groups in childcare centers. Thus, data analyses will be conducted in a multilevel modeling framework to account for nonindependence of the participants at center level.

Sample Size and Power

Sample size and power was calculated using SPSS SamplePower (IBM). Based on previous studies [6], we choose a conservative estimate of expected effect of 0.30 (Cohen *d*). With a power of 0.80 and α=.05, we need 352 individuals if the randomization was performed individually. We plan to include data from 16 children from each childcare center. In a similar research [44], the intraclass correlation coefficient (ICC) was reported to be approximately 0.05. However, because several children will be evaluated by the same caregiver, we estimate with an ICC as high as 0.10. The resulting design effect with ICC=0.05 (or 0.10) D=1.75 (or 2.5), and the total required sample size is Nc=352 × 1.75 = 616 (or 352 × 2.5 = 880) individuals. We plan to include 1100 individuals, and 1100/16=69 childcare centers, to account for possibly 20% missing data on individual level, and uncertainty in the effect size and ICC. The planned selection will be in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines for clustered randomized trials [45].

Planned Statistical Analysis

To determine the effect of the intervention regression analyses, mixed model analyses or structural equation modeling as appropriate will be conducted, taking into account the clustered or multilevel structure of the data and data related to background factors. Because children are of different ages at study enrollment, some children will stay in intervention classrooms for 2 years, while some for just 1. We will adjust for child age in the analyses to account for these differences in "treatment exposure." Missing data will be estimated in the models using a well-established technique that allows for the inclusion of all available data and estimation of missing values.

Qualitative Analysis

Qualitative analysis of interviews will focus on meaning of texts [46]. Elements from the thematic analysis will therefore be used to analyze the interviews [47]. Analysis will first focus on identifying relevant codes in the text [46]. The next phase will involve sorting the codes into potential overarching themes. The themes will then be reviewed and refined using constant comparative methods to reduce data into essential concepts and relationships. Internal homogeneity and external heterogeneity among themes will be considered in this phase. Three coders will independently categorize the interviews and their coding will be combined [48].

Cost

The costs of the intervention will be evaluated by calculating the hours that childcare staff, leaders, CLASS observers, and mentors have donated to the project in relation to the number of toddler groups and children exposed to the intervention. An estimate of per-child cost will be included in the final report to funders, along with additional estimates of costs incurred by the trial research team.

National Collaboration

This project represents a shared effort and close collaboration between the RBUP (East/South), The Master's Program for Preschool Leadership at the Norwegian Business School (BI), The National Network for Infant Mental Health in Oslo, Regional Centre for Child and Youth Mental Health and Child Welfare (RKBU) Central Norway at the Norwegian University of Science and Technology (NTNU), and The Psychology Department at NTNU.

International Collaboration

Professor Robert Pianta (University of Virginia), who led the team that developed CLASS, is a consultant for the research group. The national research team has extensive collaboration with Assistant Professor Gail E. Joseph and her associates. She is the director of the Early Childhood and Family Studies program at the University of Washington and the Principal Investigator and Director of the Childcare Quality and Early Learning Center for Research and Professional Development [49], which is the institute currently investigating effects of the broadband implementation of the quality building and quality control of childcare centers in Washington state. She is also coprincipal investigator and codirector of the National Center for Quality Teaching and Learning.

Availability of Data and Materials

The data sets or other material used during this study are available from the principal investigator (Elisabet Solheim Buøen) on reasonable request.

Ethics Approval and Consent to Participate

Ethics approval for the study was given by Regional Committees for Medical and Health Research [40], reference number 2017/430 [49]. We anticipate low risk of harm for participating in the intervention since the work on employee process quality is based on literature and previous research that have shown to be positive for children's development. In addition, education and guidance for employees is not likely to be harmful for children's development. Consent was given written by municipalities, childcare centers, and parents. Childcare centers volunteered to participate. All parents of children in the toddler groups of the participating childcare centers were invited to participate and gave a written consent. Consent was given by childcare staff throughout the year.

Results

Trial Status

As of August 2020, in total, 1531 children and 769 staff from 187 toddler groups have been recruited. Due to turnover, staff recruitment will be ongoing until August 2020. As of January 2020, the intervention group has been working with Thrive by Three for 1.5 years. Data collection at T1, T2, and T3 from both the intervention and control groups has been completed and T4 will be completed in August 2020. We expect to find an increase in childcare quality and better mental health and development outcomes for children in the intervention group. The reporting of these results will be made in accordance with the CONSORT guidelines [45]. The trial began recruitment in February 2017 and finished in August 2018. Data collection will finish in August 2020.

Changes to the Protocol

Changes to the project are made in the standard operating procedure. These changes are recorded and maintained by the principal investigator for RBUP East and South. Changes which are merely procedural but may impact the experience of the participants in the study are reported to the Regional Committees for Medical and Health Research ethics for approval.

Confidentiality

Study participants are provided anonymous ID. A study key with the participants' name and ID is stored in a separate, encrypted file on an internal server at RBUP East and South.

Dissemination of Results

Dissemination will be done though scientific publications in well-regarded journals for child mental health and development as well as preventive science journals. Project newsletters and press releases, as well as 2 PhD theses will also be used to disseminate our results. Planned scientific publications include primary outcomes, secondary outcomes, fidelity, and the intervention and implementation. Publication of the data will be in accordance with CONSORT guidelines. The project team has adopted the Vancouver protocol for determination of authorship of scientific publications.

Discussion

Protocol Overview

This study is an important contribution to the field regarding the quality of childcare settings in Norway. The results of the study will provide an indication as to whether or not the model for quality building, Thrive by Three, is effective to promote childcare quality within Norwegian childcare toddler groups. The study will also provide information about the effects of Thrive by Three on child development, mental health, and well-being. Finally, the results will provide insight into the implementation of a system for quality building in childcare centers and as such be of great value for Norwegian society, on individual, family, community, and national level.

Limitations

As with any study, there may be potential limitations and challenges. One of the challenges we anticipate is high dropout from the control group. To counteract this, we are working to motivate the control group by offering them the intervention 1 year later as well as a cash incentive. Another limitation we anticipate is that because the intervention only lasts 1 year, the long-term effects of the intervention are not completely followed up. We do, however, aim to follow the children in the intervention group to see if the positive effects do persist even after the intervention.

Conclusion

The results of this study will offer a greater understanding of how high-quality childcare can be achieved and the effects of such care on children's mental health. The study will present significant contributions to the field and present policymakers and the greater Norwegian society with important evidence on quality in childcare.

Acknowledgments

Additional funding is provided by the Regional Center for Child and Adolescent Mental Health, Eastern and Southern Norway (RBUP East and South), RKBU Central Norway, and the BI. The NFR has peer-reviewed the study protocol and is not involved in the design, analysis, nor interpretation of the study results. RBUP East and South Norway, RKBU Central Norway, BI are host organizations of the authors; the authors are solely responsible for the design, analysis, and interpretation of the study results.

Authors' Contributions

All authors are familiar with the final version of the study protocol, having read and provided substantial contributions. RL is responsible for contributing to initial project proposal and drafting the final protocol for publication. MD is head of the intervention in central Norway and responsible for contributing to the study proposal and protocol. TB is responsible for contributing to initial project proposal and drafting the protocol for publication. EB is the chief investigator of the project and is responsible for drafting the initial protocol in addition to contributing to the protocol for publication. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Original peer-review reports from the funding agency.
[PDF File (Adobe PDF File), 30 KB - resprot_v9i10e17726_app1.pdf]

References

1. Burchinal M, Kainz K, Cai Y. How well do our measures of quality predict child outcomes? A meta-analysis and coordinated analysis of data from large-scale studies of early childhood settings. In: Quality Measurement in Early Childhood Settings. Baltimore, MD: Paul H Brookes Publishing; 2011:11-31.
2. Belsky J, Vandell DL, Burchinal M, Clarke-Stewart KA, McCartney K, Owen MT, NICHD Early Child Care Research Network. Are there long-term effects of early child care? Child Dev 2007;78(2):681-701. [doi: 10.1111/j.1467-8624.2007.01021.x] [Medline: 17381797]
3. Ursache A, Noble KG. Neurocognitive development in socioeconomic context: Multiple mechanisms and implications for measuring socioeconomic status. Psychophysiology 2016 Jan;53(1):71-82 [FREE Full text] [doi: 10.1111/psyp.12547] [Medline: 26681619]
4. Schore AN. Back to basics: attachment, affect regulation, and the developing right brain: linking developmental neuroscience to pediatrics. Pediatr Rev 2005 Jun;26(6):204-217. [doi: 10.1542/pir.26-6-204] [Medline: 15930328]
5. Burchinal M, Vernon-Feagans L, Vitiello V, Greenberg M. Thresholds in the association between child care quality and child outcomes in rural preschool children. Early Childhood Research Quarterly 2014 Jan;29(1):41-51 [FREE Full text] [doi: 10.1016/j.ecresq.2013.09.004]
6. Landry SH, Zucker TA, Taylor HB, Swank PR, Williams JM, Assel M, School Readiness Research Consortium. Enhancing early child care quality and learning for toddlers at risk: the responsive early childhood program. Dev Psychol 2014 Feb;50(2):526-541. [doi: 10.1037/a0033494] [Medline: 23772822]
7. McCartney K, Burchinal M, Clarke-Stewart A, Bub KL, Owen MT, Belsky J, NICHD Early Child Care Research Network. Testing a series of causal propositions relating time in child care to children's externalizing behavior. Dev Psychol 2010 Jan;46(1):1-17. [doi: 10.1037/a0017886] [Medline: 20053002]
8. Sagi A, Koren-Karie N, Gini M, Ziv Y, Joels T. Shedding further light on the effects of various types and quality of early child care on infant-mother attachment relationship: the Haifa Study of Early Child Care. Child Dev 2002;73(4):1166-1186. [doi: 10.1111/1467-8624.00465] [Medline: 12146741]
9. Statistics Norway. Barnehager [Kindergarten]. 2018. URL: https://www.ssb.no/utdanning/statistikker/barnehager/aar-endelige [accessed 2020-09-07]
10. Layzer JI, Goodson BD. The "quality " of early care and education settings: definitional and measurement issues. Eval Rev 2006 Oct;30(5):556-576. [doi: 10.1177/0193841X06291524] [Medline: 16966676]
11. Phillips DA, Lowenstein AE. Early care, education, and child development. Annu Rev Psychol 2011;62:483-500. [doi: 10.1146/annurev.psych.031809.130707] [Medline: 20822436]
12. NICHD Early Child Care Research Network. Child-care structure-->process-->outcome: direct and indirect effects of child-care quality on young children's development. Psychol Sci 2002 May;13(3):199-206. [doi: 10.1111/1467-9280.00438] [Medline: 12009038]
13. Bierman KL, Domitrovich CE, Nix RL, Gest SD, Welsh JA, Greenberg MT, et al. Promoting academic and social-emotional school readiness: the head start REDI program. Child Dev 2008;79(6):1802-1817 [FREE Full text] [doi: 10.1111/j.1467-8624.2008.01227.x] [Medline: 19037951]
14. Lekhal R, Vartun M, Gustavson K, Saugestad Helland S, Schjølberg S, Vaage Wang M. Den Norske Mor Og Barn-Undersøkelsen. Variasjon i Barnehagekvalitet. Beskrivelser Fra Første Datainnsamling Fra Barnehagene. [The Norwegian Mother Child Cohort Study]. Oslo: Folkehelseinstituttet; 2013.
15. Barnehage.no. Barnehagen Ikke så Bra Som Ventet [Kindergarten, Not as Good as Expected]. 2015. URL: http://barnehage.no/forskning/2015/10/barnehagen-ikke-sa-bra-som-ventet/ [accessed 2019-10-17]
16. Norwegian Directorate of Education (UDIR). Ansattes Utdanning I Barnehagen – Andel [Staff Education in Kindergarten]. 2019. URL: https://www.udir.no/tall-og-forskning/statistikk/statistikk-barnehage/ansattes-utdanning-andel/ [accessed 2019-10-17]
17. Haug P. Startalder for Barnehagebarn [Starting Age for Kindergarten]. 2014. URL: https://www.forskningsradet.no/prognett-finnut/Nyheter/Mange_tilsette_i_barnehagen_meiner_15_ar_er_rett_startalder/1253995921050?lang=no [accessed 2015-02-10]
18. Webster-Stratton C, Reid MJ. Treating Conduct Problems and Strengthening Social and Emotional Competence in Young Children. Journal of Emotional and Behavioral Disorders 2003 Sep 14;11(3):130-143. [doi: 10.1177/10634266030110030101]
19. Bayer JK, Rapee RM, Hiscock H, Ukoumunne OC, Mihalopoulos C, Clifford S, et al. The Cool Little Kids randomised controlled trial: population-level early prevention for anxiety disorders. BMC Public Health 2011 Jan 05;11:11 [FREE Full text] [doi: 10.1186/1471-2458-11-11] [Medline: 21208451]
20. Conner J, Kelly-Vance L, Ryalls B, Friehe M. A Play and Language Intervention for Two-Year-Old Children: Implications for Improving Play Skills and Language. Journal of Research in Childhood Education 2014 Mar 26;28(2):221-237. [doi: 10.1080/02568543.2014.883452]
21. URL: http://www.del.wa.gov/development/guidelines/ [accessed 2015-08-01]

22. URL: http://www.researchconnections.org/childcare/resources?publisher=Thrive+By+Five+Washington [accessed 2015-08-01]
23. URL: https://depts.washington.edu/cqel/current-reseach/ [accessed 2015-08-01]
24. Shonkoff JP, Phillips D. From Neurons to Neighborhoods: The Science of Early Childhood Development. Washington, DC: National Academy Press; 2000.
25. Sameroff AJ. Developmental systems and psychopathology. Dev Psychopathol 2000 Sep 01;12(3):297-312. [doi: 10.1017/s0954579400003035] [Medline: 11014740]
26. Sroufe LA. Early relationships and the development of children. Infant Ment. Health J 2000 Jan;21(1-2):67-74. [doi: 10.1002/(sici)1097-0355(200001/04)21:1/2<67::aid-imhj8>3.0.co;2-2]
27. Pianta RC, Hamre BK, Stuhlman M. Relationships between teachers and children. In: Handbook of Psychology. Hoboken, NJ: John Wiley & Sons, Inc; 2003:199-234.
28. La Paro K, Pianta R, Stuhlman M. The Classroom Assessment Scoring System: Findings from the Prekindergarten Year. The Elementary School Journal 2004 May;104(5):409-426 [FREE Full text] [doi: 10.1086/499760]
29. Burchinal M, Magnuson K, Powell D, Soliday HS. Early childcare and education. In: Handbook of Child Psychology and Developmental Science (Vol 4). Hoboken, NJ: John Wiley & Sons Inc; 2015:223-267.
30. Lisøy C, Holme H, Solheim E. Den utviklingsstøttende barnehagen i Sandnes [The Developmentally Supportive Kindergarten in Sandnes]. Oslo: Regionsenter for barn og unges psykiske helse, helseregion Sør Øst; 2018.
31. La Paro KM, Hamre BK, Pianta RC. Classroom Assessment Scoring System (CLASS) Manual, Toddler. Baltimore, MD: Paul H. Brookes Publishing Co; 2012.
32. Hamre BK, La Paro K, Pianta R, Locasale-Crouch J. Classroom Assessment Scoring System (CLASS), Infant. Baltimore, MD: Brookes Publishing; 2011.
33. Solheim E, Berg-Nielsen TS, Wichstrøm L. The Three Dimensions of the Student–Teacher Relationship Scale. Journal of Psychoeducational Assessment 2011 Dec 05;30(3):250-263. [doi: 10.1177/0734282911423356]
34. Pianta RC. STRS Student-Teacher Relationship Scale. Lutz, FL: Psychological Assessment Resources, Inc; 2001.
35. Wachs TD, Gurkas P, Kontos S. Predictors of preschool children's compliance behavior in early childhood classroom settings. Journal of Applied Developmental Psychology 2004 Jul;25(4):439-457. [doi: 10.1016/j.appdev.2004.06.003]
36. Giserman KI, Carter AS. Brief Infant-Toddler Social and Emotional Assessment (BITSEA). In: Encyclopedia of Autism Spectrum Disorders. Berlin, Germany: Springer; 2017:1-5.
37. Achenbach TM, Rescorla LA. Manual for ASEBA Preschool Forms & Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families; 2000.
38. Schipper JCD, IJzendoorn MHV, Tavecchio LWC. Stability in Center Day Care: Relations with Children's Well-being and Problem Behavior in Day Care1. Social Development 2004 Nov;13(4):531-550 [FREE Full text] [doi: 10.1111/j.1467-9507.2004.00282.x]
39. De Schipper JC, Schuengel C. Secure Base Safe Haven Observation List for Child Attachment Behaviour. Amsterdam, The Netherlands: VU University Amsterdam; 2006.
40. Regionale komiteer for medisinsk og helsefaglig forskningsetikk (REK). The Regional Committees for Medical and Health Research Ethics (REC). URL: https://helseforskning.etikkom.no [accessed 2020-09-07]
41. Proctor E, Silmere H, Raghavan R, Hovmand P, Aarons G, Bunger A, et al. Outcomes for implementation research: conceptual distinctions, measurement challenges, and research agenda. Adm Policy Ment Health 2011 Mar;38(2):65-76 [FREE Full text] [doi: 10.1007/s10488-010-0319-7] [Medline: 20957426]
42. Putnam SP, Gartstein MA, Rothbart MK. Measurement of fine-grained aspects of toddler temperament: the early childhood behavior questionnaire. Infant Behav Dev 2006 Jul;29(3):386-401 [FREE Full text] [doi: 10.1016/j.infbeh.2006.01.004] [Medline: 17138293]
43. Buss AH, Plomin R. EAS Temperament Survey for Children. Temperament: Early Developing Personality Traits. Hillsdale, NJ: Lawrence Erlbaum Associates; 1984.
44. Lekhal R, Zachrisson HD, Solheim E, Moser T, Drugli MB. Barnehagen: Betydningen av Kvalitet i Barnehagen. Oslo: Gyldendal Akademisk; 2016.
45. Campbell MK, Elbourne DR, Altman DG, CONSORT group. CONSORT statement: extension to cluster randomised trials. BMJ 2004 Mar 20;328(7441):702-708 [FREE Full text] [doi: 10.1136/bmj.328.7441.702] [Medline: 15031246]
46. Kvale S, Brinkmann S. Learning the Craft of Qualitative Research Interviewing. Thousand Oaks, CA: Sage Publications; 2009.
47. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology 2006 Jan;3(2):77-101. [doi: 10.1191/1478088706qp063oa]
48. Clark VLP, Creswell JW. Designing and Conducting Mixed Method Research. Thousand Oaks, CA: Sage Publications; 2011.
49. Regionale komiteer for medisinsk og helsefaglig forskningsetikk (REK). Forskningsprosjekt Trygg før 3 [Research project Thrive by three]. URL: https://helseforskning.etikkom.no/prosjekterirek/prosjektregister/prosjekt?p_document_id=826817&p_parent_id=832732&_ikbLanguageCode=n [accessed 2020-09-07]

Abbreviations

ASEBA: Achenbach System of Empirically Based Assessment
BI: Norwegian Business School
BITSEA: The Brief Infant Toddler Social and Emotional Assessment
CBCL: Child Behavior Checklist
CLASS: Classroom Assessment Scoring System
CONSORT: Consolidated Standards of Reporting Trials
C-TRF: The Caregiver–Teacher Report Form
EAS: The Emotionality, Activity, Sociability Temperament Survey for Children
ECBQ: The Early Childhood Behaviour Questionnaire, Short Form
ICC: intraclass correlation coefficient
LDS: Language Development Survey
LECP: Life in Early Childhood Programs
LICW-D: Leiden Inventory for Child's Well-Being in Day Care
NFR: Norwegian Research Council
NTNU: Norwegian University of Science and Technology
RBUP: Centre for Child and Adolescent Mental Health
RKBU: Regional Centre for Child and Youth Mental Health and Child Welfare
SBSHO: Secure Base Safe Haven Observation Unit
STRS-SF: Student–Teacher Relationship Scale, Short Form

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Protocol

The Effect of Multi-Parametric Magnetic Resonance Imaging in Standard of Care for Nonalcoholic Fatty Liver Disease: Protocol for a Randomized Control Trial

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Abstract

Background: The rising prevalence of nonalcoholic fatty liver disease (NAFLD) and the more aggressive subtype, nonalcoholic steatohepatitis (NASH), is a global public health concern. Left untreated, NAFLD/NASH can lead to cirrhosis, liver failure, and death. The current standard for diagnosing and staging liver disease is a liver biopsy, which is costly, invasive, and carries risk for the patient. Therefore, there is a growing need for a reliable, feasible, and cost-effective, noninvasive diagnostic tool for these conditions. LiverMultiScan is one such promising tool that uses multi-parametric magnetic resonance imaging (mpMRI) to characterize liver tissue and to aid in the diagnosis and monitoring of liver diseases of various etiologies.

Objective: The primary objective of this trial (RADIcAL1) is to evaluate the cost-effectiveness of the introduction of LiverMultiScan as a standardized diagnostic test for liver disease in comparison to standard care for NAFLD, in different EU territories.

Methods: RADIcAL1 is a multi-center randomized control trial with 2 arms conducted in 4 European territories (13 sites, from across Germany, Netherlands, Portugal, and the United Kingdom). In total, 1072 adult patients with suspected fatty liver disease will be randomized to be treated according to the result of the mpMRI in the intervention arm, so that further diagnostic evaluation is recommended only when values for metrics of liver fat or fibro-inflammation are elevated. Patients in the control arm will be treated as per center guidelines for standard of care. The primary outcome for this trial is to compare the difference in the proportion of patients with suspected NAFLD incurring liver-related hospital consultations or liver biopsies between the study arms, from the date of randomization to the end of the study follow-up. Secondary outcomes include patient feedback from a patient satisfaction questionnaire, at baseline and all follow-up visits to the end of the study, and time, from randomization to diagnosis by the physician, as recorded at the final follow-up visit.

Results: This trial is currently open for recruitment. The anticipated completion date for the study is December 2020.

Conclusions: This randomized controlled trial will provide the evidence to accelerate decision making regarding the inclusion of mpMRI-based tools in existing NAFLD/NASH clinical care. RADIcAL1 is among the first and largest European health economic studies of imaging technologies for fatty liver disease. Strengths of the trial include a high-quality research design and an in-depth assessment of the implementation of the cost-effectiveness of the mpMRI diagnostic. If effective, the trial may

highlight the health economic burden on tertiary-referral hepatology clinics imposed by unnecessary consultations and invasive diagnostic investigations, and demonstrate that including LiverMultiScan as a NAFLD diagnostic test may be cost-effective compared to liver-related hospital consultations or liver biopsies.

Trial Registration: ClinicalTrials.gov NCT03289897 https://clinicaltrials.gov/ct2/show/NCT03289897

International Registered Report Identifier (IRRID): DERR1-10.2196/19189

(JMIR Res Protoc 2020;9(10):e19189) doi:10.2196/19189

KEYWORDS

NAFLD; NASH; multiparametric MRI; health economics; biomarker

Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of abnormal liver blood tests with an estimated prevalence of between 20%-30% in Europe, and higher in the United States [1,2]. The condition is associated with obesity, insulin resistance, and heart disease, resulting in patients with fatty liver disease being twice as likely to get early coronary artery disease compared to the healthy population [3,4]. If left untreated, NAFLD can progress to nonalcoholic steatohepatitis (NASH), characterized by tissue scarring steatosis, lobular inflammation, fibrosis, and ballooning, before the ultimate development of cirrhosis and liver failure. Due to the steady increase of NALFD over the years, NASH has now become the leading cause of liver failure in the developed world, with reported predictions that it will become the leading cause of liver transplant over the coming decades [5]. NASH is a major public health concern and, with a global prevalence of 1.5%-6.5% [6,7] (and 12% in Western populations [8]), poses a significant economic burden on health care institutions.

Similar to most liver diseases, the diagnostic gold standard for NAFLD/NASH is percutaneous liver biopsy [5,9,10]. However, biopsies are painful and carry risk, as 1 out of 1000 people experience serious adverse events, including bleeding, infection, and bowel perforation [11-13]. Biopsies only sample a small part of the liver (approximately $1/50000^{th}$ of the liver volume) [14] and suffer from sampling location variability, thus affecting the reported stage of fibrosis in up to 50% of cases [15,16], as well as inter-reader variability, which can result in biopsy-finding disagreements amongst pathologists [17-19]. Thus, biopsies alone are not enough to obtain a diagnosis or to monitor liver disease [20,21]. In addition, with the advance of various pathophysiological changes exhibited through liver disease etiologies, some patients experience impaired clotting of their blood due to liver dysfunction [22] and are consequently at a higher risk of experiencing a combination of the risk factors associated with biopsy [8]. The resulting longer hospital stays and increased socioeconomic burden after the procedure make biopsy an unpopular option amongst patients, clinicians, and payers [9]. Although recommended by clinical guidelines as the gold standard for diagnosis and monitoring [10], in practice, liver biopsies are not routinely used unless the patient presents with moderate to severe liver disease or when there is a need to exclude other liver diseases such as autoimmune hepatitis [23]. In light of these factors, health institutions deviate from diagnostic pathways to stratify the risk of advanced liver disease and to postpone, or even replace, biopsy within this population, which has resulted in a nonstandardized care pathway. Therefore, in the absence of biopsy and a universal ground truth in routine care, there is a clear need for noninvasive, objective, discriminatory tests that can stratify normal liver, simple steatosis, steatohepatitis, and cirrhosis. These tests can then be used as a common reference point for clinical care.

Over the years, various noninvasive techniques such as ultrasound, transient elastography (FibroScan; Echosens), diffuse-weighted imaging, magnetic resonance elastography, T1 mapping, and multi-parametric magnetic resonance imaging (mpMRI) have been developed for use as surrogate markers to both diagnose and monitor NAFLD/NASH disease alongside blood tests [24,25]. mpMRI (Liver*MultiScan*; Perspectum Ltd) is an emerging quantitative mpMRI test, the first to combine corrected T1, proton density fat fraction (PDFF), and T2-star, and which can identify the early stages of liver disease [26,27] and predict clinical outcomes accurately [8]. mpMRI also has the potential to become a standardized, consistent step along the NASH clinical diagnostic pathway in multiple health care systems across Europe, as it is cost-saving, noninvasive, fast, repeatable, reliable, and standardized across multiple magnetic resonance vendors [8,9,27-30].

The cost benefits of introducing a noninvasive diagnostic test that detects earlier stage disease may be especially beneficial in the clinical care of people suspected of having fatty liver disease or diabetes [27,31]. The absence of a clear consensus over patient clinical management for suspected fatty liver disease [9,29] necessitates an assessment of mpMRI within existing health care systems to identify potential real-world cost-effectiveness of new imaging technologies and streamline health care for patients. Thus, to investigate the utility and cost-benefit of adding mpMRI into the care pathway of those with suspected NAFLD in Europe (European Union territories and United Kingdom [UK]), this randomized, multi-center, phase 4 control trial to investigate the use of mpMRI as a standardized diagnostic test for NAFLD/NASH was designed. With up to 13 sites across Europe included in this trial, the primary outcome is to compare between the study arms the difference in proportion of patients with suspected NAFLD incurring liver-related hospital consultations or liver biopsies, from the date of randomization to the end of the study follow-up. This will highlight the health economic burden on tertiary-referral hepatology clinics imposed by unnecessary additional consultations.

Methods

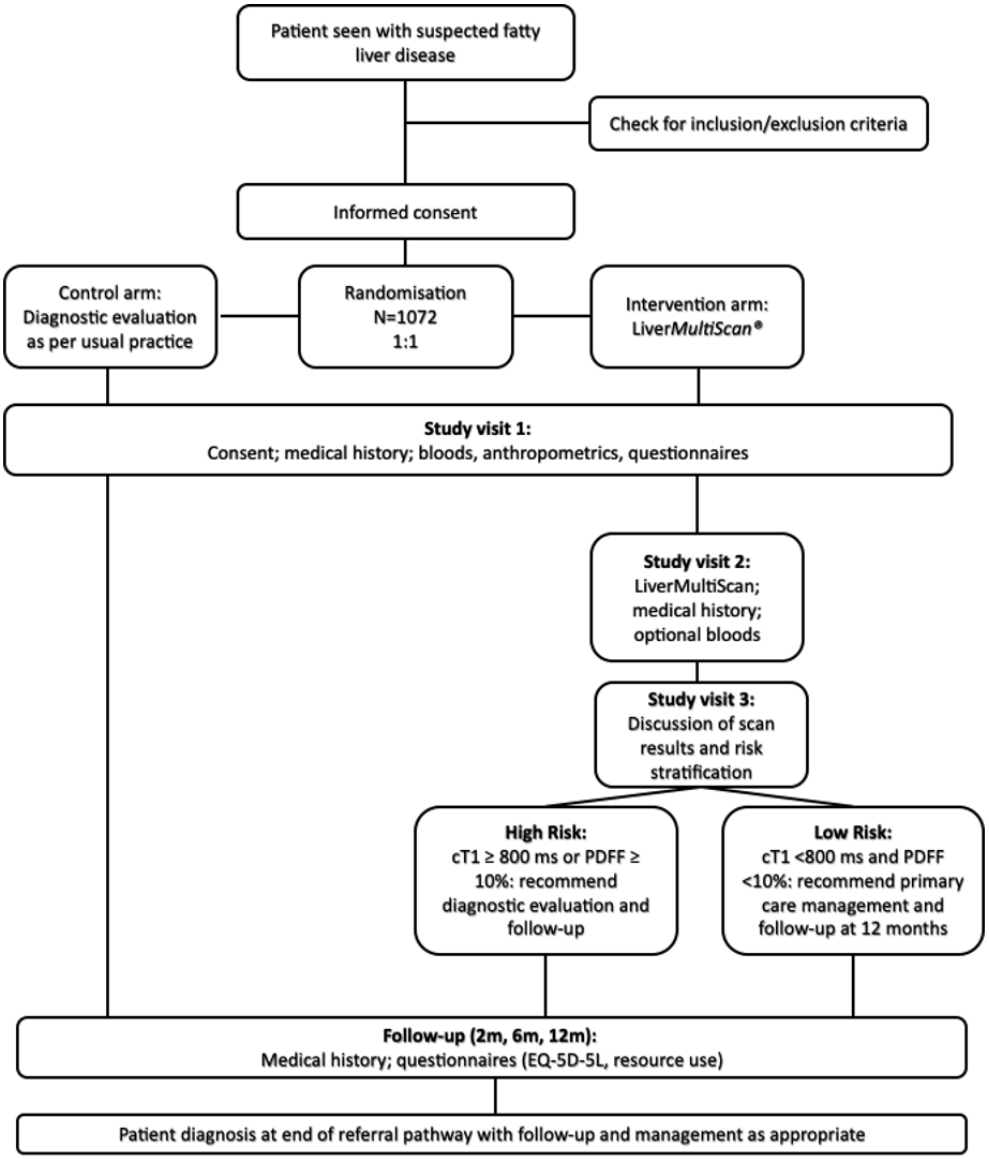
The Study

RADIcAL1 is a multi-center, phase 4, randomized controlled trial (NCT03289897) which aims to recruit 1072 patients from 13 sites in 4 different European territories, namely Ulm (Germany), Leiden (Netherlands), Coimbra (Portugal), and the UK (Liverpool, Southampton, Dundee, Glasgow, London, Manchester). The 5-year study consists of a 1-year study setup, a 3-year recruitment phase, and an up-to-12-months follow-up. The protocol, informed consent form, participant information sheet, and any proposed advertising material was submitted to each host institution's appropriate research ethics committee for written approval; a favorable (and granted) response was received in Ulm (198/17), Leiden (P17.076), Coimbra (CE-030/2017), and UK (18/SC/0725).

Patient Randomization and Study Participants

Patients will be randomized using a 1:1 allocation, without blinding, into an intervention arm (with mpMRI intervention) and a control arm (Figure 1). Randomization is automatically calculated using a random number generator on patients that have been already stratified based on a combination of the inclusion criteria (Textbox 1) and the recruitment site. Patients in the control arm will be treated as per center standard of care, with patients following local practice for NAFLD to potentially include physician consultations and anthropometric blood, imaging, and histological assessments [32-34].

Figure 1. Summary of study visits for participants in the RADIcAL1 clinical trial. m: months; PDFF: proton density fat fraction.



Textbox 1. Inclusion and exclusion criteria used during recruitment in the RADIcAL1 trial. NAFLD: nonalcoholic fatty liver disease.

Inclusion Criteria

- Male and female patients, aged 18-75 years, due to undergo an evaluation for suspected NAFLD
- Within standard of care, presence of either (1) elevated liver function tests (ALT, AST, or GGT ≥1.5 x upper limit of normal, and ALT, AST ≤5 x upper limit of normal) up to 1 year prior to patient recruitment, OR (2) imaging suggestive of fatty liver disease up to 3 years prior to patient recruitment
- OR presence of ≥ 3 of the following criteria: (1) insulin resistance or type 2 diabetes mellitus, (2) obesity (BMI >30 or waist-to-hip ratio > 1.00 for men / >0.85 for women), (3) hypertension (≥130/85 mmHg), (4) elevated triglycerides (≥1.7 mmol/l), (5) low HDL-cholesterol (<1.05 mmol/l for men / <1.25 mmol/l for women)
- Participant is willing and able to give informed consent for participation in the study

Exclusion Criteria

- Participants may not enter the study if they have any contraindication to magnetic resonance imaging (including pregnancy, extensive tattoos, pacemaker, shrapnel injury, severe claustrophobia)
- Patients with proven liver disease other than NAFLD
- Liver transplantation
- Patients that present with clinical signs of chronic liver failure (variceal bleeding, ascites, overt encephalopathy)
- Alcohol overuse/abuse as determined by local guidelines
- Patient with known malignant liver tumors and those with any malignancy with life expectancy <36 months
- Heart failure (New York Heart Association: stages II-IV)
- Severe mental illness
- Any other cause, including a significant disease or disorder which, in the opinion of the investigator, may either put the participant at risk because of participation in the study or may influence the result of the study, or the participant's ability to participate in the study

Those in the intervention arm will be treated according to the result of the mpMRI scan; if the liver fat is ≥10% or fibro-inflammation is identified (corrected T1 (cT1)≥800 ms), then further diagnostic evaluation will be recommended (such as further monitoring of liver enzymes, repeat mpMRI assessment at 6-12 months, assessment of liver stiffness, or assessment of response to lifestyle management activities) [10,35]. Otherwise, management in primary care for 12 months will be recommended. In both arms, clinical choices will be patient and site-specific in adherence with NAFLD guideline recommendations [32-34].

Potential participants will be recruited from (1) general practitioners or specialists from tertiary care hospital consultations (eg, obesity consultation); (2) secondary care clinics, and (3) databases from previous ethically approved studies where patients have consented to have their contact details retained in order to be contacted if eligible to take part in other studies.

During recruitment, the inclusion and exclusion criteria highlighted in Textbox 1 will be used to identify potential participants.

Once a potential participant expresses interest in the study, they will be provided with a patient information leaflet for a minimum of 24 hours and an opportunity to discuss their eligibility and the details of the study. In accordance with good clinical practice, the participant is free to withdraw from the study at any time for any reason without prejudice to current or future care. For those participants who wish to withdraw from the study, the option to permit ongoing use of data and samples which have already been collected, as well as future recording and usage of routinely collected clinical data and results, will be given. This will be clearly documented in the patient consent form. In addition to this, patients who are unable to undergo the magnetic resonance imaging (MRI) scan (eg, due to claustrophobia) may also be withdrawn from the study.

Study Visits

Patients will be required to attend their respective clinical centers for up to 3 dedicated study visits, as summarized in Figure 1. At Visit 1, informed consent, medical history, anthropometric readings, and blood will be taken. Visit 2 is for the intervention arm only; patients will be required to fast for 4 hours before the Liver*MultiScan* MRI scan (standardized imaging protocol in a 1.5 or 3T MRI scanner following the Perspectum protocol), which will involve lying supine in the MRI scanner for 10-15 minutes. At this visit, optional blood samples for further tests may be taken. Visit 3 is for the intervention arm only, during which clinicians will discuss the results of the MRI scan with the patients and change patient management if appropriate.

Once they have had their scan, patients will be followed up for a period of 6-12 months. In this trial, patients will also be requested to complete questionnaires at recruitment 2, 6, and 12 months after entering the study. In this trial, patients will also be requested to complete a resource use and quality of life (EQ-5D-5L [36]) questionnaire at recruitment and 2, 6, and 12 months after entering the study. Those in the intervention arm will also be asked to complete an MRI satisfaction questionnaire after having their mpMRI.

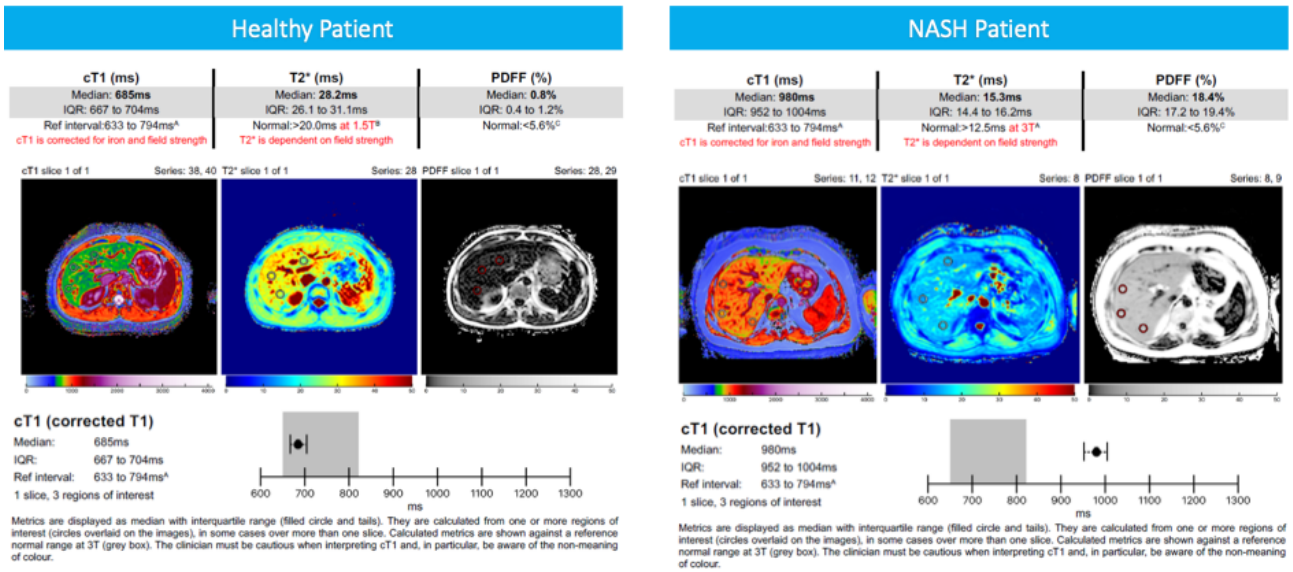
The resource use questionnaires completed at randomization will cover information such as appointments that the participant has had with a health care professional (inpatient and outpatient), medication usage, diet and physical exercise, paid and unpaid help the participant may require, and their insurance coverage. Furthermore, at the 2-, 6-, and 12-month follow-up visits, participants will be asked to answer additional questions regarding changes in medication and medical examinations they received as an outpatient. These examinations include blood tests, ultrasounds, other imaging (eg, endoscopy, CT scan, and MRI), and biopsies.

The EQ-5D-5L questionnaire [36] asks participants to describe their health on the day of questionnaire completion in order to assess the impact on quality of life. Each participant must rate their mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. The participant has 5 options to pick from for each parameter or question: no problem, slight problem, moderate problem, severe problem, or unable to carry out the task. Finally, participants are asked to indicate how they think their health is on that day, on a scale of 0 to 100.

Intervention

MRI-derived biomarkers provide many opportunities for diagnostic enrichment. MRI exploits the magnetic properties of hydrogen nuclei protons within a determined magnetic field. T1 mapping measures longitudinal relaxation time and, thus, is a surrogate measure of the amount of water present or the structural distribution of water molecules (ie, T1 can be used to indicate whether tissue water is freely moving, is structured within cells, or is bound to macromolecules). Therefore, as T1 relaxation time lengthens with increases in extracellular fluid, it has shown promise as an effective biomarker of inflammation and fibrosis in several organs [37,38]. The presence of iron in the liver, however, which can be accurately measured from MRI-T2-star relaxation time, shortens the T1 and thus must be accounted for [39]. An algorithm has been created by Perspectum Ltd that allows for the bias introduced by elevated iron to be removed from the T1 measurements, yielding the iron-corrected T1 (cT1) [14,39]. MRI-PDFF is a ratio expressed as a percentage of the fraction of the MRI-visible protons attributable to fat divided by all MRI-visible protons in that region of the liver attributable to fat and water. Taking advantage of the chemical shift between fat and water, pulse sequences (including fast spin-echo and gradient-recalled echo sequences) can be used to acquire images at multiple echo times at which fat and water signals have different phases relative to each other. cT1 maps have been shown to be correlated with fibro-inflammation and predictive of clinical events [8,14]. PDFF has been shown to have an excellent correlation with histologically graded steatosis across the clinical range seen in NASH and high diagnostic accuracy in stratification of all grades of liver steatosis. Hence, together, PDFF and cT1 hold promise to accurately assess all relevant aspects of liver disease: fat, inflammation, and fibrosis [25,40]. The sample reports shown in Figure 2 demonstrate the information that can be derived from the use of mpMRI to aid as a diagnostic tool for clinicians, highlighting the differences between a healthy patient with low cT1 and a patient with suspected NAFLD and high cT1. The high repeatability and reproducibility of mpMRI (both coefficients of variation equalling 3.3% for cT1 [25,28,41]) and predefined diagnostic thresholds for an mpMRI recommendation make clinical misinterpretation of the mpMRI unlikely.

Figure 2. Sample reports that demonstrate the information that can be derived from the use of mpMRI to aid as a diagnostic tool for clinicians, highlighting the differences between a healthy patient with low cT1 and a patient with suspected nonalcoholic fatty liver disease (NAFLD) and high cT1. PDFF: proton density fat fraction.



Objectives and Outcomes

All primary and secondary objectives and outcome measures are outlined in Table 1. The primary objective of the study is to compare the cost-effectiveness of the standard of care received by patients with suspected NAFLD in the stated EU territories compared to the care such patients will receive when Liver*MultiScan* is introduced as a standardized diagnostic test. The primary endpoint of the study utilizes health care resource use data to compare the difference in proportion of patients incurring liver-related hospital consultations or liver biopsies, from the date of randomization to the end of the study follow-up,

with cost-effectiveness dependent on local jurisdiction. One secondary objective will be based on data from patient satisfaction questionnaires to explore the implementation of the intervention. Another secondary objective investigating the certainty and frequency of diagnosis is based on clinician response to a specific question ("Using all the information obtained to date, how certain are you to make a diagnosis of NAFLD today?") posed at each diagnostic visit in the patient's journey. The 4 possible predefined responses are further subgrouped into binary categories, one subgroup for certainty and another for frequency of diagnosis. Other secondary objectives include a comparison of the time to diagnosis, which utilizes data based on any liver-related diagnosis [from 7 options: primary nonalcoholic fatty liver (NAFL), secondary NAFL, primary NASH, secondary NASH, mixed-etiology NAFL, mixed-etiology NASH, other etiology]. Additionally, the use of resources, the actual costs over a 12-month period, and the level of skill or clinical specialization required within each study arm will be investigated as secondary objectives, based on the resource use questionnaires and study case report forms. Exploratory objectives include a model looking at long-term cost-effectiveness based on quality of life over a lifetime horizon, using the EQ-5D-5L data and an analysis of the diagnostic accuracy of mpMRI and other study biomarkers.

Table 1. RADIcAL1 primary and secondary objectives.

Criteria	Primary	Secondary
Objectives	To investigate whether the introduction of mpMRI as a standardized diagnostic test for liver disease can prove a cost-effective method in different European territories	To investigate patient satisfaction with mpMRI instead of existing care (with other liver investigations)
		To investigate the certainty and frequency of diagnosis at points of time in the patient pathway
		To investigate which pathway is quicker to get to the diagnosis as recorded at the final follow-up visit (including all corrections and additional investigations)
		To measure which health care resources and costs are required in the 2 diagnostic pathways
		To investigate the cost-effectiveness of mpMRI against standard of care
		To investigate skills/specialization required
Outcome measures/ endpoints	The proportion of patients with suspected NAFLD incurring liver-related hospital consultations and/or liver biopsies, from the date of randomization to the end of the study follow-up	Patient feedback from patient satisfaction questionnaire, at baseline and all follow-up visits to the end of the study
		Certainty of diagnosis is defined as a binary (*yes/no*, as opposed to *unlikely/probable*) and frequency (*yes/probable*, as opposed to *no/unlikely*), at baseline and all follow-up visits to the end of the study
		Time, from randomization to diagnosis by the physician, as recorded at the final follow-up visit
		Rates of liver-related outpatient investigations/ consultations/hospital admissions per 400 patients during the study
		Cost of mpMRI based on randomized comparison
		Personnel required to perform procedures and tasks, from the date of randomization to the end of the study follow-up

Sample Size Calculation

In a study by Blake et al [9], it was identified that the use of Liver*MultiScan* can result in a decrease in biopsy of 18%. Adopting a conservative target of identifying a 14% decrease across different regions, to maintain statistical significance [with more than 80% power (α=.05) to show a difference in proportion of patients having consultations between the 2 pathways), each randomization arm is required to have 402 patients. Moreover, due to the size of the trial, the final recruitment target was powered to include a 25% dropout rate (including those lost to follow-up during the completion of the study). Thus, a total cohort of 1072 patients with suspected fatty liver disease will need to be recruited into the trial.

Statistical Methods and Data Management Plan

Statistical support for all primary and secondary analyses will be provided by Perspectum Ltd. Detailed health economic and statistical analysis plans [42] (Multimedia Appendix 1) describe the required analyses to investigate the study objectives. These include details of standard statistical analyses [*t* test, analysis of variance, area under the receiver operating curve (AUROC)] and data analysis packages [such as R (R Core Team), MATLAB (MathWorks), and Python (Python Software Foundation)], which will be used to report summary statistics for patients in both arms of the study. Moreover, summary statistics will be reported (number of observations, mean, standard deviation, or percentages, as relevant) for the demographic variables, clinical variables, and outcomes for the

total group, and comparisons with any noninvasive tests offered in their care.

The health economic analysis will evaluate changes in resource use and costs for data collected from randomization to the end of the study. Within this evaluation, the determination of the cost-effectiveness of mpMRI from the perspective of each health care system following the intention-to-treat principle will be derived. Health care resource use (including diagnostic procedures, health care consultations, and hospital admissions) will be obtained from medical records as well as via patient self-reported data during follow-up visits. A detailed health economic analysis plan, detailing the methods used and models developed using study data, will also be agreed upon and developed prior to the end of the study (Carolan et al., unpublished data).

Additional exploratory analysis will evaluate the diagnostic performance of cT1 and PDFF using AUROC, and will assess the concurrence of mpMRI metrics with other surrogate biomarkers associated with NAFLD/NASH used more regularly in clinical practice, such as glucose and hemoglobin A1C (HbA1c, a measure of glycated hemoglobin which contributes to diabetes diagnosis), enhanced liver fibrosis tests (used to test for advanced liver fibrosis in patients with NALFD), and cholesterol, utilizing correlation analyses (Pearson correlation for normally distributed data, and Spearman rho for non-normally distributed data). The concordance of mpMRI metrics and biopsy data will be assessed using Cohen kappa (κ) statistic, Bland-Altman analysis (bias, limits of agreement, and the corresponding 95% confidence interval), Pearson correlation, and mean coefficient of variation, which will be estimated.

In this trial, all data collected will be documented in electronic case report forms. In addition to this, all patient-related data will be handled and stored according to the European and national data protection laws [42]. All outcome data will be analyzed using an intention-to-treat principle, where data from participants shall be analyzed according to the group in which they were randomized, even if they did not receive the allocated intervention.

Results

RADIcAL1 has been funded from May 2016, and ethics approval was granted in April 2017 (Portugal), July 2017 (Germany, Netherlands), and June 2018 (UK). Data collection began in September 2017 and is estimated to be complete by the end of December 2020. As of April 2020, a total of 726 patients with suspected NAFLD or metabolic syndrome or both have been enrolled. Results will be analyzed by the end of the study, and publication of the results is expected by March 2021.

Discussion

Nonalcoholic fatty liver disease (NAFLD) and its more progressive form, nonalcoholic steatohepatitis (NASH), are emerging as the most important cause of liver disease worldwide, thought to potentially become the number 1 cause of end-stage liver disease [5]. Their increasing prevalence also share demographic and epidemiological parallels with the worldwide epidemic of obesity and type 2 diabetes mellitus [8,43,44], and the presence of these comorbidities are thought to further increase the risk of cardiovascular disease [44,45]. Due to the increased numbers of patients now requiring both diagnosis and regular monitoring for NAFLD/NASH, great economic and time-related burdens are now being placed upon already strained health care systems [5,44]. Current clinical guidelines and care pathways require patients to undergo liver biopsy for the diagnosis and monitoring of NAFLD/NASH, which is risky, painful, and costly, leading to a reluctance from both patients and clinicians to engage in such procedures with regularity [9], thus highlighting an increasingly urgent requirement for a cost-effective, repeatable, reproducible, and noninvasive tool to aid the diagnostic pathway [41].

To the best of our knowledge, this will be the first large-scale, multi-center study to evaluate the cost-effectiveness of mpMRI within the diagnostic pathway for patients with NAFLD/NASH across multiple European territories. The primary objective of the RADIcAL1 trial is to evaluate the cost-effectiveness of mpMRI within tertiary care units within Europe, assessing the impact of its utility upon the number of unnecessary consultations and biopsies that patients must attend, and the economic burden faced by health care systems. From these findings, RADIcAL1 has the potential to produce concordance and optimization of the diagnosis and monitoring pathways for patients whom, with better knowledge of their NAFLD/NASH status, may be able to undertake informed lifestyle changes and prevent further progression of comorbidities, potentially producing further health-economic savings [5,9]. Qualitative data in RADIcAL1, such as the patient satisfaction survey, will provide patient experience insights directly from a population the mpMRI technology is designed to benefit. Furthermore, due to data collection throughout the clinical care pathway, RADIcAL1 also has the potential to assess both the diagnostic accuracy and speed in which care is received in both study arms, adding further evidence to the requirement for a singular, agreed-upon, ideal diagnostic pathway.

mpMRI is well placed to provide accurate monitoring of individual patient responses to drugs in trials and within the care pathway, allowing researchers and clinicians to make informed decisions regarding patient care, with the potential to optimize the allocation of expensive treatments. We expect the introduction of mpMRI into the standard care pathway for patients with NAFLD/NASH to provide health and socioeconomic benefits to patients in addition to cost-savings for health care providers, and this will be evaluated in RADIcAL1.

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Authors' Contributions

RB, SR, HL, MD, MC, MB, MCB, and FCA developed the study concept and protocols and were involved in the funding and initiation of the project. MK and CF assisted with further development of the protocol. MD, SR, MB, MC, HL, CF, MCB, FCA, and RB drafted the clinical study protocol. The principal investigator at each center (MC, MD, MCB, and DT) applied for the ethics application. ES, LAT, LH, MF, HTB, and SR drafted the manuscript. Additional members of the RADIcAL1 team include Lucy Walker, Neelam Hassanali, and Rexford Newbould. All authors contributed and approved the final manuscript.

Conflicts of Interest

DT, ES, LAT, LH, MF, SR, HTB, CF, MK, and RB are affiliated with Perspectum Ltd. Perspectum Ltd is a privately funded commercial enterprise that develops medical devices to address unmet clinical needs, including LiverMultiScan. Perspectum Ltd is the sponsor of this study. MCB, FCA, MC, HL, MB, and MD have no conflicts of interest to declare.

Multimedia Appendix 1
Statistical analysis plan.
[PDF File (Adobe PDF File), 699 KB - resprot_v9i10e19189_app1.pdf]

Multimedia Appendix 2
Grant Protocol Peer Review.
[PDF File (Adobe PDF File), 89 KB - resprot_v9i10e19189_app2.pdf]

References

1. Blachier M, Leleu H, Peck-Radosavljevic M, Valla D, Roudot-Thoraval F. The burden of liver disease in Europe: a review of available epidemiological data. J Hepatol 2013 Mar;58(3):593-608 [FREE Full text] [doi: 10.1016/j.jhep.2012.12.005] [Medline: 23419824]
2. Levelt E, Pavlides M, Banerjee R, Mahmod M, Kelly C, Sellwood J, et al. Ectopic and Visceral Fat Deposition in Lean and Obese Patients With Type 2 Diabetes. J Am Coll Cardiol 2016 Jul 05;68(1):53-63 [FREE Full text] [doi: 10.1016/j.jacc.2016.03.597] [Medline: 27364051]
3. Mahfood Haddad T, Hamdeh S, Kanmanthareddy A, Alla VM. Nonalcoholic fatty liver disease and the risk of clinical cardiovascular events: A systematic review and meta-analysis. Diabetes Metab Syndr 2017 Nov;11 Suppl 1:S209-S216. [doi: 10.1016/j.dsx.2016.12.033] [Medline: 28017631]
4. Tana C, Ballestri S, Ricci F, Di Vincenzo A, Ticinesi A, Gallina S, et al. Cardiovascular Risk in Non-Alcoholic Fatty Liver Disease: Mechanisms and Therapeutic Implications. Int J Environ Res Public Health 2019 Aug 26;16(17) [FREE Full text] [doi: 10.3390/ijerph16173104] [Medline: 31455011]
5. Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2018 Jan;15(1):11-20. [doi: 10.1038/nrgastro.2017.109] [Medline: 28930295]
6. Wilman HR, Kelly M, Garratt S, Matthews PM, Milanesi M, Herlihy A, et al. Characterisation of liver fat in the UK Biobank cohort. PLoS One 2017;12(2):e0172921 [FREE Full text] [doi: 10.1371/journal.pone.0172921] [Medline: 28241076]
7. Jayakumar S, Middleton MS, Lawitz EJ, Mantry PS, Caldwell SH, Arnold H, et al. Longitudinal correlations between MRE, MRI-PDFF, and liver histology in patients with non-alcoholic steatohepatitis: Analysis of data from a phase II trial of selonsertib. J Hepatol 2019 Jan;70(1):133-141 [FREE Full text] [doi: 10.1016/j.jhep.2018.09.024] [Medline: 30291868]
8. Pavlides M, Banerjee R, Sellwood J, Kelly CJ, Robson MD, Booth JC, et al. Multiparametric magnetic resonance imaging predicts clinical outcomes in patients with chronic liver disease. J Hepatol 2016 Feb;64(2):308-315 [FREE Full text] [doi: 10.1016/j.jhep.2015.10.009] [Medline: 26471505]
9. Blake L, Duarte RV, Cummins C. Decision analytic model of the diagnostic pathways for patients with suspected non-alcoholic fatty liver disease using non-invasive transient elastography and multiparametric magnetic resonance imaging. BMJ Open 2016 Sep 20;6(9):e010507. [doi: 10.1136/bmjopen-2015-010507] [Medline: 27650757]
10. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018 Jan;67(1):328-357. [doi: 10.1002/hep.29367] [Medline: 28714183]
11. Kim KR, Ko G, Sung K, Yoon H, Shin JH, Song H, et al. Transjugular liver biopsy in patients with living donor liver transplantation: comparison with percutaneous biopsy. Liver Transpl 2008 Jul;14(7):971-979 [FREE Full text] [doi: 10.1002/lt.21448] [Medline: 18581512]

12. Kalambokis G, Manousou P, Vibhakorn S, Marelli L, Cholongitas E, Senzolo M, et al. Transjugular liver biopsy--indications, adequacy, quality of specimens, and complications--a systematic review. J Hepatol 2007 Aug;47(2):284-294. [doi: 10.1016/j.jhep.2007.05.001] [Medline: 17561303]
13. West J, Card TR. Reduced mortality rates following elective percutaneous liver biopsies. Gastroenterology 2010 Oct;139(4):1230-1237. [doi: 10.1053/j.gastro.2010.06.015] [Medline: 20547160]
14. Banerjee R, Pavlides M, Tunnicliffe EM, Piechnik SK, Sarania N, Philips R, et al. Multiparametric magnetic resonance for the non-invasive diagnosis of liver disease. J Hepatol 2014 Jan;60(1):69-77 [FREE Full text] [doi: 10.1016/j.jhep.2013.09.002] [Medline: 24036007]
15. Regev A, Berho M, Jeffers LJ, Milikowski C, Molina EG, Pyrsopoulos NT, et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. Am J Gastroenterol 2002 Oct;97(10):2614-2618. [doi: 10.1111/j.1572-0241.2002.06038.x] [Medline: 12385448]
16. Morisaka H, Motosugi U, Glaser KJ, Ichikawa S, Ehman RL, Sano K, et al. Comparison of diagnostic accuracies of two- and three-dimensional MR elastography of the liver. J Magn Reson Imaging 2017 Apr;45(4):1163-1170 [FREE Full text] [doi: 10.1002/jmri.25425] [Medline: 27662640]
17. Goodman ZD. Grading and staging systems for inflammation and fibrosis in chronic liver diseases. J Hepatol 2007 Oct;47(4):598-607. [doi: 10.1016/j.jhep.2007.07.006] [Medline: 17692984]
18. Kleiner DE, Brunt EM, Van NM, Behling C, Contos MJ, Cummings OW, Nonalcoholic Steatohepatitis Clinical Research Network. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology 2005 Jun;41(6):1313-1321. [doi: 10.1002/hep.20701] [Medline: 15915461]
19. Standish RA, Cholongitas E, Dhillon A, Burroughs AK, Dhillon AP. An appraisal of the histopathological assessment of liver fibrosis. Gut 2006 Apr;55(4):569-578 [FREE Full text] [doi: 10.1136/gut.2005.084475] [Medline: 16531536]
20. Afdhal NH. Fibroscan (transient elastography) for the measurement of liver fibrosis. Gastroenterol Hepatol (N Y) 2012 Sep;8(9):605-607 [FREE Full text] [Medline: 23483859]
21. Castera L, Pinzani M. Biopsy and non-invasive methods for the diagnosis of liver fibrosis: does it take two to tango? Gut 2010 Jul;59(7):861-866. [doi: 10.1136/gut.2010.214650] [Medline: 20581229]
22. Flores B, Trivedi HD, Robson SC, Bonder A. Hemostasis, bleeding and thrombosis in liver disease. J Transl Sci 2017 May;3(3) [FREE Full text] [doi: 10.15761/JTS.1000182] [Medline: 30221012]
23. Nalbantoglu ILK, Brunt EM. Role of liver biopsy in nonalcoholic fatty liver disease. World J Gastroenterol 2014 Jul 21;20(27):9026-9037 [FREE Full text] [doi: 10.3748/wjg.v20.i27.9026] [Medline: 25083076]
24. Castera L. Non-invasive tests for liver fibrosis in NAFLD: Creating pathways between primary healthcare and liver clinics. In: Liver Int. Oxford, UK: John Wiley & Sons Ltd; Feb 01, 2020:77-81.
25. Thomaides-Brears H, Lepe R, Banerjee R, Duncker C. Multiparametric MR mapping in clinical decision-making for diffuse liver disease. Abdom Radiol 2020 Aug 5. [doi: 10.1007/s00261-020-02684-3]
26. Ludwig J, Viggiano TR, McGill DB, Oh BJ. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. Mayo Clin Proc 1980 Jul;55(7):434-438. [Medline: 7382552]
27. Pavlides M, Banerjee R, Tunnicliffe EM, Kelly C, Collier J, Wang LM, et al. Multiparametric magnetic resonance imaging for the assessment of non-alcoholic fatty liver disease severity. Liver Int 2017 Jul;37(7):1065-1073 [FREE Full text] [doi: 10.1111/liv.13284] [Medline: 27778429]
28. Harrison SA, Dennis A, Fiore MM, Kelly MD, Kelly CJ, Paredes AH, et al. Utility and variability of three non-invasive liver fibrosis imaging modalities to evaluate efficacy of GR-MD-02 in subjects with NASH and bridging fibrosis during a phase-2 randomized clinical trial. PLoS One 2018;13(9):e0203054 [FREE Full text] [doi: 10.1371/journal.pone.0203054] [Medline: 30192782]
29. Eddowes PJ, McDonald N, Davies N, Semple SIK, Kendall TJ, Hodson J, et al. Utility and cost evaluation of multiparametric magnetic resonance imaging for the assessment of non-alcoholic fatty liver disease. Aliment Pharmacol Ther 2018 Mar;47(5):631-644 [FREE Full text] [doi: 10.1111/apt.14469] [Medline: 29271504]
30. Breen DJ. Multiparametric MRI for early detection of diffuse liver disease: an interview with David Breen. Biomark Med 2018 Feb;12(2):105-106. [doi: 10.2217/bmm-2017-0368] [Medline: 29318905]
31. Roeb E, Steffen HM, Bantel H, Baumann U, Canbay A, Demir M, et al. [S2k Guideline non-alcoholic fatty liver disease]. Z Gastroenterol 2015 Jul;53(7):668-723. [doi: 10.1055/s-0035-1553193] [Medline: 26167698]
32. Sberna AL, Bouillet B, Rouland A, Brindisi MC, Nguyen A, Mouillot T, et al. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO) clinical practice recommendations for the management of non-alcoholic fatty liver disease: evaluation of their application in people with Type 2 diabetes. Diabet Med 2018 Mar;35(3):368-375. [doi: 10.1111/dme.13565] [Medline: 29247558]
33. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016 Jun;64(6):1388-1402. [doi: 10.1016/j.jhep.2015.11.004] [Medline: 27062661]

34. NICE. Nonalcoholic fatty liver disease (NAFLD): assessment and management Internet. National Institute for Health and Care Excellence. URL: https://www.nice.org.uk/guidance/ng49/chapter/recommendations [accessed 2020-06-06]
35. Mojtahed A, Kelly CJ, Herlihy AH, Kin S, Wilman HR, McKay A, et al. Reference range of liver corrected T1 values in a population at low risk for fatty liver disease-a UK Biobank sub-study, with an appendix of interesting cases. Abdom Radiol (NY) 2019 Jan;44(1):72-84 [FREE Full text] [doi: 10.1007/s00261-018-1701-2] [Medline: 30032383]
36. Jin X, Al Sayah F, Ohinmaa A, Marshall DA, Johnson JA. Responsiveness of the EQ-5D-3L and EQ-5D-5L in patients following total hip or knee replacement. Qual Life Res 2019 Sep;28(9):2409-2417. [doi: 10.1007/s11136-019-02200-1] [Medline: 31089988]
37. Everett RJ, Treibel TA, Fukui M, Lee H, Rigolli M, Singh A, et al. Extracellular Myocardial Volume in Patients With Aortic Stenosis. Journal of the American College of Cardiology 2020 Jan;75(3):304-316. [doi: 10.1016/j.jacc.2019.11.032]
38. Bradley CR, Cox EF, Scott RA, James MW, Kaye P, Aithal GP, et al. Multi-organ assessment of compensated cirrhosis patients using quantitative magnetic resonance imaging. Journal of Hepatology 2018 Nov;69(5):1015-1024. [doi: 10.1016/j.jhep.2018.05.037]
39. Tunnicliffe E, Rajarshi B, Pavlides M, Neubauer S, Robson M. A model for hepatic fibrosis: the competing effects of cell loss and iron on shortened modified Look-Locker inversion recovery T1 (shMOLLI-T1) in the liver. J. Magn. Reson. Imaging 2016 Jul;45(2):450-462. [doi: 10.1002/jmri.25392]
40. Schaapman JJ, Tushuizen ME, Coenraad MJ, Lamb HJ. Multiparametric MRI in Patients With Nonalcoholic Fatty Liver Disease. J Magn Reson Imaging 2020 Aug 21. [doi: 10.1002/jmri.27292]
41. Bachtiar V, Kelly MD, Wilman HR, Jacobs J, Newbould R, Kelly CJ, et al. Repeatability and reproducibility of multiparametric magnetic resonance imaging of the liver. PLoS One 2019;14(4):e0214921 [FREE Full text] [doi: 10.1371/journal.pone.0214921] [Medline: 30970039]
42. Regulation (EU) 2016/679 of the European Parliament and of the Council. EUR-Lex 2016. 2016. URL: http://data.europa.eu/eli/reg/2016/679/oj [accessed 2020-06-06]
43. Samuel VT, Shulman GI. Nonalcoholic Fatty Liver Disease as a Nexus of Metabolic and Hepatic Diseases. Cell Metab 2018 Jan 09;27(1):22-41 [FREE Full text] [doi: 10.1016/j.cmet.2017.08.002] [Medline: 28867301]
44. Younossi ZM. Non-alcoholic fatty liver disease - A global public health perspective. J Hepatol 2019 Mar;70(3):531-544. [doi: 10.1016/j.jhep.2018.10.033] [Medline: 30414863]
45. Hodson L, Banerjee R, Rial B, Arlt W, Adiels M, Boren J, et al. Menopausal Status and Abdominal Obesity Are Significant Determinants of Hepatic Lipid Metabolism in Women. J Am Heart Assoc 2015 Oct 02;4(10):e002258-e002105 [FREE Full text] [doi: 10.1161/JAHA.115.002258] [Medline: 26432801]

Abbreviations

AUROC: area under the receiver operating curve
cT1: corrected T1
mpMRI: multi-parametric magnetic resonance imaging
NAFLD: nonalcoholic fatty liver disease
NASH: nonalcoholic steatohepatitis
PDFF: proton density fat fraction

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Protocol

Virtual Reality–Based Treatment for Military Members and Veterans With Combat-Related Posttraumatic Stress Disorder: Protocol for a Multimodular Motion-Assisted Memory Desensitization and Reconsolidation Randomized Controlled Trial

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Abstract

Background: Military members are at elevated risk of operational stress injuries, including posttraumatic stress disorder (PTSD) and moral injury. Although psychotherapy can reduce symptoms, some military members may experience treatment-resistant PTSD. Multimodular motion-assisted memory desensitization and reconsolidation (3MDR) has been introduced as a virtual reality (VR) intervention for military members with PTSD related to military service. The 3MDR intervention incorporates exposure therapy, psychotherapy, eye movement desensitization and reconsolidation, VR, supportive counselling, and treadmill walking.

Objective: The objective of this study is to investigate whether 3MDR reduces PTSD symptoms among military members with combat-related treatment-resistant PTSD (TR-PTSD); examine the technology acceptance and usability of the Computer Assisted Rehabilitation ENvironment (CAREN) and 3MDR interventions by Canadian Armed Forces service members (CAF-SMs), veterans, 3MDR clinicians, and operators; and evaluate the impact on clinicians and operators of delivering 3MDR.

Methods: This is a mixed-methods waitlist controlled crossover design randomized controlled trial. Participants include both CAF-SMs and veterans (N=40) aged 18-60 years with combat-related TR-PTSD (unsuccessful experience of at least 2

evidence-based trauma treatments). Participants will also include clinicians and operators (N=12) who have been trained in 3MDR and subsequently utilized this intervention with patients. CAF-SMs and veterans will receive 6 weekly 90-minute 3MDR sessions. Quantitative and qualitative data will be collected at baseline and at 1, 3, and 6 months postintervention. Quantitative data collection will include multiomic biomarkers (ie, blood and salivary proteomic and genomic profiles of neuroendocrine, immune-inflammatory mediators, and microRNA), eye tracking, electroencephalography, and physiological data. Data from outcome measures will capture self-reported symptoms of PTSD, moral injury, resilience, and technology acceptance and usability. Qualitative data will be collected from audiovisual recordings of 3MDR sessions and semistructured interviews. Data analysis will include univariate and multivariate approaches, and thematic analysis of treatment sessions and interviews. Machine learning analysis will be included to develop models for the prediction of diagnosis, symptom severity, and treatment outcomes.

Results: This study commenced in April 2019 and is planned to conclude in April 2021. Study results will guide the further evolution and utilization of 3MDR for military members with TR-PTSD and will have utility in treating other trauma-affected populations.

Conclusions: The goal of this study is to utilize qualitative and quantitative primary and secondary outcomes to provide evidence for the effectiveness and feasibility of 3MDR for treating CAF-SMs and veterans with combat-related TR-PTSD. The results will inform a full-scale clinical trial and stimulate development and adaptation of the protocol to mobile VR apps in supervised clinical settings. This study will add to knowledge of the clinical effectiveness of 3MDR, and provide the first comprehensive analysis of biomarkers, technology acceptance and usability, moral injury, resilience, and the experience of clinicians and operators delivering 3MDR.

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KEYWORDS

3MDR; posttraumatic stress disorder; military; veteran; psychotherapy; virtual reality

Introduction

Background

Posttraumatic stress disorder (PTSD), a mental health condition triggered by experiencing or witnessing a terrifying event, can be life-altering. Characterized by enduring symptoms related to negative cognitive intrusions, avoidance, hypervigilance, and alterations in mood, arousal, and reactivity [1], PTSD is the most common mental illness experienced by military members and veterans [2-4], and remains the predominant focus of most military and veteran health research and care [5-8]. PTSD prevalence is persistent and may increase over time [9], characterized by complexity and a wide variance internationally within military and veteran populations [10]. Among US military members deployed during the War on Terror, PTSD prevalence estimates reach up to 19% [10] compared to 5.3% for Canadians [11], 2.7% to 4% in UK military members [12], and 3% for military members from the Netherlands [13]. A recent meta-analysis reported that overall rates remained high (at approximately 23%) for US veterans following 9-11 [14] and the incidence of PTSD increased to 16% for Canadian veterans [15].

Isolated or cumulative traumatic experiences can also cause long-term psychological and spiritual struggles, including depression, anxiety, moral injury [5,16], and suicide [17]. Moral injury—a separate trauma syndrome that results from exposure to ethically or virtuously injurious experiences such as witnessing or participating in acts that transgress personal morals and values [18]—has been posited as a potential key comorbidity, and a compounding and complicating factor of PTSD [19,20].

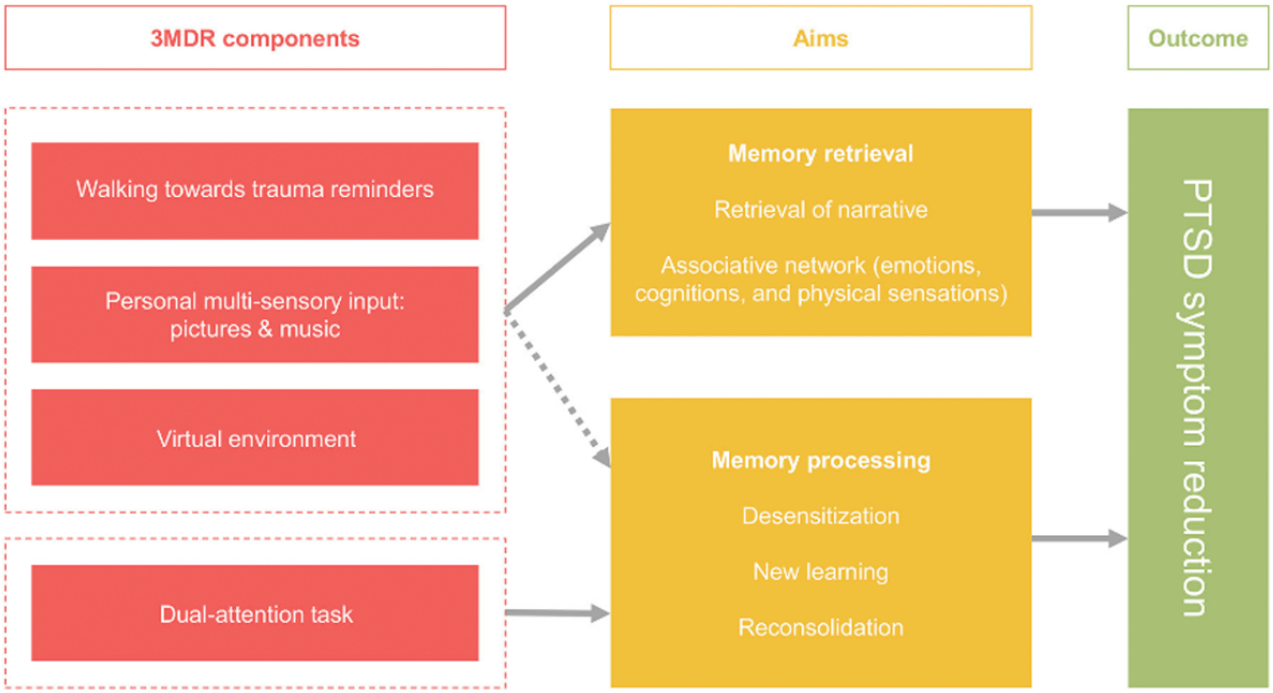
The classification of treatment-resistant PTSD (TR-PTSD) has been adopted for the many veterans who do not experience a clinically significant reduction in symptoms following receipt of evidence-based treatment. International PTSD guidelines consistently demonstrate trauma-focused cognitive behavioral therapy, cognitive processing therapy, prolonged exposure, and eye-movement desensitization and reprocessing (EMDR) to be the gold-standard and first-line treatments for PTSD. However, it is equally acknowledged that military members and veterans consistently have poorer clinical outcomes than their civilian counterparts in these treatments [21-23]. Although general recommendations for optimizing psychotherapies (ie, using untried or complementary modalities) and utilizing secondary pharmacological interventions (ie, mood stabilizers, antiadrenergic agents/hypnotics, or atypical antipsychotic agents) have been suggested [24], specific evidence-based TR-PTSD therapies or protocols are lacking.

Multimodular Motion-Assisted Memory Desensitization and Reconsolidation

Multimodular motion-assisted memory desensitization and reconsolidation (3MDR) is an emerging virtual reality (VR)-assisted therapy being studied with military members and veterans in the Netherlands, United States, United Kingdom, and Canada. It is hypothesized that the combination of trauma modalities in 3MDR may contribute to its potential effectiveness. The key elements of 3MDR therapy include: (1) engaging in exposure to traumatic material whereby avoidance patterns are minimized or broken; (2) experiencing emotions in the here and now that are evoked while the traumatic memories are being retrieved, and giving expression to these; and (3) reintegrating (reconsolidating) memories and sensory

along with affective information associated with the trauma via a dual task (Figure 1) [25,26]. It is also thought that the combination of elements involved in 3MDR work collectively to facilitate the memory reconsolidation necessary to reduce the intensity of traumatic memories and subsequent PTSD symptoms. These include (1) exposure to VR visual imagery and auditory input, (2) walking, (3) a dual-attention task, and (4) therapeutic context and relationship [25,26]. A brief description of each element follows.

Figure 1. Schematic overview of the augmentation strategies applied in the framework of the multimodular motion-assisted memory desensitization and reconsolidation (3MDR) intervention and its outcomes. Used with permission [25]. PTSD: posttraumatic stress disorder.



Exposure to Visual and Auditory Input

Emotional dysregulation and numbing are increasingly being considered as crucial components to address in PTSD treatment, especially for veterans who appear to more actively withhold emotional responses and use numbing as a coping mechanism [27]. Viewing affective pictures is thought to increase emotional engagement, and has been found to elicit physiological response patterns, which are higher for unpleasant pictures [28,29]. However, in addition to looking at affective pictures [30], auditory input such as music is noted to be a strong emotional trigger [31]. As self-selected music can elicit the retrieval of significantly more autobiographical memories in people with dementia [32,33], it is considered that optimal memory recollection may likewise be elicited by music for those with PTSD. Patients diagnosed with PTSD have indicated that music evokes (traumatic) memories, and enables them to access and discuss these memories [25,34,35]. Visual and auditory components are therefore central to 3MDR because of their believed ability to evoke potentially repressed or numbed emotions.

Walking

Among those with PTSD, walking toward an image of a traumatic memory has been found to increase engagement, decrease avoidance [36], potentially support the formation of new cognitive and emotional experiences related to the traumatic event, and contribute to reconsolidation of the traumatic memory [25]. Walking seems to facilitate consolidation of fear-related and traumatic memories. This occurs through bilateral movement [25], associated increases in brain-derived neurotrophic factor levels [37], approach behaviors toward feared cues and challenging working memory [33], increasing expression of associative memory [38], enhancing divergent thinking (which facilitates accessing emotional and cognitive networks associated with the traumatic memory) [37,39], allowing for new memories to surface [39], and reducing somatic and dissociative symptoms [40]. Walking throughout 3MDR's platform phase is thought to be foundational to the therapy.

Dual-Attention Task

The dual-attention task component of 3MDR aims to facilitate processing and reconsolidation of traumatic memories and utilizes aspects of EMDR [31,41,42]. In traditional EMDR interventions, participants are asked to retrieve aversive memories and rate their vividness and emotional intensity [41-45]. They are then asked to recall the memories while making eye movements or performing a bilaterally stimulating task [41-45]. Within the 3MDR intervention, this task requires the participant to visually track a horizontally moving ball across the screen in the foreground of a traumatic image while calling out numbers displayed on this ball. Reconsolidation theory posits that a memory, while it is being recalled, becomes pliable for some time in which new information may be added [25,43]. Working memory is considered to be taxed when the brain is required to simultaneously perform two tasks. The first task (ie, viewing a traumatic picture) receives less attention and

attenuates the vividness and emotional tone of the memory [44-46]. While participants are recalling traumatic memories in the course of 3MDR, more context or new information can be consolidated so that memories are not experienced as a current threat or as emotionally charged [25].

Therapeutic Context and Relationship

The therapeutic setting of 3MDR is an active side-by-side rather than passive position, which impacts both the physical context and therapeutic alliance. The patient is supported throughout the process by a therapist who is standing alongside, and, more importantly, is also viewing the same traumatic material while the patient is recalling their traumatic event. This emotional participation in treatment is increased by the psychotherapeutic approach where the therapist asks the patient to describe the image, and their memory, somatic responses, cognitions, and emotions. Lower emotional valence and processing of the traumatic memories is expected, with new learning and the full traumatic network activated along with intervening in the reconsolidation process [25].

Findings from a 3MDR proof-of-concept study [40] and two initial randomized controlled trials (RCTs) [26,47] involving military members and veterans with combat-related TR-PTSD have been promising. In the published RCTs, decreases in PTSD symptom severity from baseline to the trial end point were significantly greater for the 3MDR group as compared to those of the control group with medium to large effect sizes [26,47]. Notably, these effects were maintained for weeks after the conclusion of the 3MDR intervention and a low dropout rate was noted in both studies. Although the results of the primary outcome, a reduction in PTSD symptoms, were favorable, variable results in the secondary outcomes were obtained, and many questions about 3MDR remain, warranting further examination.

Overall Aims

This protocol describes a novel study to assist with the knowledge translation of the underpinnings of 3MDR as a therapeutic intervention. The primary study aim is to investigate whether the 3MDR intervention reduces symptoms of combat-related TR-PTSD and moral injury compared with treatment as usual among Canadian Armed Forces service members (CAF-SMs) and veterans. The study will be the first of its kind to examine the technology acceptance and usability of the Computer-Assisted Rehabilitation ENvironment (CAREN) VR system for 3MDR by participants, 3MDR clinicians and operators, as well as the impact of delivering 3MDR on clinicians and operators. Further, the longitudinal nature of the study will facilitate analysis of the longevity of possible 3MDR treatment effects for up to 6 months postintervention. This study will also address the possible effect of 3MDR on the constructs of moral injury and resilience. Further, as examination of relationships of psychological and biological factors to effective PTSD treatment has become critically important in attempts to understand the pathogenesis of TR-PTSD and to identify novel therapeutic targets [48-50], biomarker measurements and machine learning will be employed. Classifying neuropsychiatric disorders on the basis of objective and practical biomarkers aims to inform the diagnosis and selection of therapeutic approaches [51-54]. Machine-learning analysis will attempt to develop predictive models that can be used for individual diagnosis and prediction of the course of illness and effectiveness of treatment. Biomarker and machine learning utilization is a unique and novel addition to the study of 3MDR that has yet to be incorporated into other 3MDR studies internationally.

The main research questions to be addressed include: (1) Will participants' combat-related TR-PTSD and moral injury symptoms, and associated behavior and physiology, change after an intervention of 3DMR therapy compared with treatment as usual? (2) Will peripheral multiomic biomarkers related to traumatic stress (ie, blood and salivary proteomic and genomic profiles of neuroendocrine, immune-inflammatory responses, and microRNA) be modified by the 3MDR intervention and show utility for predicting patient outcomes posttreatment? (3) What are the 3MDR clinicians', operators', and participants' perceived technology acceptance and usability of 3MDR on the CAREN system? (4) What is the overall participant experience of the 3MDR intervention and comparability to PTSD therapies that the participants had previously engaged in? (5) Will 3MDR clinicians and operators experience perceived or secondary traumatic stress, or a change in their professional quality of life as a result of delivering 3MDR?

Specific Objectives

The first objective of the study is to examine the effect of 3MDR therapy on combat-related TR-PTSD and moral injury symptoms, behaviors, and physiological measures for CAF-SMs and veterans who have not benefited from other trauma therapies. The second objective is to examine the perceived technological acceptance and usability of 3MDR by CAF-SMs and veterans with combat-related TR-PTSD as well as 3MDR clinicians and operators. The third objective is to examine the effects of 3MDR on the operators and clinicians who provide this intervention to military members and veterans with combat-related TR-PTSD. In addition to conventional statistical analyses, the final objective of this study is to explore the application of machine learning in an attempt to identify individual data patterns that may predict diagnosis, severity, and potential treatment outcomes.

Hypotheses

Related to the objectives above, we have derived the following four hypotheses for this study.

Hypothesis 1: Participants' symptoms of combat-related TR-PTSD will decrease during the 3DMR therapy compared with treatment as usual.

Hypothesis 2: CAF-SMs, veterans, 3MDR clinicians, and operators will perceive 3MDR to be a novel intervention with adequate perceived technology acceptance and usability.

Hypothesis 3: 3MDR operators and clinicians will not experience adverse mental health effects, including secondary trauma and stress, that affect their daily functioning as a result of 3MDR delivery.

Hypothesis 4: Machine-learning analysis will generate two accurate predictive models that may portend diagnosis, severity,

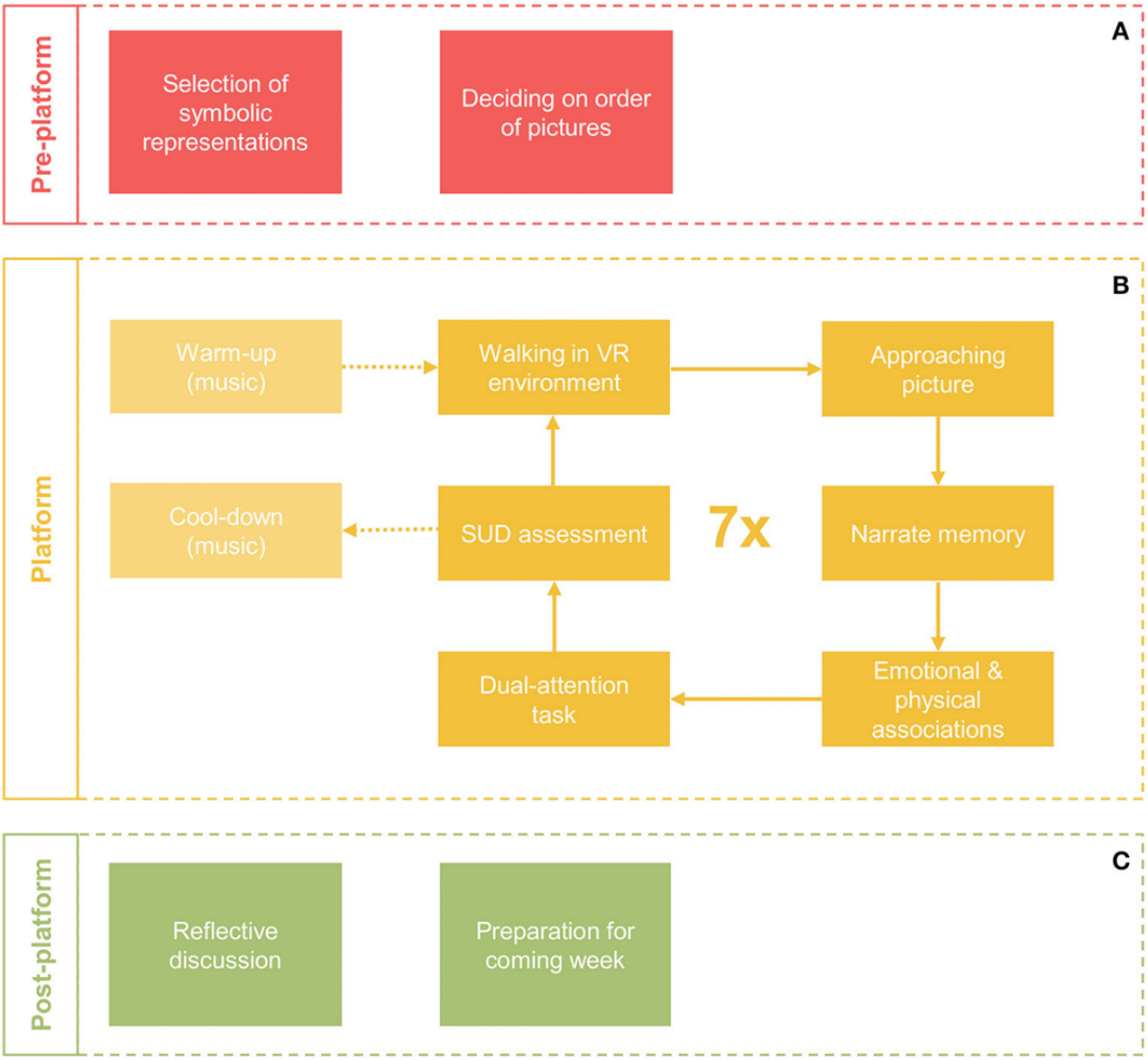
and potential treatment outcomes in CAF-SMs and veterans with combat-related TR-PTSD.

Methods

Intervention

The 3MDR intervention takes place in an immersive CAREN, a room-sized, three-dimensional VR system that facilitates full engagement. A treadmill located in a central platform in the CAREN is surrounded by 240° floor-to-ceiling screens with motion-capture technology. In each session, the participant continually walks on the treadmill while briefly listening to self-selected music reminiscent of their military deployment(s) prior to viewing a series of 7 self-selected images related to their traumatic events projected onto the screen. The participant is directed to engage in their selected image and walk toward it. Each 3MDR session follows a repetitive cycle of a preplatform phase (A), which is a mental and physical warm up; a platform phase (B) when the VR environment changes, providing a visual and auditory cue of movement into cycles of active therapy; and, following a mental cool-down period, a postplatform phase (C), during which the participant and clinician reflect on the session, and focus on important or newly arisen cognitive and emotional associations (Figure 2). A self-care plan is also reviewed prior to the participant leaving the CAREN. A typical 3MDR session lasts 90 minutes, including the participant walking on the platform for 45-60 minutes (equivalent to 3-4 km).

Figure 2. Schematic overview of a single multimodular motion-assisted memory desensitization and reconsolidation (3MDR) session. A session consists of a preplatform phase (A), platform phase (B), and postplatform phase (C). Used with permission [25]. VR: virtual reality; SUD: Subjective Units of Distress scale.



In the context of the full-service hospital setting, a risk mitigation strategy will be implemented. Clinicians providing 3MDR who have vast experience with trauma-affected populations, including CAF-SMs and veterans, will be authorized to provide mental health services. Clinicians and operators will continually assess the safety of participants during sessions, and will stop the intervention and implement codes or safety protocols if required. Participants will be debriefed after therapy to determine if they are safe to leave the site and prepared to follow their self-care and safety plan. Alternate participant transportation will be utilized for participants if required.

Study Design and Setting

This study will be a nonblinded mixed-methods waitlist controlled staggered entry RCT with a crossover design. An experimental group (n=20) will receive 6 sessions of 3MDR once a week followed by treatment as usual. The definition of treatment as usual for the purpose of this study will include other evidence-based psychotherapeutic interventions such as cognitive behavioral therapy, cognitive processing therapy, prolonged exposure, EMDR, and medications.

A waitlist control group (n=20) will initially receive treatment as usual for 9 weeks before being offered the opportunity to receive the 3MDR intervention. Those agreeable to the 3MDR intervention will then receive 6 sessions of 3MDR before resuming treatment as usual. Assignment to the initial experimental group versus the waitlist control group will be randomized. Participants will receive an introductory session prior to commencement of the 3DMR intervention and a follow-up session after completion of the intervention. All participants will provide informed written consent. For the projected timeline of this study, refer to Table 1.

This study has been approved by the University of Alberta Research Ethics Board (Pro00084466) and Canadian Armed Forces Surgeon General (E2019-02-250-003-0003).

Table 1. Time points of data collection for participants in the intervention group (1) and control group (2).

Construct to be measured	Measure	Week 1 (Baseline)	Week 3	Weeks 4-8	Week 9 (Post)	1 Month Post	3 Months Post	6 Months Post	12 Months Post
PTSD[a]	LEC5[b]	1, 2							
PTSD	CAPS5[c]	1, 2			1, 2		1, 2	1, 2	1
PTSD	PCL-5[d]		1	1	1, 2	1, 2	1, 2	1, 2	1
Demographic Information	Questionnaire	2	1						
Anxiety	GAD-7[e]		1	1	1, 2	1, 2	1, 2	1, 2	1
Depression	PHQ-9[f]		1	1	1, 2	1, 2	1, 2	1, 2	1
Avoidance	PABQ[g]		1	1	1, 2	1, 2	1, 2	1, 2	1
Dissociation	PDEQ[h]		1	1	1, 2	1, 2	1, 2	1, 2	1
Alcohol Use	AUDIT[i]		1	1	1, 2	1, 2	1, 2	1, 2	1
Moral Injury	MISS-M[j]		1	1	1, 2	1, 2	1, 2	1, 2	1
Emotional Regulation	DERS-18[k]		1	1	1, 2	1, 2	1, 2	1, 2	1
Resilience	CD RISC-25[l]		1	1	1, 2	1, 2	1, 2	1, 2	1
Social Functioning	OQ-45[m]		1	1	1, 2	1, 2	1, 2	1, 2	1
Quality of Life	EQ-5D[n]/EQ VAS[o]		1	1	1, 2	1, 2	1, 2	1, 2	1
Neurofunctional Performance	BrainFX Screen	1, 2			1, 2				
Technology Acceptance and Usability	UTAUT[p] Questionnaire		1		1				
Subjective Distress	SUDS[q]	1, 2	1	1	1, 2	1, 2	1, 2	1, 2	1
Client Satisfaction	CSQ-8[r]			1	1				
3MDR[s] Satisfaction	3MDR-Q[t]			1	1				
3MDR Satisfaction	Subjective Interview		1	1	1	1	1	1	1

[a]PTSD: posttraumatic stress disorder.

[b]LEC5: Life Events Checklist for DSM-5.

[c]CAPS5: Clinically Administered PTSD Scale for DSM-5.

[d]PCL-5: PTSD Checklist for DSM-5.

[e]GAD-7: Generalized Anxiety Disorder Scale, 7-item.

[f]PHQ-9: Patient Health Questionnaire, 9-item.

[g]PABQ: Posttraumatic Avoidance Behavior Questionnaire.

[h]PDEQ: Dissociative Experiences Questionnaire.

[i]AUDIT: Alcohol Use Disorder Identification Test.

[j]MISS-M: Moral Injury Symptom Scale for Military.

[k]DERS-18: Difficulties in Emotional Regulation Scale.

[l]CD RISC-25: Connor-Davidson Resilience Scale.

[m]OQ-45: Outcome Questionnaire 45.

[n]EQ-5D: EuroQol-5D-5L.

[o]EQVAS: EuroQol-Visual Analog Scale.

[p]UTAUT: Unified Theory of Acceptance and Usability of Technology.

[q]SUDS: Subjective Units of Distress Scale.

[r]CSQ-8: Client Satisfaction Questionnaire.

[s]3MDR: multimodular motion-assisted memory desensitization and reconsolidation.

[t]3MDR-Q: multimodular motion-assisted memory desensitization and reconsolidation questionnaire.

Recruitment

Regular and reserve CAF-SMs and veterans will be recruited through established relationships with the CAF, Operational Stress Injury Clinics, the Royal Canadian Legion Alberta/Northwest Territories Command, and local community service providers supporting CAF-SMs and veterans. Participants will also be recruited through word of mouth among potential participants. Eligible participants include English-speaking regular and reserve CAF-SMs and veterans aged 18-60 years who meet the Diagnostic and Statistical Manual-5 (DSM-5) criteria for a diagnosis of PTSD. This includes: (1) symptoms lasting more than 3 months; (2) a score of 30 or higher on the DSM-5 Clinician-Administered PTSD Scale, Fifth Edition (CAPS-5) interview; (3) trauma related to combat experiences; and (4) have had a nonresponse to at least two types of evidence-based PTSD treatments where at least one of these treatments was a psychotherapeutic intervention. It is permitted that the second treatment is a pharmacological intervention. Participants must also be stable on their psychotropic medication for a period of 4 weeks before entering the trial and agree to notify researchers of medication adjustments during the course of the trial. Participants with comorbidities will be included if they satisfy the other criteria and PTSD is considered the primary diagnosis. Participants must also have the cognitive capacity to provide informed consent. Participants will be excluded from the study if they demonstrate signs of acute suicidality, psychosis, or reduced cognitive processing that would exclude them from following directions or providing informed consent. Participants will also be excluded if it is determined that they are unable to walk at a normal pace for 30-45 minutes on a treadmill, or if their physical size or abilities are not compatible with the CAREN system. For CAF-SMs and veterans, screening by a research team member will consist of an interview to discuss their previous military employment/deployments, current and past medical history, history and experiences of previous PTSD interventions, and overall suitability for the study.

Recruitment of 3MDR clinicians and operators (N=12) will be conducted through word of mouth among the six international 3MDR research teams located in the Netherlands, the United States (California and Maryland), the United Kingdom (Wales), and Canada (Alberta and Ontario). Clinicians and operators who have received training for 3MDR and completed 6 weeks of interventions will be eligible for a pre/post evaluation. Voluntary written informed consent will be obtained from all participants.

The control group will undergo screening for eligibility and baseline assessment, followed by 9 weeks of treatment as usual while the intervention group receives the 3MDR intervention. They will then be provided an opportunity to cross over into the intervention group.

For the introductory session, intervention group participants will become accustomed to the CAREN system by practicing the process associated with 3MDR, including walking on the treadmill while looking at a neutral image as the clinician guides them through the 3MDR protocol. The participant will be asked to provide (1) images reminiscent of the traumatic deployment event that preceded a PTSD diagnosis, ranked according to the emotional distress that each elicits (ie, from least to greatest level of distress); and (2) digital music tracks of a song that reminds them of their deployment and other sounds or music that provide positive feelings. A secondary purpose of this introductory session is also to transfer trust from their service provider to the 3MDR researchers and clinicians. One week after the introductory session, the 3MDR therapy will be initiated and participants will undergo 6 90-minute sessions.

Randomization and Blinding

Participants will be randomized to the 3MDR or treatment as usual groups in a parallel design. A research assistant will utilize computerized random number allocation to assign participants to either the 3MDR or treatment as usual groups and maintain a confidential log of which participants are assigned to the respective groups. In addition, participants will be randomly assigned to the clinician that they will be engaging with for 3MDR. Participants, assessors, 3MDR clinicians, and other health care providers will not be blinded to the group allocation.

Sample Size

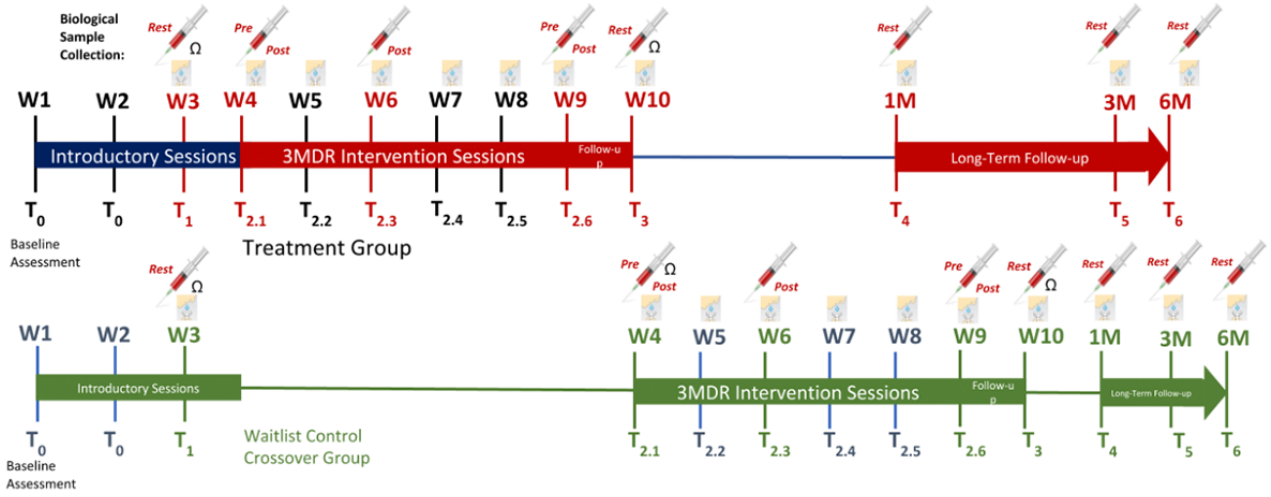
A sample size calculation was conducted using G*Power 3 [55], based on the primary hypothesis that 3MDR would result in significantly lower clinician-rated PTSD symptoms as compared to treatment as usual. To detect a significant interaction with at least a medium effect size, a minimal sample size of 17 participants was determined for each group. Because of an estimated 10% dropout and some attrition at measurements, the sample size was set at 20 participants in each group (Cohen f=1.0) using general linear modeling with one within-subjects factor (2 time points) and one between-subjects factor (2 interventions), and assuming a correlation of r=0.5 between the repeated measures, an α-level of .05, and a power ($1 - \beta$) of 0.8.

Study Timeline and Data Collection

Objective 1: Effectiveness of 3MDR

Data will be collected from intervention and control group participants at initial assessment (T0), prior to delivery of 3MDR (T1), pre/post 3MDR sessions (T2.1-2.6), and at 1 week (T3), 1 month (T4), 3 months (T5), and 6 months (T6) postintervention (Figure 3).

Figure 3. Multimodular motion-assisted memory desensitization and reconsolidation (3MDR) data collection time points for the intervention (treatment; blue/red) and waitlist control (green) groups. The syringe icon denotes blood collection and the square icon denotes saliva collection.



Clinical outcome measures will be collected at each time point using the questionnaires listed in Table 1. Qualitative interviews will occur at T3 through T6. Physiological, biometric, and qualitative audio/video data will be collected at T2.1-T2.6. Blood and saliva samples will be collected at baseline (T1), before (pre) and immediately after (post) 3MDR sessions at T2.1 and T2.6, post 3MDR sessions at T2.3 and T2.4, at 1-week follow up (T3), and at 1-, 3-, and 6-month follow ups (T4, T5, T6) for the analyses of peripheral blood and salivary biomarkers, including inflammatory mediators, neuroendocrine hormones, and microRNAs (see Multimedia Appendix 1).

Demographic information will include gender, age, ethnicity, marital status, military branch (ie, army, navy, or air force), and occupation. Psychological outcomes will be assessed through paper-based questionnaires administered during each contact with participants (Table 1). For further information on each outcome measure, refer to Multimedia Appendix 2.

Physiological Data

Walking and eye-scanning patterns, as well as physiological data (eg, heart rate, breathing rate, gait pattern, force plate analysis) will be collected during the training session through the CAREN system, Tobii Mobile eye-tracking glasses, Muse electroencephalogram (EEG), and Zephyr BioHarness 3.

Subjective Measures

Video recording of each session will capture qualitative data of the exchange between the clinician and participant during the 3MDR session. Audio recordings of the therapeutic debriefs will also occur, during which the clinician and patient will discuss the experience of any remarkable or meaningful aspects of the session. The clinician will also share observations. Upon completion of the 3MDR intervention, audio-recorded iterative semistructured interviews will be conducted with all participants at week 10, and 1, 3, and 6 months postintervention to explore their experience of 3MDR, its impact on their PTSD symptoms and overall function, and participation in the research study.

Objective 2: Measure of Technology Acceptance and Usability

To measure the perceived technology acceptance and usability of 3MDR and the CAREN, two 15-question surveys based on the Unified Theory of Acceptance and Usability of Technology (UTAUT) model [56] will be administered pre/post exposure to CAREN and 3MDR. The surveys utilized Likert scores ranging from 15 to 105 points, with high scores indicating increased perceived technology acceptance and usability.

Objective 3: 3MDR Operators and Clinicians

The impact of delivering 3MDR will be examined with clinicians and operators using questionnaires related to technological acceptance, perceived stress, and professional quality of life prior to 3MDR training and on completion of a full course of 3MDR with a study participant (Table 2).

Table 2. Time points of data collection for multimodular motion-assisted memory desensitization and reconsolidation (3MDR) clinicians and operators.

Construct to be measured	Measure	Week 1 (Baseline)	Week 9 (Post)
Technology Acceptance and Usability	UTAUT[a] Questionnaire	X	X
Perceived Stress	PSS[b]	X	X
	SUDS[c]	X	X
	Subjective Interview		X
Professional Quality of Life	PQoL[d]	X	X
Secondary Stress	STSS[e]	X	X

[a]UTAUT: Unified Theory of Acceptance and Usability of Technology.

[b]PSS: Perceived Stress Scale.

[c]SUDS: Subjective Units of Distress Scale.

[d]PQoL: Professional Quality of Life Scale.

[e]STSS: Secondary Traumatic Stress Scale.

Objective 4: Machine Learning

Although group-based statistical analysis is useful for drawing conclusions about general trends, it has limited utility for guiding individual diagnostic and treatment choices.

As a result, in addition to conventional statistical analysis, this study will explore the application of machine learning in an attempt to identify individual data patterns that may predict diagnosis, severity, and potential treatment outcomes. Physiological, biometric, biological, and qualitative data from T0 to T3 will be used to predict psychological outcome measures at week 9 plus follow-up sessions. A model that can compute sequential, multimodal data is needed to autonomously observe and learn the variability of the relevant feature sets and its association with outcome measures [57,58]. Deep neural networks will be applied for this task [57,58].

Data Analysis

Objective 1: Effectiveness of 3MDR

The quantitative analysis strategy for this study will include a variety of descriptive, parametric, nonparametric, univariate, and multivariate approaches, as well as machine-learning techniques.

Descriptive statistics will be used to summarize demographic data of participants, including mean values, frequencies, and proportions.

Baseline between-group differences in sociodemographic, clinical, and neuropsychological variables will be assessed. For psychological outcomes, including self-reported PTSD symptom severity, anxiety and depression symptoms, and avoidance behavior, analyses will be conducted using mixed linear models. All of the analyses above will be carried out on an intent-to-treat basis. A two-tailed $P<.05$ will be considered statistically significant.

For preliminary assessment of the relation between treatment outcomes and relevant predicting

variables, exploratory regression analyses will be performed and a predicting variable will be considered to have potential predicting value in cases of $P<.20$. Predictors will then be combined in a regression model to determine which variables most strongly predict 3MDR treatment success. Missing data points, potentially due to missed visits or outcome measure abnormalities, will be handled with the last observation carried forward analysis of covariance [59].

A partial least squares (PLS) regression [60] will be used to identify combinations of blood biomarker concentrations that may distinguish the three treatment groups. PLS is a multivariate data reduction technique that creates orthogonal latent variables describing the maximal covariance between a set of predictors (biomarkers) and response (patient outcome) variables [61]. Between-group comparisons will be evaluated post hoc by generating bootstrapped mean differences of the group saliences for all group pairs, followed by the derivation of bootstrap ratios and empirical *P* values. In addition, model prediction performance will be quantitated by evaluating the prediction accuracy and posterior probability from separate PLS-discriminant analyses (PLSDA) on each group pair. PLSDA will also be used to evaluate the differences in biomarker profiles between groups. For both tasks, PLS and PLSDA, the weighted contribution of individual biomarker loadings will be quantitated by bootstrapped resampling (5000 iterations), followed by the generation of bootstrapped ratios and empirical *P* values. For evaluation of correlations between blood biomarkers and patient outcomes, an out-of-sample, leave-two-out cross-correlation (R2) value will be calculated on the PLS model. Random forest–based feature selection will be used to select the most relevant biomarkers that could be used to differentiate treatment groups. The random forest machine-learning algorithm is robust, with low bias and a reduced chance for overfitting.

For qualitative data analysis, audio recordings will be professionally transcribed and thematically analyzed in NVivo 12 software [62]. Thematic analysis involves examining text in detail to identify recurring patterns (“themes”) through both inductive and deductive reasoning [63]. Open codes will be combined into preliminary patterns that focus on similarities and differences within and between audio recordings to reduce the number of codes and provide more focus for the secondary

level of coding [63]. Within the secondary level of coding, more abstract concepts will be assigned to broader categories of themes, and the relations between these concepts will be explored and verified through key quotes. Results will be distributed to a sample of the participants for member checking to assure the accuracy and trustworthiness of the research team's interpretation of themes.

Objective 2: Measure of Technology Acceptance and Usability

The UTAUT questionnaires measure performance expectancy, effort expectancy, social influence, and facilitating conditions, and behavioral intention with respect to 3MDR and the CAREN [56]. Differences in the medians between groups (ie, performance expectancy, effort expectancy, social influence, and facilitating conditions, and the behavioral intention responses of intervention and control groups) will be analyzed by nonparametric tests. Acceptance will be assessed using the PLS structural equation model to determine reliability measurements for each construct (Cronbach α).

Objective 3: 3MDR Operators and Clinicians

Owing to the small anticipated sample size, nonparametric statistical analysis with the Wilcoxon signed-rank test will be employed to assess the outcome measures addressing clinician and operator stress. Qualitative interviews will be thematically analyzed as described above.

Objective 4: Machine Learning

In a supervised regression learning approach, the input of the machine-learning pipeline is considered to be the various types of data collected for each individual across every session. If the performance task is predicting reductions in symptom severity, then the output will contain psychological outcome measures. Such data will be divided into training and testing examples, whereby the statistical model will learn on the training set and then make data-driven predictions on the testing set to gauge how accurate those predictions were. During this process, the learner will optimize its predictions by comparing the predicted output with the observed output and then updating the parameters based on the severity of the errors made. Ultimately, the learned model will make individualized predictions about how a patient may respond to the treatment of 3MDR at a given time point.

Triangulation of Data

A concurrent parallel approach following a data transformation model will be utilized in the data analysis process to converge the data for comparing and contrasting the quantitative statistical results with qualitative findings [64,65]. Integration will be scheduled at approximately every 5 participants during the data collection period to assist with the assurance of clinical appropriateness for the participants of the study and provide preliminary results. The final point of integration and analysis will take place at the conclusion of data collection.

Results

The trial is currently underway with 11 CAF-SMs/veterans having completed the intervention protocol. Additionally, 5 clinicians and 4 operators have completed pre/post outcome measures or the interview component of the trial. Data will be analyzed with the goal of publication at the completion of the study within 2 years.

Discussion

Projected Outcomes

Effective evidence-based interventions are needed for the treatment of TR-PTSD experienced by military members and veterans. This 3MDR study, one of the first international studies of its kind, will investigate whether 3MDR reduces symptoms of combat-related TR-PTSD. This 3MDR study protocol has roots in previous 3MDR studies from Canada, the Netherlands, and the United Kingdom [25,40,48,66]. Ideally, the combined international efforts of multiple research teams could lead to a meta-analysis of 3MDR in the military and veteran populations. If 3MDR is found to be effective, study findings will support making 3MDR more accessible nationally and internationally as an intervention for CAF-SMs and veterans. If indicated, 3MDR trials could be extended to other trauma-affected populations (eg, public safety personnel, marginalized groups, some indigenous communities, victims of violent crime, immigrants, refugees, victims of natural disasters) with PTSD and various mental health conditions.

Although some alterations and additions have been incorporated in this study that make it distinct from other international studies, an effort has also been made to standardize various components across all studies. This includes consistency with 3MDR clinician and operator training, a 3MDR manual as a standardized intervention, 3MDR fidelity checklists, use of similar outcome measures where appropriate, and standardization of mixed-methods data analysis wherever possible.

This Canadian 3MDR study is the first to include a number of novel components. Uniquely, this longitudinal study will address resilience, moral injury, inflammatory mediators, neuroendocrine hormones, and microRNA via measurements of blood-based biomarkers. Collection of physiological data using novel technology such as eye tracking and EEG is also unique and will provide valuable insight into the mechanisms by which 3MDR may be effective. Expanding the knowledge of the efficacy of psychological treatments such as 3MDR specific to combat-related TR-PTSD is unique, as this population is rarely included in clinical trials [67].

The 3MDR intervention itself will be delivered by members of a multidisciplinary team of registered trauma-informed clinicians (ie, psychologists, social workers, occupational therapists, CAF mental health chaplains, psychiatrists) who have variable experience working with military members and veterans. The study will also examine secondary stress that may be experienced by clinicians and operators as a result of delivering 3MDR. Further, the acceptance and usability of technology by participants, and 3MDR clinicians and operators regarding the use of the CAREN for delivery of 3MDR will be studied.

It is predicted that a novel and synergistic effect between components of the 3MDR intervention and treatment outcomes

for combat-related TR-PTSD will be apparent. This project will expand knowledge of the underlying mechanisms of TR-PTSD. Additionally, through machine learning, successful model development may predict changes in PTSD symptom severity in this context [68]. It is also hoped that prognostic models will be developed based on the study data from this protocol [61]. These models will enable clinical decisions—based on cognitive, biological, and psychological markers and symptom severity—to signal treatment responsiveness at the individual therapy client level [67].

The importance of determining effective components of 3MDR has value not only for this modality but also more broadly regarding PTSD treatment effectiveness. As veterans seem to gain limited progress in traditional trauma modalities, it may be that combat-related trauma necessitates the engagement of multiple biological, cognitive, and affective systems simultaneously to produce the effects found in civilian populations. If the combination of multiple efficacious components (eg, bilateral movement, dual-task attention, emotional engagement, visual and auditory stimulation) is effective at reducing PTSD symptoms, significant evaluation of the means by which currently accepted PTSD treatment modalities are delivered, most often including office environments and stationary physical positions, is warranted.

Moreover, if moral injury is also identified as a pertinent comorbid component of combat-related TR-PTSD, key insights may be gained as to why military members and veterans did not have an adequate response to previous treatments. Although research on moral injury is still burgeoning, this study has significant potential to further elucidate the overlap and difference between PTSD and moral injury, particularly in relation to Criterion D of the PTSD diagnosis [1]. Equally, as evidence-based interventions are currently very limited for moral injury, using 3MDR to treat moral injury may have a unique advantage as comorbid PTSD pathologies could be concurrently addressed, thus not requiring military members and veterans to undergo multiple psychotherapeutic interventions. The question of resilience is also relevant to the broader conversation, particularly if once the acute PTSD and moral injury symptoms are addressed, military members and veterans experience a sense of resilience in relation to any remaining pathology, social engagement, and improved quality of life.

Limitations

Despite the many strengths of this study, some limitations must be noted. First, the limited intervention timeline (ie, a total of 6 sessions) may not be sufficient for changes to occur, particularly within participants who have had combat-related TR-PTSD for a significant period of time; however, similar studies for the treatment of combat-related TR-PTSD using 3MDR have shown positive and statistically significant changes in PTSD symptoms [25,47]. Second, it is unlikely that the results will apply to the general population for PTSD; larger clinical trials will be necessary for generalization as the intervention to date has been exclusively piloted with military members and veterans with combat-related TR-PTSD. Third, it is possible that participant engagement in this intervention may depend on their level of comfort with a VR environment, their readiness to address problematic components of their trauma, or challenges associated with forming a meaningful therapeutic alliance with the 3MDR clinician. Although this is not expected to be the case, and the research team has incorporated proactive steps into the protocol and procedures (ie, introductory session to familiarize the participant with the CAREN system and to develop rapport with their clinician), assessing individual readiness will be more challenging. Fourth, it is not possible to stratify randomization by gender given the limited number of women in combat roles; this is an important limitation to address in future work. Moreover, it is not possible to standardize the treatment as usual that the participants receive, which adds some variability that cannot be controlled for. Finally, as a characteristic of many rehabilitation intervention trials, participants blinding themselves to the intervention, or having a true placebo group, is not possible with current approaches. As assessors and health care professionals will work closely with the participants in the same hospital setting, blinding of these personnel is also unlikely.

Conclusion

This RCT will provide a useful evaluation of 3MDR as a potentially effective treatment for combat-related TR-PTSD among CAF-SMs and veterans. With military members and veterans experiencing reduced effectiveness with traditional "gold-standard" PTSD interventions, there is an immediate need for creation of an effective manualized combat-related TR-PTSD intervention. This 3MDR study protocol honors previously published international studies while incorporating concepts of resilience, moral injury, technology acceptance and usability, multiomic biomarker data, machine learning, and the 3MDR clinician and operator experience. The addition of novel technologies such as eye tracking and EEG, as well as data analysis techniques such as PLS-SEM and machine learning will push the knowledge of 3MDR effectiveness as well as elucidating by what mechanisms this may be caused. It is hoped that the results of this 3MDR study will contribute to future evidence-based research and clinical accessibility to the intervention as indicated for multiple trauma-affected populations.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Details of the biomarker collection protocol.
[DOCX File , 24 KB - resprot_v9i10e20620_app1.docx]

Multimedia Appendix 2
Description of the outcome measures planned for this study.
[DOCX File , 33 KB - resprot_v9i10e20620_app2.docx]

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: 5th Edition. Arlington, VA: American Psychiatric Association Publications; 2013.
2. McFarlane AC. The impact of war on mental health: lest we forget. World Psychiatry 2015 Oct 25;14(3):351-353. [doi: 10.1002/wps.20253] [Medline: 26407792]
3. Congretional Research Service. A Guide to U.S. Military Casualty Statistics: Operation Freedoms Sentinel, Operation Inherent Resolve, Operation New Dawn, Operation Iraqi Freedom,Operation Enduring Freedom. 2015 Aug 07. URL: https://www.everycrsreport.com/reports/RS22452.html [accessed 2020-10-15]
4. Levy BS, Sidel VW. Health effects of combat: a life-course perspective. Annu Rev Public Health 2009 Apr;30(1):123-136. [doi: 10.1146/annurev.publhealth.031308.100147] [Medline: 18925871]
5. Vermetten E, Greenberg N, Boeschoten MA, Delahaije R, Jetly R, Castro CA, et al. Deployment-related mental health support: comparative analysis of NATO and allied ISAF partners. Eur J Psychotraumatol 2014 Aug 14;5(1):23732 [FREE Full text] [doi: 10.3402/ejpt.v5.23732] [Medline: 25206953]
6. Department of National Defense. Strong, Secure, Engaged: Canada's Defence Policy. Ottawa, ON: Government of Canada; 2017. URL: https://www.canada.ca/en/department-national-defence/corporate/policies-standards/canada-defence-policy.html [accessed 2020-10-15]
7. Thompson J, MacLean M, Roach M, Banman M, Mabior J, Pedlar D. A Well-Being Construct for Veterans Policy, Programming and Research. Research Directorate Technical Report. Charlottetown, PE: Research Directorate, Veterans Affairs Canada; 2007. URL: https://www.veterans.gc.ca/eng/about-vac/research/research-directorate/publications/reports/well-being-construct [accessed 2020-10-15]
8. Department of National Defense, Veteran Affairs Canada. Canadian Armed Forces and Veteran Affairs Canada Joint Suicide Prevention Strategy. Ottawa, ON: Government of Canada; 2017. URL: https://www.canada.ca/en/department-national-defence/corporate/reports-publications/caf-vac-joint-suicide-prevention-strategy.html [accessed 2020-10-15]
9. Milliken CS, Auchterlonie JL, Hoge CW. Longitudinal assessment of mental health problems among active and reserve component soldiers returning from the Iraq war. JAMA 2007 Nov 14;298(18):2141-2148. [doi: 10.1001/jama.298.18.2141] [Medline: 18000197]
10. Wagner A, Jakupcak M. Chapter 3: Combat-related stress reactions among U.S. Veterans of Wartime Service. In: Laurence JH, Matthew MD, editors. The Oxford Handbook of Military Psychology. Oxford, UK: Oxford University Press; 2012.
11. Zamorski MA, Boulos D. The impact of the military mission in Afghanistan on mental health in the Canadian Armed Forces: a summary of research findings. Eur J Psychotraumatol 2014 Aug 14;5(1):23822 [FREE Full text] [doi: 10.3402/ejpt.v5.23822] [Medline: 25206951]
12. Jones N, Seddon R, Fear NT, McAllister P, Wessely S, Greenberg N. Leadership, cohesion, morale, and the mental health of UK Armed Forces in Afghanistan. Psychiatry 2012 Mar;75(1):49-59. [doi: 10.1521/psyc.2012.75.1.49] [Medline: 22397541]
13. Eekhout I, Reijnen A, Vermetten E, Geuze E. Post-traumatic stress symptoms 5 years after military deployment to Afghanistan: an observational cohort study. Lancet Psychiatry 2016 Jan;3(1):58-64. [doi: 10.1016/S2215-0366(15)00368-5] [Medline: 26681368]
14. Fulton JJ, Calhoun PS, Wagner HR, Schry AR, Hair LP, Feeling N, et al. The prevalence of posttraumatic stress disorder in Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) Veterans: a meta-analysis. J Anxiety Disord 2015 Apr;31:98-107. [doi: 10.1016/j.janxdis.2015.02.003] [Medline: 25768399]
15. Van TL, Sweet J, Poirier A, McKinnon K, Sudom K, Dursun S, et al. Well-Being of Canadian Regular Force Veterans: Findings from LASS 2016 Survey. Research Directorate Technical Report. Charlottetown, PE: Veteran Affairs Canada;

2016 Jun 23. URL: https://cimvhr.ca/vac-reports/data/reports/VanTil%202017_Well-Being%20of%20CAF%20Veterans%20LASS%202016.pdf [accessed 2020-10-15]
16. Hoencamp R, Vermetten E, Tan ECTH, Putter H, Leenen LPH, Hamming JF. Systematic review of the prevalence and characteristics of battle casualties from NATO coalition forces in Iraq and Afghanistan. Injury 2014 Jul;45(7):1028-1034. [doi: 10.1016/j.injury.2014.02.012] [Medline: 24878294]
17. Vermetten E, Jetly R. A Critical Outlook on Combat-Related PTSD: Review and Case Reports of Guilt and Shame as Drivers for Moral Injury. Military Behav Health 2018 May 23;6(2):156-164. [doi: 10.1080/21635781.2018.1459973]
18. Jinkerson J. Defining and assessing moral injury: A syndrome perspective. Traumatology 2016 Jun;22(2):122-130. [doi: 10.1037/trm0000069]
19. Koenig HG, Youssef NA, Pearce M. Assessment of Moral Injury in Veterans and Active Duty Military Personnel With PTSD: A Review. Front Psychiatry 2019 Jun 28;10:443. [doi: 10.3389/fpsyt.2019.00443] [Medline: 31316405]
20. Koenig HG, Youssef NA, Ames D, Teng EJ, Hill TD. Examining the Overlap Between Moral Injury and PTSD in US Veterans and Active Duty Military. J Nerv Ment Dis 2020 Jan;208(1):7-12. [doi: 10.1097/NMD.0000000000001077] [Medline: 31738222]
21. Hamblen JL, Norman SB, Sonis JH, Phelps AJ, Bisson JI, Nunes VD, et al. A guide to guidelines for the treatment of posttraumatic stress disorder in adults: An update. Psychotherapy (Chic) 2019 Sep;56(3):359-373. [doi: 10.1037/pst0000231] [Medline: 31282712]
22. Forbes D, Pedlar D, Adler AB, Bennett C, Bryant R, Busuttil W, et al. Treatment of military-related post-traumatic stress disorder: challenges, innovations, and the way forward. Int Rev Psychiatry 2019 Feb 02;31(1):95-110. [doi: 10.1080/09540261.2019.1595545] [Medline: 31043106]
23. Rehman Y, Sadeghirad B, Guyatt GH, McKinnon MC, McCabe RE, Lanius RA, et al. Management of post-traumatic stress disorder: A protocol for a multiple treatment comparison meta-analysis of randomized controlled trials. Medicine (Baltimore) 2019 Sep;98(39):e17064. [doi: 10.1097/MD.0000000000017064] [Medline: 31574805]
24. Hamner MB, Robert S, Frueh BC. Treatment-resistant posttraumatic stress disorder: strategies for intervention. CNS Spectr 2004 Oct 07;9(10):740-752. [doi: 10.1017/s1092852900022380] [Medline: 15448585]
25. van Gelderen MJ, Nijdam MJ, Vermetten E. An Innovative Framework for Delivering Psychotherapy to Patients With Treatment-Resistant Posttraumatic Stress Disorder: Rationale for Interactive Motion-Assisted Therapy. Front Psychiatry 2018 May 4;9:176. [doi: 10.3389/fpsyt.2018.00176] [Medline: 29780334]
26. van Gelderen MJ, Nijdam M, Haagen J, Vermetten E. Interactive Motion-Assisted Exposure Therapy for Veterans with Treatment-Resistant Posttraumatic Stress Disorder: A Randomized Controlled Trial. Psychother Psychosom 2020 Mar 23;89(4):215-227 [FREE Full text] [doi: 10.1159/000505977] [Medline: 32203971]
27. Roemer L, Litz B, Orsillo S, Wagner A. A preliminary investigation of the role of strategic withholding of emotions in PTSD. J Traum Stress 2001 Jan;14(1):149-156. [doi: 10.1023/a:1007895817502]
28. Schnyder U, Cloitre M. Evidence Based Treatments for Trauma-Related Psychological Disorders: A Practical Guide for Cliniciians. Switzerland: Springer International Publishing; 2015.
29. Bradley MM, Codispoti M, Cuthbert BN, Lang PJ. Emotion and motivation I: Defensive and appetitive reactions in picture processing. Emotion 2001;1(3):276-298. [doi: 10.1037/1528-3542.1.3.276]
30. Belfi AM, Karlan B, Tranel D. Music evokes vivid autobiographical memories. Memory 2016 Aug 10;24(7):979-989. [doi: 10.1080/09658211.2015.1061012] [Medline: 26259098]
31. Janata P, Tomic ST, Rakowski SK. Characterization of music-evoked autobiographical memories. Memory 2007 Nov;15(8):845-860. [doi: 10.1080/09658210701734593] [Medline: 17965981]
32. El Haj M, Postal V, Allain P. Music Enhances Autobiographical Memory in Mild Alzheimer's Disease. Educ Gerontol 2012 Jan;38(1):30-41. [doi: 10.1080/03601277.2010.515897]
33. El Haj M, Antoine P, Nandrino JL, Gély-Nargeot M, Raffard S. Self-defining memories during exposure to music in Alzheimer's disease. Int Psychogeriatr 2015 May 28;27(10):1719-1730. [doi: 10.1017/s1041610215000812]
34. Bensimon M, Amir D, Wolf Y. Drumming through trauma: Music therapy with post-traumatic soldiers. Art Psychother 2008 Jan;35(1):34-48. [doi: 10.1016/j.aip.2007.09.002]
35. Carr C, d'Ardenne P, Sloboda A, Scott C, Wang D, Priebe S. Group music therapy for patients with persistent post-traumatic stress disorder--an exploratory randomized controlled trial with mixed methods evaluation. Psychol Psychother 2012 Jun;85(2):179-202. [doi: 10.1111/j.2044-8341.2011.02026.x] [Medline: 22903909]
36. Wolitzky KB, Telch MJ. Augmenting in vivo exposure with fear antagonistic actions: a preliminary test. Behav Ther 2009 Mar;40(1):57-71. [doi: 10.1016/j.beth.2007.12.006] [Medline: 19187817]
37. Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, et al. Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci U S A 2011 Feb 15;108(7):3017-3022. [doi: 10.1073/pnas.1015950108] [Medline: 21282661]
38. Chang Y, Labban J, Gapin J, Etnier J. The effects of acute exercise on cognitive performance: a meta-analysis. Brain Res 2012 May 09;1453:87-101. [doi: 10.1016/j.brainres.2012.02.068] [Medline: 22480735]
39. Oppezzo M, Schwartz DL. Give your ideas some legs: the positive effect of walking on creative thinking. J Exp Psychol Learn Mem Cogn 2014 Jul;40(4):1142-1152. [doi: 10.1037/a0036577] [Medline: 24749966]

40. Vermetten E, Meijer L, van der Wurff P, Mert A. The effect of military motion-assisted memory desensitization and reprocessing treatment on the symptoms of combat-related post traumatic stress disorder: first preliminary results. Stud Health Technol Inform 2013;191:125-127. [Medline: 23792857]
41. Lewis C, Roberts NP, Andrew M, Starling E, Bisson JI. Psychological therapies for post-traumatic stress disorder in adults: systematic review and meta-analysis. Eur J Psychotraumatol 2020 Mar 10;11(1):1729633 [FREE Full text] [doi: 10.1080/20008198.2020.1729633] [Medline: 32284821]
42. Steenkamp MM, Litz BT, Hoge CW, Marmar CR. Psychotherapy for Military-Related PTSD: A Review of Randomized Clinical Trials. JAMA 2015 Aug 04;314(5):489-500. [doi: 10.1001/jama.2015.8370] [Medline: 26241600]
43. Nader K. Reconsolidation and the Dynamic Nature of Memory. Cold Spring Harb Perspect Biol 2015 Sep 09;7(10):a021782 [FREE Full text] [doi: 10.1101/cshperspect.a021782] [Medline: 26354895]
44. Gunter RW, Bodner GE. How eye movements affect unpleasant memories: support for a working-memory account. Behav Res Ther 2008 Aug;46(8):913-931. [doi: 10.1016/j.brat.2008.04.006] [Medline: 18565493]
45. van den Hout MA, Engelhard IM, Beetsma D, Slofstra C, Hornsveld H, Houtveen J, et al. EMDR and mindfulness. Eye movements and attentional breathing tax working memory and reduce vividness and emotionality of aversive ideation. J Behav Ther Exp Psychiatry 2011 Dec;42(4):423-431. [doi: 10.1016/j.jbtep.2011.03.004] [Medline: 21570931]
46. Engelhard IM, van den Hout MA, Dek EC, Giele CL, van der Wielen J, Reijnen MJ, et al. Reducing vividness and emotional intensity of recurrent "flashforwards" by taxing working memory: an analogue study. J Anxiety Disord 2011 May;25(4):599-603. [doi: 10.1016/j.janxdis.2011.01.009] [Medline: 21376527]
47. Bisson J, van Deursen R, Hannigan B, Kitchiner N, Barawi K, Jones K, et al. Randomized controlled trial of multi-modular motion-assisted memory desensitization and reconsolidation (3MDR) for male military veterans with treatment-resistant post-traumatic stress disorder. Acta Psychiatr Scand 2020 Aug;142(2):141-151. [doi: 10.1111/acps.13200] [Medline: 32495381]
48. García-Gutiérrez MS, Navarrete F, Sala F, Gasparyan A, Austrich-Olivares A, Manzanares J. Biomarkers in Psychiatry: Concept, Definition, Types and Relevance to the Clinical Reality. Front Psychiatry 2020 May 15;11:432. [doi: 10.3389/fpsyt.2020.00432] [Medline: 32499729]
49. Rhind S, Wynn G, Vermetten E, Jetly R. Biomarkers for military mental health: Insights, challenges, and future prospects. J Military Vet Fam Health 2020 Mar 01;6(S1):51-67. [doi: 10.3138/jmvfh.2019-0036]
50. Dean KR, Hammamieh R, Mellon SH, Abu-Amara D, Flory JD, Guffanti G, PTSD Systems Biology Consortium, et al. Multi-omic biomarker identification and validation for diagnosing warzone-related post-traumatic stress disorder. Mol Psychiatry 2019 Sep 10. [doi: 10.1038/s41380-019-0496-z] [Medline: 31501510]
51. Wshah S, Skalka C, Price M. Predicting Posttraumatic Stress Disorder Risk: A Machine Learning Approach. JMIR Ment Health 2019 Jul 22;6(7):e13946 [FREE Full text] [doi: 10.2196/13946] [Medline: 31333201]
52. Shim M, Jin M, Im C, Lee S. Machine-learning-based classification between post-traumatic stress disorder and major depressive disorder using P300 features. Neuroimage Clin 2019;24:102001 [FREE Full text] [doi: 10.1016/j.nicl.2019.102001] [Medline: 31627171]
53. Schultebraucks K, Galatzer-Levy IR. Machine Learning for Prediction of Posttraumatic Stress and Resilience Following Trauma: An Overview of Basic Concepts and Recent Advances. J Trauma Stress 2019 Apr;32(2):215-225. [doi: 10.1002/jts.22384] [Medline: 30892723]
54. Ramos-Lima L, Waikamp V, Antonelli-Salgado T, Passos I, Freitas LHM. The use of machine learning techniques in trauma-related disorders: a systematic review. J Psychiatr Res 2020 Feb;121:159-172. [doi: 10.1016/j.jpsychires.2019.12.001] [Medline: 31830722]
55. Erdfelder E, Faul F, Buchner A. GPOWER: A general power analysis program. Behav Res Method Instr Comput 1996 Mar;28(1):1-11 [FREE Full text] [doi: 10.3758/bf03203630]
56. Venkatesh V, Morris M, Davis G, Davis F. User Acceptance of Information Technology: Toward a Unified View. MIS Quart 2003;27(3):425. [doi: 10.2307/30036540]
57. Galatzer-Levy IR, Karstoft K, Statnikov A, Shalev AY. Quantitative forecasting of PTSD from early trauma responses: a Machine Learning application. J Psychiatr Res 2014 Dec;59:68-76 [FREE Full text] [doi: 10.1016/j.jpsychires.2014.08.017] [Medline: 25260752]
58. Dwyer DB, Falkai P, Koutsouleris N. Machine Learning Approaches for Clinical Psychology and Psychiatry. Annu Rev Clin Psychol 2018 May 07;14(1):91-118. [doi: 10.1146/annurev-clinpsy-032816-045037] [Medline: 29401044]
59. DeSouza CM, Legedza ATR, Sankoh AJ. An overview of practical approaches for handling missing data in clinical trials. J Biopharm Stat 2009 Nov 21;19(6):1055-1073. [doi: 10.1080/10543400903242795] [Medline: 20183464]
60. Hair J, Hult G, Ringle C, Sarstedt M. A primer on partial least squares structural equation modeling (PLS-SEM) Second edition. Los Angeles: Sage; 2017.
61. Di Battista AP, Churchill N, Rhind S, Richards D, Hutchison MG. The relationship between symptom burden and systemic inflammation differs between male and female athletes following concussion. BMC Immunol 2020 Mar 12;21(1):11 [FREE Full text] [doi: 10.1186/s12865-020-0339-3] [Medline: 32164571]
62. NVivo Qualitative Data Analysis Software. Timberlake. Doncaster, Australia: QSR International URL: https://www.qsrinternational.com/nvivo-qualitative-data-analysis-software/home [accessed 2020-10-15]

63. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006 Jan;3(2):77-101. [doi: 10.1191/1478088706qp063oa]
64. Creswell J, Plano CV. Designing and Conducting Mixed-Methods Research. Thousand Oaks, CA: SAGE Publications; 2011:58-88.
65. Schoonenboom J, Johnson RB. How to Construct a Mixed Methods Research Design. Kolner Z Soz Sozpsychol 2017;69(Suppl 2):107-131 [FREE Full text] [doi: 10.1007/s11577-017-0454-1] [Medline: 28989188]
66. Jetly R, Meakin C, Sinitski E, Blackburn L, Menard J, Vincent M, et al. Multi-Modal Virtual-Reality Based Treatment for Members with Combat Related Post-Traumatic Stress Disorder: Canadian Armed Forces Pilot Study. 2017 Presented at: International Conference on Virtual Rehabilitation; June 2017; Montreal, QC URL: https://ieeexplore.ieee.org/xpl/conhome/8000694/proceeding [doi: 10.1109/ICVR.2017.8007474]
67. Sippel LM, Holtzheimer PE, Friedman MJ, Schnurr PP. Defining Treatment-Resistant Posttraumatic Stress Disorder: A Framework for Future Research. Biol Psychiatry 2018 Sep 01;84(5):e37-e41. [doi: 10.1016/j.biopsych.2018.03.011] [Medline: 29752073]
68. Dwyer DB, Falkai P, Koutsouleris N. Machine Learning Approaches for Clinical Psychology and Psychiatry. Annu Rev Clin Psychol 2018 May 07;14(1):91-118. [doi: 10.1146/annurev-clinpsy-032816-045037] [Medline: 29401044]

Abbreviations

3MDR: Modular Motion-assisted Memory Desensitization and Reconsolidation
CAF: Canadian Armed Forces
CAF-SMs: Canadian Armed Forces service members
CAREN: Computer Assisted Rehabilitation ENvironment
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EEG: electroencephalography
EMDR: eye movement desensitization and reconsolidation
PLS: partial least squares
PLSDA: partial least squares-discriminant analysis
PTSD: posttraumatic stress disorder
RCT: randomized controlled trial
TR-PTSD: treatment-resistant posttraumatic stress disorder
UTAUT: unified theory of acceptance and usability of technology
VR: virtual reality

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Protocol

AQUEDUCT Intervention for Crisis Team Quality and Effectiveness in Dementia: Protocol for a Feasibility Study

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Abstract

Background: Specialist community teams often support people with dementia who experience crisis. These teams may vary in composition and models of practice, which presents challenges when evaluating their effectiveness. A best practice model for dementia crisis services could be used by teams to improve the quality and effectiveness of the care they deliver.

Objective: The aim of this study is to examine the feasibility of conducting a large-scale randomized controlled trial comparing the AQUEDUCT (Achieving Quality and Effectiveness in Dementia Using Crisis Teams) Resource Kit intervention to treatment as usual.

Methods: This is a multisite feasibility study in preparation for a future randomized controlled trial. Up to 54 people with dementia (and their carers) and 40 practitioners will be recruited from 4 geographically widespread teams managing crisis in dementia. Quantitative outcomes will be recorded at baseline and at discharge. This study will also involve a nested health economic substudy and qualitative research to examine participant experiences of the intervention and acceptability of research procedures.

Results: Ethical approval for this study was granted in July 2019. Participant recruitment began in September 2019, and as of September 2020, all data collection has been completed. Results of this study will establish the acceptability of the intervention, recruitment rates, and will assess the feasibility and appropriateness of the outcome measures in preparation for a large-scale randomized controlled trial.

Conclusions: There is a need to evaluate the effectiveness of crisis intervention teams for older people with dementia. This is the first study to test the feasibility of an evidence-based best practice model for teams managing crisis in dementia. The results of this study will assist in the planning and delivery of a large-scale randomized controlled trial.

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KEYWORDS

dementia; crisis; mental health; community services; feasibility study

Introduction

Background

Dementia is a progressive condition that affects over 850,000 people in the United Kingdom [1]. The cognitive, behavioral, and psychological symptoms of dementia include memory loss, changes in reasoning and planning skills, and communication difficulties that may impair ability to perform daily activities [2]. Improving dementia care remains a key priority from the Prime Minister's Challenge on Dementia [3]. Community support, with the aim of reducing hospital admissions, is one way to respond to this policy initiative; however, fluctuations in the health and social circumstances of the person with dementia may cause a breakdown in care which could lead to crisis.

A dementia mental health crisis can be defined as "a need for urgent mental health assessment and intervention for people with dementia who live in the community" (from Hoe J, Ledgerd R, Devine M, Toot S, Challis D, Orrell M. Home Treatment Manual 2012 Version 4. Support at Home: Interventions to Enhance Life in Dementia (SHIELD); unpublished). Crisis situations in dementia are common and often result in a hospital admission. Risk factors for breakdown of care at home include increased carer burden and inadequate social support [4]. Increased contact with general practitioners and case manager consultations are recommended to help manage instances of crisis [5]. Support for people with dementia and their carers at a time of crisis is often managed through secondary mental health services. These services involve teams that vary in name and composition and may include crisis resolution and home treatment teams and dementia rapid response teams, though in some instances, there are no suitable services. Some teams may be commissioned to specifically provide support for older people, while others may be nonage-defined. From here on in, these services will be referred to as *teams managing crisis in dementia*. A recent scoping survey [6] highlighted the disparity in services across England; teams managing crisis in dementia vary in terms of name, set-up, delivery, policy, and procedures. Further high-quality evidence is required to support the effectiveness of teams managing crisis in dementia in reducing hospital admissions and preventing breakdown of care at home, and to improve knowledge on how teams can be supported to deliver care for people with dementia in crisis.

Preliminary Work

The Achieving Quality and Effectiveness in Dementia Using Crisis Teams (AQUEDUCT) program comprises 3 work packages following the Medical Research Council's Framework for the Development and Evaluation of Randomized Controlled Trials for Complex Interventions [7]. The first work package (WP1) consisted of 2 strands: a systematic literature review to examine the effectiveness of crisis interventions for older people and a scoping review to map and understand operational procedures in current services [6], and subsequently, qualitative work (including interviews; focus groups; consultations; and a consensus conference involving people with dementia, carers, practitioners, and stakeholders) was used to identify and establish agreement about key elements of best practice in teams managing crisis in dementia.

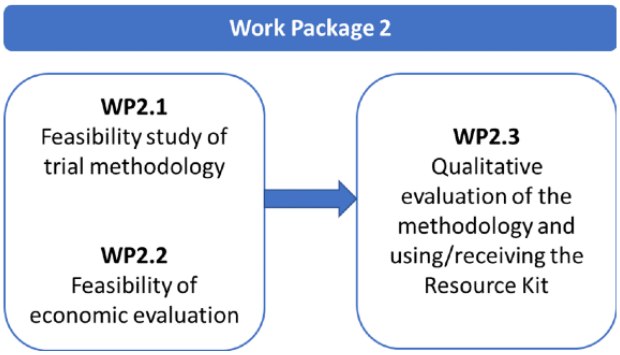
The strands from WP1 contributed to the development of a model of best practice comprising 50 best practice statements, a best practice tool, and a resource kit [8], after which, 12 teams managing crisis in dementia and 5 noncrisis older adult mental health teams field-tested the AQUEDUCT best practice tool and resource kit. The feedback from these teams was used to amend the resource kit for future use in the second work package (WP2)—the feasibility study. Findings from this feasibility study will be used to inform the future large-scale randomized controlled trial in the third work package (WP3). This paper describes the protocol for WP2 only.

Aims and Objectives

The aims of WP2 of the AQUEDUCT research program were to (1) conduct a feasibility study of use of the resource kit in relation to practice, care outcomes, and costs; (2) gather feedback from participants about the acceptability and feasibility of the research procedures; and (3) refine the resource kit for use in the randomized controlled trial in order to (1) determine the feasibility of recruitment to a large-scale randomized controlled trial; (2) refine the eligibility criteria for teams managing crisis in dementia for a future definitive randomized controlled trial; (3) determine the relevance and acceptability to National Health Service (NHS) practitioners; (4) determine the acceptability to people with dementia, carers, and NHS practitioners of the trial procedures; (5) assess the ability of the NHS sites to implement the resource kit; (6) assess the training and support needs for NHS practitioners using the resource kit; (7) evaluate resource kit uptake and fidelity when used through NHS services; (8) assess follow-up and outcome completion rates; (9) determine the relevance and acceptability of a range of outcome measures to inform selection of the primary outcome for the main trial; and (10) evaluate the utility and acceptability of resource use questionnaires for use in an economic evaluation in a future randomized controlled trial.

The design of WP2 is illustrated in Figure 1. The main component—WP2.1—is the overall feasibility study; WP2.2 will examine the feasibility of an economic evaluation of the resource kit, and WP2.3 is a qualitative evaluation of the experience of using the resource kit and its acceptability.

Figure 1. Design and components of WP2.



Methods

Site Selection

This is a multisite pre–post feasibility study with all sites allocated to the AQUEDUCT resource kit intervention. Recruitment will take place at 4 sites which will be purposively selected from across England to ensure a diverse range of teams managing crisis in dementia models and service user demographics. The number of teams approached and reasons for teams declining to participate will be documented. This will allow structural or process issues which influence participation to be identified and considered for how they may impact site selection in the main trial.

Criteria

Inclusion criteria will be as follows: (1) teams managing mental health crises in dementia in community settings, (2) people with dementia receiving input from the teams managing crisis in dementia during the team's use of the resource kit, and (3) carers providing support for a person with dementia in receipt of input (using the resource kit) from the teams managing crisis in dementia.

Exclusion criteria will be as follows: (1) team is not defined by NHS Trust as having a role in dementia mental health crisis management, (2) team does not meet the following definition for mental health crisis management—providing urgent mental health assessment and intervention for people with dementia in the community, and (3) team is not able to demonstrate capacity and capability to complete required research activities.

Participant Recruitment

This study will recruit 3 different groups of participants: teams managing crisis in dementia practitioners, people living with dementia, and carers. Recruitment will take place in different ways. All participants will be asked to consent separately, by signing relevant consent forms for each stage of the research with which they wish to engage. This section presents the recruitment pathway for WP2.1, the main feasibility study. Recruitment for WP2.2 and WP2.3 will be outlined later in the protocol.

Practitioners will be identified and recruited from participating teams managing crisis in dementia. Once the NHS Trust has formally agreed to participate in the study, each team manager or senior practitioner will receive an information pack which will include an information sheet for potential practitioner participants. The team manager will identify 2 practitioners who will act as research coordinators for the site; these practitioners will be given up to 3 days to decide whether or not they wish to participate. A member of the AQUEDUCT research team will then conduct a site set-up visit to answer any questions and seek written informed consent. From this point, the research coordinators will be responsible for arranging and confirming consent with other practitioners at the site. All teams will complete good clinical practice [9] training before their study start date.

People with dementia and carers who are referred to the teams managing crisis in dementia caseload during the first 2 weeks of each team's implementation of the resource kit will be identified and recruited by participating practitioners. Potentially eligible participants will be approached by the practitioner who will give them an appropriate information sheet and explain to them that the team managing crisis in dementia has agreed to participate in the AQUEDUCT research program. Potential participants will be given up to 3 days to decide whether or not they wish to participate; if in agreement, they will then sign a consent form.

Where a carer also agrees to participate in the study, the carer will be asked to provide written informed consent for their own participation in the feasibility study. A carer's decision to participate or not will not affect the involvement of a consenting person with dementia.

Sample Size

The aim of this feasibility study is to estimate rates of recruitment and completion rates, and to refine eligibility criteria and other research procedures; therefore, no formal sample size calculation is required. The proposed sample size includes a total of 40 teams managing crisis in dementia practitioners and 54 people with dementia and carers across the 4 NHS sites; this is considered sufficient to establish feasibility and to inform the future large-scale randomized controlled trial.

Ethics and Mental Capacity

Ethical approval was given by the West Midlands–Coventry and Warwickshire Research Ethics Committee (19/WM/0132) on July 14, 2019 and Health Research Authority approval was given on July 15, 2019. The study sponsor is Nottinghamshire Health care NHS Foundation Trust.

On first contact with the person with dementia, and at every subsequent meeting with a person with dementia, the teams

managing crisis in dementia practitioner will determine the mental capacity (according to the Mental Capacity Act 2005 [10]) of the person with dementia to give informed consent to take part in the research. Where the person with dementia is thought not to have the mental capacity to give informed consent, the view of the person with dementia's carer will be taken into account as they will have a greater knowledge of the person with dementia's abilities over time. The carer consultee will be asked to consider what would be in the best interests of the person with dementia according to their previous or currently expressed views. In these instances, the carer will be provided with a consultee information sheet and a carer consultee declaration form.

Withdrawal

People with dementia can withdraw from the study at any time without any impact on their current or future care. Carers may also withdraw from the study, and this will not affect the person with dementia's continued involvement in the study. Participant information sheets and consent forms will inform participants of their right to withdraw from the research for any reason (which does not need to be stated) and at any time, without any effect on their employment (for teams managing crisis in dementia practitioners) or input from services (for people with dementia and carers).

Patient and Public Involvement

Throughout the development of the AQUEDUCT research program, the research team has extensively consulted with people with dementia and their carers. Patient and public involvement was integrated throughout WP1, to inform development of the AQUEDUCT resource kit. The protocol for WP2 has been developed in consultation with the AQUEDUCT patient and public involvement reference group, and all study documentation and participant recruitment procedures have been reviewed by patient and public involvement representatives.

AQUEDUCT Intervention

The AQUEDUCT resource kit is an online resource for teams managing crisis in dementia, designed to assist teams in evaluating and improving their practice according to the best practice model developed in WP1 of the research program. The resource kit comprises 3 components: the best practice tool which enables teams managing crisis in dementia to evaluate their practice according to 50 best practice statements, the home treatment package developed during the National Institute for Health Research (NIHR)–funded Support at Home—Interventions to Enhance Life in Dementia study (from Hoe J, Ledgerd R, Devine M, Toot S, Challis D, Orrell M. Home Treatment Manual 2012 Version 4. Support at Home: Interventions to Enhance Life in Dementia (SHIELD); unpublished), and a collection of templates and documents that can be used directly or adapted by teams to suit their practice.

At the set-up visit, or subsequently, participating practitioners will complete online training on use of the AQUEDUCT resource kit. They will then complete a posttraining self-assessment to provide information about the effectiveness of the online training. The self-assessment consists of multiple-choice questions that assess the ability, training, and support needs of NHS practitioners using the resource kit. The aim of this assessment is to identify any misunderstandings or areas that require further explanation. Topics focus on study procedures and the best practice toolkit.

For the purpose of the feasibility study, each team will be given 3 weeks to complete the best practice tool before the implementation phase, to determine areas in which the teams managing crisis in dementia could improve practice. The team will then implement relevant elements of the resource kit that will assist them in improving practice during an 8-week implementation phase. The team will recomplete the best practice tool at the end of the implementation phase.

The AQUEDUCT research team will have weekly contact with team practitioners to obtain feedback and provide support for implementation of the resource kit. Support elements will be monitored by the research team to identify usage and costs. teams managing crisis in dementia practitioners will maintain activity records to monitor time spent implementing the resource kit in practice during the implementation phase.

Study Outcomes

Feasibility Study Outcomes (WP2.1)

One of the main aims of the feasibility study is to determine the most suitable outcome measures for the proposed randomized controlled trial. The primary outcome measure to be used in the main trial will be selected from among those described below, based on relevance and acceptability in this feasibility study.

Outcome Measures for the Person With Dementia

Both the self-completed and proxy versions of the Dementia Quality of Life Questionnaire [11], measuring quality of life for people with dementia, will be used. The Client Satisfaction Questionnaire [12], measuring user satisfaction of service received; the Neuropsychiatric Inventory [13], a carer-completed measure that assesses neuropsychiatric symptoms for the person with dementia rating the frequency of the symptoms on a 4-point Likert scale, and severity on a 3-point scale; and the Bristol Activities of Daily Living Scale, a carer-rated measure that assesses daily living activities [14] will also be used.

Outcome Measures for the Carer

European Quality of Life 5 Dimensions questionnaire [15], measuring health-related quality of life; Hospital Anxiety and Depression Scale, a self-completed measure that assesses anxiety and depression [16]; the Neuropsychiatric Inventory severity of symptoms (3-point scale) and the impact of symptoms manifestations (5-point scale) to determine caregiver distress associated with neuropsychiatric symptoms [13]; and Client Satisfaction Questionnaire [12] will be used.

Outcome Measures for Teams Managing Crisis in Dementia

The following data will be collected: initial best practice tool score for the teams managing crisis in dementia; final best practice tool score for the teams managing crisis in dementia; number of hospital admissions for the teams managing crisis in dementia over the study period; total number of referrals

received by the teams managing crisis in dementia over the study period (to include nondementia referrals); number of specific dementia crisis referrals received by the teams managing crisis in dementia over the study period; number of inappropriate referrals to the teams managing crisis in dementia over the study period; teams managing crisis in dementia practitioner absenteeism over the study period; total number of hospital beds available to the service or organization during the study period; and number of hospital beds available to the teams managing crisis in dementia over the study period.

Health Economic Outcomes (WP2.2)

This substudy will test the feasibility of conducting a full economic evaluation of the resource kit in the future randomized controlled trial. The aim will be to test the relevance and acceptability to people with dementia and carers of the questionnaires to be considered for the full economic evaluation in the large-scale randomized controlled trial. It will include at least 4 carers of people with dementia recruited by each of the 4 teams to reflect living arrangements such as a spouse living with a person with dementia or an adult-child living elsewhere. It will involve an analysis of the specific cost of the resource kit, identify appropriate sources of data to be used in the full economic evaluation, and how best to collect these data.

To assess the feasibility of the economic evaluation, carers who are taking part in WP2.1 will be approached by team practitioners and asked if they will consider participating in the feasibility study of the economic evaluation as well. If agreeable, potential participants will then be contacted by a member of the AQUEDUCT research team and will be provided with an information sheet, given an opportunity to ask questions, and given up to 3 days to decide whether or not they wish to participate in this part of the research. If they wish to be involved, participants will sign the relevant consent form.

To calculate the cost of the resource kit, the following components will be considered: (1) the cost of producing and maintaining the resource kit, including the cost of producing and maintaining the best practice tool, all resource materials in the resource kit, all guidance and explanatory information, and the website which supports the resource kit and (2) the cost of skills training for teams managing crisis in dementia practitioners in the use of the resource kit, including all training materials.

It will be assumed that, in the large-scale randomized controlled trial, the lifetime incremental cost per quality-adjusted life year gained for the resource kit versus treatment as usual will be estimated from NHS and Personal Social Services perspectives and from a societal perspective. The resources used and unit cost data for these components will be collected through a modified version of the Clinical Service Receipt Inventory [17]. Potential sources of health-related quality of life data suitable for estimating quality-adjusted life years for people with dementia and carers will also be collected.

Qualitative Evaluation of Participant Experience (WP2.3)

This part of the study will evaluate the experience of applying the research methodology and the acceptability and relevance to participants of using or receiving input from the teams managing crisis in dementia with the resource kit. Findings from the qualitative substudy will be used to modify the resource kit and research methods to be used in the large scale randomized controlled trial. Team practitioners who were involved in the main part of the feasibility study will be approached by a member of the AQUEDUCT research team to invite them to participate in the qualitative evaluation. Potential participants will be given a relevant information sheet, an opportunity to ask questions, and up to 3 days to decide whether or not they wish to participate in advance of giving consent.

All potentially eligible people with dementia and carers will be provided with a relevant information sheet; the research will be explained to them verbally, and potential participants will have the opportunity to ask questions and will be given up to 3 days to decide whether or not they wish to participate in advance of giving consent.

Once informed consent has been provided, team practitioners, people with dementia, and carers will complete bespoke questionnaires to explore their perspectives of how the research procedures were applied and of the acceptability and relevance of using, or receiving input on, the resource kit. Practitioners will be asked to answer statements such as “Was the Best Practice Toolkit training an appropriate length of time?’” with either yes, somewhat, or no. The questionnaire also includes some open-ended questions such as “If you answered no, please provide further details.” The framework for the bespoke questionnaires is outlined Textbox 1.

Textbox 1. Framework for qualitative substudy.

Experience of

- online training and related activities (teams managing crisis in dementia only)
- completing the best practice tool (teams managing crisis in dementia only)
- recruiting people with dementia or carers and of being recruited (all participants)
- using the resource kit (teams managing crisis in dementia only)
- completing other research-related activity (teams managing crisis in dementia only)
- completing the questionnaires (all relevant participants)
- contact with the AQUEDUCT research team (all relevant participants)
- clinical team input (people with dementia and carers only)

Data Collection

Table 1 outlines procedures and assessments at each time point during the study. Upon recruitment, team practitioners will complete a demographic information sheet. Each team will complete the best practice tool at 2 time points: baseline (preimplementation) and study close (postimplementation). The qualitative questionnaires will be completed by team practitioners at the end of the 8-week implementation phase.

Table 1. Study procedures for WP2.

Assessments and procedures	Study set-up (3 weeks)	Baseline	Implementation phase (8 weeks)	Study close (2 weeks)
WP2.1[a]				
Practitioners				
Informed consent	X			
Demographic information	X			
Best practice tool intervention	X			X
People with dementia				
Eligibility screen		X		
Informed consent		X		
Demographic information		X		
Dementia Quality of Life Questionnaire		X	X	
Client Satisfaction Questionnaire			X	
Carers				
Eligibility screen		X		
Informed consent		X		
Demographic information		X		
European Quality of Life 5 Dimensions Questionnaire		X	X	
Hospital Anxiety and Depression Scale		X	X	
Client Satisfaction Questionnaire		X	X	
Bristol Activities of Daily Living Scale		X	X	
Dementia Quality of Life Questionnaire-Proxy		X	X	
Neuropsychiatric Inventory symptom frequency and severity		X	X	
WP2.2				
Carers				
Informed consent		X		
Demographic information		X		
Client Service Receipt Inventory		X		X
Experience questionnaire				X
WP2.3				
Practitioners				
Informed consent				X
Demographic information				X
Experience questionnaire				X
People with dementia and carers				
Informed consent				X
Demographic information				X
Experience questionnaire				X

[a]WP: work package.

Data will be collected at 2 time points for people with dementia and carers. Upon recruitment, demographic information and baseline questionnaires will be completed; follow-up questionnaires will be completed at the end of the period during which the person with dementia and the carer has received team input. Participants not included in the study will be recorded on the Person with Dementia and Carer data summary sheet. The reason for noninclusion or the reason for declining to participate will be recorded where possible.

Data Management

Upon signing a consent form, all participants will be allocated a unique identification code to ensure anonymity. Individual participant information obtained as a result of this research will be considered strictly confidential. Confidentially will be maintained through ongoing use of unique identifiers. All data will be treated as confidential and the NHS Code of Confidentiality [18], 2016 General Data Protection Regulation [19], and 2005 Good Clinical Practice guidelines [9] will be adhered to. Insurance and indemnity arrangements will be covered by the study sponsor (Nottinghamshire Health care NHS Foundation Trust).

Data Analysis

Data analysis to address the feasibility aims of this study will be primarily descriptive. Feasibility outcomes will be estimated using descriptive statistics (with 95% confidence intervals) and will consider recruitment rates, retention rates, amount of missing data, and intervention adherence. The rate of protocol adherence will be reported in terms of participants (practitioners, people with dementia, and carers) who adhere to the required research activities. Key characteristics (personal, demographic and, where appropriate, clinical information from the case report form) will be compared between participants and those who are ineligible or who do not consent to take part, to ascertain adequacy of inclusion and exclusion criteria and likely generalizability of this research to the required targeted populations. The same characteristics will be compared between those who complete all required research activities and those who do not.

Process data will also be collected by the teams managing crisis in dementia and the AQUEDUCT research team. This will include the number of sites approached, the number of participants approached as well as the number recruited, and reasons for not participating given by those who decline to participate. The teams managing crisis in dementia will also record time spent on research activities and on implementing the resource kit.

Adverse Events

No adverse events are anticipated. All adverse events will be recorded in the case report form and the Person with Dementia and Carer data summary sheet. Participants will be informed that they can stop their participation at any time without any impact on their employment or clinical input.

Results

Ethical approval for this study was granted in July 2019. Participant recruitment began in September 2019, and as of September 2020, all data collection has been completed.

Discussion

This protocol describes a multisite feasibility study of an evidence-based best practice model for teams managing crisis in dementia. Previous research revealed only limited evidence in support of crisis teams reducing hospital admission rates, and despite an increase in the number of published studies, their designs remain methodologically limited [6]. The AQUEDUCT resource kit addresses the current care gap by providing more robust evidenced-based dementia crisis care model. This study will add to knowledge concerning the feasibility and acceptability of implementing a model of best practice for teams managing crisis in dementia. Data gathered in this study will also provide an opportunity to modify the AQUEDUCT resource kit.

We anticipate that this information can be used to improve the quality and effectiveness of crisis teams that work with people with dementia. If the AQUEDUCT intervention is found to be effective, this program could influence how services are organized, with benefits for people with dementia and their carers. The long-term impact of a standardized model of dementia crisis care working may be to reduce hospital admissions and to reduce care costs. These impacts may improve quality of life for people with dementia and carers.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review reports.
[PDF File (Adobe PDF File), 222 KB - resprot_v9i10e18971_app1.pdf]

References

1. Prince M, Knapp M, Guerchet M, McCrone P, Prina M, Comas-Herrera M, et al. Dementia UK: Update. London: Alzheimer's Society; 2014:1-113.
2. Pink J, O'Brien J, Robinson L, Longson D. Dementia: assessment, management and support for people living with dementia and their carers. National Institute for Health and Care Excellence. 2018. URL: https://www.nice.org.uk/guidance/ng97/resources/dementia-assessment-management-and-support-for-people-living-with-dementia-and-their-carers-pdf-1837760199109 [accessed 2020-03-15]
3. The prime ministers challenge on dementia: delivering major improvements in dementia care and research by 2015. Department of Health. 2015. URL: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/215101/dh_133176.pdf [accessed 2020-02-01]
4. Spitznagel MB, Tremont G, Davis JD, Foster SM. Psychosocial predictors of dementia caregiver desire to institutionalize: caregiver, care recipient, and family relationship factors. J Geriatr Psychiatry Neurol 2006 Mar 29;19(1):16-20 [FREE Full text] [doi: 10.1177/0891988705284713] [Medline: 16449755]
5. MacNeil Vroomen J, Bosmans JE, van Hout HP, de Rooij SE. Reviewing the definition of crisis in dementia care. BMC Geriatr 2013 Mar 01;13(1):10 [FREE Full text] [doi: 10.1186/1471-2318-13-10] [Medline: 23374634]
6. Streater A, Coleston-Shields DM, Yates J, Stanyon M, Orrell M. A scoping review of crisis teams managing dementia in older people. CIA 2017 Oct;Volume 12:1589-1603. [doi: 10.2147/cia.s142341]
7. Campbell M, Fitzpatrick R, Haines A, Kinmonth AL, Sandercock P, Spiegelhalter D, et al. Framework for design and evaluation of complex interventions to improve health. BMJ 2000 Sep 16;321(7262):694-696 [FREE Full text] [doi: 10.1136/bmj.321.7262.694] [Medline: 10987780]
8. Stanyon M, Streater A, Coleston-Shields D, Yates J, Challis D, Dening T, et al. Protocol for the development of an evidence-based 'Best Practice Model' for Teams Managing Crisis in Dementia. JMIR Research Protocols 2019 Nov 05:14951 (forthcoming/in press). [doi: 10.2196/14781]
9. Handbook for good clinical research practice (GCP): guidance for implementation. World Health Organization. 2005. URL: http://apps.who.int/iris/bitstream/10665/43392/1/924159392X_eng.pdf [accessed 2020-02-01]
10. Mental Capacity Act. Department of Health. 2005. URL: https://www.legislation.gov.uk/ukpga/2005/9/contents [accessed 2019-02-01]
11. Banerjee S. DEMQOL: A patient reported outcome measure for use in dementia—development to address the need for evaluations of cost effectiveness as well as clinical effectiveness. Journal of Mental Health Policy and Economics 2012;15(1):S1.
12. Attkisson C, Greenfield T. The UCSF Client Satisfaction Scales: the Client Satisfaction Questionnaire-8. In: Maruish ME, editor. The Use of Psychological Testing for Treatment Planning and Outcomes Assessment (3rd Edition). New Jersey: Lawrence Erlbaum Associates; 2004:799-811.
13. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994 Dec 01;44(12):2308-2314. [doi: 10.1212/wnl.44.12.2308] [Medline: 7991117]
14. Bucks RS, Ashworth DL, Wilcock GK, Siegfried K. Assessment of activities of daily living in dementia: development of the Bristol Activities of Daily Living Scale. Age Ageing 1996 Mar;25(2):113-120. [doi: 10.1093/ageing/25.2.113] [Medline: 8670538]
15. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011 Dec 9;20(10):1727-1736 [FREE Full text] [doi: 10.1007/s11136-011-9903-x] [Medline: 21479777]
16. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983 Jun;67(6):361-370. [doi: 10.1111/j.1600-0447.1983.tb09716.x] [Medline: 6880820]
17. Beecham J, Knapp M. Costing psychiatric interventions. Measuring Mental Health Needs 2001;2:200-224 [FREE Full text]
18. NHS Confidentiality Code of Practice. Department of Health. 2003. URL: https://www.gov.uk/government/publications/confidentiality-nhs-code-of-practice [accessed 2019-02-01]
19. Magdziarczyk M. Right to be forgotten in light of Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation). In: International Scientific Conference on Social Sciences and Arts-SGEM. 2019 Presented at: 6th International Scientific Conference on Social Sciences and Arts SGEM 2019; April 11-14, 2019; Vienna, Austria p. 177-184. [doi: 10.5593/sgemsocial2019v/1.1/s02.022]

Abbreviations

AQUEDUCT: Achieving Quality and Effectiveness in Dementia Using Crisis Teams
NHS: National Health Service
NIHR: National Institute for Health Research

WP: work package

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Original Paper

Use of a Smartphone App to Increase Physical Activity Levels in Insufficiently Active Adults: Feasibility Sequential Multiple Assignment Randomized Trial (SMART)

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Abstract

Background: The sequential multiple assignment randomized trial (SMART) design allows for changes in the intervention during the trial period. Despite its potential and feasibility for defining the best sequence of interventions, so far, it has not been utilized in a smartphone/gamified intervention for physical activity.

Objective: We aimed to investigate the feasibility of the SMART design for assessing the effects of a smartphone app intervention to improve physical activity in adults. We also aimed to describe the participants' perception regarding the protocol and the use of the app for physical activity qualitatively.

Methods: We conducted a feasibility 24-week/two-stage SMART in which 18 insufficiently active participants (<10,000 steps/day) were first randomized to group 1 (smartphone app only), group 2 (smartphone app + tailored messages), and a control group (usual routine during the protocol). Participants were motivated to increase their step count by at least 2000 steps/day each week. Based on the 12-week intermediate outcome, responders continued the intervention and nonresponders were rerandomized to subsequent treatment, including a new group 3 (smartphone app + tailored messages + gamification) in which they were instructed to form groups to use several game elements available in the chosen app (Pacer). We considered responders as those with any positive slope in the linear relationship between weeks and steps per day at the end of the first stage of the intervention. We compared the accelerometer-based steps per day before and after the intervention, as well as the slopes of the app-based steps per day between the first and second stages of the intervention.

Results: Twelve participants, including five controls, finished the intervention. We identified two responders in group 1. We did not observe relevant changes in the steps per day either throughout the intervention or compared with the control group. However, the rerandomization of five nonresponders led to a change in the slope of the steps per day (median −198 steps/day [IQR −279 to −103] to 20 steps/day [IQR −204 to 145]; *P*=.08). Finally, in three participants from group 2, we observed an

increase in the number of steps per day up to the sixth week, followed by an inflection to baseline values or even lower (ie, a quadratic relationship). The qualitative analysis showed that participants' reports could be classified into the following: (1) difficulty in managing the app and technology or problems with the device, (2) suitable response to the app, and (3) difficulties to achieve the goals.

Conclusions: The SMART design was feasible and changed the behavior of steps per day after rerandomization. Rerandomization should be implemented earlier to take advantage of tailored messages. Additionally, difficulties with technology and realistic and individualized goals should be considered in interventions for physical activity using smartphones.

Trial Registration: Brazilian Registry of Clinical Trials RBR-8xtc9c; http://www.ensaiosclinicos.gov.br/rg/RBR-8xtc9c/.

(JMIR Res Protoc 2020;9(10):e14322) doi:10.2196/14322

KEYWORDS

tailored messages; gamification; steps per day

Introduction

In Brazil, despite the economic crisis, the demand for smartphones has increased dramatically. There are approximately 324 million mobile devices connected to the internet in Brazil, of which 230 million are smartphones [1]. There is an enormous potential for smartphones to improve cardiovascular health in Brazil. Accordingly, efforts to engage people who do not meet physical activity recommendations have been made using popular emerging technologies, including mobile devices such as smartphones and their apps. There is evidence in the literature that app-based interventions to promote physical activity can be useful in yielding an overall moderate effect [2]. Regarding physical activity, a recent systematic review and meta-analysis reported that the use of wearables and smartphone apps led to a small to moderate increase in physical activity in minutes per day, and a moderate increase in daily step count [3]. However, recent evidence suggests that smartphone apps have been most effective in the short term (eg, up to 3 months), indicating the need for future research to establish the paths to improve physical activity in the long term [4].

In order to optimize app-based interventions for physical activity, a novel research design, namely the sequential multiple assignment randomized trial (SMART) design, might be a rational strategy. SMART is an adaptive design, which allows for alternative treatments depending on observed success in the intervention during the research period. This strategy brings the intervention more in line with real-life situations, helping to identify people who benefit from interventions differentially and individualize the treatment. Another benefit of this intervention design is the evaluation of multiple interventions and responses in one trial. In addition, the SMART design has been recommended over the classical randomized controlled trial for technology-based interventions [5,6], as it allows for adaptations over time based on the response to the intervention. This strategy may be beneficial, as the effectiveness of an app might diminish over time, because of losing interest in the app or its elements.

For example, consider a SMART to evaluate behavioral interventions in eHealth for scope and intensity. Assume that there are three types of strategies (A, B, and C), which are listed in order of dose and range. In this study, each participant would be randomized to one of two possible initial interventions (A or B). After a pre-established period, participants would be classified as nonresponders or responders, according to a previously defined criterion. Thereafter, nonresponders would be rerandomized to a subsequent intervention more rigorous in terms of the intensity and range of the initial intervention. Responders to treatments A and B would continue in their treatments to investigate the longer follow-up effect. Nonresponders to treatment A would be rerandomized to both receive treatment C and experience treatment B. Nonresponders in B, in turn, would be rerandomized to C or would change treatment by going to A. Six interventions are embedded in this design.

Given the need to evaluate the SMART design development and implementation process, as well as the preliminary results of each participant's response to the proposed intervention, a feasibility study is appropriate and allows the identification of methodological aspects that may be adapted before more extensive randomized controlled trials. Moreover, conducting a pilot study favors the exploration of crucial outcomes beyond the evaluation of the study protocol implementation process [7].

Despite the high potential and feasibility [8] of a SMART design, so far it has hardly been utilized in smartphone and gamified interventions, especially for increasing physical activity. Accordingly, the primary objective of this study was to investigate the feasibility of a SMART design for assessing the effects of a community-based smartphone app intervention to improve physical activity in insufficiently active adults. We also aimed to describe the participants' perceptions regarding the protocol and the use of the app for physical activity qualitatively. Moreover, we aimed to analyze the participants' responses to the intervention.

Methods

Study Design

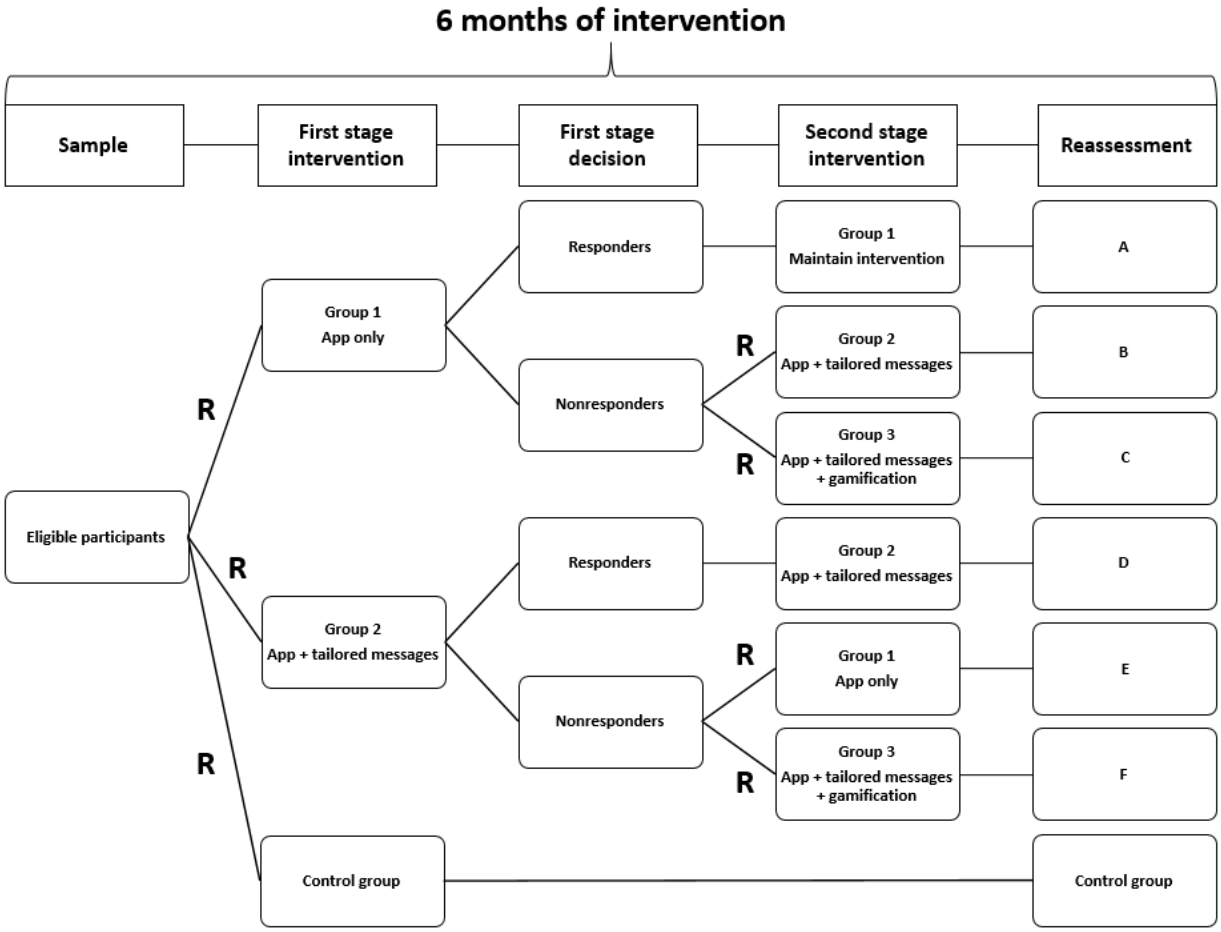
We conducted a feasibility study about the effectiveness of the SMART protocol using a smartphone app (free of charge) for the level of physical activity in adults. Our feasibility study expected to evaluate the recruitment capacity and resulting characteristics of sampling, evaluation, and refinement of data collection procedures; outcome measures; intervention and study acceptance and adequacy procedures; resources and ability

to manage and implement the study and intervention; and preliminary responses to the intervention. The interdisciplinary team that developed the feasibility SMART study protocol included a psychologist, physical therapists, and professionals in physical education.

This feasibility trial was a 24-week intervention with a two-stage SMART in which the allocation sequence of the randomization was concealed using opaque envelopes. An independent researcher performed this phase of the protocol. In the first stage of treatment decision, participants were randomized to group 1 (smartphone app only), group 2 (smartphone app + weekly tailored text messages), or a control group. After 12 weeks, based on the intermediate assessment (maintenance and increase or decrease in the number of steps), participants were classified as responders or nonresponders. The nonresponders were rerandomized into the two pre-existing groups (group 1 and group 2), and a new intervention group (group 3: smartphone app + weekly tailored text messages + gamification) was added to the protocol (Figure 1). Participants in the control group were advised to maintain their usual routine. The text messages sent to participants throughout the intervention are presented in Multimedia Appendix 1.

The ethics committee of the university approved this study (number: 0499/2018), and the trial was registered at the Brazilian Clinical Trials Registry (ReBEC #RBR-8xtc9c).

Figure 1. The sequential multiple assignment randomized trial (SMART) design applied in this study. Letters at the end of the flowchart indicate the way of the intervention. A: app only during 24 weeks; B: app only during 12 weeks and app + tailored messages in the last 12 weeks; C: app only during 12 weeks and app + tailored messages + gamification in the last 12 weeks; D: app + tailored messages during 24 weeks; E: app + tailored messages during 12 weeks and app only in the last 12 weeks; F: app + tailored messages during 12 weeks and app + tailored messages + gamification in the last 12 weeks; R: randomization and rerandomization.



Participants and Recruitment

As a rule of thumb, it has been recommended to recruit 30 participants for both pilot and feasibility studies, with samples between 24 and 50 being mathematically recommended to both calculate the standard deviation of a predetermined outcome and evaluate the rates of adherence and involvement (responder and nonresponder), as well as drop-out (for example) [9].

We invited 39 volunteers who presented to another ongoing study called the Epidemiology and Human Movement (EPIMOV) Study. Briefly, the EPIMOV Study is another study of our research team being carried out since 2013 in the city of Santos, Sao Paulo, Brazil. It is a prospective epidemiological study to investigate the association of physical activity and sedentary behavior with the incidence of cardiorespiratory and locomotor diseases. EPIMOV Study participants were recruited

through social networks, folders displayed in the community, local magazines, and newspapers. In the EPIMOV Study, we included adults (age ≥18 years) who did not have cardiopulmonary diseases, locomotor disturbances, known electrocardiographic abnormalities, or other problems that would preclude them from safely performing physical exercises. EPIMOV Study exclusion criteria were regular use of assistive gait devices, recent respiratory infections, unstable or stable angina in the last 4 weeks, bradyarrhythmia or tachyarrhythmia, and abnormalities in lung function evaluated through spirometry. Thus, we used the participants of the EPIMOV Study in the sample of this SMART design study. All eligible participants, consecutively enrolled in the EPIMOV Study, were invited to participate in this feasibility trial, and upon agreeing to participate, they were randomized to one of the groups of the SMART design (Figure 1). In order to be eligible for the feasibility SMART study, the participants of the EPIMOV Study were required to be 30 years or older, be digitally engaged with their smartphones, and have a minimal behavioral change status (ie, higher than the precontemplative profile) for physical activity, based on the transtheoric model of behavior change at baseline [10].

The exclusion criteria for the feasibility SMART study were as follows: walking an average of ≥10,000 steps/day (assessed by a triaxial accelerometer) and/or a score of ≥3000 metabolic equivalents (METs)/min/week in the International Physical Activity Questionnaire (IPAQ) [11]. We set the limit of 10,000 steps/day since this is a well-recognized threshold for improving health [12] and more than 3000 METs/min/week in the IPAQ because it is related to the international recommendation for physical activity.

Study Interventions

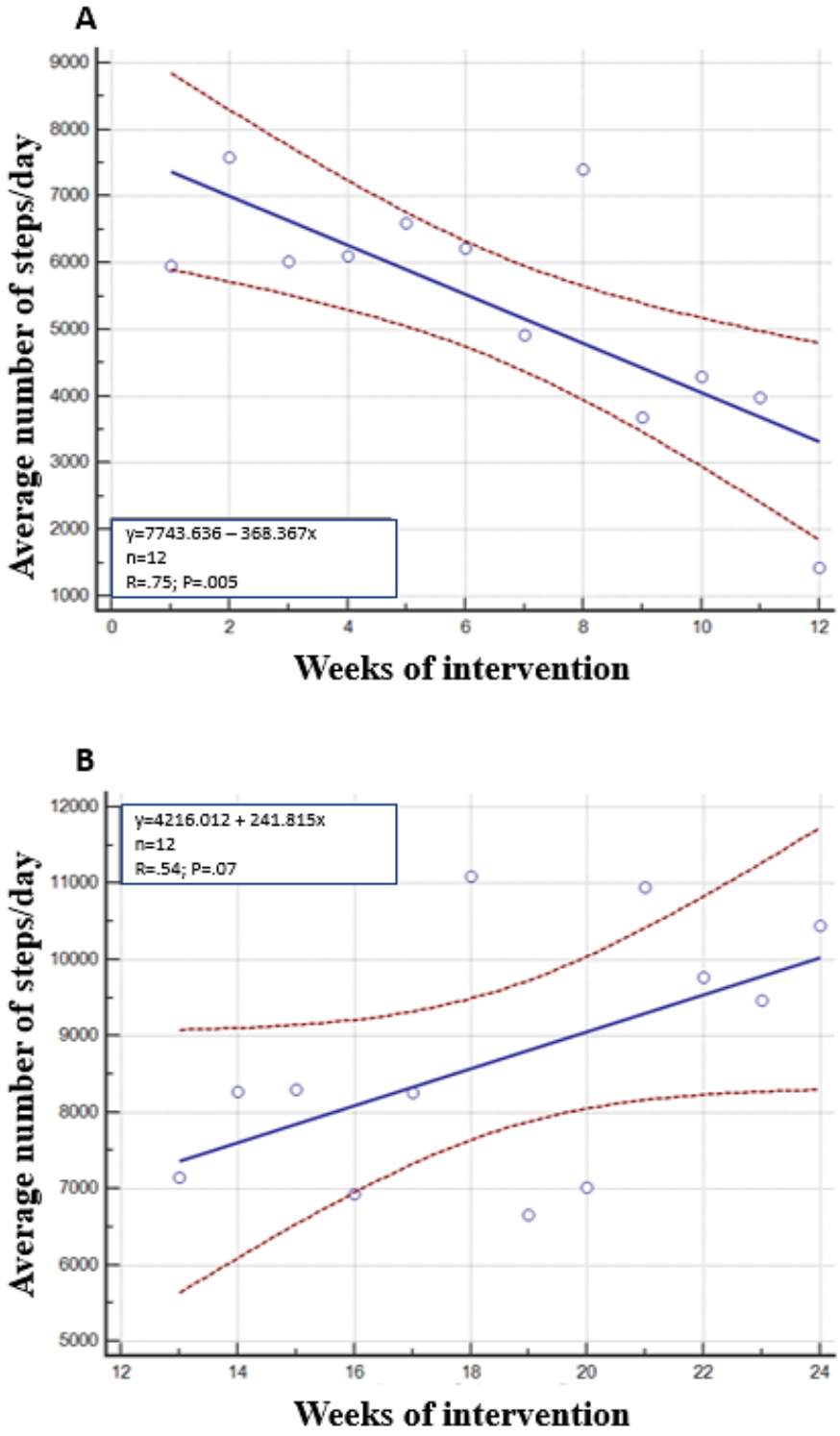
Tailoring Variables

We considered as the primary tailoring variable the increase in the average number of steps per day in comparison with baseline. Participants were rerandomized after 12 weeks from the beginning of the intervention, based on their response to the first stage of the intervention. In case of reaching the goal in the first stage, they remained in the same group; otherwise, they were exposed to a new intervention (Figure 1). The participants were informed that they would be joining an adaptive trial and that there was potential for rerandomization if they did not respond to or use their first intervention condition.

We asked participants to increase their average daily step count by 2000 steps as much as possible. There is no consensus about the minimum increase in the number of steps (per day or per week) related to cardiovascular health improvement, although one study found that a change by 2000 steps/day was inversely associated with the risk of a cardiovascular event [13]. Moreover, the American College of Sports Medicine recommendations on the quantity and intensity of physical activity suggests an increase of an average of 2000 steps/day for benefits in cardiovascular health [14].

However, at the very beginning of the intervention (third week of the sixth participant assessment), we decided not to use the increase of 2000 steps/day for identifying responders and nonresponders in order to avoid making participants feel discouraged or uncomfortable by reaching the goal only a few times. Thus, the goal for each participant was any increase in the daily step count compared with the initial assessment. In this way, to define responders and nonresponders in this study, we fitted a linear regression for each participant with the relationship between weeks on the x-axis and the number of steps per day on the y-axis (Figure 2). Thereafter, we considered responders as those with any positive slope at the end of the 12-week first stage of the intervention. Those with zero or negative slopes were considered as nonresponders.

Figure 2. The method developed in this study to define responders and nonresponders to the smartphone app intervention for physical activity. (A) An unresponsive participant in the smartphone app only intervention; (B) The same participant after rerandomization to an intervention combining the app with gamification features.



Group 1

In group 1 (smartphone app only), participants were instructed to monitor their daily steps using the Pacer app. Additional instructions on app features were not provided, and encouraging text messages were not sent. In order to record the average number of steps per week, initially, participants were instructed to send a print screen of their step counts every Monday. After it was possible, we began to collect this information using the app interface by verifying each participant profile on the app with their agreement. Participants also received weekly questionnaires with questions, such as how they felt about that week, what was the appropriateness of the goal imposed on them, and how much they would like to remain in the study.

Group 2

In group 2 (smartphone app + weekly tailored messages), participants used the app to track the number of daily steps, and they received weekly text messages on their smartphones with information about their performance in the previous week and motivational messages according to their behavior change status [15]. We prepared a series of 48 messages (24 directed to participants with a contemplative behavior change profile and 24 directed to those with preparation and action behavior change profiles). The 24 messages included 12 for those who reached the goal and 12 for those who did not reach the goal. We sent the messages on the same weekday using a free app. Furthermore, the weekly questionnaires were sent in the same way as in group 1.

Control Group

Participants in the control group were instructed to maintain their usual routine.

Group 3

In group 3 (smartphone app + weekly tailored text messages + gamification), in addition to app use and tailored text messages, participants were instructed to form groups with researchers to use the functions available in the app as described above. The researchers in this group acted both as dummy participants and as social moderators, competing and giving encouragement to the real participants. Apart from step monitoring and individual messages, participants were encouraged to join virtual challenges. For each challenge they completed, they were rewarded with a virtual badge on the app. Challenges available were as follows: target number of steps per day, target distance walked in the month, and group competitions where the total number of steps was compared among different groups of app users. In addition, there were rankings of the number of steps among all users, as well as running challenges.

At the end of the sixth month, there were seven possible ways of the intervention. These ways were identified as the way in the control group (one way) and ways with the letters A to F (six different ways) as follows: A, app only during 24 weeks; B, app only during 12 weeks and app + tailored messages in the last 12 weeks; C, app only during 12 weeks and app + tailored messages + gamification in the last 12 weeks; D, app + tailored messages during 24 weeks; E, app + tailored messages during 12 weeks and app only in the last 12 weeks; F, app + tailored messages during 12 weeks and app + tailored messages + gamification in the last 12 weeks (Figure 1).

Outcomes and Assessments

Study outcomes were assessed at baseline and after 12 and 24 weeks by researchers blinded to group allocation. All researchers who did the assessments were blinded. The researchers who did the group allocation, sent messages, and participated in gamification were not blinded. At each scheduled assessment period, study measurements were carried out during two visits, spaced 7 days apart. In all three assessments, participants repeated the protocol of the two visits. In the first visit, participants underwent general health screening (clinical and sociodemographic characteristics), assessment of the behavior change status for physical activity [15], anthropometric assessment, lung function assessment, and cardiorespiratory fitness assessment. At the end of the first assessment, participants were informed about using the triaxial accelerometer for the subsequent 7 days for the assessment of the average number of steps per day. At the end of the first visit, they were also instructed to install a smartphone app for physical activity monitoring and to use it throughout the subsequent 7 days, so that we could establish a personalized goal regarding the increase in steps per day. In the second visit, they returned the accelerometer, and we assessed the physical activity levels and body composition.

Clinical and Sociodemographic Assessments

Baseline assessments included the age, sex, race, and educational level of the participants. We measured height (m) and body mass (kg) in all participants. Thereafter, we calculated the BMI and defined obesity as a BMI30 kg/m^2. We also investigated by self-report the presence of previous diagnoses of the main risk factors for cardiovascular disease, including systemic arterial hypertension, diabetes/hyperglycemia, and dyslipidemia/hypercholesterolemia. A family history of premature coronary heart disease was defined as myocardial infarction or sudden death before 55 years of age in the father or another male first-degree relative, or before 65 years of age in the mother or other female first-degree relatives. We also asked participants about current smoking.

Physical Activity Behavior Change Status

We assessed participants' behavior change status for physical activity according to a previously validated questionnaire [15]. This questionnaire provides information about the physical activity habits of the volunteers and the plans to start a physical activity behavior, which was used to develop personalized messages, as will be described later.

Sedentary Behavior and Physical Activity Levels

We performed this evaluation with a validated triaxial accelerometer (ActiGraph GT3X+, MTI) [16]. Participants wore the device for 7 consecutive days of assessment during the waking hours. To be considered valid, days of data collection needed to have at least 10 hours of continuous monitoring, starting at the moment of awakening. Participants used the accelerometer until bedtime, except during showering and aquatic activities. Nonwearing time and the thresholds for the intensity of physical activity were evaluated as previously described [17]. We defined wearing time as 24 hours minus nonwearing time. Periods of zero counts for 60 or more consecutive minutes were considered as nonwearing time. To be considered as valid data for analysis, volunteers needed to use the device for at least 4 days (10 hours/day), including a weekend day.

The total amount of sedentary behavior was considered based on the minutes with less than 100 counts/minute (cpm), which represents <1.5 METs of energy expenditure. We evaluated sedentary behavior, light-intensity physical activity, and moderate to vigorous physical activity at baseline and at the end of the 24-week intervention. The measurements were calculated in hours per day considering the total wear time and the number of calendar days of use, as well as in percentage of

the total time. The thresholds for the intensity of physical activity were as follows [17]: (1) light physical activity (100-1951 cpm) and (2) moderate to vigorous physical activity (>1951 cpm). Physically inactive participants were considered as those participants with less than 150 minutes/week of moderate to vigorous physical activity or less than 75 minutes/week of vigorous physical activity [14].

Daily Step Count and Smartphone App

We obtained the baseline average daily step count by using a smartphone app. Before starting the intervention, we tested several smartphone apps. Researchers installed on their smartphones the most popular free physical activity apps with a step-monitoring function that worked correctly in both Android and iOS operating systems. After a meeting, we decided to use the Pacer app. We agreed on this choice based on some features of this app. First, it handles well on the two most popular operating systems. Second, it accurately monitors daily steps. Third, it has gamification features, such as goal setting, rewards, virtual badges, progress bars, walking/running rankings, and group formation possibility. Finally, the app has social network and coaching functions.

Data Analysis

Qualitative Data Analysis

We performed qualitative analysis of the perceptions of all participants included in the SMART in terms of the protocol and the use of the app for physical activity. The exchange of text messages with participants was performed through the free instant messaging app WhatsApp. We transcribed to text all the text messages exchanged between participants and researchers. The proceedings used were adapted from qualitative research in health [18]. To assimilate the content of the material, we conducted a free-floating reading of the transcribed material, followed by an exhaustive reading until recording units were extracted. Finally, we organized and analyzed the material according to the literature recommendations.

Conversations with participants via the app occurred two times a week and were usually initiated by the researcher. The content of these conversations started with an initial greeting, talked about the participant's inclusion, and included instructions on using the step counter app and instructions on sending a print screen with weekly steps. Conversations also involved reports on performance of the participants, health situations, and difficulties in handling the app, where assistance was provided. Participants could answer the messages sent by researchers through text and emojis (message app feature).

Quantitative Data Analysis

Quantitative analysis involved comparison between the slopes of the average number of steps per day obtained in the first stage of the intervention (12 weeks) and the second stage (24 weeks). Because of the small sample size, we chose the following statistical procedures. We performed a Mann-Whitney test to investigate the differences in the study groups. We compared the average number of steps per day at baseline and after 12 and 24 weeks of the intervention using the Kruskal-Wallis test. We also used an independent samples *t* test for comparisons between intervention groups and the control group at baseline and at the end of the 24-week intervention. Finally, we fit linear and quadratic regressions both during the first 12 weeks of the intervention and overall to investigate the behavior of changes in the average number of steps per day throughout the intervention. As for the linear trend in the number of steps, we calculated the slopes for each participant who finished the protocol (stages one and two) and then compared the median of the slopes using the Mann-Whitney test. Moreover, we calculated the median of the weekly number of steps of the five participants who completed the protocol and compared the slopes of the step trends between the initial 12 weeks and the final 12 weeks using analysis of covariance. We used the number of steps as the dependent variable, the intervention stage as a fixed factor, and the intervention weeks as a covariate. We set the alpha level at 5% for all analyses.

Results

In total, we invited 39 participants from the EPIMOV Study. Among them, 14 were not included (presented a high physical activity level, ie, >10,000 steps/day or >3000 METs in the IPAQ) and seven were excluded (two refused to participate, four reported not using a smartphone in daily life, and one did not complete the assessments) (Figure 3). Of the 18 participants randomized, seven in the intervention groups and five in the control group finished the 24-week intervention protocol (Figure 3). We found no relevant differences between groups regarding the general characteristics at baseline (Table 1).

Figure 3. Flow chart of the feasibility sequential multiple assignment randomized trial (SMART) utilized in this study.

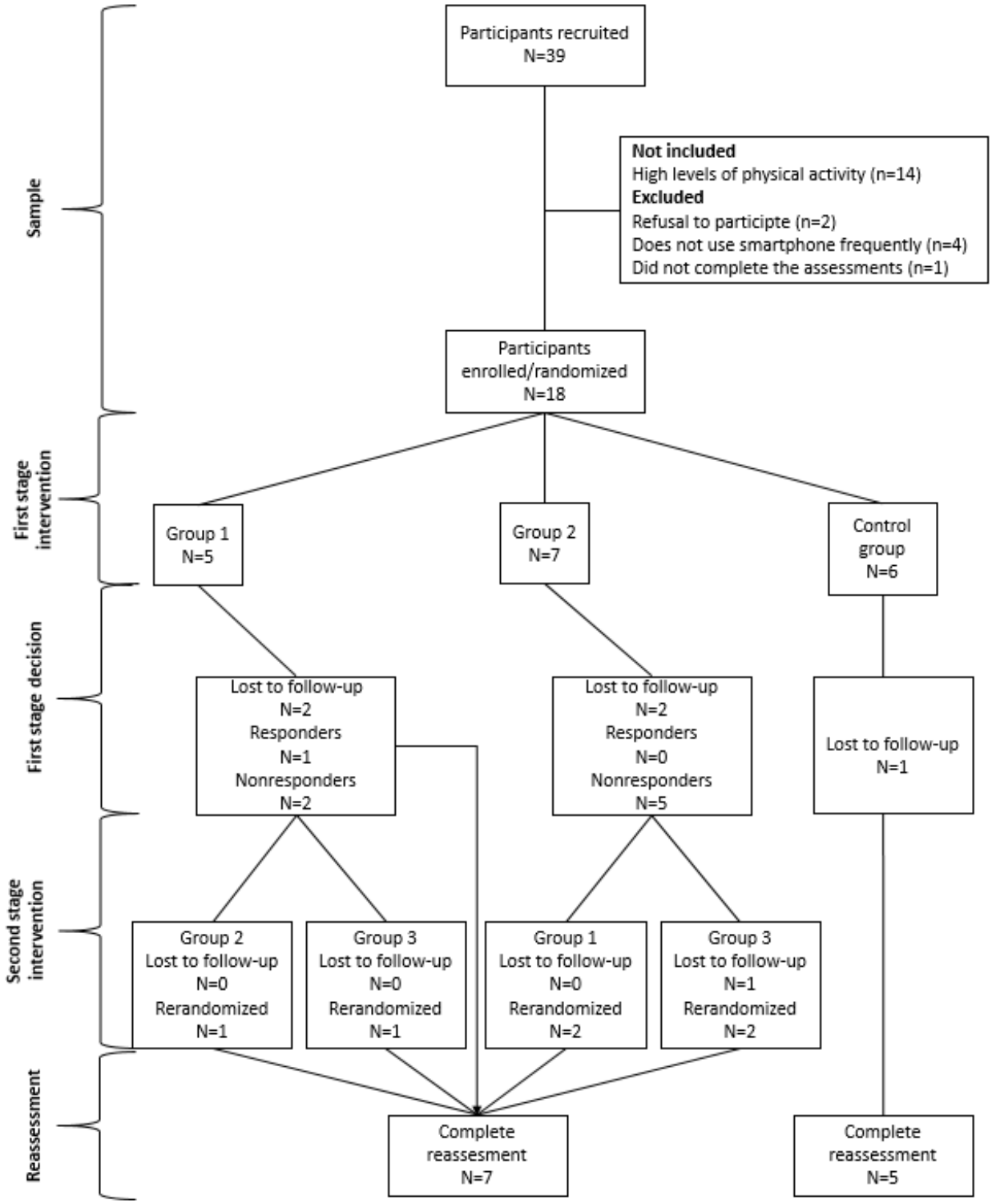


Table 1. General characteristics of the study participants.

Characteristic	Intervention groups[a]	Control group[a]	*P*
Age (years)	44 (7)	42 (7)	.64
Sex (male/female)	4/3	4/1	.54
Weight (kg)	90 (27)	89 (25)	.95
Height (m)	1.69 (0.11)	1.63 (0.12)	.39
BMI (kg/m^2)	31.3 (9.0)	33.2 (8.9)	.71
Physical activity			
Sedentary (h/week)	55.2 (12.4)	55.7 (12.6)	.68
Light intensity (h/week)	19.9 (5.8)	24.7 (6.6)	.28
Moderate to vigorous intensity (h/week)	2.95 (1.19)	2.55 (1.54)	.62
Average number of steps/day	3910 (2097)	4170 (2024)	.27

[a]Data are presented as mean (SD) or n/n.

We successfully adopted the SMART design, performed randomization and rerandomization among all groups, and delivered the proposed intervention for a feasibility study. The technology-based intervention allied with the SMART design may have created conditions to favor participants' behavior change. The delivery of tailored messages, identification and rerandomization of nonresponders, and interaction between participants and researchers were feasible. The average number of daily steps was a feasible measure of the level of physical activity for this study design.

The qualitative analysis showed that participants' reports could be classified into the following three categories: (1) difficulties in managing the app and technology or problems with the device, (2) good responses to the app, and (3) difficulties in achieving the goals (Table 2). An example of a participant-researcher interaction is shown in Textbox 1.

Table 2. Qualitative data results.

Category	Participants' quotes
(1) Difficulties in managing the app and technology or problems with the device	*I think there's some problem. It's zero for some days. Back to normal.* [Participant #01, male, 37 years old]
	I changed the phone and could not use the app. Do you know how could I restore the data? I tried but couldn't do it. [Participant #14, female, 37 years old]
	But the data won't be correct because the app hasn't been working well, that's why I don´t have it with me all the time. When I go out for a walk, it does not work, and at home, it sometimes does. Also, there are some clothes it doesn't fit in the pocket… got it? [Participant #11, female, 52 years old]
(2) Good responses to the app	*This week I'm doing well, I've been hiking and running 6k.* [Participant #04, female, 33 years old]
	I have a friend who would like to [participate], is there any chance? [Participant #07, female, 62 years old]
	Still trying to commit me to the goals and my work schedule and the knees... [Participant #09, female, 47 years old]
(3) Difficulties in achieving the goals	*Good morning! I know I have to improve and also that it is a shame these steps, but it's not because I want to, unfortunately, if it's not one thing it's another but I'll try.* [Participant #04, female, 33 years old]
	Good afternoon. Rainy week. Cut me some slack. Hugs. [Participant #06, male, 51 years old]
	I didn't reach the proposed goal, and health is so-so. [Participant #09, female, 47 years old]
	And I've been very busy with my orders, thank you and have a great day. [Participant #11, female, 52 years old].
	Vacation last week. [Participant #14, female, 37 years old]

Textbox 1. Example of participant-researcher interaction messages.

Researcher: Good morning! Your average number of steps this week was 8,281/8,208.

Participant #14 (female, 37 years old): Good morning.

Researcher: [emoji reinforcing the participant's behavior]

Participant #14: [emoji expressing happiness]

Participant #14: I started a bodybuilding program.

Researcher: Cool! Congratulations!

Only one out of 12 participants achieved the goal of increasing 2000 steps/day in the first 12 weeks of the intervention and presented a positive slope. Therefore, the participant was classified as a responder and was not rerandomized. Among nonresponders, one out of seven participants achieved the goal in the remaining 12 weeks after rerandomization. On occasions when the goal was not reached, in 66.7% of responses, participants reported feeling bad or very bad about it. Interestingly, in 72% of weekly questions, they reported that the 2000-step goal was adequate at the time they did not achieve it. In addition, in 99% of cases, participants reported being willing to continue the study. In 95% of cases, participants reported feeling well or very well when they reached the goal of increasing 2000 steps/week. They also reported performing physical activities alone 66% of the time. Walking for exercise and leisure were the most prevalent types of physical activity.

We did not observe significant changes (P=.10) in the average number of steps per day on comparing baseline, week 12, and week 24 (Figure 4). Moreover, we found no differences in the average number of steps per day among groups at baseline (Table 1) and at the end of 24 weeks of the intervention (intervention groups: mean 3995, SD 3204 vs control group: mean 4250, SD 4204). However, we observed that after rerandomization (week 12), participants tended to change the slope of the average number of steps per day (from median −198 steps/day [IQR −279 to −103] to median 20 steps/day [IQR −204 to 145]; P=.08). Comparing the trend of the median number of steps between the first and second stages of the intervention in the total sample, we found a relevant inflection (Figure 5). Considering all 24 weeks of the intervention, we observed that four out of five nonresponders presented a quadratic relationship between the average number of steps per day, with positive inflection after rerandomization (Figure 6). We observed these results regardless of the sequence of interventions.

Figure 4. The average number of steps per day at baseline, after 12 weeks of the intervention, and after rerandomization and new intervention adoption up to 24 weeks of the study protocol.

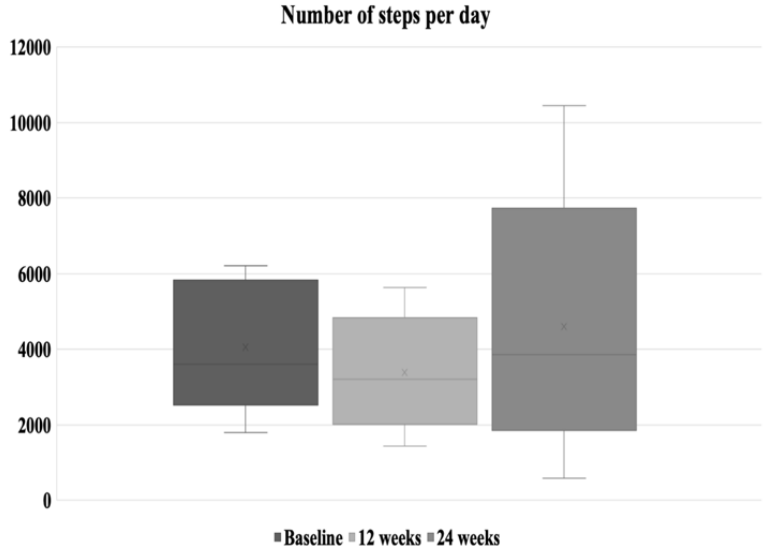


Figure 5. Linear regressions with the slopes of the relationships between the median number of steps per day of the five participants who finished the protocol and weeks of the intervention. The slope of the second stage of the intervention (weeks 13 to 24) was significantly different compared with the first stage of the intervention (P=.02).

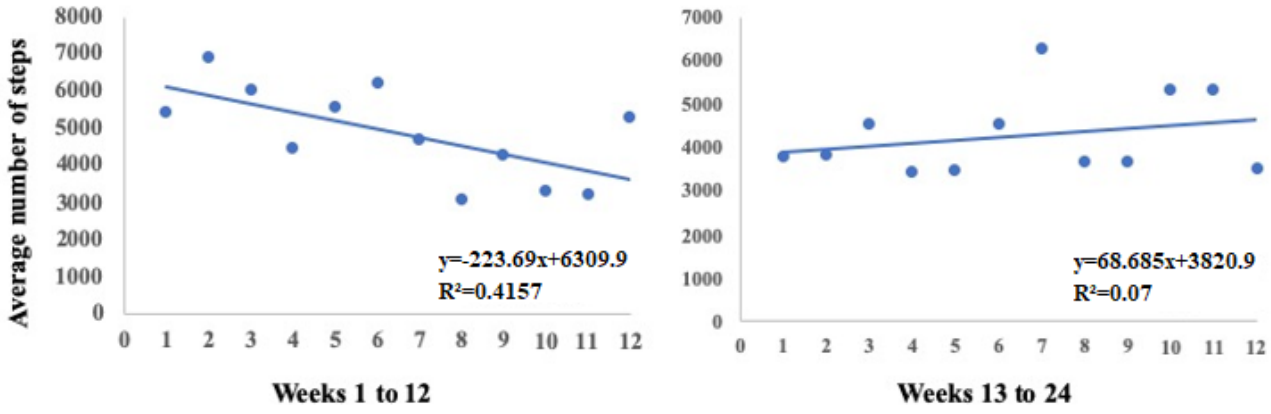
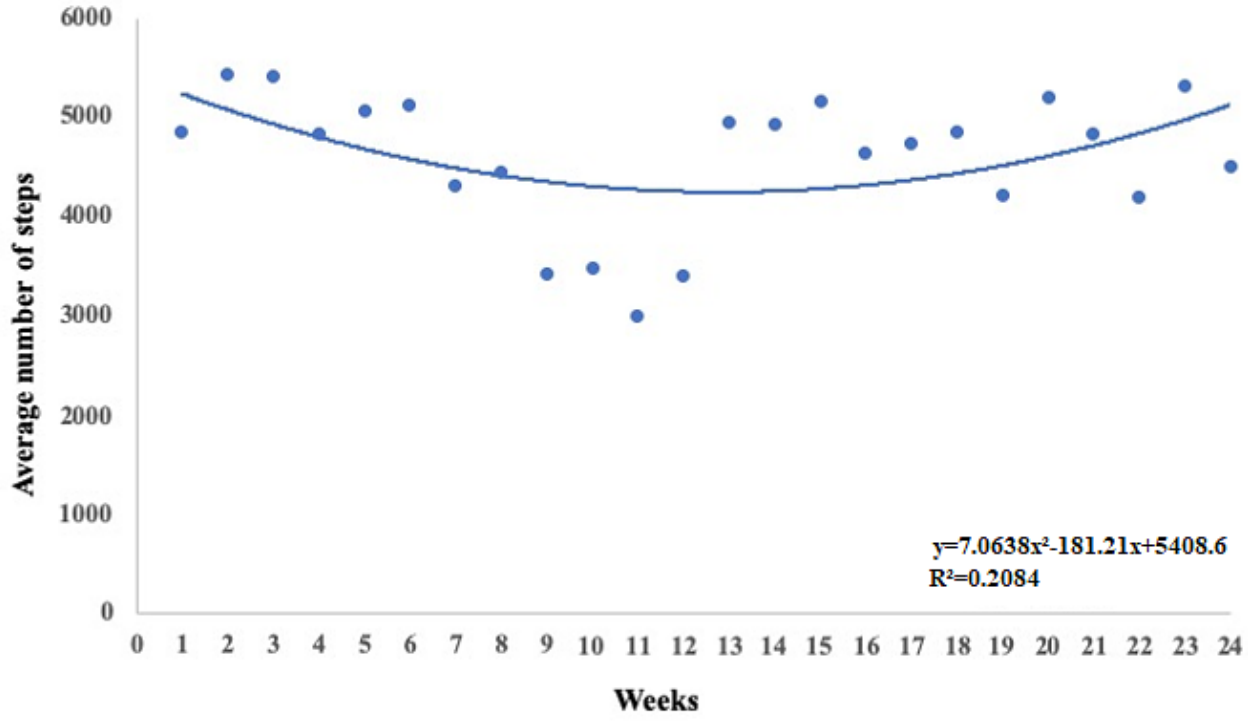


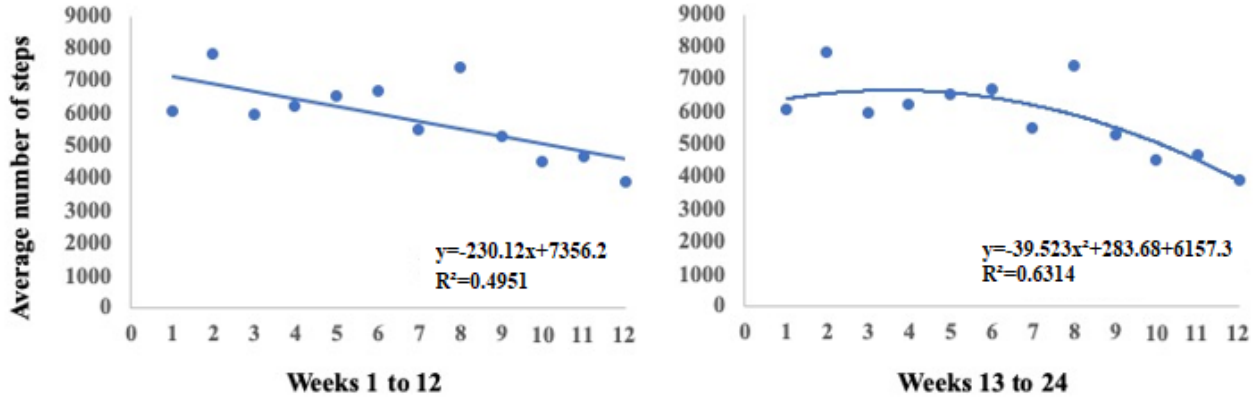
Figure 6. The average number of steps per day throughout the 24-week intervention showing a quadratic relationship in the total sample of participants who finished the protocol.



As for responders, we identified one participant with a slope showing an increase of 8 steps/week in the first stage of the intervention, who maintained a positive slope of 26 steps/week in the second stage of the intervention. Another participant in group 1 showed an increase in the number of steps with a slope of 1341 steps up to the sixth week of the intervention before dropping out of the study.

Finally, we observed that for three nonresponders from group 2 (smartphone app + tailored messages), a quadratic rather than a linear regression was better to predict the behavior of the average number of steps during the first 12 weeks of the intervention (Figure 7). They showed an increase in the number of steps up to the sixth week and then presented an inflection to baseline values or even lower.

Figure 7. Examples of better fit using quadratic regression (A) compared with linear regression (B) for predicting the behavior of weekly changes in the average number of steps per day.



Discussion

Principal Findings

The primary objective of this study was to investigate the feasibility of a SMART design for assessing the effects of a community-based smartphone app intervention to improve physical activity in insufficiently active adults. We also described the participants' perceptions regarding the protocol qualitatively. Moreover, we aimed to analyze the participants' responses to the intervention. Supporting the primary purpose, we observed that this study design was feasible for interventions

promoting behavior change in physical activity. Furthermore, multicomponent app-based interventions seem to be more effective than app-based interventions alone [19].

We showed that the SMART design, in association with behavior change techniques and technology-based features, is feasible and shows potential to be effective in promoting more active lifestyles. The study design worked correctly and called for participants to experience positive effects on physical activity levels. Thus, the SMART protocol required adequate planning and a dedicated interdisciplinary team to deliver the intervention. Interdisciplinary interventions increase the chances of achieving the different dimensions of change and sustenance of complex behaviors, as in physical activity [20].

After we finished this feasibility SMART study, we made changes to the protocol, and the full trial is ongoing. For the adaptive intervention trial itself, we will change the way we recruit volunteers. Initially, we were inviting participants from another study with a different focus (EPIMOV Study) to be part of the SMART study. However, we realized that we need to broadly publicize the SMART study (social media, networks, and newspapers) to recruit volunteers interested in increasing their levels of daily physical activity, which we hope will contribute to decreasing the drop-out rate.

The qualitative analyses showed that participants presented an excellent response to the app, as well as important issues such as difficulty in managing the technology and difficulties in achieving the goals, which could be addressed in a future large-scale clinical trial. The possibility of interaction with the team had an essential role among participants. It is interesting to observe that participants tried to report their difficulties or their achievements/progress to the researcher. The sensibility and acceptance of the participants' demands had an essential role in the process of behavior change among the participants of this study. Some people need more support and incentive to start the change, and some recent evidence showed that self-efficacy is a potent mediator for improving physical activity, especially considering meaning in life and peer support [21,22]. The researcher-participant interaction reinforces the positive effect for the participant trying to change behavior.

Researchers in the field of psychology point out the complexity and importance of therapeutic alliance research in psychotherapy [23,24]. Therefore, broadening the understanding of such variables in intervention programs that seek to change behavior is relevant. Although it is a topic that needs to be better understood, we believe that considering the importance of the quality of the relationship established between the researcher and participant is a crucial aspect in the process of change of human behavior.

Smartphone devices and apps provide more awareness than motivation in practicing physical activity [25]. The interaction of a participant with a professional evaluator in physical activity and health brings higher reliability and promotes the overcoming of physical barriers or geographic isolation. It has been shown to increase adherence and involvement in physical activity intervention programs, overcome barriers, and increase motivation to achieve goals [25]. This intervention proved to be effective in a 10-week physical training program submitted through WhatsApp, along with sending encouraging messages and responses to any questions from participants. Muntaner-Mas et al proved that it was feasible and had good adherence, even without the use of behavior change techniques, although the researchers emphasized the importance of such techniques [26]. This result is in line with our study design, in which we performed a SMART owing to the adaptive characteristic of this design.

Furthermore, the availability of researchers allied with the weekly text messages may have contributed to participants' adhesion to the intervention since they could stop using the app or stop monitoring or trying to increase their daily steps. Although electronic devices and apps are essential tools for health interventions, real-time feedback is crucial for behavior change [27].

In a small sample, we found a tendency to increase the average number of steps per day throughout 24 weeks of the intervention, especially in the last 12 weeks. Moreover, the tailored messages seemed to have a positive impact on the physical activity level; however, our results demonstrated that rerandomization to a new treatment strategy would be better implemented before 12 weeks of the intervention. These findings confirm previous research about the importance of the social environment [28,29] and the use of messages as strategy motivation to increase the physical activity level [30]. Given that levels of motivation may vary across the lifespan [31], a combination of strategies to keep individuals physically active seems to be more effective [32]. Studies have shown that the social environment has an essential influence on the psychological and behavioral aspects related to the level of physical activity [33].

Our findings suggest that the rerandomization itself seemed to play an important role in participants' behavior, leading to an inversion of the tendency to decrease physical activity over a short period. While most participants were not able to achieve the goal of increasing 2000 steps/day, we observed, intriguingly, that they reported that this goal was adequate.

After about 3 weeks of the intervention, we decided to redefine the goal to avoid making participants feel discouraged or uncomfortable by reaching the goal only a few times. The importance of goal setting has been discussed in the field of sports psychology. Weinberg [34] argues that, for setting a goal, an important principle is that it should be challenging and realistic. If goals are too complicated, the tendency is that individuals lose motivation and give up, and if it is too easy and does not present a challenge, individuals become complacent and do not reach maximum effort [34].

Thus, the goal for each participant was to increase their daily steps by any count compared with the initial assessment. This goal can be an essential strategy to encourage self-regulation, which plays a vital role in behavior change. Buckley et al [35] showed that cognitive control abilities play an important role in the self-regulation of physical activity and sedentary behavior. Self-regulation may be defined as a process that permits an individual to guide his activities over time and circumstances. It consists of the modulation of thoughts, attention, affects, or behavior by deliberate or automated use of cognition [36].

In addition, we consider that the presentation of personalized messages sensitive to the stage of behavior change can generate a higher positive response and incentive in the search for a goal. In the initial stage of behavior change, the possibility of the individual perceiving himself/herself as supported and encouraged is of fundamental importance for the construction of a more effective behavior change [37]. Sending automated messages produced a null effect on increasing physical activity in patients with type 2 diabetes [38].

Finally, our results showed a decline in the average number of steps of participants in the first stage of the intervention with relevant positive inflection in the second stage. However, it is worth noting that an essential part of the sample that received personalized messages showed quadratic behavior in the step trend with an evident decline from the sixth week. These results suggest that if rerandomization was performed earlier, our results could have been even more consistent. Our intervention currently provides for rerandomization in the sixth week. Adaptations in technology intervention are dynamic and must be implemented quickly. In this sense, an application with sufficient artificial intelligence could automate and individualize the adaptive process to increase physical activity.

Strengths and Limitations

As a strength of our study, we highlight its novelty. To our knowledge, this is the first study to develop an adaptive intervention based on behavior change techniques to increase the level of physical activity in adults. In addition, an interdisciplinary team was mandatory for the proposed intervention (ie, behavior change for physical activity). We showed that the SMART design, in association with behavior change techniques and technology-based features, is feasible and shows potential to be effective in promoting a more active lifestyle. In addition, few participants reported problems using the app. The Pacer app was useful for step counting, as expected. Even with limited accuracy, the number of steps taken in the Pacer app was reproducible and able to predict the distance traveled during walking [39]. Therefore, continuous monitoring of the number of steps through the app in this study was adequate. We were able to conduct the SMART design study, which required adequate planning and a dedicated team to deliver the intervention. The study design worked correctly and called for participants to have positive effects on the physical activity level. Finally, the qualitative analysis provided relevant information that may be useful to plan interventions on physical activity behavior change.

We are aware that the 34% drop-out rate of participants in this study is a possible limitation. However, this proportion has been described in other physical activity interventions in primary health care, even with a shorter intervention period (eg, 12 months) [39-41]. Moreover, we recognize the small number of participants, which limits pre- and postintervention comparisons, but this was a feasibility study, and we worked on improvements before beginning the full trial. Finally, we had no information about more specific feedback from participants on how they felt about achieving the increase in the physical activity level proposed. However, we intend to improve this point by forming focus groups with participants who go through the design of the study.

Conclusion

The SMART design was feasible for assessing the effects of a community-based smartphone app intervention to improve physical activity in insufficiently active adults. Our results suggest that rerandomization should be implemented earlier to take advantage of tailored messages.

Additionally, difficulties with technology and a realistic and individualized goal should be considered in interventions for physical activity using smartphones. We found a tendency to increase the average number of steps per day throughout the 24 weeks of the intervention, especially in the last 12 weeks. The results from the feasibility study contributed greatly to the final design of the SMART.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Text messages sent to participants throughout the intervention.
[DOCX File , 19 KB - resprot_v9i10e14322_app1.docx]

References

1. Meirelles FS. Pesquisa Anual do Uso de TI. Fundação Getúlio Vargas. 2019. URL: https://eaesp.fgv.br/producao-intelectual/pesquisa-anual-uso-ti [accessed 2020-09-23]
2. Fanning J, Mullen SP, McAuley E. Increasing physical activity with mobile devices: a meta-analysis. J Med Internet Res 2012 Nov 21;14(6):e161 [FREE Full text] [doi: 10.2196/jmir.2171] [Medline: 23171838]

3. Gal R, May AM, van Overmeeren EJ, Simons M, Monninkhof EM. The Effect of Physical Activity Interventions Comprising Wearables and Smartphone Applications on Physical Activity: a Systematic Review and Meta-analysis. Sports Med Open 2018 Sep 03;4(1):42 [FREE Full text] [doi: 10.1186/s40798-018-0157-9] [Medline: 30178072]
4. Romeo A, Edney S, Plotnikoff R, Curtis R, Ryan J, Sanders I, et al. Can Smartphone Apps Increase Physical Activity? Systematic Review and Meta-Analysis. J Med Internet Res 2019 Mar 19;21(3):e12053 [FREE Full text] [doi: 10.2196/12053] [Medline: 30888321]
5. Collins LM, Murphy SA, Strecher V. The multiphase optimization strategy (MOST) and the sequential multiple assignment randomized trial (SMART): new methods for more potent eHealth interventions. Am J Prev Med 2007 May;32(5 Suppl):S112-S118 [FREE Full text] [doi: 10.1016/j.amepre.2007.01.022] [Medline: 17466815]
6. Kumar S, Nilsen WJ, Abernethy A, Atienza A, Patrick K, Pavel M, et al. Mobile health technology evaluation: the mHealth evidence workshop. Am J Prev Med 2013 Aug;45(2):228-236 [FREE Full text] [doi: 10.1016/j.amepre.2013.03.017] [Medline: 23867031]
7. Orsmond GI, Cohn ES. The Distinctive Features of a Feasibility Study: Objectives and Guiding Questions. OTJR (Thorofare N J) 2015 Jul 06;35(3):169-177. [doi: 10.1177/1539449215578649] [Medline: 26594739]
8. Martin SS, Feldman DI, Blumenthal RS, Jones SR, Post WS, McKibben RA, et al. mActive: A Randomized Clinical Trial of an Automated mHealth Intervention for Physical Activity Promotion. JAHA 2015 Oct 29;4(11). [doi: 10.1161/jaha.115.002239]
9. Hooper R. Justifying sample size for a feasibility study. National Institute for Health Research. 2019. URL: https://www.rds-london.nihr.ac.uk/resources/justify-sample-size-for-a-feasibility-study/ [accessed 2020-09-23]
10. Prochaska JO, Velicer WF. The transtheoretical model of health behavior change. Am J Health Promot 1997 Aug 26;12(1):38-48. [doi: 10.4278/0890-1171-12.1.38] [Medline: 10170434]
11. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003 Aug;35(8):1381-1395. [doi: 10.1249/01.MSS.0000078924.61453.FB] [Medline: 12900694]
12. Tudor-Locke C, Bassett DR. How many steps/day are enough? Preliminary pedometer indices for public health. Sports Med 2004;34(1):1-8. [doi: 10.2165/00007256-200434010-00001] [Medline: 14715035]
13. Yates T, Haffner SM, Schulte PJ, Thomas L, Huffman KM, Bales CW, et al. Association between change in daily ambulatory activity and cardiovascular events in people with impaired glucose tolerance (NAVIGATOR trial): a cohort analysis. The Lancet 2014 Mar;383(9922):1059-1066. [doi: 10.1016/s0140-6736(13)62061-9]
14. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee I, et al. Quantity and Quality of Exercise for Developing and Maintaining Cardiorespiratory, Musculoskeletal, and Neuromotor Fitness in Apparently Healthy Adults. 2011;43(7):1334-1359. [doi: 10.1249/mss.0b013e318213fefb]
15. Prochaska JO, DiClemente CC, Norcross JC. In search of how people change: Applications to addictive behaviors. American Psychologist 1992;47(9):1102-1114. [doi: 10.1037/0003-066x.47.9.1102]
16. Troiano RP, Berrigan D, Dodd KW, Mâsse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. Med Sci Sports Exerc 2008 Jan;40(1):181-188. [doi: 10.1249/mss.0b013e31815a51b3] [Medline: 18091006]
17. Matthew CE. Calibration of accelerometer output for adults. Med Sci Sports Exerc 2005 Nov;37(11 Suppl):S512-S522. [doi: 10.1249/01.mss.0000185659.11982.3d] [Medline: 16294114]
18. Minayo MCDS. O desafio do conhecimento. In O desafio do conhecimento 2011:269. [doi: 10.1590/s0102-311x1992000300013]
19. Schoeppe S, Alley S, Van Lippevelde W, Bray NA, Williams SL, Duncan MJ, et al. Efficacy of interventions that use apps to improve diet, physical activity and sedentary behaviour: a systematic review. Int J Behav Nutr Phys Act 2016 Dec 07;13(1):127 [FREE Full text] [doi: 10.1186/s12966-016-0454-y] [Medline: 27927218]
20. Haggis C, Sims-Gould J, Winters M, Gutteridge K, McKay HA. Sustained impact of community-based physical activity interventions: key elements for success. BMC Public Health 2013 Sep 27;13(1):892 [FREE Full text] [doi: 10.1186/1471-2458-13-892] [Medline: 24069938]
21. Rush CL, Hooker SA, Ross KM, Frers AK, Peters JC, Masters KS. Brief report: Meaning in life is mediated by self-efficacy in the prediction of physical activity. J Health Psychol 2019 Feb 22:1359105319828172. [doi: 10.1177/1359105319828172] [Medline: 30791727]
22. Chen H, Sun H, Dai J. Peer Support and Adolescents' Physical Activity: The Mediating Roles of Self-Efficacy and Enjoyment. J Pediatr Psychol 2017 Jun 01;42(5):569-577. [doi: 10.1093/jpepsy/jsw103] [Medline: 28158660]
23. Horvath AO, Del Re AC, Flückiger C, Symonds D. Alliance in individual psychotherapy. Psychotherapy (Chic) 2011 Mar;48(1):9-16. [doi: 10.1037/a0022186] [Medline: 21401269]
24. Flückiger C, Del Re AC, Wampold BE, Symonds D, Horvath AO. How central is the alliance in psychotherapy? A multilevel longitudinal meta-analysis. J Couns Psychol 2012 Jan;59(1):10-17. [doi: 10.1037/a0025749] [Medline: 21988681]
25. Chang RC, Lu H, Yang P, Luarn P. Reciprocal Reinforcement Between Wearable Activity Trackers and Social Network Services in Influencing Physical Activity Behaviors. JMIR Mhealth Uhealth 2016 Jul 05;4(3):e84 [FREE Full text] [doi: 10.2196/mhealth.5637] [Medline: 27380798]

26. Muntaner-Mas A, Vidal-Conti J, Borràs PA, Ortega FB, Palou P. Effects of a Whatsapp-delivered physical activity intervention to enhance health-related physical fitness components and cardiovascular disease risk factors in older adults. J Sports Med Phys Fitness 2017 Jan;57(1-2):90-102. [doi: 10.23736/S0022-4707.16.05918-1] [Medline: 26364690]
27. O'Reilly GA, Spruijt-Metz D. Current mHealth technologies for physical activity assessment and promotion. Am J Prev Med 2013 Oct;45(4):501-507 [FREE Full text] [doi: 10.1016/j.amepre.2013.05.012] [Medline: 24050427]
28. Priebe CS, Spink KS. Using messages promoting descriptive norms to increase physical activity. Health Commun 2012 Apr;27(3):284-291. [doi: 10.1080/10410236.2011.585448] [Medline: 21899404]
29. Zhang J, Brackbill D, Yang S, Becker J, Herbert N, Centola D. Support or competition? How online social networks increase physical activity: A randomized controlled trial. Prev Med Rep 2016 Dec;4:453-458 [FREE Full text] [doi: 10.1016/j.pmedr.2016.08.008] [Medline: 27617191]
30. Priebe CS, Spink KS. Less sitting and more moving in the office: Using descriptive norm messages to decrease sedentary behavior and increase light physical activity at work. Psychology of Sport and Exercise 2015 Jul;19:76-84. [doi: 10.1016/j.psychsport.2015.02.008]
31. Brunet J, Sabiston CM. Exploring motivation for physical activity across the adult lifespan. Psychology of Sport and Exercise 2011 Mar;12(2):99-105. [doi: 10.1016/j.psychsport.2010.09.006]
32. Bauman AE, Reis RS, Sallis JF, Wells JC, Loos RJ, Martin BW. Correlates of physical activity: why are some people physically active and others not? The Lancet 2012 Jul;380(9838):258-271. [doi: 10.1016/s0140-6736(12)60735-1]
33. Hofmann SG, Asmundson GJ, Beck AT. The science of cognitive therapy. Behav Ther 2013 Jun;44(2):199-212. [doi: 10.1016/j.beth.2009.01.007] [Medline: 23611069]
34. Weinberg R. Goal Setting in Sport and Exercise: Research and Practical Applications. R Educ Fís UEM 2013 Jul 04;24(2). [doi: 10.4025/reveducfis.v24i2.17524]
35. Buckley J, Cohen JD, Kramer AF, McAuley E, Mullen SP. Cognitive control in the self-regulation of physical activity and sedentary behavior. Front Hum Neurosci 2014 Sep 29;8:747 [FREE Full text] [doi: 10.3389/fnhum.2014.00747] [Medline: 25324754]
36. Karoly P. Mechanisms of Self-Regulation: A Systems View. Annu. Rev. Psychol 1993 Jan;44(1):23-52. [doi: 10.1146/annurev.ps.44.020193.000323]
37. Pope JP, Pelletier L, Guertin C. Starting Off on the Best Foot: A Review of Message Framing and Message Tailoring, and Recommendations for the Comprehensive Messaging Strategy for Sustained Behavior Change. Health Commun 2018 Sep 16;33(9):1068-1077. [doi: 10.1080/10410236.2017.1331305] [Medline: 28622007]
38. Alghafri TS, Alharthi SM, Al-Farsi Y, Alrawahi AH, Bannerman E, Craigie AM, et al. 'MOVEdiabetes': a cluster randomized controlled trial to increase physical activity in adults with type 2 diabetes in primary health in Oman. BMJ Open Diabetes Res Care 2018 Oct 31;6(1):e000605. [doi: 10.1136/bmjdrc-2018-000605] [Medline: 30487976]
39. Jancey J, Lee A, Howat P, Clarke A, Wang K, Shilton T. Reducing attrition in physical activity programs for older adults. J Aging Phys Act 2007 Apr;15(2):152-165. [doi: 10.1123/japa.15.2.152] [Medline: 17556782]
40. Wade M, Brown N, Dancy B, Mann S, Gissane C, Majumdar A. Identification of dropout predictors to a community-based physical activity programme that uses motivational interviewing. J Public Health (Oxf) 2020 Feb 28;42(1):3-11. [doi: 10.1093/pubmed/fdy206] [Medline: 30452650]
41. Samdal GB, Meland E, Eide GE, Berntsen S, Abildsnes E, Stea TH, et al. The Norwegian Healthy Life Centre Study: A pragmatic RCT of physical activity in primary care. Scand J Public Health 2019 Feb 03;47(1):18-27. [doi: 10.1177/1403494818785260] [Medline: 30074437]

Abbreviations

cpm: counts per minute
EPIMOV: Epidemiology and Human Movement Study
IPAQ: International Physical Activity Questionnaire
MET: metabolic equivalent
SMART: sequential multiple assignment randomized trial

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Original Paper

Intervention to Improve Preschool Children's Fundamental Motor Skills: Protocol for a Parent-Focused, Mobile App–Based Comparative Effectiveness Trial

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Abstract

Background: Preschool age is an important time to master fundamental motor skills (FMS) through structured physical activity, yet many young children lag behind in motor skill development.

Objective: The Promoting Lifelong Activity in Youth (PLAY) study is a pilot comparative effectiveness trial to test the acceptability, feasibility, and preliminary effectiveness of a mobile app delivered to parents to promote FMS development in their preschool children (aged 3-5 years).

Methods: We conducted a 2-arm, parallel-design, randomized comparative effectiveness trial in 72 parent-child dyads from the southeastern United States. Experts in motor development and developmental psychology developed an app designed to deliver a 12-week program to parents of preschoolers using 1 of 2 curricula: an FMS program (intervention) that involved peer modeling, parent engagement, and structured skills-based activities and an unstructured physical activity (comparator) curriculum that provided suggestions for child-led physical activity (ie, free play). Primary outcomes are feasibility and acceptability of the app and child's FMS measured at end of intervention (week 12). Exploratory outcomes are child's objective physical activity, perceived movement competence, and parent report of self-regulation at the end of treatment (week 12) and sustained outcomes at follow-up (week 24).

Results: This project was funded in September 2018, with institutional review board approval in August 2018. Data collection took place from May 2019 through February 2020. To date, the project team has completed data collection on 69 preschool-age children, and results are expected to be published by 2021.

Conclusions: The PLAY study examines the feasibility and preliminary effectiveness of a mobile app, parent-led curricula to promote FMS proficiency for preschool children. If found to be effective, the app has the potential for wide-scale dissemination to parents of preschoolers and to provide a model for the utilization of mobile apps to promote young children's motor skill development.

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KEYWORDS

children; technology; family; motor skills; physical activity

Introduction

Background

Physical activity (PA) is vital to early childhood physical and mental development [1]. Yet a third of children aged 3-5 years do not engage in the recommended 3 hours of daily PA [2]. Structured PA promotes the development of fundamental motor skills (FMS) like running, jumping, or throwing a ball. These skills are basic, goal-directed movement patterns that provide a foundation for children to be physically active and competent movers [3] and enable a child to build the confidence and ability to be physically active [3,4]. These skills are not innately acquired and instead must be modelled and practiced for mastery. Evidence has shown that children must establish a minimal level of FMS proficiency to continue being physically active as they age [4-8].

FMS and PA behaviors have a dynamic and reciprocal relationship [4,7]. Children with higher levels of FMS are more physically active both during childhood [9-11] and into adolescence [12-15] compared to those with lower levels of FMS competency. Research has indicated that the preschool years are an opportune time for children to learn and reinforce these skills [16]. With inadequate FMS competency, a child is less likely to engage in PA based on a lack of prerequisite skills and abilities that are foundational to FMS [4-8], whereas a child with adequate FMS competency tends to be more physically active [17]. Moreover, FMS promote self-regulatory abilities including managing emotions, focusing attention, and inhibiting behavior [18]. Behavioral self-regulation is important for academic readiness [19] and regulating health behaviors that may also contribute to obesity [20]. Therefore, interventions for preschool children should focus on developing FMS competence.

As children and their parents spend a significant amount of time viewing screens [21], it may be opportune to leverage screen-time as a tool to increase preschool children's PA. Specifically, PA interventions delivered over digital devices, such as mobile apps, can provide encouragement in real-world settings for children to be physically active. The use of mobile-based interventions (eg, on a smartphone or tablet) has been recognized as a promising avenue to substantially affect levels of PA, especially in high-income countries such as the United States [22]. However, few mobile-based interventions have been developed that specifically focus on increasing PA in children [23,24], while several weight management apps include PA as a secondary component [25,26].

Comparable mobile health (mHealth) programs that focus on increasing PA in preschoolers are promising: A 6-month mobile app intervention delivered to parents of preschoolers improved children's PA, particularly among those with higher fat mass [27]. A 7-week intervention that involved cognitive behavioral skills training over text messaging to parents of preschoolers observed improved PA in the target child, but this intervention also included face-to-face visits with a counselor [28]. Only one of these studies delivered the intervention exclusively to parents, and the PA results were not reported [29]. In a slightly older age group (6-10 years of age), a mobile-based PA promotion program (P-Mobile) was delivered to parents and resulted in increased objectively measured steps/day [30]. The present intervention, the Promoting Lifelong Activity in Youth (PLAY) study, is focused on modeling FMS as a way to increase preschool-aged children's FMS, PA levels, perceived motor competence, and academic readiness.

Study Aims

The goal of PLAY is to test a developmentally appropriate intervention delivered on a mobile app to parents, with the goal of teaching FMS proficiency to their preschool-aged children (aged 3-5 years). The specific aims are described in the following sections.

Aim 1

The first aim is to examine the feasibility and acceptability of a 12-week FMS intervention delivered through a mobile app to parents and children.

Aim 2

The second aim is to test the hypothesis that a 12-week FMS intervention delivered through a mobile app will improve children's FMS, compared to the unstructured PA (UPA) app comparator group.

Exploratory Aim 1

The first exploratory aim is to test the hypothesis that a 12-week FMS intervention delivered through a mobile app will improve children's PA levels, perceived movement competence, and academic readiness (ie, self-regulation skills), compared to the UPA app comparator group.

Exploratory Aim 2

The second exploratory aim is to test the potential mediating or moderating effect of FMS on changes in exploratory outcomes.

Exploratory Aim 3

The third exploratory aim is to test the hypothesis that the effects of the FMS intervention will be sustained through week 24.

Methods

Study Design

The PLAY study was designed as an attention-matched randomized controlled trial, with the intervention arm receiving FMS instruction and the comparator arm receiving instruction on UPA. The PLAY study sought to recruit 72 child-parent dyads (children 3 to 5 years of age), with the goal of 36 dyads per arm. Parents were targeted to guide the intervention, as parental support, modeling, and co-participation predict children's engagement in PA [31-34]. Pennington Biomedical Research Center's Institutional Review Board approved this study (2018-041).

Sample Size and Power Calculation

The estimated effect size is based on a meta-analysis of FMS interventions (overall effect size d=0.39) [35,36]. A group size of 28 dyads/arm was originally planned to provide 80% power to detect an effect size of 0.33 for change in FMS score at week

12 (α=0.05). The research team enrolled and randomized 72 parent-child dyads to allow for a ~22% drop out by week 12 (based on previous studies by the multi-primary investigators), so that there would be at least 28 dyads/group at the end of the intervention (week 12).

Participants, Eligibility, and Recruitment

Parents of preschool children in a southeastern state of the United States were recruited between May 2019 and August 2019. Parents were recruited using advertisements via local childcare centers, community events, email listserv, and social media. Inclusion criteria for the child were age between 3 and 5 years, physically capable of exercise, and no mobility limitations that would impair PA based on parent report. Child exclusionary criterion was gross motor quotient at "gifted" or "very advanced" based on the Test of Gross Motor Development - 3rd edition (TGMD-3) [37] at baseline screening; the rationale was to avoid ceiling effects in the primary outcome. Inclusion criteria for parents included having a smartphone, willing to download and use the mobile app, having no plans to move during the study period (24 weeks), and having no self-reported mobility limitations that impaired modelling of FMS. Families were compensated US $25 upon completion of the baseline visit, week 12 visit, and week 24 visit, for a total of US $75.

Randomization and Blinding

Dyads were randomized in a 1:1 ratio to the FMS or UPA condition after all baseline assessments were complete. The statistician (RB) generated a sex-stratified adaptive randomization taking into account baseline FMS. Investigators were blinded. Data assessors were blinded at each assessment visit. Families discovered which condition they were assigned to following the completion of baseline data collections.

Procedures

After an initial phone screen, eligible preschool children and parents were asked to attend a screening visit. All study visits occurred at a local recreational facility or at the biomedical research center.

Screening Visit

Parents received detailed information about the study and provided written informed consent. Eligibility measures were also completed. Parents completed a weekly availability worksheet to identify available times and opportunities to practice lessons with their children using the mobile app at least 5 days per week. The preschool child performed the TGMD-3. TGMD-3 assessments were scored by a trained coder before the baseline visit to determine eligibility. The child was fitted for a hip-worn accelerometer (ActiGraph GT3X+BT), and parents were asked to have their child wear the accelerometer for 24 hours/day for 7 days while the parent completed a wear-time log. The parent was present when the child was fitted for their accelerometer to assist in appropriate placement while at home; parents were also given informational handouts on how to complete the parental log and when and how to take the monitors off.

Baseline Visit (Week 0)

The baseline visit was scheduled within 2-3 weeks of the screening visit. Parents returned the accelerometer at the baseline visit. If the child did not have adequate accelerometer wear during the time period, the parent was asked to have the child wear the accelerometer for an additional 7 days. Parents completed questionnaires at the baseline visit, which included parent and child demographics and child self-regulation. A trained research assistant measured the child's height and weight and conducted the Pictorial Scale of Perceived Movement Skill Competence for Young Children (PMSC) [38,39].

After the collection of baseline data, the trained research assistant revealed randomization from an opaque envelope provided by the statistician. The trained research assistant helped download the PLAY study mobile app onto the parent's smartphone and selected the FMS version or UPA version based on randomization. The trained research assistant familiarized the parent with the PLAY study mobile app by using the first weekly lesson as an example, showing the videos and explaining the points system.

Follow-Up Visits (Weeks 12 and 24)

The parent and child returned for 2 follow-up visits at 12 weeks (end of intervention) and 24 weeks (follow-up) after baseline. The parent was mailed the accelerometer and wear-time log 2 weeks ahead of these visits to provide adequate time for the child to wear the accelerometer for 7 days. Parents returned the accelerometer in-person for each visit. At both follow-up visits, parents completed questionnaires including child self-regulation and acceptability. Anthropometry, PMSC, and TGMD-3 were conducted with the preschool child and in that specific order. A trained research assistant deleted the PLAY study mobile app from the parent's smartphone at the week 24 visit.

Intervention

App Development

The PLAY app was developed by research scientists with expertise in FMS, developmental psychology, and behavior change and programmed by CyberFision, an app development company. Because the app is web-based, the app can function on a smartphone, tablet, or other mobile internet-enabled device. Parents in both conditions downloaded the PLAY study mobile app. To standardize the appearance and usability of the mobile app across the two conditions, one mobile app was created to house all components of the intervention, with specific features turned on for each condition (ie, parents of the FMS intervention did not see the UPA intervention components and vice versa).

Weekly Lessons

Parents in both conditions were instructed to first read the lesson each week, which detailed the purpose and goals for the activity breaks, and then to have their child perform the respective activity break (which was either the FMS or UPA suggested activities). Parents were asked to have their child engage in the activity breaks for at least 12 minutes/day, 5 days a week, for 12 weeks. This resulted in a total of 720 minutes of time directed toward either the FMS or UPA activity breaks. If the child was unable to obtain 12 minutes in one bout, the parent was asked

to obtain that total amount within the day (eg, two 6-minute sessions).

Reminders and Reinforcement Schedule

One-way SMS or text messages were sent 5 times each week via the mobile app to prompt the parent to read each week's lesson (1 time/week) and to prompt the parent and child to engage in the activity break (5 times/week). Parents selected times at their screening visit of when they wanted to receive these reminders. Additionally, a reinforcement schedule was built into the PLAY study mobile app by a point system in which the child pressed a star on the screen for each day that they performed the activity break (5 stars available for each week). Parents were encouraged to reward their child with non-food–based rewards such as small toys or non-tangible items such as a high-five. A new lesson was available every 7 days for 12 weeks for 12 lessons total. Lessons were unlocked regardless of the number of activity breaks completed; parents had access to previous lessons but were unable to access future lessons until the respective week. Research assistants also monitored parents' usage of the app weekly by monitoring whether the parents reported that the child engaged in at least one activity break through the star reporting system. The research assistants telephoned the parent when this information was missing to inquire if there were technical difficulties accessing the app.

Fundamental Motor Skill (FMS) Condition

The PLAY app provided parents in the FMS condition with brief instructional lessons, peer modeling videos of FMS, and peer modeling videos of activity breaks to deliver targeted, structured FMS instruction time. The FMS condition was built on a curriculum focused on 6 key FMS (3 locomotor, 3 object control) that were selected to be challenging but developmentally appropriate (hop, throw, slide, kick, jump, catch; each repeated twice). Activity breaks were developed and tested previously in a preschool-age population, demonstrating effectiveness to improve children's motor skill competence with good adherence [40,41]. Each week's lesson included 6 videos; 5 videos (approximately 5 seconds in length) showed preschool-aged children performing different aspects of an FMS (eg, stepping with opposition, bending knees). These series of videos were intended to help the parent select components of the FMS to focus on to shape the child's skill towards mastery [42]. A final video each week (<1 minute in length) showed children demonstrating activities for the activity break, which included activities that reinforced the week's selected skill. This final video was narrated by children.

For example, on Week 1 Day 1, the parent received a notification to open the app and access the first themed lesson, "Hop." The parent was asked to read a brief instructional lesson about the targeted FMS (including a description of a proficient "hop"), view the brief videos of the demonstrated FMS and suggested activity break activities, and then engage in a 12-minute activity break designed to help the parent model the skill and provide the preschool child with practice for the targeted FMS. Given the complexity of each FMS, parents were given 5 videos of the subcomponents of completing each FMS and asked to practice the progression that fit the child. For example, for overhand throwing, the child would practice winding up, stepping forward with the opposite foot, following through across their body, and aiming either for distance or accuracy. Therefore, the child and parent had video examples of child peers completing these FMS subcomponents. The goal was to obtain a total exposure of 720 minutes of directed instruction over 12 weeks, a dosage that aligns with prior interventions that effectively improved children's FMS [35,43].

Behavioral scaffolding [44] and social cognitive theory [44,45] informed the FMS approach. Behavioral scaffolding is a cognitive learning approach to problem solving that allows children to master skills beyond his or her current ability [46,47] and was implemented through video segments of children performing motor skills that increase in complexity. According to social cognitive theory, for modeling to effectively elicit behavior change, the child must undergo a process involving attention, retention, reproduction, and motivation [44,45]. This was accomplished through viewing of peers performing and narrating skills (attention), repeated practice and reminders (retention), replication of modeled activities (reproduction), and perceived competence and video and text files providing intrinsic and extrinsic motivation, respectively (motivation).

Unstructured Physical Activity (UPA) Condition

Parents in the UPA (defined as child-led free play) condition had access to the UPA lessons and UPA activity breaks to promote the equivalent amount of UPA time for the child (ie, 720 minutes over 12 weeks). The lessons were adapted to be developmentally appropriate for preschool children using a curriculum previously developed and tested based on social cognitive theory [30]. This comparator arm was selected as it has shown to increase children's PA levels [30] but does not explicitly target FMS or provide structured lessons to parents on how to model these skills. The following 6 topics were covered: setting goals, making time for child's free play, being active indoors and outdoors (eg, dancing), reinforcing PA, reducing sedentary behaviors (eg, screen-time), and parental co-participation. The activity breaks provided specific strategies to encourage the child's UPA (eg, take your child to the park or outside, use your phone alarm to remind your child to be physically active) with an accompanying video narrated by an adult that read aloud the lesson and featured photos depicting images that aligned with the lesson (eg, a photo of a park). There were no children featured in the photos so that the UPA group did not receive any peer modeling. Features of each condition may be found in Table 1.

Table 1. PLAY app: features of each condition.

Features	Fundamental motor skills (FMS)	Unstructured physical activity (PA)
Child physical activity	720 minutes of directed instruction on FMS over 12 weeks (12 minutes/day, 5 days/week)	720 minutes of unstructured PA over 12 weeks (12 minutes/day, 5 days/week)
Parent lesson	Parent reads lesson once a week on each targeted FMS (eg, description of a proficient "hop")	Parent reads lesson on PA support once a week (eg, how to make time for PA)
Peer modeling videos	Parent and child watch video of peers modeling each targeted FMS (eg, a child performing a "hop")	None
Activity break	Practice, modeling, and reinforcement of each targeted FMS (eg, hopping game)	Activity breaks of unstructured PA (eg, take child to the park, play songs for a dance party)
Push notifications	Once per week to notify of lesson availability; 5 times per week to prompt each 12-minute activity break	Once per week to notify of lesson availability; 5 times per week to prompt each 12-minute activity break
Rewards and reinforcement	Point system reinforcement schedule	Point system reinforcement schedule

Measures

Primary Outcomes

Feasibility was measured as adherence to the mobile app intervention, including objective data on the number of lessons, videos, and activity breaks accessed, and self-reported frequency of interaction with the app through the reinforcement schedule (ie, star reporting system). These data were provided on an ongoing basis by CyberFision. Acceptability was captured at weeks 4, 8, and 12 with an in-app parent survey that assessed satisfaction with the intervention in 4 domains (overall satisfaction, helpfulness, ease of use, and perceived change in child's motor skills) using a Likert-type scale. The System Usability Scale [48] and a satisfaction scale [49] were completed by the parents at the week 12 and 24 assessment visits. Additional usage data were captured via weekly parent surveys embedded within the app: the context of the activity breaks including the parent's location, the child's location, and who participated (weeks 1, 5, 9); barriers to performing the activity breaks and the use of equipment during the breaks (weeks 2, 6, 10); and engagement with the mobile app (weeks 3, 7, 11).

FMS were assessed using the TGMD-3, a direct observation assessment used with children aged 3-10 years [37]. The TGMD-3 is a process-oriented and product-oriented assessment to evaluate FMS performance in 2 subscales: locomotor (run, gallop, one-legged hop, skip, jump, and slide) and ball skills (two-hand strike, one-hand strike, catch, kick, dribble, overhand throw, and underhand throw). By design, these include skills targeted in the intervention. Previous research has demonstrated that the TGMD-3 is a valid and reliable assessment tool [50,51]. Assessments were filmed in an open space and coded by trained research assistants blinded to the purpose of this project. An FMS expert (EKW), who previously attained 99% reliability coding with the author of the TGMD-3 assessment, coded the administrations and was blinded to the experimental condition of the participants.

Exploratory Outcomes

To measure PA, the child was asked to wear an Actigraph GT3X+BT accelerometer for 7 days on the right hip, which has been previously validated in preschool children [52]. Minimal wear time was accepted as 4 days at ≥10 hours/day (≥1 weekend day) and 15-second epoch length [53] were used. Cutpoints by Pate et al [52] were used to classify moderate and vigorous PA, and cutpoints by Evenson et al [54] were used to classify sedentary time.

The PMSC [38] was used to examine the child's perceived movement competence on the 13 skills assessed with the TGMD-3 and took approximately 10 minutes for the child to complete. Previous research has established validity and reliability with this scale in this age range [39].

Self-regulation skills were reported by the parent using the Devereux Early Childhood Assessment, 2nd Edition, which is a 38-item proxy report with good validity and reliability to measure self-regulation and behavioral concerns in children aged 3-5 years [55].

Descriptive Characteristics and Potential Covariates

For anthropometry, height and weight were measured using a stadiometer and portable scale, respectively, without shoes, and recorded to the nearest 1.0 cm and 0.1 kg, respectively. A third measurement was taken if the 2 measurements differed by more than 0.5 units. BMI z-score was calculated [56].

To collect sociodemographic data, parents reported information on child and parent age, sex, race/ethnicity, parental education, family structure, childcare or away-from-home care, home environment [57], and household income. To collect health behavior information, parents reported the child's screen use, sleep, and prior experience of the preschool child and parent with mobile apps. The parent also completed a short questionnaire related to child diet, including intake frequency of specific food groups (high fat foods and sugary drinks), that has been previously validated in this age range [58].

Statistical Analysis

Intent-to-treat analyses will be used to include all participants with baseline and at least one follow-up value. Additional analyses will be conducted per protocol based on intervention adherence. Final selection of covariates included in the models will be based on model fit statistics, such as AIC.

Aim 1

Initial results for feasibility, broken down separately for number of lessons and videos accessed, activity breaks accessed, and

frequency of interaction, will be expressed using contingency tables. Rates, based on a generalized linear model with a Poisson distribution, will be used to both adjust for covariates and compare the 2 versions of the app (FMS vs UPA). Each of the 4 domains of acceptability will be treated independently and considered as a continuous response, analyzed with a linear model for covariate and app effects.

Aim 2

FMS results will be estimated using a linear mixed effect model with the baseline and follow-up scores at week 12 (end of intervention) and week 24 (end of study) as the outcome. This model will use random effects to account for the correlation in a participant over time. Results from the model will be reported as least square means, with *P* values based on *t* tests.

Exploratory Aims

PA levels, perceived movement competence, and self-regulation will be analyzed similarly as for Aim 2. FMS will be tested as a potential mediator and moderator. Mediations will investigate how the covariates affect the relationship between the condition and each outcome variable (for the exploratory analyses, these include PA levels, perceived movement competence, and academic readiness or self-regulation). Mediation analyses will be applied using both structural mean models and principal stratification [59].

Sustained effects will be estimated using a similar linear mixed model as described in an earlier section. However, time will be considered a continuous covariate in order to estimate the rate of sustained effect. This allows the interaction of app and time to test for rate differences between the 2 apps on outcomes of interest through the follow-up at weeks 12 and 24 (separate models conducted for each dependent variable measured continuously over time: FMS, PA levels, perceived movement competence, and self-regulation).

Results

This project was funded from September 2018 through 2021 by the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health. Pennington Biomedical Research Center's Institutional Review Board approved this study in August 2018. Recruitment occurred between May 2019 and August 2019. Accordingly, data collection happened from May 2019 through February 2020, including all baseline, week 12, and week 24 visits. To date, the project team has completed data collection on 69 parent-child dyads and is currently analyzing the primary and exploratory outcomes. Results of the current study are expected to be published in 2021.

Discussion

PLAY is a parent-targeted, theoretically grounded, mobile-based intervention designed to teach parents how to model, support, and guide their preschool-aged children's FMS competence. The scientific premise for the protocol is based on: (1) evidence showing that children must establish a minimal level of FMS proficiency to continue participating in PA opportunities as they age [4-8]; (2) longitudinal data linking FMS proficiency in childhood with higher levels of PA and lower adiposity 4 y later [15] and into adolescence [12], including an FMS intervention that increased preschoolers' PA [60]; (3) the lack of published mHealth interventions that specifically focus on parents of preschool-aged children or on PA promotion or FMS development; (4) the mixed results of prior mHealth interventions, which are at least partially attributable to previous efforts failing to fully capitalize on behavior change theory and maintain treatment intensity; and (5) the desire of parents to have family-focused interventions that are convenient to access [61].

Unlike other interventions that are primarily in childcare settings [11,62], this intervention utilizes parents to deliver the FMS curriculum, as parents serve an important role to enable early PA behaviors [63]. Previous work in low-income populations found that some of parents' PA was related to their preschool children's PA, providing more evidence that these behaviors could be modeled from parent to child [64]. Given the ubiquity of digital devices in parents' and children's daily lives [21], this study will leverage this existing screen-time and mobile app use to promote FMS development and healthy development in children.

The use of a mobile app to deliver the intervention offers the unique opportunity to distribute evidence-based content in a succinct and easily accessible manner to parents. This mode of delivery directly to the hands of the parent offers many advantages compared to receiving this instruction at in-person classes or health clinics, reducing barriers such as transportation, time commitment, and other family priorities [65]. The app offers ecological validity, so the child is practicing FMS and engaging in PA in the real-world setting of their own home rather than in a research laboratory. Further, the curriculum delivered on the mobile app is grounded in behavior change techniques, such as behavioral scaffolding and peer modelling, whereas many other mobile apps incorporate few behavior change techniques to shape behaviors [66]. Apps also offer the opportunity to incorporate real-time feedback through wearable devices, such as step counters and accelerometers, which are growing in popularity and acceptability by parents [67] but may or may not be acceptable or feasible for preschool-aged children.

One of the key strengths of using a mobile app is the opportunity for dissemination and implementation (ie, scaling up the intervention). The mobile app may be readily updated from parents' feedback and thereby adapted in a timely manner. This adaptability allows the study to bypass challenges in dissemination and implementation commonly presented in school and health care interventions, such as structural and personnel limitations. For example, the PLAY study mobile app delivers lessons that require little to no equipment and provides lessons directly to the parent and child. These two components decrease the potential for organizational challenges, along with hiring and training personnel to implement the intervention. Additionally, mobile apps allow accessibility to families and individuals living in rural areas where access to appropriate curriculum and health-enhancing activities is limited. A FMS curriculum delivered on a smartphone app is an innovative and potentially acceptable way to create a social

learning environment that can benefit young children and their parents from their homes.

There are potential limitations to the PLAY study. The parents were provided with videos that demonstrate each level of FMS progression divided into skill components and expected to determine their child's ability and adjust the activities for their child's current FMS level. An important consideration is that previous studies indicate parents do not provide a valid report of their child's FMS [68,69], which may lead to parents delivering content or curriculum that is not developmentally appropriate for their child. While the study outcome data on FMS were collected using a valid and reliable test and scored by a trained expert, future iterations may share these data directly with the parent to assist their intervention delivery.

One challenge is potential malfunction of the mobile app that can influence delivery and lesson implementation during the trial. The research study team conducted usability testing prior to use and also contacted parents with technical support if they did not engage with the mobile app (via reporting participation) at least once per week. This communication was intended to allow any mobile app errors to be found in real-time and quickly addressed. Another limitation is a concern in app research, which is differentiating between adherence to protocol (ie, completing the activity breaks) and engagement with the mobile app (ie, opening and utilizing the mobile app) [70]. This study used mobile app data (eg, viewing videos) as objective measurements of utilization of the app, but adherence to the protocol was limited to parent-report based on the family selecting stars each week to indicate completed activity breaks. Finally, as these data were collected in the southeastern United States, generalizability of the results of this feasibility study will be limited to this region. Future work will be needed to assess the feasibility in different regions, as well as to examine the effectiveness of this intervention in different subgroups (eg, sex, race/ethnicity, income level).

Overall, parents and preschool children spend much of their time using screens, and this existing screen-time may provide an opportunity to deliver beneficial and developmentally appropriate content to enhance FMS proficiency in young children. The PLAY study examines the feasibility and preliminary effectiveness of a mobile app and parent-led curricula to promote FMS proficiency for preschool children. If found to be effective, the app has the potential for wide-scale dissemination to parents of preschoolers and to provide a model for the utilization of mobile apps to promote young children's motor skill development.

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Conflicts of Interest

None declared.

References

1. Janssen I, Leblanc AG. Systematic review of the health benefits of physical activity and fitness in school-aged children and youth. Int J Behav Nutr Phys Act 2010 May 11;7:40 [FREE Full text] [doi: 10.1186/1479-5868-7-40] [Medline: 20459784]
2. Guidelines on physical activity, sedentary behaviour and sleep for children under 5 years of age. World Health Organization. 2019 Apr 2. URL: https://www.who.int/publications/i/item/guidelines-on-physical-activity-sedentary-behaviour-and-sleep-for-children-under-5-years-of-age [accessed 2020-10-03]
3. Clark JE, Metcalfe JS. The mountain of motor development: A metaphor. Motor development: research and review 2002;2:163-190.
4. Stodden DF, Goodway JD, Langendorfer SJ, Roberton MA, Rudisill ME, Garcia C, et al. A developmental perspective on the role of motor skill competence in physical activity: an emergent relationship. Quest 2008 May;60(2):290-306. [doi: 10.1080/00336297.2008.10483582]
5. De Meester A, Stodden D, Goodway J, True L, Brian A, Ferkel R, et al. Identifying a motor proficiency barrier for meeting physical activity guidelines in children. J Sci Med Sport 2018 Jan;21(1):58-62. [doi: 10.1016/j.jsams.2017.05.007] [Medline: 28595871]
6. Logan SW, Webster EK, Getchell N, Pfeiffer KA, Robinson LE. Relationship between fundamental motor skill competence and physical activity during childhood and adolescence: a systematic review. Kinesiology Review 2015;4(4):416-426. [doi: 10.1123/kr.2013-0012]
7. Robinson LE, Stodden DF, Barnett LM, Lopes VP, Logan SW, Rodrigues LP, et al. Motor competence and its effect on positive developmental trajectories of health. Sports Med 2015 Sep;45(9):1273-1284. [doi: 10.1007/s40279-015-0351-6] [Medline: 26201678]
8. Seefeldt V. Developmental Motor Patterns: Implications for Elementary School Physical Education. In: Nadeau WHC, Newell K, Roberts G, editors. Psychology of Motor Behavior and Sport. Champaign, IL: Human Kinetics; 1980:314-323.

9. Williams HG, Pfeiffer KA, O'Neill JR, Dowda M, McIver KL, Brown WH, et al. Motor skill performance and physical activity in preschool children. Obesity (Silver Spring) 2008 Jun;16(6):1421-1426 [FREE Full text] [doi: 10.1038/oby.2008.214] [Medline: 18388895]
10. Cliff DP, Okely AD, Smith LM, McKeen K. Relationships between fundamental movement skills and objectively measured physical activity in preschool children. Pediatr Exerc Sci 2009 Nov;21(4):436-449. [doi: 10.1123/pes.21.4.436] [Medline: 20128363]
11. Jones RA, Riethmuller A, Hesketh K, Trezise J, Batterham M, Okely AD. Promoting fundamental movement skill development and physical activity in early childhood settings: a cluster randomized controlled trial. Pediatr Exerc Sci 2011 Nov;23(4):600-615. [doi: 10.1123/pes.23.4.600] [Medline: 22109783]
12. Barnett LM, van Beurden E, Morgan PJ, Brooks LO, Beard JR. Childhood motor skill proficiency as a predictor of adolescent physical activity. J Adolesc Health 2009 Mar;44(3):252-259. [doi: 10.1016/j.jadohealth.2008.07.004] [Medline: 19237111]
13. Barnett LM, Van Beurden E, Morgan PJ, Brooks LO, Beard JR. Does childhood motor skill proficiency predict adolescent fitness? Med Sci Sports Exerc 2008 Dec;40(12):2137-2144. [doi: 10.1249/MSS.0b013e31818160d3] [Medline: 18981934]
14. Hands B. Changes in motor skill and fitness measures among children with high and low motor competence: a five-year longitudinal study. J Sci Med Sport 2008 Apr;11(2):155-162. [doi: 10.1016/j.jsams.2007.02.012] [Medline: 17567536]
15. Lopes VP, Maia JAR, Rodrigues LP, Malina R. Motor coordination, physical activity and fitness as predictors of longitudinal change in adiposity during childhood. European Journal of Sport Science 2012 Jul;12(4):384-391. [doi: 10.1080/17461391.2011.566368]
16. Clark J. Motor Development. In: Ramachandran VS, editor. Encyclopedia of Human Behavior (Vol. 3). San Diego, CA: Academic Press; 1994:245-255.
17. Logan SW, Scrabis-Fletcher K, Modlesky C, Getchell N. The relationship between motor skill proficiency and body mass index in preschool children. Res Q Exerc Sport 2011 Sep;82(3):442-448. [doi: 10.1080/02701367.2011.10599776] [Medline: 21957702]
18. Robinson LE, Palmer KK, Bub KL. Effect of the children's health activity motor program on motor skills and self-regulation in head start preschoolers: an efficacy trial. Front Public Health 2016;4:173 [FREE Full text] [doi: 10.3389/fpubh.2016.00173] [Medline: 27660751]
19. Raver CC, Jones SM, Li-Grining C, Zhai F, Bub K, Pressler E. CSRP's Impact on low-income preschoolers' preacademic skills: self-regulation as a mediating mechanism. Child Dev 2011;82(1):362-378 [FREE Full text] [doi: 10.1111/j.1467-8624.2010.01561.x] [Medline: 21291447]
20. Miller AL, Horodynski MA, Herb HEB, Peterson KE, Contreras D, Kaciroti N, et al. Enhancing self-regulation as a strategy for obesity prevention in Head Start preschoolers: the growing healthy study. BMC Public Health 2012 Nov 30;12:1040 [FREE Full text] [doi: 10.1186/1471-2458-12-1040] [Medline: 23194185]
21. Webster EK, Martin CK, Staiano AE. Fundamental motor skills, screen-time, and physical activity in preschoolers. J Sport Health Sci 2019 Mar;8(2):114-121 [FREE Full text] [doi: 10.1016/j.jshs.2018.11.006] [Medline: 30997257]
22. Pratt M, Sarmiento OL, Montes F, Ogilvie D, Marcus BH, Perez LG, et al. The implications of megatrends in information and communication technology and transportation for changes in global physical activity. The Lancet 2012 Jul 21;380(9838):282-293. [doi: 10.1016/S0140-6736(12)60736-3] [Medline: 22818940]
23. Newton KH, Wiltshire EJ, Elley CR. Pedometers and text messaging to increase physical activity: randomized controlled trial of adolescents with type 1 diabetes. Diabetes Care 2009 May;32(5):813-815 [FREE Full text] [doi: 10.2337/dc08-1974] [Medline: 19228863]
24. Shapiro JR, Bauer S, Hamer RM, Kordy H, Ward D, Bulik CM. Use of text messaging for monitoring sugar-sweetened beverages, physical activity, and screen time in children: a pilot study. J Nutr Educ Behav 2008;40(6):385-391 [FREE Full text] [doi: 10.1016/j.jneb.2007.09.014] [Medline: 18984496]
25. Bauer S, de Niet J, Timman R, Kordy H. Enhancement of care through self-monitoring and tailored feedback via text messaging and their use in the treatment of childhood overweight. Patient Educ Couns 2010 Jun;79(3):315-319. [doi: 10.1016/j.pec.2010.03.014] [Medline: 20418046]
26. de Niet J, Timman R, Bauer S, van den Akker E, Buijks H, de Klerk C, et al. The effect of a short message service maintenance treatment on body mass index and psychological well-being in overweight and obese children: a randomized controlled trial. Pediatr Obes 2012 Jun;7(3):205-219. [doi: 10.1111/j.2047-6310.2012.00048.x] [Medline: 22492669]
27. Nyström CD, Sandin S, Henriksson P, Henriksson H, Trolle-Lagerros Y, Larsson C, et al. Mobile-based intervention intended to stop obesity in preschool-aged children: the MINISTOP randomized controlled trial. Am J Clin Nutr 2017 Jun;105(6):1327-1335. [doi: 10.3945/ajcn.116.150995] [Medline: 28446496]
28. Militello L, Melnyk BM, Hekler EB, Small L, Jacobson D. Automated behavioral text messaging and face-to-face intervention for parents of overweight or obese preschool children: results from a pilot study. JMIR Mhealth Uhealth 2016 Mar 14;4(1):e21 [FREE Full text] [doi: 10.2196/mhealth.4398] [Medline: 26976387]
29. Haines J, McDonald J, O'Brien A, Sherry B, Bottino CJ, Schmidt ME, et al. Healthy habits, happy homes: randomized trial to improve household routines for obesity prevention among preschool-aged children. JAMA Pediatr 2013 Nov;167(11):1072-1079. [doi: 10.1001/jamapediatrics.2013.2356] [Medline: 24019074]

30. Newton RL, Marker AM, Allen HR, Machtmes R, Han H, Johnson WD, et al. Parent-targeted mobile phone intervention to increase physical activity in sedentary children: randomized pilot trial. JMIR Mhealth Uhealth 2014 Nov 10;2(4):e48 [FREE Full text] [doi: 10.2196/mhealth.3420] [Medline: 25386899]
31. Maitland C, Stratton G, Foster S, Braham R, Rosenberg M. A place for play? The influence of the home physical environment on children's physical activity and sedentary behaviour. Int J Behav Nutr Phys Act 2013 Aug 17;10:99 [FREE Full text] [doi: 10.1186/1479-5868-10-99] [Medline: 23958282]
32. Davison KK, Cutting TM, Birch LL. Parents' activity-related parenting practices predict girls' physical activity. Med Sci Sports Exerc 2003 Sep;35(9):1589-1595 [FREE Full text] [doi: 10.1249/01.MSS.0000084524.19408.0C] [Medline: 12972881]
33. Crawford D, Cleland V, Timperio A, Salmon J, Andrianopoulos N, Roberts R, et al. The longitudinal influence of home and neighbourhood environments on children's body mass index and physical activity over 5 years: the CLAN study. Int J Obes (Lond) 2010 Jul;34(7):1177-1187 [FREE Full text] [doi: 10.1038/ijo.2010.57] [Medline: 20351728]
34. Fuemmeler BF, Anderson CB, Mâsse LC. Parent-child relationship of directly measured physical activity. Int J Behav Nutr Phys Act 2011 Mar 08;8:17 [FREE Full text] [doi: 10.1186/1479-5868-8-17] [Medline: 21385455]
35. Logan SW, Robinson LE, Wilson AE, Lucas WA. Getting the fundamentals of movement: a meta-analysis of the effectiveness of motor skill interventions in children. Child Care Health Dev 2012 May;38(3):305-315. [doi: 10.1111/j.1365-2214.2011.01307.x] [Medline: 21880055]
36. Ignico AA. Effects of competency-based instruction on kindergarten children's gross motor development. Physical Educator 1991;48(4):188.
37. Ulrich DA. Test of Gross Motor Development (3rd ed.). Austin, TX: Pro-Ed; 2019.
38. Barnett LM, Ridgers ND, Zask A, Salmon J. Face validity and reliability of a pictorial instrument for assessing fundamental movement skill perceived competence in young children. J Sci Med Sport 2015 Jan;18(1):98-102. [doi: 10.1016/j.jsams.2013.12.004] [Medline: 24485803]
39. Barnett LM, Robinson LE, Webster EK, Ridgers ND. Reliability of the pictorial scale of perceived movement skill competence in 2 diverse samples of young children. J Phys Act Health 2015 Aug;12(8):1045-1051. [doi: 10.1123/jpah.2014-0141] [Medline: 25243542]
40. Wadsworth D, Robinson L, Beckham K, Webster K. Break for physical activity: incorporating classroom-based physical activity breaks into preschools. Early Childhood Educ J 2011 Oct 15;39(6):391-395 [FREE Full text] [doi: 10.1007/s10643-011-0478-5]
41. Webster EK, Wadsworth DD, Robinson LE. Preschoolers' time on-task and physical activity during a classroom activity break. Pediatr Exerc Sci 2015 Feb;27(1):160-167. [doi: 10.1123/pes.2014-0006] [Medline: 25249496]
42. Galbicka G. Shaping in the 21st century: moving percentile schedules into applied settings. J Appl Behav Anal 1994;27(4):739-760 [FREE Full text] [doi: 10.1901/jaba.1994.27-739] [Medline: 16795849]
43. Robinson LE, Palmer KK, Meehan SK. Dose–response relationship: the effect of motor skill intervention duration on motor performance. Journal of Motor Learning and Development 2017;5(2):280-290. [doi: 10.1123/jmld.2016-0004]
44. Bandura A, National Institute of Mental Health. Social Foundations of Thought and Action: A Social Cognitive Theory. Englewood Cliffs, NJ: Prentice Hall; 1986.
45. Bandura A. Social cognitive theory of self-regulation. Organizational Behavior and Human Decision Processes 1991 Dec;50(2):248-287 [FREE Full text] [doi: 10.1016/0749-5978(91)90022-l]
46. Wood D, Bruner JS, Ross G. The role of tutoring in problem solving. J Child Psychol Psychiatry 1976 Apr;17(2):89-100. [doi: 10.1111/j.1469-7610.1976.tb00381.x] [Medline: 932126]
47. Wood D, Middleton D. A study of assisted problem-solving. Br J Psychol 1975;66(2):181-191 [FREE Full text]
48. Bangor A, Kortum PT, Miller JT. An empirical evaluation of the system usability scale. International Journal of Human-Computer Interaction 2008 Jul 30;24(6):574-594. [doi: 10.1080/10447310802205776]
49. Newton RL, Perri MG. A randomized pilot trial of exercise promotion in sedentary african-american adults. Ethn Dis 2004;14(4):548-557. [Medline: 15724775]
50. Ulrich D. Spor Bilimleri Dergisi 2013;24:27-33.
51. Webster EK, Ulrich DA. Evaluation of the psychometric properties of the test of gross motor development-third edition. Journal of Motor Learning and Development 2017;5(1):45-58. [doi: 10.1123/jmld.2016-0003]
52. Pate RR, Almeida MJ, McIver KL, Pfeiffer KA, Dowda M. Validation and calibration of an accelerometer in preschool children. Obesity (Silver Spring) 2006 Nov;14(11):2000-2006 [FREE Full text] [doi: 10.1038/oby.2006.234] [Medline: 17135617]
53. Cliff DP, Reilly JJ, Okely AD. Methodological considerations in using accelerometers to assess habitual physical activity in children aged 0-5 years. J Sci Med Sport 2009 Sep;12(5):557-567. [doi: 10.1016/j.jsams.2008.10.008] [Medline: 19147404]
54. Evenson KR, Catellier DJ, Gill K, Ondrak KS, McMurray RG. Calibration of two objective measures of physical activity for children. J Sports Sci 2008 Dec;26(14):1557-1565. [doi: 10.1080/02640410802334196] [Medline: 18949660]
55. Barbu OC, Levine-Donnerstein D, Marx RW, Yaden DB. Reliability and validity of the devereux early childhood assessment (DECA) as a function of parent and teacher ratings. Journal of Psychoeducational Assessment 2012 Dec 20;31(5):469-481. [doi: 10.1177/0734282912467758]

56. A SAS program for the CDC growth charts. Centers for Disease Control and Prevention. 2011. URL: http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm [accessed 2015-07-09]
57. Matheny AP, Wachs TD, Ludwig JL, Phillips K. Bringing order out of chaos: psychometric characteristics of the confusion, hubbub, and order scale. Journal of Applied Developmental Psychology 1995 Jul;16(3):429-444. [doi: 10.1016/0193-3973(95)90028-4]
58. Henry BW, Smith TJ, Ahmad S. Psychometric assessment of the behavior and attitudes questionnaire for healthy habits: measuring parents' views on food and physical activity. Public Health Nutr 2014 May;17(5):1004-1012. [doi: 10.1017/S136898001200554X] [Medline: 23332083]
59. Hayes AF. Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach. New York, NY: Guilford Publications; 2017.
60. Cohen KE, Morgan PJ, Plotnikoff RC, Callister R, Lubans DR. Physical activity and skills intervention: SCORES cluster randomized controlled trial. Med Sci Sports Exerc 2015 Apr;47(4):765-774. [doi: 10.1249/MSS.0000000000000452] [Medline: 25051389]
61. Staiano AE, Marker AM, Comeaux J, Frelier JM, Hsia DS, Broyles ST. Family-based behavioral treatment for childhood obesity: caretaker-reported barriers and facilitators. Ochsner J 2017;17(1):83-92 [FREE Full text] [Medline: 28331454]
62. Wasenius NS, Grattan KP, Harvey ALJ, Naylor P, Goldfield GS, Adamo KB. The effect of a physical activity intervention on preschoolers' fundamental motor skills - a cluster RCT. J Sci Med Sport 2018 Jul;21(7):714-719. [doi: 10.1016/j.jsams.2017.11.004] [Medline: 29150312]
63. Carson V, Langlois K, Colley R. Associations between parent and child sedentary behaviour and physical activity in early childhood. Health Rep 2020 Feb 19;31(2):3-10 [FREE Full text] [doi: 10.25318/82-003-x202000200001-eng] [Medline: 32073643]
64. Barkin SL, Lamichhane AP, Banda JA, JaKa MM, Buchowski MS, Evenson KR, et al. Parent's physical activity associated with preschooler activity in underserved populations. Am J Prev Med 2017 Apr;52(4):424-432 [FREE Full text] [doi: 10.1016/j.amepre.2016.11.017] [Medline: 28081998]
65. Barber SE, Jackson C, Hewitt C, Ainsworth HR, Buckley H, Akhtar S, et al. Assessing the feasibility of evaluating and delivering a physical activity intervention for pre-school children: a pilot randomised controlled trial. Pilot Feasibility Stud 2016;2:12 [FREE Full text] [doi: 10.1186/s40814-016-0052-4] [Medline: 27965832]
66. McKay FH, Wright A, Shill J, Stephens H, Uccellini M. Using health and well-being apps for behavior change: a systematic search and rating of apps. JMIR Mhealth Uhealth 2019 Jul 04;7(7):e11926 [FREE Full text] [doi: 10.2196/11926] [Medline: 31274112]
67. Mackintosh KA, Chappel SE, Salmon J, Timperio A, Ball K, Brown H, et al. Parental perspectives of a wearable activity tracker for children younger than 13 years: acceptability and usability study. JMIR Mhealth Uhealth 2019 Nov 04;7(11):e13858 [FREE Full text] [doi: 10.2196/13858] [Medline: 31682585]
68. Maher S, Schott N, Lander NJ, Hinkley T, Barnett LM. A comparison of parent report and actual motor competence in young children. Aust Occup Ther J 2018 Oct;65(5):387-394. [doi: 10.1111/1440-1630.12486] [Medline: 29926927]
69. Zysset AE, Kakebeeke TH, Messerli-Bürgy N, Meyer AH, Stülb K, Leeger-Aschmann CS, et al. The validity of parental reports on motor skills performance level in preschool children: a comparison with a standardized motor test. Eur J Pediatr 2018 May;177(5):715-722 [FREE Full text] [doi: 10.1007/s00431-017-3078-6] [Medline: 29427041]
70. Sieverink F, Kelders SM, van Gemert-Pijnen JE. Clarifying the concept of adherence to eHealth technology: systematic review on when usage becomes adherence. J Med Internet Res 2017 Dec 06;19(12):e402 [FREE Full text] [doi: 10.2196/jmir.8578] [Medline: 29212630]

Abbreviations

FMS: fundamental motor skills
mHealth: mobile health
PA: physical activity
PLAY: Promoting Lifelong Activity in Youth
PSMC: Pictorial Scale of Perceived Movement Skill Competence for Young Children
TGMD-3: Test of Gross Motor Development – 3rd edition
UPA: unstructured physical activity

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Protocol

Comparing Conventional Chemotherapy to Chronomodulated Chemotherapy for Cancer Treatment: Protocol for a Systematic Review

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Abstract

Background: Chronomodulated chemotherapy aims to achieve maximum drug safety and efficacy by adjusting the time of treatment to an optimal biological time as determined by the circadian clock. Although it is a promising alternative to conventional (non–time-stipulated) chemotherapy in several instances, the lack of scientific consensus and the increased logistical burden of timed administration limit the use of a chronomodulated administration protocol.

Objective: With the goal to increase scientific consensus on this subject, we plan to conduct a systematic review of the current literature to compare the drug safety and efficacy of chronomodulated chemotherapy with those of conventional chemotherapy.

Methods: This systematic review will comply with the PRISMA (Preferred Reporting Items for the Systematic Reviews and Meta-Analysis) guidelines. In order to identify relevant studies, we conducted a comprehensive search in PubMed and Embase on May 18, 2020. We included clinical studies that compare either the safety or efficacy of chronomodulated chemotherapy with that of conventional chemotherapy. Potential studies will be reviewed and screened by 2 independent reviewers. Quality assessment will be performed using the National Institutes of Health's Study Quality Assessment Tool (Quality Assessment of Controlled Intervention Studies). Disagreements will be resolved by consulting a third independent reviewer.

Results: This protocol has received funding, and the search for studies from databases commenced on May 18, 2020. The systematic review is planned to be completed by October 31, 2020.

Conclusions: In this systematic review, we will compare drug safety and drug efficacy for cancer patients who were administered either chronomodulated chemotherapy or conventional chemotherapy. Moreover, we will highlight the outcomes and quality of the selected trials for this review.

Trial Registration: PROSPERO International Prospective Register of Systematic Reviews CRD42020177878; https://tinyurl.com/y53w9nq6

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KEYWORDS

cancer; chemotherapy; chronotherapy; circadian clock; efficacy; overall survival; safety; systematic review

Introduction

Circadian rhythms (circa: about, dia: a day) organize biological functions in living organisms around an approximate 24-hour period to adjust organ and tissue physiology to the ever-changing demands of day and night [1]. Controlled by a molecular clockwork, they drive oscillations in a broad range of biological processes, ranging from the cellular level (eg, cell cycle regulation [2] and cellular metabolism [3]) to whole body physiology (eg, liver and renal activity [4]), which can therefore greatly affect drug responses [5].

Chemotherapy is used to treat many cancers and involves administration of cytotoxic drugs that either kill or interfere with the proliferation of rapidly dividing cells. The principle of conventional chemotherapy is to increase the chemotherapy dose until maximum cytotoxicity occurs and a maximum tolerated dose is reached. However, as both malignant and normal cells are affected, severe toxicities are often developed, in turn leading to interruption of chemotherapy treatments and decreased survival rates [6]. Therefore, finding ways to increase efficacy and reduce side effects would greatly improve cancer therapy potential.

The molecular mechanisms involved in regulating pharmacological processes such as drug absorption, distribution, metabolism, and excretion are controlled by the circadian clock. The clock thereby determines when the anticancer drug treatment should ideally be delivered as it controls the drug's elimination and detoxification, affecting the efficacy and toxicity on tumor cells and healthy cells, respectively [7]. In addition to this, the sensitivity of molecular drug targets shows diurnal variations [7]. The tolerability of more than 40 anticancer drugs such as oxaliplatin have demonstrated a 10-fold variability in rodents as a function of dosing time [7]. Anticancer drugs have shown to have a 24-hour variability in drug toxicity as well as improved efficacy and tolerability in rodents kept in alternate exposure to 12h light and 12h darkness (LD12:12) [7]. The circadian rhythms of both drug toxicity and efficacy are defined in preclinical studies, and the optimal circadian time from rodents is extrapolated and translated to the most suitable time to administer chemotherapy according to the human's circadian rhythms [8]. Together, these findings have led to the investigation of the time-dependent changes in the efficacy and safety of anticancer drug therapies [7].

Chronomodulated chemotherapy aims to exploit the circadian variation in drug response by administering anticancer drugs at specific times of the day, thereby hitting cancer cells when they are most vulnerable or normal cells when they are least vulnerable [9,10]. The terms chronomodulated and circadian-based have been used to describe similar strategies using parenteral or oral administration. For the sake of clarity, we will use the term chronomodulation for all therapeutic routes.

The goal of chronomodulated chemotherapy is to minimize toxic side effects while promoting the maximum achievable efficacy of the chemotherapy regimen to improve the cancer patients' quality of life, survival time that is based on the different circadian rhythms of DNA synthesis, and cell growth between tumor and normal cells [11,12]. The impact of circadian rhythms on the outcome of cancer therapy has been the subject of several clinical trials over the past two decades. While conventional chemotherapy generally consists of constant-rate drug delivery, chronomodulated chemotherapy is administered as a variable rate infusion with peak drug delivery times set to vary according to circadian time or delivery restricted to specific time windows [13].

To date, several studies have established the association between circadian disruption caused by shiftwork and increased cancer risk [14-17]. In 2007, the International Agency for Research on Cancer classified "shiftwork that involves circadian disruption" as a probable carcinogenic risk [18]. Furthermore, both cancer and chemotherapy have been found to disturb circadian rhythmicity independently of each other [19]. These factors may be causing interpatient variability of circadian rhythms to a yet unknown extent. This leaves room for the exploration of optimizing chronotherapy by adjusting administration time to each patient's individual circadian clock.

Although chronomodulated chemotherapy is a promising avenue of research that could contribute significantly to improve existing and future cancer treatments, no medical consensus has been reached to implement chronomodulated chemotherapy regimens, and conventional chemotherapy is most often administered in accordance with the hospital schedule and staff working hours [10]. Before this approach is integrated into clinical practice, its benefits must be adequately supported with evidence from well-designed randomized clinical trials.

This systematic review will evaluate the findings of randomized controlled trials (RCTs) that compare the safety and efficacy of chronomodulated chemotherapy with those of conventional chemotherapy administration in adult cancer patients.

Methods

The systematic review and its protocol will comply with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines [20].

Inclusion and Exclusion Criteria

Studies in English, Dutch, or German will be included in the systematic review. Clinical trials that compare the safety or efficacy of chemotherapy administered to adult cancer patients in accordance with conventional and chronomodulated chemotherapy regimens will be included. Only RCTs will be included in the systematic review. There will be no restrictions on inclusion of studies by time frame or type of setting. We will provide a list of all excluded clinical trials as a supplemental file.

Participants

Adult patients (≥18 years old) of all ethnicities and genders that are diagnosed with any type of cancer will be included. No

restrictions will be imposed with respect to participants having received other treatment prior to inclusion in the trial.

Interventions

RCTs that compare the clinical safety or efficacy of chemotherapy administered according to circadian delivery schedules with standard delivery schedules will be included. Single agent and combination chronotherapy regimens delivered through oral administration, bolus injection, or infused according to a flat or sinusoidally chronomodulated schedule will be included. In addition, trials with concomitant radiotherapy will be included in this systematic review.

Outcome Measures

The outcome of this systematic review will be analyzed as per the following measures.

Safety

This will include changes in chemotherapy administration, like a delay or a reduction of chemotherapy treatment, maximum tolerable dose, termination of treatment, or early withdrawal from the clinical trial. Toxicity will be assessed by either of the following toxicity grading scales: World Health Organization standard toxicity criteria [21], Common Toxicity Criteria [22], Eastern Cooperation Oncology Group criteria for toxicity [23], Radiation Therapy Oncology Group criteria [24], and Gynecologic Oncology Group standard toxicity criteria.

Efficacy

This will include objective response rate (also known as response rate), disease control rates, progression free survival, and overall survival, taking into account salvage therapies if reported. In the case of neoadjuvant and adjuvant studies, efficacy will be measured by recurrence rate and disease-free and overall survival.

Search Strategy

Studies published on or before May 18, 2020, were identified by performing a comprehensive search in PubMed and Embase (Elsevier). A literature search strategy was developed in collaboration with an information specialist from Utrecht University unconnected to this study. The search strategy was composed of the following terms and their synonyms: cancer, circadian rhythms, and chemotherapy. For chemotherapy, alongside its synonyms, specific terms for chemotherapy classes, individual drug names, and brand names were included. The World Health Organization's list of essential medicines 2019 [25] was utilized to confirm inclusion of all essential chemotherapies. Appropriate MeSH (Medical Subject Headings) and Embase subjects headings (Emtree terms) were added to the search strategy for PubMed and Embase searches, respectively. No limits on publication dates were imposed on the search. The search results were narrowed down to show only articles in English, Dutch, or German, due to resource limits. For Embase, conference abstracts were filtered from the search results. The complete search is listed in Multimedia Appendix 1. The reference lists of all selected articles were handsearched, and their titles and abstracts will be assessed based on the inclusion and exclusion criteria.

Study Selection

The appropriate references and trials for the review will be deduplicated in Endnote (Clarivate Analytics) and afterwards uploaded to Rayyan [26] to be screened on title and abstract and will be reviewed independently by 2 different reviewers (ABK and MIP). Disagreements will be resolved by consulting a third independent reviewer (LWL). Full texts that contain studies that could be suitable for the systematic review will be screened based on the inclusion and exclusion criteria. If there is no full text available for a relevant trial, the corresponding author(s) will be contacted in order to request it.

Risk of Bias and Quality Assessment

The quality and the risk of bias for selected trials and studies will be assessed using the Quality Assessment of Controlled Intervention Studies tool from the National Heart, Lung, and Blood Institute [27]. All included studies will be categorized as being of good, fair, or poor quality. Studies judged as being of poor quality will be excluded from this review. The risk of bias and quality assessment will be performed by 2 reviewers (ABK and MIP). Any inconsistencies between the 2 reviewers will be resolved by consulting a third reviewer (LWL).

Selective reporting within studies will be assessed by verifying if a protocol was published for each included study and evaluating whether all specified outcomes were published. Other possible risks of meta-bias such as publication bias will be discussed appropriately.

The confidence in the cumulative evidence obtained will be assessed using GRADE (Grading of Recommendations, Assessment, Development and Evaluations) [28] for each primary outcome measure.

Data Extraction

A data extraction sheet will be developed to store information about the selected studies and trials. Each paper will be assessed independently by 2 reviewers (MIP and ABK) to reduce bias. Data from the selected studies and trials will be extracted independently by the 2 reviewers. The data extraction form will be made and piloted before final implementation by both reviewers. The following parameters will be extracted:

1. Publication information: authors, year, country, and journal.
2. Study information: trial size, subject characteristics, type of cancer, duration and frequency of follow-up, chemotherapy, and trial objectives.
3. Treatment information: type of treatment schedule for each patient.
4. Primary outcome variables: efficacy (objective response rate, overall survival, and progression-free survival); toxicity (incidence of side effects and severity of side effects based on either World Health Organization's standard toxicity criteria [21] or the National Cancer Institute's Common Terminology Criteria for Adverse Events [22]).
5. Secondary outcome variables: efficacy (disease control rate, reduction in tumor marker, complete response, pathological complete response, disease-free survival, event-free survival, recurrence rate, reoperation rate, rate of microscopically complete resection, time to progression of

cancer symptoms, subjective tumor-related symptoms, minimal residual disease, metastasis-free survival); toxicity (duration of side effect, reversibility of side effect, dose limiting toxicity, treatment modifications, treatment delays, and treatment discontinuations); efficacy and toxicity (quality of life, time to treatment failure).

All factors influencing toxicity and efficacy will be explored appropriately. In order to compare the endpoints in both study arms, we will collect the corresponding hazard ratios, relative risks, risk differences, mean/median differences, and their statistical significance, as far as availability allows.

Amendments

Any amendments made to the protocol will be documented in PROSPERO (the International Prospective Register of Systematic Reviews) by MIP. The methods section of the systematic review will include a summary of any protocol amendments accompanied by date and rationale.

Results

The search for the relevant studies on databases was performed on May 18, 2020. The systematic review is intended to be completed and ready for submission for publication by October 31, 2020.

Discussion

This systematic review will have some limitations that will be discussed appropriately. The exclusion of papers not written in English, Dutch, and German may inhibit the identification of all important findings, and this will be taken into consideration in the discussion of the systematic review. However, the database searches of the appropriate studies will be extensive to ensure the required studies are captured for the systematic review.

We will produce a table with patient characteristics, including gender, age, ethnicity, and different cancer types. In this table, we will also include the type of chemotherapy used in the trial, the dose and half-life of these cytotoxic drugs, any significant differences between the conventional and chronomodulated chemotherapy treatment groups, optimal delivery time to administer the chemotherapeutic drug of choice, and the treatment group that produces the least side effects. In case of a sinusoidal infusion schedule, we will also state the circadian timing system function. The selected studies included in this review will provide information required to conclude whether chemotherapy regimens should be administered in accordance with the circadian clock and highlight the findings and quality of reporting these particular clinical trials. This systematic review will provide vital information on drug safety and drug efficacy in cancer patients administered chronomodulated chemotherapy versus conventional chemotherapy.

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Authors' Contributions

LWL is the guarantor of this review. LWL conceived the study and acquired funding. ABK, US, and MIP developed and drafted the protocol. AMM, CJAP, MP, JPGS, and LWL critically revised the protocol and manuscripts and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search terms.
[PDF File (Adobe PDF File), 65 KB - resprot_v9i10e18023_app1.pdf]

References

1. Roenneberg T, Merrow M. The Circadian Clock and Human Health. Curr Biol 2016 May 23;26(10):R432-R443 [FREE Full text] [doi: 10.1016/j.cub.2016.04.011] [Medline: 27218855]
2. Chaix A, Zarrinpar A, Panda S. The circadian coordination of cell biology. J Cell Biol 2016 Oct 10;215(1):15-25 [FREE Full text] [doi: 10.1083/jcb.201603076] [Medline: 27738003]
3. Putker M, Crosby P, Feeney KA, Hoyle NP, Costa ASH, Gaude E, et al. Mammalian Circadian Period, But Not Phase and Amplitude, Is Robust Against Redox and Metabolic Perturbations. Antioxid Redox Signal 2018 Mar 01;28(7):507-520 [FREE Full text] [doi: 10.1089/ars.2016.6911] [Medline: 28506121]
4. Marcheva B, Ramsey K, Peek C, Affinati A, Maury E, Bass J. Circadian clocks and metabolism. Handbook of Experimental Pharmacology 2013:127-155. [doi: 10.1007/978-3-642-25950-0_6] [Medline: 23604478]

5. Musiek ES, Fitzgerald GA. Molecular clocks in pharmacology. Handb Exp Pharmacol 2013(217):243-260 [FREE Full text] [doi: 10.1007/978-3-642-25950-0_10] [Medline: 23604482]
6. Aldred EM. Chapter 39 - Chemotherapy. In: Pharmacology: A Handbook for Complementary Healthcare Professionals. Edinburgh; New York: Churchill Livingstone, Elsevier; 2009:307-313.
7. Ozturk N, Ozturk D, Kavakli IH, Okyar A. Molecular Aspects of Circadian Pharmacology and Relevance for Cancer Chronotherapy. Int J Mol Sci 2017 Oct 17;18(10) [FREE Full text] [doi: 10.3390/ijms18102168] [Medline: 29039812]
8. Hrushesky WJ. Circadian timing of cancer chemotherapy. Science 1985 Apr 05;228(4695):73-75. [doi: 10.1126/science.3883493] [Medline: 3883493]
9. Eriguchi M, Levi F, Hisa T, Yanagie H, Nonaka Y, Takeda Y. Chronotherapy for cancer. Biomed Pharmacother 2003 Oct;57 Suppl 1:92s-95s. [doi: 10.1016/j.biopha.2003.08.012] [Medline: 14572683]
10. Ballesta A, Innominato PF, Dallmann R, Rand DA, Lévi FA. Systems Chronotherapeutics. Pharmacol Rev 2017 Apr;69(2):161-199 [FREE Full text] [doi: 10.1124/pr.116.013441] [Medline: 28351863]
11. Lévi F, Okyar A, Dulong S, Innominato PF, Clairambault J. Circadian timing in cancer treatments. Annu Rev Pharmacol Toxicol 2010;50:377-421. [doi: 10.1146/annurev.pharmtox.48.113006.094626] [Medline: 20055686]
12. Lévi F. Chronotherapeutics: the relevance of timing in cancer therapy. Cancer Causes Control 2006 May;17(4):611-621. [doi: 10.1007/s10552-005-9004-7] [Medline: 16596317]
13. Erkekoglu P, Baydar T. Chronopharmacodynamics of drugs in toxicological aspects: A short review for clinical pharmacists and pharmacy practitioners. J Res Pharm Pract 2012 Oct;1(2):41-47 [FREE Full text] [doi: 10.4103/2279-042X.108369] [Medline: 24991588]
14. Lie JS, Roessink J, Kjaerheim K. Breast cancer and night work among Norwegian nurses. Cancer Causes Control 2006 Feb;17(1):39-44. [doi: 10.1007/s10552-005-3639-2] [Medline: 16411051]
15. Schernhammer ES, Laden F, Speizer FE, Willett WC, Hunter DJ, Kawachi I, et al. Rotating night shifts and risk of breast cancer in women participating in the nurses' health study. J Natl Cancer Inst 2001 Oct 17;93(20):1563-1568. [doi: 10.1093/jnci/93.20.1563] [Medline: 11604480]
16. Papantoniou K, Castaño-Vinyals G, Espinosa A, Aragonés N, Pérez-Gómez B, Burgos J, et al. Night shift work, chronotype and prostate cancer risk in the MCC-Spain case-control study. Int J Cancer 2015 Sep 01;137(5):1147-1157 [FREE Full text] [doi: 10.1002/ijc.29400] [Medline: 25530021]
17. Papantoniou K, Castaño-Vinyals G, Espinosa A, Turner MC, Alonso-Aguado MH, Martin V, et al. Shift work and colorectal cancer risk in the MCC-Spain case-control study. Scand J Work Environ Health 2017 May 01;43(3):250-259 [FREE Full text] [doi: 10.5271/sjweh.3626] [Medline: 28251241]
18. Palmer K. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 98: Painting, Firefighting and Shiftwork. International Agency for Research on Cancer. Occupational Medicine 2011 Oct 04;61(7):521-522. [doi: 10.1093/occmed/kqr127]
19. Innominato PF, Roche VP, Palesh OG, Ulusakarya A, Spiegel D, Lévi FA. The circadian timing system in clinical oncology. Ann Med 2014 Jun;46(4):191-207. [doi: 10.3109/07853890.2014.916990] [Medline: 24915535]
20. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009 Aug 18;151(4):264-9, W64. [Medline: 19622511]
21. World Health Organization. WHO handbook for reporting results of cancer treatment.: World Health Organization; 1979. URL: https://apps.who.int/iris/handle/10665/37200 [accessed 2020-02-04]
22. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 5. 2017 Nov 27. URL: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf [accessed 2020-02-04]
23. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982 Dec;5(6):649-655. [Medline: 7165009]
24. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995 Mar 30;31(5):1341-1346. [doi: 10.1016/0360-3016(95)00060-C] [Medline: 7713792]
25. World Health Organization Model List of Essential Medicines: 21st List 2019. World Health Organization. Geneva: World Health Organization URL: https://apps.who.int/iris/handle/10665/325771 [accessed 2020-02-04]
26. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev 2016 Dec 05;5(1):210 [FREE Full text] [doi: 10.1186/s13643-016-0384-4] [Medline: 27919275]
27. Study Quality Assessment Tools. National Heart, Lung, and Blood Institute (NHLBI). 2014. URL: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools [accessed 2020-02-04]
28. Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE handbook for grading quality of evidence and strength of recommendations. alfkdsn: The GRADE Working Group; Oct 2013. URL: https://gdt.gradepro.org/app/handbook/handbook.html

Abbreviations

GRADE: Grading of Recommendations, Assessment, Development and Evaluations
MeSH: Medical Subject Headings
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PROSPERO: International Prospective Register of Systematic Reviews
RCT: randomized controlled trial

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Protocol

The Analgesic Effect of Electroencephalographic Neurofeedback for People With Chronic Pain: Protocol for a Systematic Review and Meta-analysis

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Abstract

Background: Chronic pain is a global health problem, affecting around 1 in 5 individuals in the general population. The understanding of the key role of functional brain alterations in the generation of chronic pain has led researchers to focus on pain treatments that target brain activity. Electroencephalographic neurofeedback attempts to modulate the power of maladaptive electroencephalography frequency powers to decrease chronic pain. Although several studies have provided promising evidence, the effect of electroencephalographic neurofeedback on chronic pain is uncertain.

Objective: This systematic review aims to synthesize the evidence from randomized controlled trials to evaluate the analgesic effect of electroencephalographic neurofeedback. In addition, we will synthesize the findings of nonrandomized studies in a narrative review.

Methods: We will apply the search strategy in 5 electronic databases (Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, PsycInfo, and CINAHL) for published studies and in clinical trial registries for completed unpublished studies. We will include studies that used electroencephalographic neurofeedback as an intervention for people with chronic pain. Risk-of-bias tools will be used to assess methodological quality of the included studies. We will include randomized controlled trials if they have compared electroencephalographic neurofeedback with any other intervention or placebo control. The data from randomized controlled trials will be aggregated to perform a meta-analysis for quantitative synthesis. The primary outcome measure is pain intensity assessed by self-report scales. Secondary outcome measures include depressive symptoms, anxiety symptoms, and sleep quality measured by self-reported questionnaires. We will investigate the studies for additional outcomes addressing adverse effects and resting-state electroencephalography analysis. Additionally, all types of nonrandomized studies will be included for a narrative synthesis. The intended and unintended effects of nonrandomized studies will be extracted and summarized in a descriptive table.

Results: Ethics approval is not required for a systematic review, as there will be no patient involvement. The search for this systematic review commenced in July 2020, and we expect to publish the findings in early 2021.

Conclusions: This systematic review will provide recommendations for researchers and health professionals, as well as people with chronic pain, about the evidence for the analgesic effect of electroencephalographic neurofeedback.

Trial Registration: International Prospective Register of Systematic Reviews (PROSPERO) CRD42020177608; https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=177608

International Registered Report Identifier (IRRID): PRR1-10.2196/22821

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KEYWORDS

EEG neurofeedback; chronic pain; meta-analysis; systematic review

Introduction

Background

Chronic pain is estimated to affect up to 50% of the adult population [1,2], and 10% to 20% experience clinically significant chronic pain [3]. Chronic pain is defined as ongoing or recurrent pain, lasting for at least three months [4,5]. It is often associated with functional limitations and psychological distress [4,6], resulting in a decreased health-related quality of life [7,8]. Chronic pain may result from an ongoing pathology (eg, cancer), damage to the central nervous system (eg, stroke and spinal cord injury) or peripheral nervous system (eg, diabetic neuropathy), tissue degeneration (eg, arthritis), and other pain syndromes with unknown pathologies (eg, fibromyalgia and complex regional pain syndrome).

The understanding of the critical role of maladaptive functional brain changes in the development and maintenance of chronic pain has led researchers to focus on pain treatments that aim to modulate brain activity [9,10]. Previously, neurosurgical methods, such as cordotomy and thalamotomy, were considered to be effective in the control of abnormal brain activity, such as increased theta frequency power, resulting in a significant pain reduction [11,12]. However, these types of surgery are costly, highly invasive, and associated with major complications such as cognitive impairment. In the past few decades, noninvasive brain stimulation techniques including transcranial direct current stimulation, cranial electrotherapy stimulation, and repetitive transcranial magnetic stimulation have been used to reduce pain by aiming to alter the maladaptive brain activity associated with chronic pain. However, there is insufficient evidence to support the efficacy of these approaches on chronic pain [13,14]. More recently, electroencephalographic (EEG) neurofeedback using brain-computer interface technology has been developed to target the maladaptive brain activity underlying chronic pain [2,15].

Description of EEG Neurofeedback

The goal of EEG neurofeedback is to modulate the targeted maladaptive EEG frequency powers to decrease chronic pain [2,15,16]. Surface EEG is recorded from 1 or more electrode sites, depending on the specific pain condition, often from the sensorimotor cortex [17]. The targeted frequency powers are extracted and processed in real time, then presented to the individual as visual or auditory feedback, or both [16,18]. For example, it has been shown that individuals with chronic neuropathic pain have increased theta and reduced alpha frequency power compared with healthy individuals without chronic pain [19,20]. In this case, EEG neurofeedback is used to suppress theta and reinforce alpha frequency power [2,16]. Using this EEG neurofeedback protocol, individuals can learn to regulate their abnormal brain activity in a way that reduces their chronic pain [2,16].

Previous Reviews and Rationale

Previous systematic reviews about the effect of EEG neurofeedback on chronic pain have mainly focused on specific pain conditions such as fibromyalgia [21,22] or cancer-related pain [23]. The results of these systematic reviews were inconclusive due to the limited data. While a recent review found a medium effect size of pain reduction favoring neurofeedback interventions in chronic pain, it included studies using functional magnetic resonance imaging-based neurofeedback [24]. Combining the results for 2 different methodologies makes it difficult to evaluate the analgesic effect of a specific intervention.

Our planned systematic review will cover all forms of chronic pain and include only EEG-based neurofeedback interventions to increase the likelihood of conclusive evidence about the analgesic effect of EEG neurofeedback. Although inclusion of a wide variety of pain conditions will increase the heterogeneity of the pooled data, the larger sample size will substantially improve the meta-analytic power. In order to distinguish the effect of EEG neurofeedback on different chronic pain types, such as neuropathic and nonneuropathic pain, we will conduct a subgroup analysis (see the Subgroup and Sensitivity Analysis subsection below). Review findings will inform researchers and health professionals, as well as people with chronic pain, about the analgesic effect of EEG neurofeedback. In addition, this review can help to identify any gaps in previous studies and provide direction for future research.

Objectives

The primary objective of this systematic review is to evaluate the evidence for the analgesic effect of EEG neurofeedback for people with chronic pain. The secondary objective is to investigate the effect of EEG neurofeedback on depressive symptoms, anxiety symptoms, and sleep quality. Further, as an additional objective of this systematic review, we will include the reports of adverse events and resting-state EEG analysis for a narrative review.

Methods

Review Registration

This systematic review protocol is prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) 2015 guidelines [25,26]. Multimedia Appendix 1 is the PRISMA-P checklist. This systematic review is registered in the International Prospective Register of Systematic Reviews with registration number CRD42020177608.

Types of Participants

We will include studies of participants with chronic pain, defined as persistent or recurrent pain for more than 3 months [4]. There will be no restriction on age or sex of the participants in the included studies.

Types of Intervention

We will include studies that investigate the analgesic effect of EEG neurofeedback for people with chronic pain, regardless of the number and duration of intervention sessions, the EEG neurofeedback protocol, and the targeted brain region.

Types of Outcome Measures

The *primary* outcome measure is pain intensity. Pain intensity may be assessed using a self-report rating scale such as the visual analog scale or the numeric rating scale. Studies that used other scales will also be included.

The *secondary* outcome measures are depressive symptoms, anxiety symptoms, and sleep quality. Depressive symptoms and anxiety symptoms may be measured by self-report questionnaires such as the Beck Depression Inventory or Beck Anxiety Inventory, or the Hamilton Depression Rating Scale or Hamilton Anxiety Rating Scale. Sleep quality may be assessed using the Medical Outcomes Study Sleep Scale or the Pittsburgh Sleep Quality Index. Studies that have used other assessments will not be excluded.

We will include studies that have assessed the primary or secondary outcome measures, or both, on at least two occasions, one before or at the beginning of the intervention and one close to or at the end of the intervention. Further, we will include additional outcome measures for the narrative review. For example, reports of any adverse effects will be included as well as the results of the resting-state EEG analysis comparing pre- versus postintervention.

Types of Studies

We will include randomized controlled trials (RCTs) if they have compared EEG neurofeedback with no treatment or any other intervention, including sham control, waitlist control, or usual care. Nonrandomized studies, defined as "any quantitative study estimating the effectiveness of an intervention that does not use randomisation to allocate subjects to comparison groups" [27], will be included for a narrative review. Comparative nonrandomized studies (eg, cross-sectional designs and controlled cohort studies) will be used to address intended effects, and noncomparative studies (eg, case reports and case series) will be reported for corroborating evidence and adverse effects. All studies must have used EEG neurofeedback as an intervention for people with chronic pain. We will exclude studies that involved the following: (1) individuals experiencing pain for less than 3 months; (2) healthy individuals with experimentally induced pain; and (3) any other intervention in conjunction with EEG neurofeedback.

Search Strategy

To identify the eligible studies, we will search 5 electronic bibliographic databases for published studies: (1) Cochrane Central Register of Controlled Trials (CENTRAL), (2) MEDLINE, EMBASE, and PsycInfo via Ovid, and (3) CINAHL via EBSCO.

Additionally, we will search the following clinical trial registries for completed unpublished studies: (1) ClinicalTrials.gov, (2) EU Clinical Trials Register, (3) Australia New Zealand Clinical Trials Registry, and (4) World Health Organization International Clinical Trials Registry Platform (ICTRP).

Search strategies will be established using Medical Subject Headings (MeSH) and related text words. We will use a combination of different keywords for chronic pain and EEG neurofeedback intervention to identify relevant literature. The search strategies will be tailored to each database. Multimedia Appendix 2 shows the search strategy according to Ovid search syntax. There will be no restriction on the publication period, but only articles in English language will be included. In addition, we will check the reference lists of the eligible studies and relevant review articles to include any missed but relevant published studies. While the review is in progress, citation searching for forward citation of recent studies and citation alerts (eg, on Google Scholar) on included studies will be used to identify new studies as they appear. The searches will be rerun prior to the final analysis and further retrieved studies will be included.

Study Selection

We will use EndNote X9 (Clarivate Analytics) reference software to store, organize, and manage all the search results and ensure an efficient study selection process by removing the duplicate records. Two reviewers will independently evaluate the title and abstract of all studies identified through the search against the inclusion and exclusion criteria. Any disagreement between the individual judgments will be resolved by an additional reviewer. The screening process will be conducted in Covidence (Veritas Health Innovation Ltd), which is systematic review management software. The full text of the selected studies will then be retrieved. In the case of trial registrations, the full text is defined as all associated files and information. If the reviewer is uncertain about the eligibility of any study, the full text will be obtained for further information. An additional reviewer will be consulted, should there be any uncertainty or disagreement of the eligibility of studies. Disagreement on study eligibility will be resolved through consensus. Excluded studies and the reasons for exclusion will be recorded and documented.

Data Extraction

We will pilot test a customized data extraction spreadsheet on 2 studies relevant to this review, and then use it to extract data from the eligible studies. Two reviewers will independently extract the data from the final list of studies. The disagreements in the extracted data will be resolved through discussion with an additional reviewer. The following information will be extracted from the eligible studies.

We will extract data on *study characteristics*, including the study design, country, and setting of the study.

We will extract *participant* data on diagnosis, age, sex, duration of pain, comorbidities, and the number of participants allocated in each intervention group. The primary and secondary outcome measures at baseline (ie, before or at the beginning of the intervention) will also be extracted (mean and measure of variability).

We will extract *intervention* data on EEG neurofeedback protocols including the targeted frequency bands, the targeted brain region, the duration of each session, the number of sessions, and the duration of the interventions. Data on the details of the comparative intervention (ie, type, dosage, frequency) in each individual study will also be extracted.

We will extract data on the type of *outcome measures* used to assess the primary and secondary outcomes, the time points from baseline to the end of interventions, and follow-ups. The postintervention assessments will be categorized into 3 groups: short-term for less than 1 week, mid-term for 1 to 6 weeks, and long-term for more than 6 weeks for follow-up assessments.

We will extract *results* of the primary and secondary outcome measures at a time point close to or at the end of the interventions, or the changes in outcome measures from baseline for each intervention group. If a study used more than 1 outcome measure of pain intensity, we will select and extract only a single measure, prioritizing them in the following order: 100-mm/10-cm visual analog scale, 11-point numeric rating scale (0 = no pain, 10 = the worst pain imaginable), and then pain intensity rating from composite measures or other scales [28].

For the secondary outcome measures, we will extract scores from each of the questionnaires for depressive symptoms, anxiety symptoms, and sleep quality if the studies used more than 1 questionnaire. We will also extract the number of participants who stopped receiving the treatment due to a rare or adverse event in each intervention group.

If data are missing, we will contact the authors of the studies a maximum of 3 times, after which we will consider the data to be irretrievable.

Study Quality and Risk of Bias

Study quality and risk of bias will be assessed by 2 independent reviewers using the first version of the Cochrane Risk of Bias (RoB 1.0) tool for RCTs [29] and the Cochrane Risk of Bias in Non-Randomised Studies - of Interventions (ROBINS-I) tool for nonrandomized studies [30]. Additionally, the quality of noncomparative studies (eg, case reports and case series) will be assessed using the Joanna Briggs Institute critical appraisal tools [31]. The inconsistencies will be resolved by an additional reviewer.

We will use the Cochrane RoB 1.0 tool to assess the study-level risk of bias for 5 domains: selection, performance, detection, attrition, and reporting bias [29]. We will use the ROBINS-I tool to assess the risk of bias for studies that have not used randomization for intervention allocations, such as cohort studies and cross-sectional designs. The risk-of-bias assessment using this tool covers 7 domains: confounding and participants' selection (preintervention), intervention classification (during intervention), and deviations, missing data, measurements, and selection of reported results (postintervention) [30]. The ROBINS-I tool includes signaling questions to provide easier judgments for each domain, as well as an overall risk-of-bias assessment. We will use the Joanna Briggs Institute critical appraisal checklists [31] for case reports and case series to assess the study-level risk of bias.

Data Synthesis

We will not combine the data extracted from RCTs and nonrandomized studies for a quantitative synthesis. The distinctions between various types of nonrandomized studies and RCTs make it methodologically indefensible to pool the results in a meta-analysis [32]. The extracted outcomes data from RCTs will be quantitatively synthesized by a meta-analysis method using R (R version 4.0.0; R Foundation for Statistical Computing) software. The population and intervention from at least two RCTs must be sufficiently similar to perform a meta-analysis. Indeed, the level of consistency and appropriateness of RCTs is key to justify pooling the results in a meta-analysis [33].

We will convert the primary and secondary outcome data to a 0- to 100-point scale (mean and standard deviation) [28]. In numerical or continuous scales, the score value is divided by the range of scale, and then multiplied by 100. For example, for a 0 to 20 scale, the score value is divided by 20 and multiplied by 100. Likert scales will be treated as numerical scales, because the scores for Likert-type questions can be summed and presented as a final scale score. Additionally, in categorical scales, the lowest value will be assigned to be 0, and then 1 additional point for each category of severity. For example, none = 0, mild = 1, moderate = 2, and high = 3. Then, these values will be treated like numerical scales.

The relative treatment effects of the compared interventions (eg, EEG neurofeedback vs control) on the outcome measures will be estimated using weighted mean difference with 95% confidence intervals [28]. We will use a threshold of 10 points on the 0- to 100-point scale to clarify the minimal clinically important effect of EEG neurofeedback on pain intensity [34]. Since a cutoff threshold has not been established for converted 0 to 100 points of the secondary outcomes, we will adopt a 10-point threshold as the clinically meaningful change for depressive symptoms, anxiety symptoms, and sleep quality.

In recognition of the likely heterogeneity of the chronic pain population and the EEG neurofeedback methodology, we will use a random-effects meta-analysis. We will assess the

heterogeneity of the study population and intervention using the χ^2 test and estimate the degree of heterogeneity using the I^2 statistic. The heterogeneity is considered significant when $P<.1$ and when $I^2 \geq 50\%$. A subgroup analysis will be performed when significant heterogeneity is present (see Subgroup and Sensitivity Analysis subsection).

We will conduct a narrative synthesis to provide additional information about EEG neurofeedback as an intervention including adverse effects. The data and methodology for the great variety of nonrandomized designs are usually not sufficiently similar to be pooled in a meta-analysis; thus, we will use a narrative approach for these studies [35]. Narrative methods of synthesis include classification of evidence from diverse studies, data reduction, data display, comparison, and conclusion [36]. The findings from the nonrandomized studies will be described and summarized in an extraction table using techniques of narrative synthesis.

Quality of Evidence

We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [37] to grade the certainty of evidence and the strength of recommendations at the outcome level. For example, the GRADE rating will be applied to the outcome of interest to estimate the certainty of the intervention effect. There are 4 levels of certainty within the GRADE approach: very low, low, moderate, and high. The level of certainty of evidence can be downgraded for the following reasons.

Risk of Bias

The rating will be downgraded by 2 levels if there is a high risk of bias for more than 25% and less than 50% of the included studies' participants. It will be 1 grade down if more than 50% of participants are from high risk-of-bias studies [38].

Imprecision

The rating will be downgraded by 1 level if the total number of participants is less than 400 for continuous data and less than 300 for dichotomous data [39].

Inconsistency

The rating will be downgraded by 1 level if significant heterogeneity is identified ($P<.1$) [40].

Indirectness

This domain will not be considered because the inclusion criteria of this review ensures a specific population and outcome interest [41].

Publication Bias

The rating will be downgraded by 1 level if a publication bias is detected using visual and statistical assessments [42].

Subgroup and Sensitivity Analysis

Where heterogeneity is identified ($P<.1$), we will conduct subgroup analysis according to the type of chronic pain and the study population age through preplanned analysis: (1) neuropathic pain versus nonneuropathic pain: neuropathic pain is defined as "pain caused by a lesion or disease of the somatosensory nervous system" [43], and nonneuropathic pain includes all other chronic pain conditions; (2) adults versus adolescents or children: studies including adults over 18 years old compared with studies with individuals under 18 years old.

Further, depending on the variability of RCTs, we will conduct a sensitivity analysis to assess the impact of excluding studies with high risk of bias.

Results

This review will not require any ethics approval, as there will be no patient involvement in the conduct, reporting, and interpretation of the review. The search for this systematic review commenced in July 2020, and we will disseminate the findings as soon as they are available, expected by early 2021.

Discussion

This protocol describes the methodology of a systematic review and meta-analysis to aggregate the evidence for analgesic effects of EEG neurofeedback for people with chronic pain. In addition to including RCTs for a meta-analysis, we will supplement the review by a narrative synthesis of nonrandomized comparative designs for intended effects and noncomparative designs for corroborating evidence and adverse effects.

The heterogeneity of the chronic pain population and the variety of EEG neurofeedback methodology might restrict the opportunities for meta-analysis and interpretation of results. However, preplanned subgroup analyses based on the pain conditions and patients' age groups will help to address the issue of population heterogeneity.

We will report the methodology and results of this review according to the PRISMA guidelines [44]. The findings will provide an evaluation of both the intended and adverse effects of EEG neurofeedback interventions. Given the debilitating impact of chronic pain on people's quality of life, this systematic review will provide recommendations for researchers, health care professionals, and people with chronic pain about the evidence for the analgesic effect of EEG neurofeedback.

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Authors' Contributions

NH-S, SMG, TN-J, and JHM conceptualized the protocol; NH-S and W-JC defined the concepts, search items, data extraction process, and methodological appraisal of the studies; NH-S drafted the manuscript; and all authors critically reviewed the manuscript. All authors have approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) checklist.
[PDF File (Adobe PDF File), 80 KB - resprot_v9i10e22821_app1.pdf]

Multimedia Appendix 2
Search strategy.
[PDF File (Adobe PDF File), 10 KB - resprot_v9i10e22821_app2.pdf]

References

1. van Hecke O, Torrance N, Smith BH. Chronic pain epidemiology and its clinical relevance. Br J Anaesth 2013 Jul;111(1):13-18 [FREE Full text] [doi: 10.1093/bja/aet123] [Medline: 23794640]
2. Jensen MP, Gertz KJ, Kupper AE, Braden AL, Howe JD, Hakimian S, et al. Steps toward developing an EEG biofeedback treatment for chronic pain. Appl Psychophysiol Biofeedback 2013 Jun;38(2):101-108. [doi: 10.1007/s10484-013-9214-9] [Medline: 23532434]
3. Goldberg DS, McGee SJ. Pain as a global public health priority. BMC Public Health 2011 Oct 06;11:770 [FREE Full text] [doi: 10.1186/1471-2458-11-770] [Medline: 21978149]
4. Treede R, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. A classification of chronic pain for ICD-11. Pain 2015 Jun;156(6):1003-1007 [FREE Full text] [doi: 10.1097/j.pain.0000000000000160] [Medline: 25844555]
5. Steingrímsdóttir Ó, Landmark T, Macfarlane GJ, Nielsen CS. Defining chronic pain in epidemiological studies: a systematic review and meta-analysis. Pain 2017 Nov;158(11):2092-2107. [doi: 10.1097/j.pain.0000000000001009] [Medline: 28767506]
6. Gatchel RJ. Comorbidity of chronic pain and mental health disorders: the biopsychosocial perspective. Am Psychol 2004 Nov;59(8):795-805. [doi: 10.1037/0003-066X.59.8.795] [Medline: 15554853]
7. Jensen MP, Chodroff MJ, Dworkin RH. The impact of neuropathic pain on health-related quality of life: review and implications. Neurology 2007 Apr 10;68(15):1178-1182. [doi: 10.1212/01.wnl.0000259085.61898.9e] [Medline: 17420400]
8. Lamé IE, Peters ML, Vlaeyen JWS, Kleef MV, Patijn J. Quality of life in chronic pain is more associated with beliefs about pain, than with pain intensity. Eur J Pain 2005 Feb;9(1):15-24. [doi: 10.1016/j.ejpain.2004.02.006] [Medline: 15629870]
9. Alshelh Z, Di Pietro F, Youssef AM, Reeves JM, Macey PM, Vickers ER, et al. Chronic neuropathic pain: it's about the rhythm. J Neurosci 2016 Jan 20;36(3):1008-1018. [doi: 10.1523/JNEUROSCI.2768-15.2016] [Medline: 26791228]
10. Prinsloo S, Gabel S, Lyle R, Cohen L. Neuromodulation of cancer pain. Integr Cancer Ther 2014 Jan;13(1):30-37. [doi: 10.1177/1534735413477193] [Medline: 23439659]
11. Jeanmonod D, Magnin M, Morel A, Siegemund M. Surgical control of the human thalamocortical dysrhythmia: I. Central lateral thalamotomy in neurogenic pain. Thalamus Related Syst 2006 Apr 12;1(1):71-79. [doi: 10.1017/s1472928801000036]
12. Meyerson BA. Neurosurgical approaches to pain treatment. Acta Anaesthesiol Scand 2001 Oct;45(9):1108-1113. [doi: 10.1034/j.1399-6576.2001.450910.x] [Medline: 11683661]
13. Boldt I, Eriks-Hoogland I, Brinkhof MWG, de Bie R, Joggi D, von Elm E. Non-pharmacological interventions for chronic pain in people with spinal cord injury. Cochrane Database Syst Rev 2014 Nov 28(11):CD009177. [doi: 10.1002/14651858.CD009177.pub2] [Medline: 25432061]
14. O'Connell NE, Marston L, Spencer S, DeSouza LH, Wand BM. Non-invasive brain stimulation techniques for chronic pain. Cochrane Database Syst Rev 2018 Mar 16;3:CD008208 [FREE Full text] [doi: 10.1002/14651858.CD008208.pub4] [Medline: 29547226]
15. Hassan MA, Fraser M, Conway BA, Allan DB, Vuckovic A. The mechanism of neurofeedback training for treatment of central neuropathic pain in paraplegia: a pilot study. BMC Neurol 2015 Oct 13;15:200 [FREE Full text] [doi: 10.1186/s12883-015-0445-7] [Medline: 26462651]
16. Vučković A, Altaleb MKH, Fraser M, McGeady C, Purcell M. EEG correlates of self-managed neurofeedback treatment of central neuropathic pain in chronic spinal cord injury. Front Neurosci 2019;13:762 [FREE Full text] [doi: 10.3389/fnins.2019.00762] [Medline: 31404253]
17. Miró J, Castarlenas E, de la Vega R, Roy R, Solé E, Tomé-Pires C, et al. Psychological neuromodulatory treatments for young people with chronic pain. Children (Basel) 2016 Dec 06;3(4) [FREE Full text] [doi: 10.3390/children3040041] [Medline: 27929419]

18. Micoulaud-Franchi J, McGonigal A, Lopez R, Daudet C, Kotwas I, Bartolomei F. Electroencephalographic neurofeedback: level of evidence in mental and brain disorders and suggestions for good clinical practice. Neurophysiol Clin 2015 Dec;45(6):423-433. [doi: 10.1016/j.neucli.2015.10.077] [Medline: 26553293]
19. Boord P, Siddall PJ, Tran Y, Herbert D, Middleton J, Craig A. Electroencephalographic slowing and reduced reactivity in neuropathic pain following spinal cord injury. Spinal Cord 2008 Feb;46(2):118-123. [doi: 10.1038/sj.sc.3102077] [Medline: 17502876]
20. Jensen MP, Sherlin LH, Gertz KJ, Braden AL, Kupper AE, Gianas A, et al. Brain EEG activity correlates of chronic pain in persons with spinal cord injury: clinical implications. Spinal Cord 2013 Jan;51(1):55-58. [doi: 10.1038/sc.2012.84] [Medline: 22801188]
21. Glombiewski JA, Bernardy K, Häuser W. Efficacy of EMG-and EEG-biofeedback in fibromyalgia syndrome: a meta-analysis and a systematic review of randomized controlled trials. Evid Based Complement Alternat Med 2013;2013:962741 [FREE Full text] [doi: 10.1155/2013/962741] [Medline: 24082911]
22. Santoro M, Cronan T. A systematic review of neurofeedback as a treatment for fibromyalgia syndrome symptoms. J Musculoskelet Pain 2014 May 19;22(3):286-300. [doi: 10.3109/10582452.2014.883037]
23. Hetkamp M, Bender J, Rheindorf N, Kowalski A, Lindner M, Knispel S, et al. A systematic review of the effect of neurofeedback in cancer patients. Integr Cancer Ther 2019;18:1534735419832361. [doi: 10.1177/1534735419832361] [Medline: 30832518]
24. Patel K, Sutherland H, Henshaw J, Taylor JR, Brown CA, Casson AJ, et al. Effects of neurofeedback in the management of chronic pain: a systematic review and meta-analysis of clinical trials. Eur J Pain 2020 Jun 05. [doi: 10.1002/ejp.1612] [Medline: 32502283]
25. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015 Jan;4:1 [FREE Full text] [doi: 10.1186/2046-4053-4-1] [Medline: 25554246]
26. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015 Jan 02;349:g7647. [Medline: 25555855]
27. Reeves BC, Higgins JPT, Ramsay C, Shea B, Tugwell P, Wells GA. An introduction to methodological issues when including non-randomised studies in systematic reviews on the effects of interventions. Res Synth Methods 2013 Mar;4(1):1-11. [doi: 10.1002/jrsm.1068] [Medline: 26053535]
28. Bagg MK, McLachlan AJ, Maher CG, Kamper SJ, Williams CM, Henschke N, et al. Paracetamol, NSAIDS and opioid analgesics for chronic low back pain: a network meta-analysis. Cochrane Database Syst Rev 2018 Jun;2018(6):CD013045. [doi: 10.1002/14651858.cd013045]
29. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Cochrane Bias Methods Group, Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928 [FREE Full text] [Medline: 22008217]
30. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016 Oct 12;355:i4919. [Medline: 27733354]
31. Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, et al. Chapter 7: Systematic reviews of etiologyrisk. In: Aromataris E, Munn M, editors. Joanna Briggs Institute Reviewer's Manual. Adelaide, Australia: The Joanna Briggs Institute; Jul 17, 2017:2019-2005.
32. Valentine JC, Thompson SG. Issues relating to confounding and meta-analysis when including non-randomized studies in systematic reviews on the effects of interventions. Res Synth Methods 2013 Mar;4(1):26-35. [doi: 10.1002/jrsm.1064] [Medline: 26053537]
33. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003 Sep 6;327(7414):557-560 [FREE Full text] [doi: 10.1136/bmj.327.7414.557] [Medline: 12958120]
34. Chou R, Deyo R, Friedly J, Skelly A, Hashimoto R, Weimer M, et al. Nonpharmacologic therapies for low back pain: a systematic review for an American College of Physicians Clinical Practice Guideline. Ann Intern Med 2017 Apr 04;166(7):493-505. [doi: 10.7326/M16-2459] [Medline: 28192793]
35. Snilstveit B, Oliver S, Vojtkova M. Narrative approaches to systematic review and synthesis of evidence for international development policy and practice. J Dev Effect 2012 Sep;4(3):409-429. [doi: 10.1080/19439342.2012.710641]
36. Whittemore R, Knafl K. The integrative review: updated methodology. J Adv Nurs 2005 Dec;52(5):546-553. [doi: 10.1111/j.1365-2648.2005.03621.x] [Medline: 16268861]
37. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008 Apr 26;336(7650):924-926 [FREE Full text] [doi: 10.1136/bmj.39489.470347.AD] [Medline: 18436948]
38. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). J Clin Epidemiol 2011 Apr;64(4):407-415. [doi: 10.1016/j.jclinepi.2010.07.017] [Medline: 21247734]

39. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. J Clin Epidemiol 2011 Dec;64(12):1283-1293. [doi: 10.1016/j.jclinepi.2011.01.012] [Medline: 21839614]
40. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. J Clin Epidemiol 2011 Dec;64(12):1294-1302. [doi: 10.1016/j.jclinepi.2011.03.017] [Medline: 21803546]
41. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 8. Rating the quality of evidence--indirectness. J Clin Epidemiol 2011 Dec;64(12):1303-1310. [doi: 10.1016/j.jclinepi.2011.04.014] [Medline: 21802903]
42. Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, et al. GRADE guidelines: 5. Rating the quality of evidence--publication bias. J Clin Epidemiol 2011 Dec;64(12):1277-1282. [doi: 10.1016/j.jclinepi.2011.01.011] [Medline: 21802904]
43. Jensen TS, Baron R, Haanpää M, Kalso E, Loeser JD, Rice ASC, et al. A new definition of neuropathic pain. Pain 2011 Oct;152(10):2204-2205. [doi: 10.1016/j.pain.2011.06.017] [Medline: 21764514]
44. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535 [FREE Full text] [Medline: 19622551]

Abbreviations

CENTRAL: Cochrane Central Register of Controlled Trials
EEG: electroencephalography
GRADE: Grading of Recommendations Assessment, Development and Evaluation
ICTRP: International Clinical Trials Registry Platform
MeSH: Medical Subject Headings
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols
RCT: randomized controlled trial
RoB 1.0: Risk of Bias version 1.0
ROBINS-I: Risk of Bias in Non-Randomised Studies - of Interventions

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Protocol

Mapping Evidence on Community-Based Clinical Education Models for Undergraduate Physiotherapy Students: Protocol for a Scoping Review

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Abstract

Background: Community-based clinical training has been advocated as an excellent approach to transformation in clinical education. Clinical education for undergraduate physiotherapy students is a hands-on practical experience that aims to provide a student with the skills necessary to enable them to be fit to practice independently. However, in many countries, including South Africa, this training has been conducted only in large urban academic hospitals. Such hospitals are not a true reflection of the environment that these students will most likely be facing as practicing health care professionals.

Objective: The objective of this scoping review is to map out existing evidence on community-based clinical education models for undergraduate physiotherapy students globally.

Methods: A systematic scoping review will be based on the 2005 Arksey and O'Malley framework. Studies involving students and stakeholders in clinical education will be included. This review will not be limited by time of publication. An electronic search of relevant literature, including peer-reviewed primary studies and grey literature, will be conducted from the PubMed, Google Scholar, Medline, CINAHL, and Cochrane Library databases. The search strategy will include keywords such as "education," "physiotherapy," "undergraduate," "community-based," "training," "decentralized," and "distributed." Boolean logic will be used for each search string. Two independent reviewers will conduct screening of titles, abstracts, and full text before extracting articles. A predesigned data-charting table will supplement the extraction of data. Version 12 NVIVO software will aide in the thematic analysis of data.

Results: Data collection will commence after publication of this protocol, and the results are expected to be obtained in the following 5 months.

Conclusions: The evidence obtained from the extracted data is expected to assist in the development of a model of community-based clinical education for undergraduate physiotherapy students in South Africa, and serve as a basis for future research. The discussion of this evidence will be guided by the research question utilizing a critical narrative approach to explore emerging themes. The enablers and barriers identified from the reviewed studies can guide the development of a community-based clinical education model.

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KEYWORDS

physiotherapy; clinical education; community-based clinical training; decentralized clinical training; primary health care

Introduction

Clinical education is the integration of theory into practice in the health care environment, with the aim of developing clinically competent health science practitioners. This type of training is imperative in health science professions as it provides hands-on practical experience with real patients in a real clinical environment [1-3]. Traditionally, this training has been centered around well-resourced academic hospitals, mainly in cities close to universities [4]. However, a global shift toward community-based clinical practice conducted away from a university setting and large academic hospitals necessitates a change toward rural and periurban clinical placements [5]. This type of training is also known as decentralized clinical training [6,7].

The primary health care approach has been identified as a "first level of contact in a health system" [8]. Therefore, it is essential for a curriculum to address the primary health care needs of the population, which are social responsiveness, inclusiveness, and participation [9]. This transformation prepares undergraduate students to be socially responsive to the needs of the communities they serve, giving them the confidence to become health advocates for their patients [4,10,11].

Physiotherapy is one of the few health science professions that manages patients from the acute hospital phase in the intensive care unit to a chronic rehabilitation phase in the primary health care setting in the communities in which patients live. Therefore, diversified clinical training of physiotherapy students is essential for a curriculum that aims to provide clinical competence and social accountability [3,12-15]. Although this is also the case for medical students [6,16], there have been extensive global debates regarding practical placements and their effectiveness in producing graduates who are prepared for the changing health needs in the developing world [5,13,17-19]. The primary purpose of a school of physiotherapy is to develop graduates that have both the clinical reasoning and practical skills required to function as competent practitioners in all levels of care [20].

Global research on health education programs [2,3,18,19,21,22] concurs that a community-based clinical training program that uses decentralized clinical training platforms is an excellent approach. This approach aims to achieve transformative learning, which enhances ethical and social accountability [17]. Decentralized clinical training in this context is defined as training closer to the community, away from universities and large academic hospitals. The changes in health education, including an increase in student intake and health systems requirements, are a driving force to ensure that students are well prepared to meet the demands of their communities. This will require an improvement, review, or change in the curriculum to ensure the preparedness of graduates to be competent professionals who can implement knowledge, skills, and values practically [3,7].

A scoping literature review conducted by De Villers et al [6] confirmed that medical training in sub-Saharan Africa conducted at different clinical settings distant from large academic hospitals is beneficial in improving core competencies for students and in retaining these graduates in rural settings. However, less is known about other health science undergraduate programs in this regard, specifically for the discipline of physiotherapy. Therefore, there is a need for evaluation of existing global community-based clinical education models to contribute toward the development of a community-based primary health care training model in the South African context. This scoping review aims to examine and map evidence related to community-based clinical education models for undergraduate physiotherapy students and highlight their ability to produce socially responsive graduates. The results of this review will contribute toward the development of a community-based primary health care training model for undergraduate physiotherapy students in the South African context.

Methods

Study Design

The methodology for this scoping review will adopt the five-stage framework developed by Arksey and O'Malley [23], which Levac and colleagues [24] further elaborated by including aspects of quality appraisal. These stages are described in more detail below, in specific relation to the primary aim of this study. A Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) extension for a scoping review checklist (Multimedia Appendix 1) will be used to ensure the inclusion of all relevant sections.

Stage 1: Identifying the Research Question

The main question that will guide this review is, "What are existing models of community- based clinical education for undergraduate physiotherapy students?"

The subsequent subquestions that will pave the way for the review are as follows: (1) What are the clinical education models that exist for the physiotherapy discipline? What is/has been the practice? (2) How have community-based clinical education models been put to practice? (3) What are the enablers and barriers of the identified clinical education models? (4) Does any clinical education model utilize decentralized training platforms to ensure clinical competence through community engagement and social learning?

The Participants-Concept-Context model will be adopted to determine the eligibility of the research question (Table 1) [25].

Table 1. Participants-Concept-Context framework for eligibility of the research question.

Components	Determinants
Participants	Physiotherapy students at the undergraduate level of study, academics, clinical supervisors
Concept	Models of community-based clinical education
Context	Global

Stage 2: Identifying Relevant Literature

A comprehensive search strategy will be developed for this review to harness related studies. The electronic databases searched will include PubMed, Pedro, MEDLINE and CINAHL, Google Scholar, an academic search using EBSCOhost via the University of Kwa-Zulu Natal (UKZN), and Cochrane Library. Keywords will be separated by Boolean terms "AND," "OR," "NOT." The final step will be the search of the reference lists. The initial list of keywords will include, but are not limited to: "clinical education," "training," "teaching and learning," "undergraduate physiotherapy education," "decentralized" OR "distributed," "community-based," "community-engaged," "primary health care," "physiotherapy"/"physical therapy," and "curriculum." A pilot study was conducted to determine the feasibility of the study. The pilot findings showed good feasibility of the study with 118 articles retrieved from PubMed and 16,616 articles obtained from EBSCOhost (Table 2).

Table 2. Results of a pilot search.

Keywords searched	Database	Date of search	Number of publications retrieved
((((((“Physiotherapy” OR “Physical Therapy”)) AND (“Training” OR “Education” OR “Teaching” OR “Teaching and Learning” OR “Curriculum”))) OR (((“education”) AND “physiotherapy”) AND “undergraduate” AND (Humans[Mesh])) AND (Humans[Mesh]))) OR (((“Decentralized” OR “Distributed” OR “Community- based” OR “Community engaged”)) OR “on the job” AND rural AND”) OR “ AND primary health care AND (Humans[Mesh])) AND (Humans[Mesh])	PubMed	September 27, 2019	118
((((((“Physiotherapy” OR “Physical Therapy”)) AND (“Training” OR “Education” OR “Teaching” OR “Teaching and Learning” OR “Curriculum”))) OR (((“education”) AND “physiotherapy”) AND “undergraduate” AND (Humans[Mesh])) AND (Humans[Mesh]))) OR (((“Decentralized” OR “Distributed” OR “Community- based” OR “Community engaged”)) OR “on the job” AND rural AND) OR AND “primary health care” AND (Humans[Mesh])) AND (Humans[Mesh])	EBSCOhost	September 27, 2019	16,616, including the following filters: human, (full text, scholarly (peer-reviewed) journal

Stage 3: Study Selection

The study research question will be utilized to guide the development of the inclusion and exclusion criteria for the proper selection of relevant studies.

Peer-reviewed articles published in English that focus on the following theory will be included: (1) models of undergraduate physiotherapy community-based clinical education, (2) undergraduate physiotherapy curricula on clinical education, and (3) decentralized clinical training (ie, training conducted away from the university and central training academic hospitals, including rural sites, primary health clinics, community health centers, district hospitals, and regional hospitals).

Opinion papers on community-based clinical education for undergraduate physiotherapy students will be excluded, such as commentaries on community-based clinical training for undergraduate physiotherapy students.

Charting of Data

A data-extracting tool will be created to organize and store all data retrieved from the articles during the scoping review. Two independent reviewers utilizing the sample of the included studies will evaluate this tool. The information from studies will consist of: author, year of publication, site location, study population, institution description (community health center, primary health clinic, hospital, community, home), site description (rural, periurban, or urban), duration of the training at the site, aim or purpose of the study, methodology, essential results, model aspects, and recommendations. This information will be continuously updated throughout the scoping review process. All eligible studies will be uploaded to Mendeley referencing software and replicate studies will be removed. PRISMA guidelines will be used to report the screening results [26].

Collating, Summarizing, and Reporting Results

This review will adopt a mixed-method analysis of the results of the selected studies, including both qualitative and quantitative analyses. Extracted data that will be analyzed quantitatively will include numerical summaries of article type, duration of rotation, site description, location (rural, urban, periurban), and the aspects of the model. A descriptive analytical method will be conducted using the Statistical Package for Social Sciences Version 23. Thematic analysis will be used for analyzing the qualitative data from the reviewed studies to synthesize and interpret critical issues and themes arising from the included studies.

Quality Appraisal

The Mixed Method Appraisal Tool (MMAT) version 2018 [25] will be used to appraise the quality of the selected studies, as recommended by Levac et al [24]. Three reviewers (NT, VC, and SC) will be involved in the critical appraisal process. Two reviewers will capture methodological quality criteria, according to MMAT [27]. A third reviewer who is an expert in MMAT application will oversee the complete process, adding rigor to the process. The MMAT allows for a concomitant appraisal of methodological quality of five study categories: qualitative research, randomized controlled trials, nonrandomized studies, quantitative descriptive studies, and mixed methods studies [25].

Ethics Approval

The study is part of doctoral work in the Department of Health Sciences at UKZN. Ethical approval was obtained from the

Humanities and Social Sciences Research Ethics Committee of UKZN (ethical clearance no. HSS/0575/018D).

Results

Data collection will commence upon protocol publication, and the results can be expected in the following 5 months.

Discussion

This scoping review aims to map out existing models of community-based clinical education and highlight their ability to produce socially responsive graduates. There is a global shift toward community-based clinical training of health care professionals with evidence supporting this approach in undergraduate medical education [19,22].

The undergraduate physiotherapy curriculum needs to produce graduates who possess the competencies of a health practitioner, professional, scholar, health advocate, collaborator, communicator, and leader. Decentralized clinical training has been reported as the best method of developing competent undergraduate students who will be socially accountable and able to advocate for their patients [6,28].

This scoping review will synthesize the evidence and reveal knowledge gaps to contribute toward the development of a community-based clinical education model for undergraduate physiotherapy students in a South African context.

Clinical education stakeholders, physiotherapist clinical supervisors in different hospital settings, and academics involved in the training of undergraduates stand to benefit from this scoping review. The review will produce consolidated evidence of various models of community-based clinical education for undergraduate students. This evidence can be employed by stakeholders to design future programs and also form a basis for future research.

This scoping review will clearly describe the global community-based clinical education models used for the training of undergraduate physiotherapy students. The empirical evidence obtained from this review will be beneficial to stakeholders in health science education, including academics, clinicians, and policymakers, contributing to the ongoing transformation of clinical training.

Acknowledgments

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Authors' Contributions

NC conceptualized the planned methodology of this study and prepared the first draft of the manuscript under the guidance and supervision of VC and SC. All authors reviewed the manuscript and approved it for submission to the journal.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist.
[PDF File (Adobe PDF File), 645 KB - resprot_v9i10e19039_app1.pdf]

References

1. Cantatore F, Crane L, Wilmoth D. Defining Clinical Education?: Parallels in Practice. Austral J Clin Educ 2016 Dec;1:1-8 [FREE Full text]
2. Diab P, Flack P. Benefits of community-based education to the community in South African health science facilities. Afr J Prim Health Care Fam Med 2013 Apr 23;5(1):474. [doi: 10.4102/phcfm.v5i1.474]
3. Ernstzen DV, Statham SB, Hanekom SD. Learning experiences of physiotherapy students during primary healthcare clinical placements. Afr J Prim Health Prof Educ 2014 Oct 23;6(2):211. [doi: 10.7196/ajhpe.530]
4. Crampton PES, McLachlan JC, Illing JC. A systematic literature review of undergraduate clinical placements in underserved areas. Med Educ 2013 Oct 09;47(10):969-978. [doi: 10.1111/medu.12215] [Medline: 24016167]
5. White S, Humphreys N. Undergraduate physiotherapy students' expectations and perceptions of rural/regional clinical placements. Aust J Rural Health 2014 Aug 13;22(4):172-178. [doi: 10.1111/ajr.12102] [Medline: 25123621]
6. de Villiers M, van Schalkwyk S, Blitz J, Couper I, Moodley K, Talib Z, et al. Decentralised training for medical students: a scoping review. BMC Med Educ 2017 Nov 09;17(1):196 [FREE Full text] [doi: 10.1186/s12909-017-1050-9] [Medline: 29121923]
7. Blose S, Chemane NCT, Chetty V, Govender P, Maddocks S. Physiotherapists' perception of a community-based primary healthcare clinical education approach to undergraduate learning. Afr J Prim Health Prof Educ 2019 Apr 03;11(1):16. [doi: 10.7196/ajhpe.2019.v11i1.1046]

8. Cott CA, Mandoda S, Landry MD. Models of integrating physical therapists into family health teams in ontario, Canada: challenges and opportunities. Physiother Can 2011 Jul;63(3):265-275. [doi: 10.3138/ptc.2010-01] [Medline: 22654231]
9. Hartman N, Kathard H, Perez G, Reid S, Irlam J, Gunston G, et al. Health Sciences undergraduate education at UCT: a story of transformation. S Afr Med J 2012 Mar 02;102(6):477-480. [doi: 10.7196/samj.5680] [Medline: 22668942]
10. Frenk J, Chen L, Bhutta Z, Cohen J, Crisp N, Evans T, et al. Health professionals for a new century: transforming education to strengthen health systems in an interdependent world. Lancet 2010 Dec 04;376(9756):1923-1958. [doi: 10.1016/S0140-6736(10)61854-5] [Medline: 21112623]
11. Birden HH, Wilson I. Rural placements are effective for teaching medicine in Australia: evaluation of a cohort of students studying in rural placements. Rural Remote Health 2012;12:2167 [FREE Full text] [Medline: 23157496]
12. Covington K, Odom C, Heflin S, Gwyer J. Student Team Learning in Practice (STEPs®): An Integrated Clinical Education Collaborative Model. J Phys Ther Educ 2017;31(2):18-29. [doi: 10.1097/00001416-201731020-00004]
13. Stiller K, Lynch E, Phillips AC, Lambert P. Clinical education of physiotherapy students in Australia: Perceptions of current models. Austral J Physiother 2004;50(4):243-247. [doi: 10.1016/s0004-9514(14)60114-8]
14. Lekkas P, Larsen T, Kumar S, Grimmer K, Nyland L, Chipchase L, et al. No model of clinical education for physiotherapy students is superior to another: a systematic review. Austral J Physiother 2007;53(1):19-28. [doi: 10.1016/s0004-9514(07)70058-2]
15. Campbell LM, Ross AJ, MacGregor RG. The Umthombo Youth Development Foundation, South Africa: Lessons towards community involvement in health professional education. Afr J Prim Health Prof Educ 2016 Mar 26;8(1):50. [doi: 10.7196/ajhpe.2016.v8i1.559]
16. Talib Z, van Schalkwyk S, Couper I, Pattanaik S, Turay K, Sagay AS, et al. Medical Education in Decentralized Settings. Acad Med 2017;92(12):1723-1732. [doi: 10.1097/acm.0000000000002003]
17. Govender P, Chetty V, Naidoo D, Pefile N. Integrated Decentralized Training for Health Professions Education at the University of KwaZulu-Natal, South Africa: Protocol for the I-DecT Project. JMIR Res Protoc 2018 Jan 25;7(1):e19 [FREE Full text] [doi: 10.2196/resprot.7551] [Medline: 29371175]
18. Mostert-Wentzel K, Africa S, Africa S. Status of undergraduate community-based and public-health physiotherapy education in South Africa. S Afr J Physiother 2013;69(1):26-35. [doi: 10.4102/sajp.v69i1.369]
19. Woolley T, Sen Gupta T, Murray R. James Cook University's decentralised medical training model: an important part of the rural workforce pipeline in northern Australia. Rural Remote Health 2016;16(1):3611 [FREE Full text] [Medline: 26992830]
20. Crosbie J, Gass E, Jull G, Morris M, Rivett D, Ruston S, et al. Sustainable undergraduate education and professional competency. Austral J Physiother 2002;48(1):5-7. [doi: 10.1016/s0004-9514(14)60276-2]
21. Swisher L, Woodard L, Quillen W, Monroe AD. Centralized and Decentralized Organizational Models of Interprofessional Education for Physical Therapist and Medical Students. J Phys Ther Educ 2010;24(1):12-18. [doi: 10.1097/00001416-201010000-00004]
22. Mlambo M, Dreyer A, Dube R, Mapukata N, Couper I, Cooke R. Transformation of medical education through Decentralised Training Platforms: a scoping review. Rural Remote Health 2018 Mar;18(1):4337 [FREE Full text] [doi: 10.22605/RRH4337] [Medline: 29522688]
23. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Method 2005 Feb;8(1):19-32. [doi: 10.1080/1364557032000119616]
24. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. Implement Sci 2010 Sep 20;5(1):69 [FREE Full text] [doi: 10.1186/1748-5908-5-69] [Medline: 20854677]
25. Hong QN, Pluye P, Fàbregues S, Bartlett G, Boardman F, Cargo M, et al. Mixed Methods Appraisal Tool (MMAT) version 2018 user guide. 2018. URL: http://mixedmethodsappraisaltoolpublic.pbworks.com/ [accessed 2019-11-18]
26. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009 Jul 21;6(7):e1000097 [FREE Full text] [doi: 10.1371/journal.pmed.1000097] [Medline: 19621072]
27. Daudt HM, van Mossel C, Scott SJ. Enhancing the scoping study methodology: a large, inter-professional team's experience with Arksey and O'Malley's framework. BMC Med Res Methodol 2013 Mar 23;13(1):48 [FREE Full text] [doi: 10.1186/1471-2288-13-48] [Medline: 23522333]
28. Woollard B, Boelen C. Seeking impact of medical schools on health: meeting the challenges of social accountability. Med Educ 2012 Jan;46(1):21-27. [doi: 10.1111/j.1365-2923.2011.04081.x] [Medline: 22150193]

Abbreviations

MMAT: Mixed Methods Appraisal Tool
PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses
UKZN: University of Kwa-Zulu Natal

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Protocol

Qualitative Evidence Synthesis on Self-Collection for Human Papillomavirus–Based Cervical Screening: Protocol for Systematic Review

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Abstract

Background: Cervical cancer is the fourth most common cancer affecting women worldwide. In the 1980s, it was found that the sexually transmitted disease human papillomavirus causes over 90% of all cervical cancer cases. Since that discovery, diagnostic technologies have been developed for the detection of human papillomavirus DNA in cervical samples. However, significant sociocultural and structural barriers remain. Considerable strides have taken place in recent years to address these barriers, such as the self-collection for human papillomavirus–based cervical screening method.

Objective: The purpose of this review is to synthesize qualitative evidence around the self-collection method and identify strategies to increase acceptability and feasibility in different settings. This qualitative synthesis will be used to better understand how to conceptualize and implement more effective, accessible, and socially and culturally acceptable cervical screening programs and policies globally.

Methods: A systematic search will be conducted in Global Health, Cochrane, CINAHL (Cumulative Index to Nursing and Allied Health Literature), ProQuest, ScienceDirect, EMBASE, EMCARE, Medline (OVID), Scopus, and Web of Science. Published and peer-reviewed articles will be included. Two reviewers will independently screen and assess the studies. The data will be coded and analyzed using a thematic synthesis process. The socioecological model will be used to organize emergent themes at the micro and macro levels. The results will be presented in narrative and tabular form.

Results: The article search and data extraction were completed in May 2020. The data were analyzed in June 2020. The review will be submitted for publication in Fall 2020.

Conclusions: This review will present the global evidence of the perspectives and experiences of various key stakeholders and how these perspectives and experiences impact their decision-making process to perform or accept self-collection for human papillomavirus–based cervical screening. The review will provide guidance to implementation researchers as well as implications for future research.

Trial Registration: PROSPERO International Prospective Register of Systematic Reviews CRD42019109073; https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=109073

International Registered Report Identifier (IRRID): DERR1-10.2196/21093

(JMIR Res Protoc 2020;9(10):e21093) doi:10.2196/21093

KEYWORDS

self-collection; HPV-based testing; cervical screening; qualitative evidence synthesis; protocol; systematic review

Introduction

Cervical cancer is the fourth leading cause of cancer affecting women in the world, with the highest burden of disease, estimated at 85% [1], occurring in low- and middle-income countries. To attenuate the global cervical cancer burden, the implementation of screening methods is a global health priority. The most commonly known screening method is cytologic screening with a Papanicolaou test (Pap smear): since its introduction in the 1940s, cervical cancer incidence and mortality have decreased by 70% in high-income countries [2]. However, Pap smears require distinctive and extensive laboratory infrastructure and capacity, making it challenging to implement in resource-limited settings [3,4].

In the early 1980s, researchers discovered the presence of human papillomavirus (HPV) DNA in cervical cancer lesions and that the sexually transmitted infection (STI) was responsible for over 90% of malignant cases [5]. Subsequent research has demonstrated that persistent HPV infection puts women at higher risk for cervical cancer [6]. These research findings have led to the development of tests for the detection of oncogenic HPV types in cervical precancerous or cancerous lesions, referred to as HPV testing. Additionally, this was an opportunity to develop technologies that are low-cost and require minimal laboratory infrastructure and training to use. Since this discovery of HPV oncogenic types, technologies for conducting HPV testing have revolutionized the way the global health community views cervical screening and its impact on global health outcomes [7]. The new screening methods offer access to screening services at a relatively low-cost via an effective and efficient process that bypasses all laboratory needs required by the Pap smear. Most of the research to date has been focused on determining the effectiveness of HPV-based cervical screening methods. A global review by Kouliopoulos et al [8] of studies conducted between 1992 and 2015 showed that HPV testing has higher sensitivity and specificity than those of conventional cytology methods and allows for less frequent screening. When provided at point-of-care, patients receive their results in a shorter time frame (60-90 minutes on average, compared to up to 2 weeks for Pap smears) allowing for faster turnaround, more timely treatment, and reduction in patients lost to follow-up [4,9,10]. Research from Goldie et al [11] demonstrated that HPV-based screening for women once they have reached 35 years of age potentially reduces the lifetime risk of cervical cancer by 36%.

The concept of self-collection (interchangeably named self-collected samples or self-sampling) was introduced in the 1970s to address the alarmingly low rates among women who lacked access to screening and health care services, often due to sociocultural, economic, and structural factors [12]. In the 1990s, Dr. Arthur Fournier noticed the concerning underutilization rates of Pap smear screening in Haiti. To circumvent the discomfort and embarrassment of pelvic examinations, a known deterrent for women seeking cervical screening services, Dr. Fournier designed a cervical self-sampling device for the detection of cancer and STIs [13]. The innovative self-sampling device that could also be used at home provided an efficient solution to screen women in resource-limited and culturally challenging settings. Since then, numerous studies [14-17] have compared the efficacy and effectiveness of self-collected samples to clinician-collected samples for cervical screening. The evidence showed that self-collected sampling not only had comparable sensitivity and specificity to those of clinician-collected sampling but was also the most-widely preferred screening method by women. Other research [18] has demonstrated that self-collection of specimens for HPV testing could potentially increase uptake for women residing in hard-to-reach settings.

With the vast and rapid progress in cervical screening methods, it is essential to recognize that, when applied in varying contexts and among different people, responses and experiences will significantly differ. In the case of self-collection for HPV screening, social values, cultural values, and understanding of the female body can each have an impact on women's acceptability of innovative cervical screening methods. To be successful, methods such as self-collection, need to be socially and culturally accepted by women, health care workers, and policymakers [19], as well as fit within settings where access to screening is scarce due to sociocultural barriers and limited resources. This requires understanding the experiences of all key actors (ie, women, health care workers, and policymakers) at all levels of the health system interacting with it.

This review aims to generate findings for further guidance to implementation researchers. It will help with the design of self-collection for HPV-based cervical screening interventions that address all factors raised by key stakeholders that could impact the acceptability and feasibility of these programs in diverse cultural and geographical settings.

To facilitate the uptake of cervical screening, thus reducing the incidence and prevalence of cervical cancer globally, this systematic review aims to identify, analyze, and synthesize the experiences and perceptions of women, health care workers, and policymakers. Consequently, it will provide evidence of factors that impact the acceptability and feasibility of self-collection for HPV-based cervical screening globally.

Methods

General

A preliminary search for existing systematic reviews on the topic has been conducted in major databases (ie, Medline; Scopus; Joanna Briggs Institute Database of Systematic Reviews and Implementation Reports; Cochrane Database; CINAHL, Cumulative Index to Nursing and Allied Health Literature; PubMed; and PROSPERO, International Prospective Register of Systematic Reviews). We found no qualitative synthesis systematic reviews that explored factors that could impact the acceptability and feasibility of self-collection for HPV-based cervical screening from the perspectives of women, health care

workers, and policymakers, globally. The protocol will follow PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [20]. Participant, interest, and context inclusion criteria [21] used for this review are detailed.

Review Questions

What are women's, health care workers', and policymakers' experiences with and perceptions of self-collection for HPV-DNA cervical cancer screening?

What are the barriers and facilitators to the acceptability and implementation of self-collection for HPV-DNA cervical cancer screening from the point of view of women, health care workers, and policymakers?

Types of Participants

The review will focus on women, health care workers, and policymakers. For women participants, there will be no age restriction since the review will focus on both perspectives and experiences of the self-collection method, albeit the HPV-DNA test is recommended for women 30 years old and above only. Also, the reviewers will allow for different terms to be used when identifying the types of participants targeted in this review: for example, health care workers could be defined differently in studies (ie, providers, health care service providers, etc).

Phenomena of Interest

The intervention of interest in this review is self-collection for HPV-based cervical screening. This review will consider all elements associated with the process of self-collection. The first outcome will be to assess the sociocultural and structural barriers and facilitators from the point of view of women (ie, patients), health care workers, and policymakers as well as to determine the feasibility factors of self-collection for HPV-based cervical screening in different settings.

Context

The review will not have a global geographical restriction: all countries with publicly available data will be included. Additionally, any setting where self-collection for HPV-based cervical screening could be performed (which includes women's homes, primary care, community health center) will also be identified and included in the review.

Study Search Methods

Types of Studies

This review will consider qualitative and mixed methods studies (Textbox 1) that draw on the experiences and perspectives of women, health care workers, and policymakers. These will include designs such as grounded theory, narratives, ethnography, phenomenology, and action research.

Two authors will independently screen the database search results, compare and discuss their findings, and resolve disagreements to reach consensus.

Textbox 1. Criteria.

Inclusion criteria

- Qualitative studies (qualitative component of mixed methods studies, interviews, focus groups, surveys, or questionnaires with open-ended questions) that explored experiences, perspectives of self-sampling or self-collection for human papillomavirus (HPV)–based cervical screening
- Studies that involve women; health care workers including physicians (obstetrics/gynecology primarily), nurses, midwives, and allied health professionals; or policymakers
- Studies published in English
- Studies in any geographical setting (high-income countries and low- and middle-income countries) and health care settings (eg, community health care centers, primary health care centers, patient's homes)
- Peer-reviewed publications published after 1986 (year of the first study on HPV-DNA testing)

Exclusion criteria

- Studies that involve stakeholders other than the ones listed in the inclusion criteria
- Studies in languages other than English
- Purely quantitative studies and quantitative components of mixed methods studies
- Nonpeer reviewed articles, theses, abstracts, reviews, or book chapters
- Any other cervical screening method that is not self-collection for HPV-based cervical screening (ie, clinician-collected cervical screening, Pap smears, visual inspection with acetic acid or visual inspection with Lugol iodine)

Search Strategy

A systematic search of the following databases will be developed in collaboration with a librarian and conducted by HC in Global Health, Cochrane, CINAHL (Cumulative Index to Nursing and Allied Health Literature), ProQuest, ScienceDirect, EMBASE, EMCARE, Medline (OVID), Scopus, and Web of Science. Published peer-reviewed articles will be included.

The literature search will be limited to studies published in English, between 1986 (year of the first study on HPV-DNA testing) to December 2019. It will ensure that both controlled vocabulary, medical subject headings (MeSH) and keywords, are tailored to each database (see an example of the draft EMBASE search strategy and keywords used in Multimedia Appendix 1.

The search strategy will include terms focused on 4 main concepts: HPV, self-collection, HPV-DNA testing, and qualitative. The primary reviewer HC will consult with the librarian for help refining the search strategy and terms to ensure the inclusion of both Medical Subject Heading (MeSH) terms and keywords relevant to this review and its aims. A preliminary list of MeSH terms and keywords are listed in Table 1.

Table 1. Terms and keywords.

Concept	Keywords	MeSH[a]
HPV[b]	*Human papillomavirus* OR *human papilloma virus*	*Papillomaviridae* OR *papillomavirus infections* OR *uterine cervical neoplasms*
	AND	AND
HPV-DNA testing	*Cervical cancer screening* OR *cervical screening* OR *cervical ADJ8 screening*	*HPV-DNA testing* OR *HPV testing* OR *HPV* primary testing OR *primary HPV testing* OR *DNA probes, HPV* OR *human papillomavirus DNA tests* OR *vaginal smears*
	AND	AND
Self-collected	*Self-sampling* OR *self-collected* OR *self-administered*	—[c]
	AND	AND
Qualitative	*Qualitative*	*Qualitative research* OR *qualitative studies* OR *qualitative study* OR *focus groups* OR *interviews as topic* OR *observation* OR *ethnography*

[a]MeSH: Medical Subject Headings.

[b]HPV: human papillomavirus.

[c]No MeSH terms were used.

All articles that are identified will be imported into EndNote (QSR International) to systematically sort, review, and select the final list of articles to be included in the synthesis. Guided by the eligibility criteria, 2 reviewers (HC and YZ) will screen each article in the Endnote library by title and abstract. The list of articles subjected to full review will be agreed upon between the 2 reviewers (HC and YZ). The 2 reviewers will proceed to review the full text of all eligible studies. The final list of included studies will be discussed and agreed upon between the 2 reviewers and an additional third reviewer (AKH).

Assessment of Methodological Quality of Included Studies

All included studies will be critically appraised using the Critical Appraisal Skills Programme tool or CASP for qualitative research [22], albeit there is no clear consensus on a standard tool applied to the methodological appraisal of qualitative studies [23]. This will be conducted independently by 2 reviewers (HC and YZ). The CASP tool consists of 10 questions that assess the essential elements of qualitative research. Each item will be scored using yes (1 point), no (0 points), or “can’t tell” (0.5 points) to score the article's quality out of 10.

The quality of the article will be determined using the following scoring guideline: a score ≤3 is of low quality, a score ranging from 4-6 is of medium quality, and a score ≥7 is of high quality. The appraisal score will not be used to exclude articles.

Data Extraction And Analysis

Data Extraction

As an initial step, an extraction exercise will be conducted to ensure accuracy, completeness, and richness of the data. An Excel (Microsoft Inc) data extraction spreadsheet will be developed to include the following study characteristics: title, authors, journal, publication date, study design, research aim, setting and study location, sample size, age group, demographics, intervention or screening type, data collection method, theoretical or conceptual framework, data analysis, outcomes, and findings.

Two reviewers (HC and YZ) will independently extract the data using the data extraction spreadsheet, and any disagreements will be discussed to reach consensus.

Data Synthesis

Qualitative research findings will be pooled using the thematic synthesis approach. This approach, developed by Thomas and Harden [24], specifically looks at individuals’ perspectives and experiences [25] using an integrative approach which considers data from comparable primary studies. For data coding, we will use NVivo (version 12.5; QSR International) qualitative data management and analysis software. Codes will inductively be identified and grouped into themes [26]. The thematic synthesis approach is comprised of 3 stages: coding text where each study will be coded line-by-line extracting data that responds to the research questions developed for this review (HC will conduct this); developing descriptive themes where the codes identified in the first stage will be categorized based on similarities to create themes (HC will conduct this); and generating analytical themes where the themes identified in the second stage will be used to develop key messages (this will be conducted by HC and discussed with and agreed upon by YZ, LL, AV, RG, and AKH).

As part of the thematic synthesis, a theoretical framework was identified to guide the data synthesis process. For this review, the socioecological model will be the a priori framework that

will need to be discussed and approved by all reviewers (HC, YZ, LL, AV, RG, and AKH), used, and adapted to identify emerging themes. Socioecological model views health behavior as being shaped by and influenced at multiple levels [27]: (1) intrapersonal, (2) interpersonal, (3) organizational, (4) community, and (5) public policy. By using the socioecological model, we aim to identify micro and macro factors that impact the perspectives and experiences of using self-collection for HPV testing, thus impacting acceptability from the point of view of all key stakeholders, as well as the implementation of the self-collection method in different settings.

The findings will provide a descriptive summary of key themes and associated quotations.

Patient and Public Involvement

This review will include solely secondary data, patients, health care workers, policymakers, and the public will not be involved in the design or conduct of the review.

Ethics and Dissemination

This review will involve the collection and analysis of publicly available secondary data, and therefore, does not require ethical approval. The review findings will be disseminated through publication in a peer-reviewed journal and scientific conference presentations. The review will include relevant discussion points to further guide implementation researchers for the prevention of cervical cancer globally as well as implications for future research.

Results

The protocol was registered on April 15, 2019 (PROSPERO CRD42019109073). The article search and data extraction were completed in May 2020. The review includes 33 papers published between 2008 and 2020. The data were analyzed in June. The review will be submitted for publication in Fall 2020.

Discussion

Qualitative research should be a priority very early on in implementation research when introducing socially and structurally sensitive screening programs. This qualitative evidence synthesis will aim to review the perspectives and experiences of key stakeholders and the impact on their decision-making process to perform or accept self-collected HPV-based cervical screening. To date, scoping and systematic reviews on cervical screening have focused on qualitative evidence about Pap smears and visual inspection with acetic acid methods, and most recently, HPV testing. This will be the first review that qualitatively explores the most recent innovative HPV-testing method of self-collection, which is being increasingly used globally. By using the socioecological model, strategies will be identified and discussed to address barriers and facilitators to increase acceptability and feasibility at every level of the system. The review will include relevant discussion points to further guide implementation researchers for the prevention of cervical cancer globally as well as implications for future research.

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Authors' Contributions

HC drafted the manuscript. HC, YZ, LL, AV, RG, and AKH contributed to the design of the review protocol. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
EMBASE draft strategy.
[DOCX File , 13 KB - resprot_v9i10e21093_app1.docx]

References

1. LaVigne AW, Triedman SA, Randall TC, Trimble EL, Viswanathan AN. Cervical cancer in low and middle income countries: Addressing barriers to radiotherapy delivery. Gynecol Oncol Rep 2017 Nov;22:16-20 [FREE Full text] [doi: 10.1016/j.gore.2017.08.004] [Medline: 28948205]
2. Safaeian M, Solomon D, Castle PE. Cervical cancer prevention--cervical screening: science in evolution. Obstet Gynecol Clin North Am 2007 Dec;34(4):739-760 [FREE Full text] [doi: 10.1016/j.ogc.2007.09.004] [Medline: 18061867]
3. Sahasrabuddhe VV, Parham GP, Mwanahamuntu MH, Vermund SH. Cervical cancer prevention in low- and middle-income countries: feasible, affordable, essential. Cancer Prev Res (Phila) 2012 Jan;5(1):11-17. [doi: 10.1158/1940-6207.CAPR-11-0540] [Medline: 22158053]

4. Sankaranarayanan R, Anorlu R, Sangwa-Lugoma G, Denny LA. Infrastructure requirements for human papillomavirus vaccination and cervical cancer screening in sub-Saharan Africa. Vaccine 2013 Dec 29;31 Suppl 5:F47-F52. [doi: 10.1016/j.vaccine.2012.06.066] [Medline: 24331747]
5. Shanmugasundaram S, You J. Targeting persistent human papillomavirus infection. Viruses 2017 Aug 18;9(8):229 [FREE Full text] [doi: 10.3390/v9080229] [Medline: 28820433]
6. Bosch FX, Lorincz A, Muñoz N, Meijer CJLM, Shah KV. The causal relation between human papillomavirus and cervical cancer. J Clin Pathol 2002 Apr;55(4):244-265. [doi: 10.1136/jcp.55.4.244] [Medline: 11919208]
7. McGraw SL, Ferrante JM. Update on prevention and screening of cervical cancer. World J Clin Oncol 2014 Oct 10;5(4):744-752 [FREE Full text] [doi: 10.5306/wjco.v5.i4.744] [Medline: 25302174]
8. Koliopoulos G, Nyaga VN, Santesso N, Bryant A, Martin-Hirsch PP, Mustafa RA, et al. Cytology versus HPV testing for cervical cancer screening in the general population. Cochrane Database Syst Rev 2017 Aug 10;8:CD008587 [FREE Full text] [doi: 10.1002/14651858.CD008587.pub2] [Medline: 28796882]
9. Denny LA, Sankaranarayanan R, De Vuyst H, Kim JJ, Adefuye PO, Alemany L, et al. Recommendations for cervical cancer prevention in sub-saharan Africa. Vaccine 2013 Dec 29;31 Suppl 5:F73-F74. [doi: 10.1016/j.vaccine.2012.11.077] [Medline: 24331750]
10. Mohammed SI, Ren W, Flowers L, Rajwa B, Chibwesha CJ, Parham GP, et al. Point-of-care test for cervical cancer in LMICs. Oncotarget 2016 Apr 05;7(14):18787-18797 [FREE Full text] [doi: 10.18632/oncotarget.7709] [Medline: 26934314]
11. Goldie SJ, Gaffikin L, Goldhaber-Fiebert JD, Gordillo-Tobar A, Levin C, Mahé C, Alliance for Cervical Cancer Prevention Cost Working Group. Cost-effectiveness of cervical-cancer screening in five developing countries. N Engl J Med 2005 Nov 17;353(20):2158-2168. [doi: 10.1056/NEJMsa044278] [Medline: 16291985]
12. Barbee L, Kobetz E, Menard J, Cook N, Blanco J, Barton B, et al. Assessing the acceptability of self-sampling for HPV among Haitian immigrant women: CBPR in action. Cancer Causes Control 2010 Mar;21(3):421-431. [doi: 10.1007/s10552-009-9474-0] [Medline: 19943103]
13. Menard JM. The Social Context of Cervical Cancer Knowledge and Prevention Among Haitian Immigrant Women. 2008. URL: https://scholarcommons.usf.edu/etd/398/ [accessed 2020-09-01]
14. Petignat P, Faltin DL, Bruchim I, Tramèr MR, Franco EL, Coutlée F. Are self-collected samples comparable to physician-collected cervical specimens for human papillomavirus DNA testing? A systematic review and meta-analysis. Gynecol Oncol 2007 May;105(2):530-535. [doi: 10.1016/j.ygyno.2007.01.023] [Medline: 17335880]
15. Ogilvie GS, Patrick DM, Schulzer M, Sellors JW, Petric M, Chambers K, et al. Diagnostic accuracy of self collected vaginal specimens for human papillomavirus compared to clinician collected human papillomavirus specimens: a meta-analysis. Sex Transm Infect 2005 Jun;81(3):207-212. [doi: 10.1136/sti.2004.011858] [Medline: 15923286]
16. Szarewski A, Cadman L, Mallett S, Austin J, Londesborough P, Waller J, et al. Human papillomavirus testing by self-sampling: assessment of accuracy in an unsupervised clinical setting. J Med Screen 2007;14(1):34-42. [doi: 10.1258/096914107780154486] [Medline: 17362570]
17. Toliman PJ, Kaldor JM, Badman SG, Gabuzzi J, Silim S, Kumbia A, et al. Performance of clinical screening algorithms comprising point-of-care HPV-DNA testing using self-collected vaginal specimens, and visual inspection of the cervix with acetic acid, for the detection of underlying high-grade squamous intraepithelial lesions in Papua New Guinea. Papillomavirus Res 2018 Dec;6:70-76 [FREE Full text] [doi: 10.1016/j.pvr.2018.10.009] [Medline: 30391365]
18. Ogilvie G, Krajden M, Maginley J, Isaac-Renton J, Hislop G, Elwood-Martin R, et al. Feasibility of self-collection of specimens for human papillomavirus testing in hard-to-reach women. CMAJ 2007 Aug 28;177(5):480-483. [doi: 10.1503/cmaj.070013] [Medline: 17724326]
19. Institute of Medicine. Leveraging Culture to Address Health Inequalities: Examples from Native Communities: Workshop Summary. National Academies Press 2013 Dec 19. [doi: 10.17226/18496] [Medline: 24830070]
20. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009 Jul 21;339:b2700 [FREE Full text] [doi: 10.1136/bmj.b2700] [Medline: 19622552]
21. Aslam S, Emmanuel P. Formulating a researchable question: a critical step for facilitating good clinical research. Indian J Sex Transm Dis AIDS 2010 Jan;31(1):47-50 [FREE Full text] [doi: 10.4103/0253-7184.69003] [Medline: 21808439]
22. CASP Systematic Review Checklist. Critical Appraisal Skills Programme. URL: https://casp-uk.net/casp-tools-checklists/ [accessed 2020-09-22]
23. Katrak P, Bialocerkowski AE, Massy-Westropp N, Kumar VS, Grimmer KA. A systematic review of the content of critical appraisal tools. BMC Med Res Methodol 2004 Sep 16;4(1):22 [FREE Full text] [doi: 10.1186/1471-2288-4-22] [Medline: 15369598]
24. Thomas J, Harden A. Methods for the thematic synthesis of qualitative research in systematic reviews. BMC Med Res Methodol 2008 Jul 10;8(1):45 [FREE Full text] [doi: 10.1186/1471-2288-8-45] [Medline: 18616818]
25. Harden A, Garcia J, Oliver S, Rees R, Shepherd J, Brunton G, et al. Applying systematic review methods to studies of people's views: an example from public health research. J Epidemiol Community Health 2004 Sep 01;58(9):794-800. [doi: 10.1136/jech.2003.014829] [Medline: 15310807]

26. Boland A, Cherry G, Dickson R, editors. Doing a Systematic Review: A Student's Guide, second edition. London: Sage Publishing; Oct 9, 2017.
27. Lee J, Carvallo M. Socioecological perspectives on cervical cancer and cervical cancer screening among Asian American women. J Community Health 2014 Oct;39(5):863-871. [doi: 10.1007/s10900-014-9887-x] [Medline: 24863746]

Abbreviations

CASP: Critical Appraisal Skills Programme
CINAHL: Cumulative Index to Nursing and Allied Health Literature
DNA: deoxyribonucleic acid
HPV: human papillomavirus
MeSH: Medical Subject Headings
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
STI: sexually transmitted infection

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Protocol

Effect of Testosterone Treatment on Cardiovascular Events in Men: Protocol for a Systematic Literature Review and Meta-Analysis

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Abstract

Background: Testosterone prescriptions have increased dramatically in recent decades, with increasing usage in men. Despite epidemiological associations reported high circulating concentrations of endogenous androgens and low risk of cardiovascular events and mortality, the effects of exogenous androgens in the form of testosterone therapy for maintaining physiological circulating androgen concentrations on the cardiovascular system remain uncertain with no published meta-analysis on this topic.

Objective: The aim of this study was to investigate the effects of prescribed testosterone treatment, in all forms and durations, from well-developed randomized controlled trials, on cardiovascular events in men aged 18 years or older.

Methods: Peer-reviewed journal articles published from 1980 to 2019 will be searched from databases (ie CINAHL [Cumulated Index to Nursing and Allied Health Literature], Embase, Medline, Scopus, Cochrane Controlled Register of Trials as well as the Clinical Trial Registry). Randomized controlled trials or cluster randomized controlled trials with at least one intervention arm of testosterone and a control group of usual care or no testosterone treatment will be included in this review and meta-analysis. Studies on men with previous cardiovascular events or cardiac vascularization (coronary bypass surgery or percutaneous coronary intervention) will be excluded. Data related to primary outcomes such as clinical events of any type of stroke or transient ischemic attack, nonfatal myocardial infarction or acute coronary syndrome, emergency coronary artery revascularization, carotid surgery, cardiac mortality, and all-cause mortality will be extracted for analysis. The criteria for PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) will be followed in the evaluation of evidence.

Results: Search terms have been piloted and finalized. This study will be completed by the end of 2020.

Conclusions: This protocol will guide a systematic literature review of the evidence around prescribed testosterone and its effect on cardiovascular events in men aged 18 years or older. The findings will inform clinical management of hypogonadal men.

Trial Registration: PROSPERO International Prospective Register of Systematic Reviews CRD42019134278; https://tinyurl.com/y6t7ggge

International Registered Report Identifier (IRRID): PRR1-10.2196/15163

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KEYWORDS

exogenous testosterone; stroke; nonfatal myocardial infarction; emergency revascularization; carotid surgery; cardiac mortality

Introduction

Epidemiological observational studies have shown that low endogenous testosterone concentrations are associated with a high incidence of cardiovascular events and cardiovascular mortality in middle-aged and older men [1-3]. Potential mechanisms by which testosterone could exert beneficial effects on the vasculature include reduction in cholesterol accumulation, modulation of inflammation, and improvement in endothelial function [4,5]. However, this causation is unproven as there has been no randomized placebo-controlled trial of testosterone sufficiently powered to examine the outcomes of cardiovascular events or mortality.

Small randomized trials of testosterone therapy have shown improvements in surrogate endpoints related to cardiovascular risk [6-9]. However, other trials of testosterone have not shown improvements in carotid atherosclerosis, which was assessed using carotid intima-media thickness. One study reported an increase in noncalcified coronary atheroma, which was assessed by coronary computed tomography angiography in older men receiving testosterone therapy over a period of 12 months [10]. While 1 randomized trial of testosterone therapy in older men with mobility limitations reported an excess of adverse events in the treatment arm [11], a recent large trial in older men did not find any excess of cardiovascular adverse events with testosterone treatment during the intervention period [12]. Indeed, the effects of exogenous androgens in the form of testosterone therapy for maintaining the physiological circulating androgen concentrations on the cardiovascular system remain uncertain.

To date, there is no meta-analysis published on this topic that focuses on the outcomes of randomized controlled trials. It is therefore challenging for clinicians to decide if any testosterone should be prescribed to hypogonadal men. Owing to this evidence gap for the current clinical management of hypogonadal men, a systematic literature review and meta-analysis of data from well-designed randomized controlled trials is needed to ascertain the beneficial, neutral, or adverse effects of testosterone treatment on cardiovascular outcomes in the general population of middle-aged and older men. The aim of this review is to systematically assess the evidence of the effects of testosterone treatment (either in the form of oral administration, transdermal application, intramuscular, or implant) in comparison to those of no testosterone treatment on cardiovascular outcomes of men aged 18 years or older.

Methods

Review Objectives and Hypotheses

This systematic review and meta-analysis will follow the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) [13] for evaluating the effect of testosterone treatment on primary cardiovascular outcomes (clinical events of stroke or transient ischemic attack, nonfatal myocardial infarction, or acute coronary syndrome, emergency coronary artery revascularization, carotid surgery, cardiac mortality, and all-cause mortality) among adult men. Three a priori hypotheses will be tested: types of testosterone treatment (oral administration, transdermal application, intramuscular injection, or implant vs no testosterone), dosage of testosterone received (total dosage [mg] received during the duration of the study vs no testosterone), and follow-up period (at least 6 months vs more than 6 months).

Inclusion Criteria

Studies need to meet the following characteristics to be eligible for this systematic review and meta-analysis.

Participants

Studies that examine men aged 18 years or older and report baseline androgen levels will be included. The participants can be overweight or obese, with or without metabolic syndrome, smokers, and of different socioeconomic status. Studies on men with previous cardiovascular events or cardiac vascularization (coronary bypass surgery or percutaneous coronary intervention) will be excluded. Studies that examine both adult men and women will only have the male population data extracted for this review and meta-analysis.

Intervention

Testosterone formulation given to humans via oral administration, transdermal application, intramuscular injection, or implant of any dosage and frequency will be examined in this review and meta-analysis.

Comparison

The effect of testosterone treatment via oral administration, transdermal application, intramuscular injection, or implant will be compared to that in a control group of usual care or no testosterone intervention.

Outcomes

Studies with at least 6-month postintervention follow-up outcomes will be included. The primary postintervention outcomes are clinical events of any type of stroke or transient ischemic attack, nonfatal myocardial infarction or acute coronary syndrome, emergency coronary artery revascularization, carotid surgery, cardiac mortality, and all-cause mortality. Emergency coronary revascularization includes percutaneous coronary intervention or coronary artery bypass graft. The secondary outcome will be any atherosclerotic cardiovascular disease, broadly defined to include events occurring in the coronary, cerebral, aortic, and peripheral vasculature. Therefore, the secondary outcomes will also include ischemic heart disease, coronary heart disease, coronary artery disease, cerebrovascular diseases, including carotid disease, and peripheral vascular disease, including aortic aneurysm. The number of events among those who received any testosterone intervention will be compared to that in the control group of usual care or no testosterone intervention.

Types of Studies

Randomized controlled trials or cluster randomized controlled trials with at least one intervention arm of testosterone and a control group of usual care or no testosterone treatment will be included. Experimental studies with no randomization (such as quasi-experimental studies) will not be included in this study. Observational cohort studies, case-control studies, nested case-control studies, cross-sectional studies, case series, and case reports will also not be included.

Search Strategy

Peer-reviewed information published in electronic databases will be searched. Search terms will include testosterone AND (cardiac OR heart OR stroke OR myocardial infarction OR atherosclerosis OR revascularization OR Agatston score OR death OR angina OR carotid OR artery OR coronary OR cerebral OR aortic OR peripheral vascular) anywhere in the text by using truncation and wildcards when available, to accommodate for different spellings. The search modes will be set to Boolean/Phrase when available. In addition, the limiters will be human studies, studies done on males, publications written in English, and publication year set to range from 1980 to 2019 and when available, and peer-reviewed randomized controlled trials. If full-text is not available, the original study authors will be contacted for the full-text of the article published in English language.

Information Sources

CINAHL (Cumulated Index to Nursing and Allied Health Literature), Embase, Medline, Scopus, and Cochrane Controlled Register of Trials will be searched using the advanced search function, where available. The following search strategy will also be applied when searching the Clinical Trial Registry (ClinicalTrials.gov) for trials with completed results. References of the selected articles will also be scanned to ensure literature saturation.

Study Selection

The number of records found from each database and the Clinical Trial Registry will be noted in the format of the PRISMA flow diagram. The full details of the articles will be imported to an EndNote library. Duplicates of identical records will be removed and the number of duplicates removed will be recorded in the PRISMA flow diagram. Two independent reviewers will screen the titles and abstracts of the remaining articles. Articles that are conference abstracts, review articles, observational studies, response or letters to the Editors, not on men, on isolated cells or artery specimens, and irrelevant outcomes will be excluded and the number recorded on the PRISMA flow diagram. If consensus is not reached at the screening phase, there will be discussion between the 2 reviewers or a third independent reviewer may be invited to screen the articles until consensus is reached. The remaining full-text articles will be screened against the selection criteria. Full-text articles that do not meet the eligibility criteria will be excluded and the number recorded on the PRISMA flow diagram. If multiple articles were produced from the same active intervention by the same group of authors at the same institution on the same outcome, only the article with the most complete follow-up data will be included in the review. Discussion between 2 independent reviewers or involvement of a third independent reviewer will resolve disagreement on the selection of the articles. References of the selected articles will also be screened as above to ensure literature saturation. The final number of the selected articles will be noted on the PRISMA flow diagram.

Assessment of the Methodological Quality

The quality of the studies will be assessed by 2 independent reviewers following the Cochrane Collaboration's tool for assessing risk of bias. The risk of bias will be assessed in terms of sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and bias that may be threats to the validity [14]. Each of these will be assessed as "low risk," "high risk," or "uncertain risk" of bias [14] at the study and outcome level. Discussion between 2 independent reviewers and involvement of a third independent reviewer will be required until consensus is reached.

Data Extraction

The number of articles retrieved and excluded will be recorded in the format of the PRISMA flow diagram. The characteristics of the included study and participants will be noted in a table, grouped by the types of testosterone therapy received. Data extraction will be piloted from a small group of studies by 2 reviewers. One reviewer will then independently extract the data from all the selected articles, which will be verified by the second reviewer. There is no plan of individual patient data meta-analysis; therefore, no further data will be sought from the original researchers. Depending on the number of selected articles, the mean or risk ratios of the outcomes will be presented in a number of tables. Data to be extracted for the review and meta-analysis will include the following: (1) general information of the article (authors, year of publication, country of origin, source of funding), (2) study characteristics (aims of the study, study design, duration of the study, recruitment criteria, sampling technique, unit of randomization [participant or general practitioner]), (3) baseline participant characteristics by intervention group and control group (sample size, age, ethnicity, comorbidities, testosterone level, plaque volume, body mass index or weight classification, smoking status), (4) intervention (generic and trade name of the testosterone therapy, dosage, frequency of administration, and duration of intervention), (5) comparator (usual care or type of placebo for the control group), and (6) outcomes (number lost to follow-up, number of cardiovascular events, odds ratio, risk ratio, hazard ratio, mean [SD] change in volume/score, and effect size). If the data of the key outcomes are not available, the authors of the selected articles will be contacted for the required information.

Data Synthesis

The quality of the evidence will be assessed against Cochrane's domains of risk of bias [15]. Meta-biases due to study design or methodological biases, reporting, and publication bias will be assessed. Publication bias will be assessed using Egger's test and funnel plots [16]. Heterogeneity across studies will be assessed through visual inspection of the forest plot, I^2 statistic, and τ^2 [13]. A fixed-effect meta-analysis using the

inverse-variance method will be performed if there is minimal heterogeneity [17]. A random-effect model following the DerSimonian and Laird method may be performed to account for heterogeneity (I^2 statistic >50%) across studies [18]. Possible small sample bias will be assessed by comparing the fixed effect estimate against that from the random effects model. The primary outcomes are the presence of clinical events of any type of stroke or transient ischemic attack, nonfatal myocardial infarction or acute coronary syndrome, emergency coronary artery revascularization, carotid surgery, cardiac mortality, and all-cause mortality. The secondary outcome is any atherosclerotic cardiovascular disease, which includes ischemic heart disease, coronary heart disease, coronary artery disease, cerebrovascular and carotid diseases, aortic aneurysm, and peripheral arterial disease. The number of events regarding primary and secondary outcomes among those who received any testosterone intervention will be compared to that of the control group of usual care or no testosterone intervention and the likelihood of events presented as risk ratios with 95% confidence intervals. Findings regarding coronary atherosclerosis will be reported as changes in the volume of calcified plaque and noncalcified coronary atheromatous plaque or coronary calcium score or Agatston score between baseline and endpoints of the studies (mean [SD]). Carotid atherosclerosis will be reported as the change in the carotid intima-media thickness and volume of carotid plaque between baseline and endpoint of the studies (mean [SD]). The presence of aortic or carotid inflammation on positron emission tomography, in absence of vasculitis, will be reported as the evidence of aortic or carotid atherosclerosis.

Three a priori hypotheses will be tested using stratified meta-analyses. These hypotheses are types of testosterone treatments (oral administration, transdermal application, intramuscular injection or implant vs no testosterone), dosage of testosterone received (total dosage [mg] received during the duration of the study vs no testosterone), and follow-up period (at least 6 months vs more than 6 months). Sensitivity analyses will be performed by excluding studies with high risk of bias and those with pharmaceutical funders. High-risk bias includes any bias rising from issues with allocation concealment (selection bias), blinding (performance bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) [14], or a combination of these issues. The strength of evidence on the effect estimate will be reported as "strong confidence" (no further research will affect the confidence of the effect estimate reported in the current findings), "moderate confidence" (further research may affect the confidence of the effect estimate reported in the current findings), or "uncertain" (further research will most definitely affect the confidence of the effect estimate reported in the current findings).

Ethics and Dissemination

All data extracted will be in aggregated form with no access to identifiable individual data. No ethics approval is required. This protocol has been registered on PROSPERO (Prospective Register of Systematic Reviews, registration number: CRD42019134278). Findings will be shared via PROSPERO and a peer-reviewed journal.

Results

The search terms have been piloted and finalized. After selecting and assessing the quality of the publications, data extraction and analyses will begin. Data synthesis and presentation of the findings will be completed by the end of 2020.

Discussion

There is a high rate of prescription of testosterone despite its unclear effect on cardiovascular events in men. A thorough evaluation of the published trials, as guided by this protocol, will provide evidence-based recommendations to ascertain the real benefits, neutral effects, or adverse effects on the cardiovascular health of men. It is anticipated that the findings will facilitate effective and safe clinical management of hypogonadal men.

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Conflicts of Interest

None declared.

References

1. Yeap BB, Alfonso H, Chubb SAP, Handelsman DJ, Hankey GJ, Almeida OP, et al. In older men an optimal plasma testosterone is associated with reduced all-cause mortality and higher dihydrotestosterone with reduced ischemic heart disease mortality, while estradiol levels do not predict mortality. J Clin Endocrinol Metab 2014 Jan;99(1):E9-18. [doi: 10.1210/jc.2013-3272] [Medline: 24257908]
2. Yeap B, Dwivedi G, Chih H, Reid C. Chapter 15: Androgens and cardiovascular disease in men. Endotext. South Dartmouth (MA): MDText.com, Inc; 2019. URL: https://www.ncbi.nlm.nih.gov/books/NBK279151/ [accessed 2020-01-03]
3. Yeap BB, Hyde Z, Almeida OP, Norman PE, Chubb SAP, Jamrozik K, et al. Lower testosterone levels predict incident stroke and transient ischemic attack in older men. J Clin Endocrinol Metab 2009 Jul;94(7):2353-2359. [doi: 10.1210/jc.2008-2416] [Medline: 19351733]

4. Jones TH, Kelly DM. Randomized controlled trials - mechanistic studies of testosterone and the cardiovascular system. Asian J Androl 2018;20(2):120-130 [FREE Full text] [doi: 10.4103/aja.aja_6_18] [Medline: 29442075]
5. Takov K, Wu J, Denvir MA, Smith LB, Hadoke PW. The role of androgen receptors in atherosclerosis. Mol Cell Endocrinol 2018 Apr 15;465:82-91. [doi: 10.1016/j.mce.2017.10.006] [Medline: 29024781]
6. Cornoldi A, Caminiti G, Marazzi G, Vitale C, Patrizi R, Volterrani M, et al. Effects of chronic testosterone administration on myocardial ischemia, lipid metabolism and insulin resistance in elderly male diabetic patients with coronary artery disease. Int J Cardiol 2010 Jun 25;142(1):50-55. [doi: 10.1016/j.ijcard.2008.12.107] [Medline: 19361872]
7. English KM, Steeds RP, Jones TH, Diver MJ, Channer KS. Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: A randomized, double-blind, placebo-controlled study. Circulation 2000 Oct 17;102(16):1906-1911. [doi: 10.1161/01.cir.102.16.1906] [Medline: 11034937]
8. Jaffe MD. Effect of testosterone cypionate on postexercise ST segment depression. Br Heart J 1977 Nov;39(11):1217-1222. [doi: 10.1136/hrt.39.11.1217] [Medline: 337982]
9. Mathur A, Malkin C, Saeed B, Muthusamy R, Jones T, Channer K. Long-term benefits of testosterone replacement therapy on angina threshold and atheroma in men. Eur J Endocrinol 2009 Sep;161(3):443-449. [doi: 10.1530/EJE-09-0092] [Medline: 19542238]
10. Budoff MJ, Ellenberg SS, Lewis CE, Mohler ER, Wenger NK, Bhasin S, et al. Testosterone Treatment and Coronary Artery Plaque Volume in Older Men With Low Testosterone. JAMA 2017 Feb 21;317(7):708-716 [FREE Full text] [doi: 10.1001/jama.2016.21043] [Medline: 28241355]
11. Basaria S, Coviello AD, Travison TG, Storer TW, Farwell WR, Jette AM, et al. Adverse events associated with testosterone administration. N Engl J Med 2010 Jul 08;363(2):109-122 [FREE Full text] [doi: 10.1056/NEJMoa1000485] [Medline: 20592293]
12. Srinivas-Shankar U, Roberts SA, Connolly MJ, O'Connell MDL, Adams JE, Oldham JA, et al. Effects of testosterone on muscle strength, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: a randomized, double-blind, placebo-controlled study. J Clin Endocrinol Metab 2010 Feb;95(2):639-650. [doi: 10.1210/jc.2009-1251] [Medline: 20061435]
13. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015 Jan 02;350:g7647. [doi: 10.1136/bmj.g7647] [Medline: 25555855]
14. Higgins J, Altman D. Assessing risk of bias in included studies. In: Higgins JP, Green S. editors. Cochrane Handbook for Systematic Reviews of Interventions. West Sussex: Wiley-Blackwell; 2008:187-242.
15. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Cochrane Bias Methods Group, Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011 Oct 18;343:d5928 [FREE Full text] [doi: 10.1136/bmj.d5928] [Medline: 22008217]
16. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997 Sep 13;315(7109):629-634 [FREE Full text] [doi: 10.1136/bmj.315.7109.629] [Medline: 9310563]
17. Deeks J, Higgins J, Altman D. Analysing dataundertaking meta-analyses. In: Higgins JP, Green S. editors. Cochrane Handbook for Systematic Reviews of Interventions. West Sussex: Wiley-Blackwell; 2008:243-197.
18. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986 Sep;7(3):177-188. [doi: 10.1016/0197-2456(86)90046-2] [Medline: 3802833]

Abbreviations

CINAHL: Cumulated Index to Nursing and Allied Health Literature
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: Prospective Register of Systematic Reviews

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Proposal

A Medical Translation Assistant for Non–English-Speaking Caregivers of Children With Special Health Care Needs: Proposal for a Scalable and Interoperable Mobile App

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Abstract

Background: Communication and comprehension of medical information are known barriers in health communication and equity, especially for non–English-speaking caregivers of children with special health care needs.

Objective: The objective of this proposal was to develop an interoperable and scalable medical translation app for non–English-speaking caregivers to facilitate the conversation between provider and caregiver/patient.

Methods: We employed user-centered and participatory design methods to understand the problems and develop a solution by engaging the stakeholder team (including caregivers, physicians, researchers, clinical informaticists, nurses, developers, nutritionists, pharmacists, and interpreters) and non–English-speaking caregiver participants.

Results: Considering the lack of interpreter service accessibility and advancement in translation technology, our team will develop and test an integrated, multimodal (voice-interactive and text-based) patient portal communication and translation app to enable non–English-speaking caregivers to communicate with providers using their preferred languages. For this initial prototype, we will focus on the Spanish language and Spanish-speaking families to test technical feasibility and evaluate usability.

Conclusions: Our proposal brings a unique perspective to medical translation and communication between caregiver and provider by (1) enabling voice entry and transcription in health care communications, (2) integrating with patient portals to facilitate caregiver and provider communications, and (3) adopting a translation verification model to improve accuracy of artificial intelligence–facilitated translations. Expected outcomes include improved health communications, literacy, and health equity. In addition, data points will be collected to improve autotranslation services in medical communications. We believe our proposed solution is affordable, interoperable, and scalable for health systems.

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KEYWORDS

medical translation; mobile app; special health care needs; pediatrics; caregiver-provider communication

Introduction

Background

Children with special health care needs have a high number of hospitalizations and require more specialized services. Due to the complexity of their conditions, transitioning children with special health care needs from inpatient care to continuing therapy in the home setting is often challenging. Despite these challenges, a successful transition of care is critical to help families of children with special health care needs optimize their child's outcome. Caregivers of children with special health care needs need to communicate with the clinical team frequently to report symptoms, request medication refills, receive care instructions, seek care advice, and discuss other health issues. Thus, ensuring that caregivers of children with special health care needs understand the discharge summaries and care plans, have timely access to communication channels to address their questions, and are given guidance to appropriate

services is essential for a smooth transition of care and to achieve the best state of health for their children.

Communication and comprehension of medical information is a known barrier for patients and their caregivers, especially for non–English-speaking caregivers [1,2]. Non–English-speaking caregivers, by definition, are caregivers who have limited proficiency and understanding of the English language. Use of professional interpreters in medical communications with non–English-speaking caregivers and patients is a standard procedure. During discharge, instructions on medications and care plans are typically delivered through a professional interpreter—in person or through phone/video services [3]. However, it is possible that non–English-speaking caregivers might not fully understand the information provided during transition of care and might not feel comfortable engaging in a conversation with the clinical team. In addition, it is not common for translated medication instructions and care plans to be provided in written format, especially for less common languages. Non–English-speaking caregivers have to rely on their own notes or memories to adhere to the care or medication guidance. There are also scenarios when public health and clinical guidelines have been disseminated broadly without support for non–English-speaking communities, which may lead to inequitable care [4,5], as evidenced by the current COVID-19 pandemic crisis [6].

Gap Analysis

Unfortunately, it can be difficult to access a certified medical interpreter whenever needed. In addition to accessibility and availability, there is the additional burden of cost to the health care system of providing interpretation services [7,8]. Another barrier to adequate interpretation for non–English-speaking caregivers is the limited engagement of interpreters at the point of care. Communication typically occurs at a single point in time and mostly focuses on specific current aspects of care without a comprehensive conversation (eg, treatment plans, assessment, diagnosis). Needing a professional interpreter creates a hurdle for patients and their caregivers outside clinical encounters, especially after hospital discharge, when non–English-speaking caregivers need information and guidance the most, including care navigation.

Under Title VI of the 1964 Civil Rights Act, public agencies are obligated to provide competent language assistance to individuals with limited proficiency in the English language. Use of certified medical interpreters is ideal, but these individuals may be limited in their availability, particularly outside of business hours, in less-resourced settings, and for less common languages or dialects. Technology-based language translation was identified as a potential approach for facilitating and improving communication among patients and health care providers [9]. Web-based translation tools, such as Google Translate, were found to be useful in patient-provider interactions [10]. However, these tools demonstrate significant quality issues in terms of discrepancy and inaccuracy for clinical communications [10-12]. Evidence suggests that significant improvements in commonly used web-based translation tools will be required before these tools can be used reliably for routine medical translation.

In summary, there is a critical need to fill this gap of translation services for non–English-speaking caregivers of children with special health care needs who need it most during transitions of care and for timely communications with providers outside of clinical settings. We propose to develop an easy-to-use mobile translation and documentation app that could be integrated with patient portals to bridge the communication gap between providers and non–English-speaking caregivers. We hypothesize that our app may reduce the dependency on medical interpreters for certain communication needs, thereby reducing potential delays in communication between non–English-speaking caregivers and their child's care team. In addition, such an app may increase the efficiency of two-way communication and documentation of non–English-speaking caregivers by enabling message archiving into both the app and the patient's electronic health record (EHR). In this study, our aim is to understand the technical feasibility and usability of the app for health translation services during the transition of children with special health care needs to home care.

Prior Works

To our knowledge, there is no existing medical translation app with translation ability for Spanish users specializing in the care of children with special health care needs. Current translation services in apps (eg, Google Translate, iTranslate, and Speak & Translate) provide very limited support with generic medical term translations. All translation apps, other than Google Translate, are accessible only by paid subscribers. Currently, voice-to-text or voice-to-voice translation services for Spanish exist, but they are not integrated with medical systems [13]. Canopy Speak was found to perform well as a medical translator app [14], but it was not capable of integration with EHRs at the time of the study. Multimedia Appendix 1 provides a list of medical diary apps available on the market as of March 2020. The majority of the apps are in the English language and few support other languages. None of the diary apps have any functionality of translation or integration to EHRs for communications.

Methods

User-Centered Approach

The Digital Health Innovation Team and the Section of Complex Care at Nationwide Children's Hospital (NCH) have collaborated to bring together multidisciplinary perspectives and expertise to develop digital health solutions in this area. We engaged with end users iteratively throughout the entire process of problem solving—from initial problem identification and formulation, ideation of possible solutions, integration with clinical workflow, testing of user acceptance, and choosing a deployment strategy to obtaining postimplementation user feedback.

During preliminary exploration and shadowing sessions in the clinical areas with providers, nurses, nutritionists, and pharmacists, multiple challenges of translation service availability and accessibility were identified. One example was when a mother of a patient called the clinic's nursing line when translation services were not available. She left a message in her native language; by the time the nurse had a medical

interpreter available to call the mother back, she was not available. This situation recurred multiple times during the observation period. There was consensus among the clinical team that only a few languages were common in their patient population but translation services for those languages may not be readily accessible. This leads to additional stress and burden for both families and clinical staff. In the case of urgent concerns, the lack of timely interpretation could have negative health consequences. We employed a user-centered design in first understanding the problems identified by our complex care team members, and then brainstorming together about potential solutions. Additionally, we interviewed complex care teams to better understand the clinical workflow and how potential solutions could fit into it.

After exploring the use of medical interpreters, the lack of interpreter service accessibility, and the lack of translation technology maturity, we propose a medical translation communication app, which we initially intend to support Spanish-speaking families. If successful, the app could be easily expanded to accommodate other languages. Since 2006, the staff at NCH has cared for more than 24,000 registered Spanish-speaking pediatric patients across 800,000 medical encounters and generated more than 2.8 million patient notes. We plan to interview non–English-speaking caregivers to understand their needs in medical communications, their challenges in using a traditional patient portal, and how a translation app could be seamlessly integrated into the existing channels of communication with their child's care team. Our previous user-centered research has been successfully implemented [15], funded (eg, Challenges of the Health Resources and Service Administration's Maternal and Child Health Bureau), and supported in complex care [16,17]. We will follow a similar strategy to engage end users and community members with our multidisciplinary stakeholder team.

Research Team

We will build the app in-house by leveraging the expertise of our experienced developers and the information systems team at NCH. We assembled an interdisciplinary stakeholder team (including caregivers, physicians, researchers, clinical informaticists, nurses, developers, nutritionists, pharmacists, and interpreters) at our hospital to better understand and outline the existing problems and opportunities, and to create the potential solutions. Supporting this team are a number of information technology (IT) personnel who have experience building Amazon Web Services (AWS) solutions, EHR analysts, physician informaticists, other clinicians, and 150 full-time care coordinators.

Proposed Solution

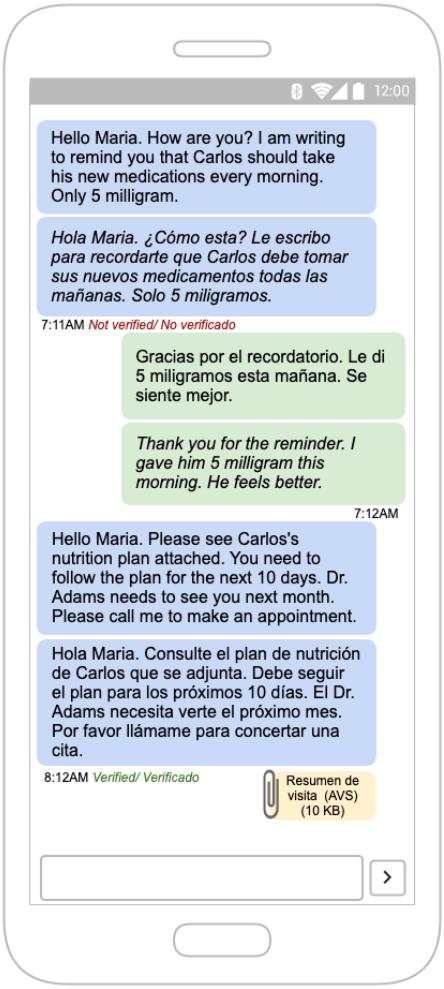
We propose to develop an EHR-integrated, multimodal (voice-interactive and text-based) communication and translation app to enable non–English-speaking caregivers and providers to communicate with one another, each in their preferred language, during transition to home care (off site). Major user functionalities are grouped into 3 categories: communication, translation, and documentation.

Communication

Non–English-speaking caregivers will be able to enter medical messages via voice or text in Spanish. Entries will be transcribed and translated online using AWS. The provider will receive an English transcribed text (with audio attachment if voice entry is used) and will be able to respond using text or voice, which will be translated into Spanish through AWS and sent as transcribed text with an audio attachment (Figure 1).

Providers will be able to initiate communication and access communication histories through the EHR with no change to their existing clinical workflow. The app will be integrated into the EHR through the patient portal, which allows providers to see patient messages in the EHR message inbox. Providers will have access to a web app to translate their messages. The translated texts will be sent over the patient portal. Figure 1 provides an example of an app interaction between a Spanish non–English-speaking caregiver and a complex care nurse. As a nurse initiates the conversation over the EHR messaging service, it will be translated into Spanish using AWS and will appear in the app interface.

Figure 1. App wireframe.



Translation

Web-based translation services through AWS will be used to translate messages and information shared by caregivers and providers. However, to reduce the number of translation errors, we will add a verification process that requires users to manually review translated messages (Figure 2). When a caregiver enters a message in Spanish, the text will be translated into English and back into Spanish in real time. The caregiver will be able to review the Spanish text and make edits, such as rephrasing the sentence or changing words, to reduce errors. This process may continue iteratively until the caregiver is satisfied with the translation. Similarly, providers will be able to enter English text through the web app and to review translated texts.

When necessary, on-site professional interpreters will be able to assist with message translations by correcting and verifying complex or crucial autotranslated messages to ensure validity. Verification will be shown on the app (Figure 1 shows verified and unverified messages). Interpreter assistance will be helpful in translating discharge documents for the caregiver. Spanish non–English-speaking caregivers will also be able to use autotranslation in their communications through the app, and to correct or verify the content (Figures 2 and 3).

Figure 2. Verification process for translation.

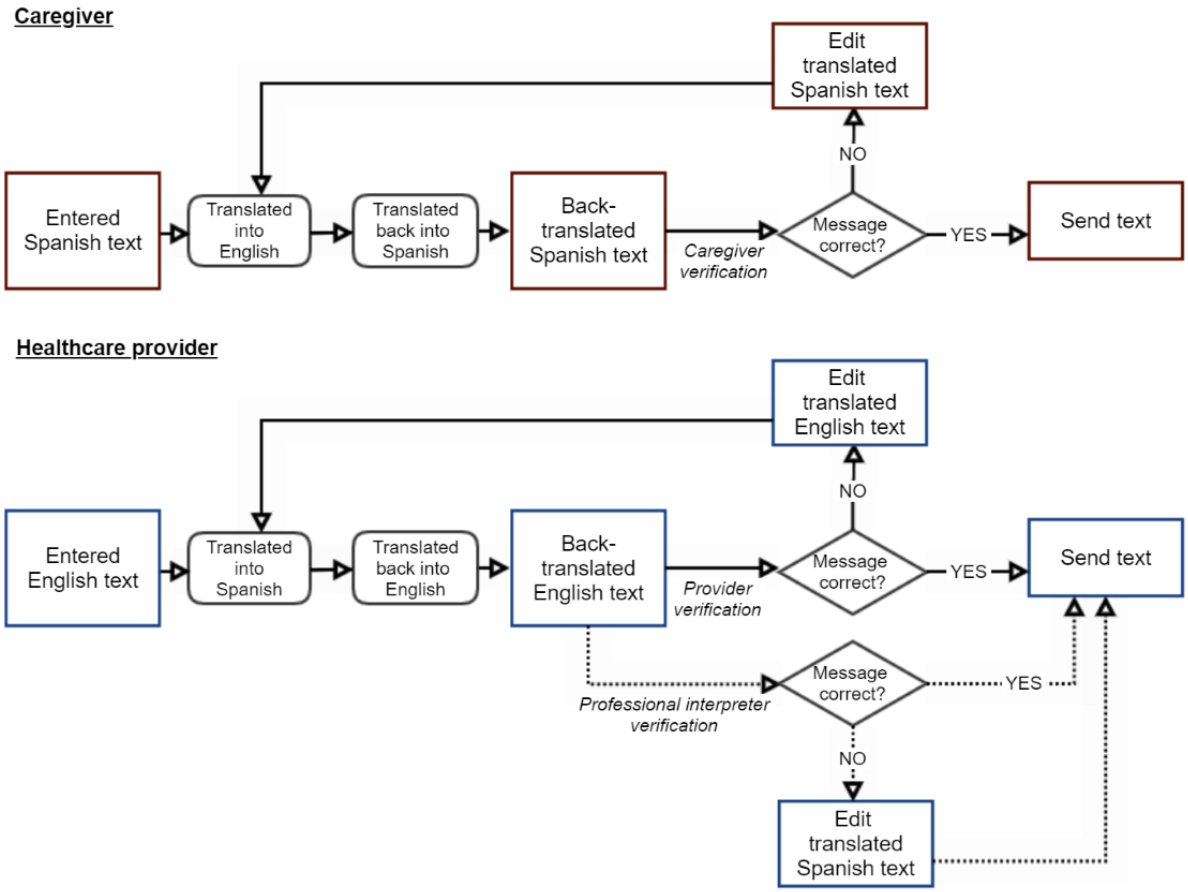
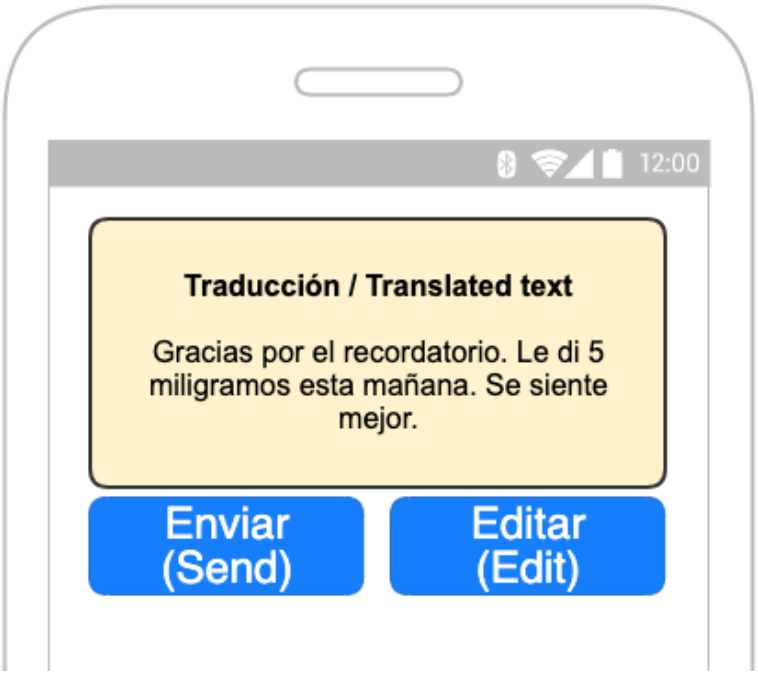


Figure 3. Verification screen.

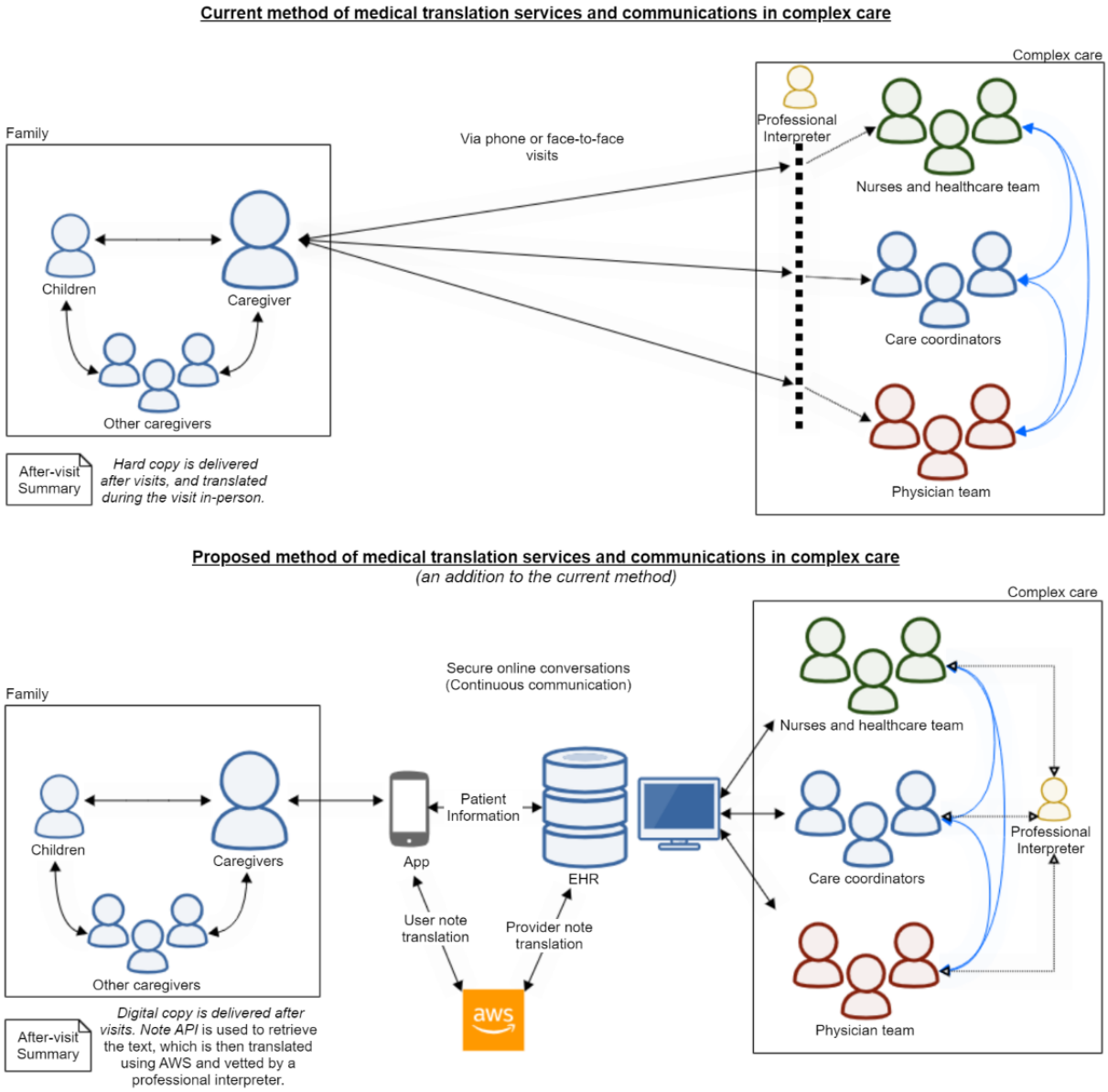


Documentation

Nurses will be able to share discharge documentation and care plans through the app, which can be translated into Spanish through AWS. The app will log each communication entry and archive it on the cloud server and in the app, which non–English-speaking caregivers can review offline. Eventually, as outlined in Figure 4, the app will take on some of the

workload of medical communication and translation. In the current practice, in each medical communication during home care transition, a professional interpreter is needed to communicate transition documentation and help with phone triaging. With the proposed model, translations will be maintained by the system (translating documents and messages), and professional interpreters will be asked to help when necessary for validation of complex communications. However, in-person communications at the hospital will still be maintained by professional interpreters.

Figure 4. Proposed framework for medical translation services. API: application programming interface; AWS: Amazon Web Services; EHR: electronic health record.



Infrastructure and Integration

To maximize access, minimize cost, and minimize disruption to the clinical or administrative workflow, we will design a scalable, extensible, and integrated solution, leveraging AWS as our backend environment for translation services, and integrate it with our EHR system through O-Auth 2.0 and Fast Healthcare Interoperability Resources (FHIR) standards. AWS has demonstrated promising developments in translation and natural language processing services, especially with medical transcription and understanding [18], with improving accuracy and expansion to additional languages. Using AWS allows us to develop a scalable infrastructure for the app. The elasticity of AWS will enable the app to be deployable to a larger user base without any code or infrastructure changes. Integration to the EHR through FHIR is also critical for a modern health application, although traditional web services may be leveraged for specific data elements to maintain compatibility with current EHR platforms. As health care provider organizations and EHR systems increasingly support these types of interoperable standards, the IT and administrative costs have been reduced to support the integration and deployment of a mobile app that interfaces with the EHR. NCH has already established guidelines and standard processes to address security and privacy issues. Some of the technical requirements are as follows: (1) infrastructure needs of AWS' web server, DynamoDB database,

and Lex/Polly services, which may affect the cost of service as more users adopt the app, (2) AWS translation application programming interfaces between Spanish and English [19], and (3) an existing iPhone operating system (iOS) device (iOS 11+; support will be extended to Android devices in later phases).

Evaluation

The usability and acceptance of the app will be measured using scientific methods. Our team has an extensive track record in acceptability and usability testing [17,20,21]. We will be employing a user-centered, participatory design and testing methodology, and widely adopted usability and acceptance scales, such as the system usability scale (SUS) and the technology acceptance model (TAM) [22,23]. The app will be tested by including non–English-speaking caregivers and the stakeholder team in the initial design, performing prototype and real-world testing, and eventually gathering their feedback through semi-structured interviews or surveys. Technical feasibility will be evaluated through internal assessment of the extent of interoperability with EHR and scalability with AWS.

The user-centered, participatory design protocol involves all stakeholders who will be invited to participate in design sessions. The initial meeting will aim to identify the problem space, current practice, needs, and expectations. An interactive design session is planned to capture stakeholder thoughts using words, color codes, and drawing boards. These projective tools are aimed to collect rich information and feedback from the participants [24]. Follow-up meetings will be held to communicate the initial design of the app prototype and to get feedback. The last session will be a testing session during which stakeholders and non–English-speaking caregiver participants will test the prototype.

Non–English-speaking caregiver participants (n=20) will be recruited from caregivers of NCH patients via email, phone call, text message, or face-to-face communications. Eligibility criteria are (1) limited English-language proficiency, (2) Spanish as the primary language, and (3) having a child receiving care at the complex care clinic at NCH. Non–English-speaking caregiver participants will be offered a gift card of up to US $30 for their participation. Their feedback will be collected through an electronic survey or interview that is guided by usability and acceptance questions and guidelines informed by the SUS and the TAM [22,23]. Given the limitations of face-to-face meetings during the COVID-19 pandemic, our backup plan is to complete all meetings and testing online. Our plan is to use virtual drawing boards and interaction materials to communicate needs and expectations and to receive feedback. In addition, we may run the app on a webpage for users to interact through browsers on their computers or mobile phones.

Overall, the expected participatory design and development timeline is 6 months. Throughout the study, we will periodically communicate with all stakeholders via email, SMS text messaging, or phone call to update them about development progress and get feedback when necessary. This study is exempt from institutional review board review.

Results

Thematic analysis will be used to identify, assess, and analyze patterns in the data [25]. We will record the audio and also keep meeting notes and observational notes during the sessions. The recorded audio will be transcribed and merged into a single document with observational notes that will be kept by at least one researcher. Thematic coding will be done by following Braun and Clarke's thematic analysis guideline: (1) familiarizing ourselves with the data, (2) generating initial codes, (3) searching for themes, (4) reviewing and refining themes, (5) defining and naming themes, and (6) reporting the findings [25]. The expected outcomes of our evaluation are qualitative input from all stakeholders and qualitative and quantitative feedback from non–English-speaking caregiver participants in response to usability and acceptability surveys. Eventually, our aim for the proposed app is to increase engagement and timely communication between caregivers and providers, which may lead to improved health outcomes [6]. A tentative timeline is shared in Table 1.

Table 1. Study timeline.

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Kickoff meeting and planning	✓					
Participatory design sessions		✓	✓		✓	
Development		✓	✓	✓	✓	
Maintenance					✓	✓
Testing					✓	✓
Reporting						✓

Discussion

Principal Findings

The proposed solution should lead to better health outcomes in both the short term and the long term, especially for patients with chronic and/or complex conditions, by empowering and engaging patients and caregivers. By overcoming the language barriers between clinical teams and non–English-speaking patients or caregivers, the proposed solution will transform the way they can communicate and how they work together to achieve the best outcome for the patients. By making information more accessible and communication easier, non–English-speaking patients and caregivers will (1) be equipped with the correct information in their own language, (2) be able to more actively engage in clinical care decision

making, (3) be more adherent to care plans, (4) carry out needed care activities outside of clinical settings, and (5) keep the clinical team informed.

The proposed solution could also lead to better health literacy. It helps caregivers to be more familiar and comfortable with medical terminology and health information, to develop a habit to document symptoms and issues, and to improve English-language proficiency. Communicating with clinical teams and revisiting these archived communication notes would help non–English-speaking caregivers to get familiar with communication language, as well as medical terms and concepts in care communications. Currently, in-person translation services may be lacking at providing transcription of communications, which may limit non–English-speaking caregivers to learning only during the engagement. The ability to access transcripts would facilitate gaining English-language proficiency. With the support of AWS medical vocabulary and increased accuracy in capturing medical terms, transcription would include accurate medical terms (such as diagnosis and medications), and would eventually help non–English-speaking caregivers to learn the correct spelling and pronunciation of medical terms and medication names (which has also been problematic in communications, especially during phone triaging). In the long term, this engagement would have a positive impact on the effectiveness of in-person communications with providers.

In addition to improving health outcomes and literacies for individual patients and caregivers, we believe this communication transformation could lead to more equitable care for non–English-speaking communities. These communities can be hard to reach for public health announcements and dissemination of general health information due to language and cultural barriers. They have a lower rate of patient portal sign-ups and may be unable to understand health-related information posted on health care organizations' websites. This proposed solution will encourage their adoption of patient portals, allowing them to have meaningful communications with their health care organizations. In turn, health care organizations could leverage this communication channel to disseminate important health information. In future work, we aim to propose the use of the translation service over patient portals once we gather evidence on the feasibility and performance of the app.

The proposed solution could improve the accuracy of automated medical translation services in the long term. The app will be able to collect information about original and revised translations, corrected sentences and words, frequency of translations, and used and modified texts with timestamps. On the provider side, we will be able to label original translations by professional interpreters. The data will be used to train and test natural language processing and natural language understanding algorithms to improve the online translation services for Spanish and complex care communication. In future phases of this research, this algorithm will add a layer between AWS and the app—as a quality check and correction service maintained by the research team.

The proposed solution is planned to be scalable and affordable. To patients and caregivers, the estimated cost is anticipated to be relatively low compared with conventional methods of translation, only requiring a download of a free mobile app on existing personal mobile phones and learning some intuitive functions of the app. Families may have an added expense related to their data plans. This solution requires minimal administrative, financial, clinical, and technical investments, thus offering greater accessibility. With the flexible back-end solutions, it can also be used by other patients and hospitals and is not limited to children with special health care needs or pediatric care. However, children with special health care needs and other patients with chronic illnesses may be the most motivated to adopt this tool and may benefit from it the most.

Challenges and Limitations

One of the main limitations with online translation services is accuracy. As mentioned previously, online translation could yield unintended translations with dire consequences in a clinical setting. To avoid that, we will translate the content back to the sender to validate if the content is accurate. Figure 2 demonstrates the process and Figure 1 shows a wireframe of the app user interface for Spanish text. It will also be applicable for English text from providers in the EHR dashboard. The translation and verification process outlined in Figure 2 could take a couple of iterations if the statements are complex. To overcome this limitation, we plan to use professional interpreters to review translations on the provider side. However, non–English-speaking caregivers and providers may need to simplify communication text to increase the accuracy of translations. We aim to improve translation services in the long term as we collect more data. We plan to keep records of translations for future efforts to develop and improve artificial intelligence algorithms in language understanding and app translations in complex care. The target population is assumed to have limited English-language proficiency and adequate literacy to engage with the app. To reduce any medicolegal risk, messages sent to providers will include a notice regarding the potential risk of translation errors and a suggestion to include an interpreter service when necessary. For non–English-speaking caregivers, users will be informed about verified and unverified messages and potential errors in translations.

Further research is planned to be inclusive of low-literacy non–English-speaking caregivers through voice assistant–based engagement. The current proposal includes voice interaction in message entry only. Future implementations would include partner hospitals and organizations, as well as public and federal funding agencies to improve the solution, scale the deployment, and sustain funding. Eventually, we plan to make the app open source and to work with commercialization support offices to plan for long-term sustainability of the app.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Consumer-level medical diary apps.
[DOCX File , 22 KB - resprot_v9i10e21038_app1.docx]

References

1. Diamond LC, Schenker Y, Curry L, Bradley EH, Fernandez A. Getting by: underuse of interpreters by resident physicians. J Gen Intern Med 2009 Feb;24(2):256-262 [FREE Full text] [doi: 10.1007/s11606-008-0875-7] [Medline: 19089503]
2. Villarruel AM, Portillo CJ, Kane P. Communicating with limited English proficiency persons: implications for nursing practice. Nurs Outlook 1999;47(6):262-270. [doi: 10.1016/s0029-6554(99)90024-6] [Medline: 10626284]
3. Using interpreter Services: Victorian Government guidelines on policy and procedures. Department of Premier and Cabinet. Melbourne: Victorian Multicultural Commission; 2019. URL: https://www.multicultural.vic.gov.au/images/2017/UsingInterpretingServicesVictorianGovernmentGuidelines.pdf [accessed 2020-06-06]
4. Cowley S, Houston A. A structured health needs assessment tool: acceptability and effectiveness for health visiting. Journal of advanced nursing 2003;43(1):92. [doi: 10.1046/j.1365-2648.2003.02675.x]
5. Rao DV, Warburton J, Bartlett H. Health and social needs of older Australians from culturally and linguistically diverse backgrounds: issues and implications. Australas J Ageing 2006 Dec;25(4):174-179. [doi: 10.1111/j.1741-6612.2006.00181.x]
6. Velasquez D, Uppal N, Perez N. Equitable Access To Health Information For Non-English Speakers Amidst The Novel Coronavirus Pandemic. Health affairs 2020. [doi: 10.1377/hblog20200331.77927]
7. Exploring Barriers and Facilitators to the Use of Qualified Interpreters in Health. The Victorian Foundation Foundation for Survivors of Torture. Melbourne: Foundation House; 2012. URL: https://refugeehealthnetwork.org.au/wp-content/uploads/Interpreters+in+health+discussion+paper+FINAL.pdf [accessed 2020-06-06]
8. O'Hagan M. Massively open translation: unpacking the relationship between technology and translation in the 21st Century. International Journal of Communication 2016;10:929-946 [FREE Full text]
9. Chang DTS, Thyer IA, Hayne D, Katz DJ. Using mobile technology to overcome language barriers in medicine. Ann R Coll Surg Engl 2014 Sep;96(6):e23-e25 [FREE Full text] [doi: 10.1308/003588414X13946184903685] [Medline: 25198966]
10. Kaliyadan F, Gopinathan Pillai S. The use of Google language tools as an interpretation aid in cross-cultural doctor-patient interaction: a pilot study. Informatics in Primary Care 2010;18(2):141-143. [doi: 10.14236/jhi.v18i2.764]
11. Patil S, Davies P. Use of Google Translate in medical communication: evaluation of accuracy. BMJ 2014;349(g7392). [doi: 10.1136/bmj.g7392]
12. Beh THK, Canty DJ. English and Mandarin translation using Google Translate software for pre-anaesthetic consultation. Anaesth Intensive Care 2015 Nov;43(6):792-793 [FREE Full text] [Medline: 26603812]
13. Panayiotou A, Gardner A, Williams S, Zucchi E, Mascitti-Meuter M, Goh AM, et al. Language Translation Apps in Health Care Settings: Expert Opinion. JMIR Mhealth Uhealth 2019 Apr 09;7(4):e11316 [FREE Full text] [doi: 10.2196/11316] [Medline: 30964446]
14. Khander A, Farag S, Chen KT. Identification and Evaluation of Medical Translator Mobile Applications Using an Adapted APPLICATIONS Scoring System. Telemedicine and e-Health 2018 Aug;24(8):594-603. [doi: 10.1089/tmj.2017.0150]
15. Sezgin E, Weiler M, Weiler A, Lin S. Proposing an Ecosystem of Digital Health Solutions for Teens With Chronic Conditions Transitioning to Self-Management and Independence: Exploratory Qualitative Study. J Med Internet Res 2018 Sep 06;20(9):e10285. [doi: 10.2196/10285]
16. HRSA. 2019 HRSA MCHB Care coordination challenge winners. 2019. URL: https://mchbgrandchallenges.hrsa.gov/challenges/care-coordination-cshcn/winners [accessed 2020-06-06]
17. Sezgin E, Noritz G, Elek A, Conkol K, Rust S, Bailey M, et al. Capturing At-Home Health and Care Information for Children With Medical Complexity Using Voice Interactive Technologies: Multi-Stakeholder Viewpoint. J Med Internet Res 2020 Feb 13;22(2):e14202. [doi: 10.2196/14202]
18. Amazon Web Services. Amazon Transcribe Medical. URL: https://aws.amazon.com/transcribe/medical/ [accessed 2020-06-06]
19. Amazon Web Services. Amazon Translate. URL: https://aws.amazon.com/translate/faqs/ [accessed 2020-06-06]
20. DeForte S, Sezgin E, Huefner J, Lucius S, Luna J, Satyapriya A, et al. Usability of a Mobile App for Improving Literacy in Children With Hearing Impairment: Focus Group Study. JMIR Hum Factors 2020 May 28;7(2):e16310 [FREE Full text] [doi: 10.2196/16310] [Medline: 32205305]

21. Militello L, Sezgin E, Huang Y, Lin S. Delivering Perinatal Health Information via a Voice Interactive App: A Mixed Method Study. JMIR Preprints. 13/02/ 2020. [doi: 10.2196/preprints.18240]
22. Lewis J, Sauro J. The factor structure of the system usability scale. 2009 Presented at: International conference on human centered design; 2009 Jul 19; Berlin, Heidelberg p. 94-103. [doi: 10.1007/978-3-642-02806-9_12]
23. Davis FD. Perceived Usefulness, Perceived Ease of Use, and User Acceptance of Information Technology. MIS Quarterly 1989 Sep;13(3):319. [doi: 10.2307/249008]
24. Sanders L. In: Stappers PJ, editor. Convivial design toolbox: generative research for the front end of design. Amsterdam: BIS; 2012.
25. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology 2006 Jan;3(2):77-101. [doi: 10.1191/1478088706qp063oa]

Abbreviations

AWS: Amazon Web Services
EHR: electronic health record
FHIR: Fast Healthcare Interoperability Resources
iOS: iPhone operating system
IT: information technology
NCH: Nationwide Children's Hospital
SUS: system usability scale
TAM: technology acceptance model

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Protocol

Video Consultations for Older Adults With Multimorbidity During the COVID-19 Pandemic: Protocol for an Exploratory Qualitative Study

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Abstract

Background: Multimorbidity, the coexistence of multiple chronic conditions in an individual, is a growing public health challenge. Amidst the COVID-19 pandemic, physical distancing remains an indispensable measure to limit the spread of the virus. This pertains especially to those belonging to high-risk groups, namely older adults with multimorbidity. In-person visits are discouraged for this cohort; hence, there is a need for an alternative form of consultation such as video consultations to continue the provision of care.

Objective: The potential of video consultations has been explored in several studies. However, the emergence of COVID-19 presents us with an unprecedented opportunity to explore the use of this technological innovation in a time when physical distancing is imperative. This study will evaluate the sustainability of video consultations on a micro-, meso-, and macro-level by assessing the views of patients, physicians, and organizational and national policymakers, respectively.

Methods: The NASSS (nonadoption, abandonment, scale-up, spread, and sustainability) framework was designed as a guide for the development of health care technologies. In this study, the implementation of and experiences related to video consultations will be studied using the NASSS framework. Individual in-depth interviews or focus group discussions will be conducted with participants using the Zoom platform. Data will be analyzed by at least two investigators trained in qualitative methodology, organized thematically, and coded in two phases—an initial phase and a focused selective phase. All disagreements will be resolved by consulting the larger research team until consensus is reached.

Results: This study was approved for funding from the Geriatric Education and Research Institute. Ethics approval was obtained from the National Healthcare Group Domain Specific Review Board (reference #2020/00760). Study recruitment commenced in July 2020. The results of the data analysis are expected to be available by the end of the year.

Conclusions: This study aims to evaluate the adoption and sustainability of video consultations for older adults with multimorbidity during the pandemic as well as post COVID-19. The study will yield knowledge that will challenge the current paradigm on how care is being delivered for community-dwelling older adults with multimorbidity. Findings will be shared with administrators in the health care sector in order to enhance the safety and quality of these video consultations to improve patient care for this group of population.

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KEYWORDS

COVID-19; multimorbidity; older adults; telemedicine; video consultation; elderly; telehealth; morbidity; protocol; chronic disease; high risk; qualitative

Introduction

Background

The utilization of remote consultations via telemedicine is not new to the health care scene [1]. Studies in several countries have discussed the benefits and challenges of remote consultations, which are often used to promote access to health care for rural and geographically isolated populations [2-5]. Other specific populations that have benefited from remote consultations are patients in palliative care [6,7], neonatal care [8,9] and postoperative care [10].

The COVID-19 pandemic has unexpectedly accentuated the need for remote consultations. In Singapore, the use of telemedicine apps has risen sharply [11], and dormitories housing foreign workers are using remote video technologies to monitor patients' well-being during the pandemic [12]. Health care professionals in public primary care have started to defer in-person consultations and replace routine in-person follow-up appointments with telephone consultations. However, telephone consultations have serious limitations compared to in-person visits, since the clinician cannot use visual information about the patient to assess well-being. Video consultations offer a means of overcoming the limitation of not being able to see the patient, allowing for a more holistic assessment [1]. Despite the advantages of video consultation, its performance in terms of safety and effectiveness to render care for older adults with multimorbidity is unknown.

The potential of video consultations is of relevance to the geriatric population. Many older adults have multiple chronic conditions or multimorbidity [13], and require regular follow-up with different clinicians. As a high-risk group, older adults have been strongly encouraged to stay home during this crisis, as catching the infection poses serious risks for them [14]. Moreover, older adults with multimorbidity may face challenges related to physical mobility because of their ill health or frailty, making traveling to the clinic both dangerous and cumbersome. In order to maintain physical distancing, video consultations serve as a means for health care providers to continue care for this group of patients. To protect this vulnerable group of patients from COVID-19 infection, many of their scheduled physical medical appointments to primary care clinics have been postponed or converted to telephone consultations since February 2020 when Singapore moved into a semilockdown. Under the Ministry of Health's regulatory sandbox for telemedicine providers, video consultation has been piloted in several private primary care clinics in Singapore since 2018 [15,16]. In the public sector, limited telemonitoring, telecollaborations, and telephone consultations have been used but video consultations have not been attempted.

In a recent online survey conducted at National Healthcare Group Polyclinics (NHGP) involving 712 patients who had telephone consultations in place of in-person consultations during the COVID-19 pandemic, approximately 95% of respondents agreed to use a telephone consultation again, and 93.1% would recommend it to another person. However, 8% of respondents preferred in-person consultations, citing a lack of personal touch as the main reason. Some of the respondents also complained that they could not see the doctor and would prefer a live video chat instead.

Conducting a video consultation may be considered a disruptive innovation since it simultaneously adheres to physical distancing measures during the COVID-19 pandemic while shifting the boundaries of doctor-patient consultations. Studies in other countries have shown that the implementation of telemedicine can be hindered by clinician nonacceptance and conflict with organization culture [17]. The successful introduction and implementation of video consultation will depend on the acceptability of the new intervention to both the intervention deliverers (ie, physicians) and the recipients (ie, patients). On a broader level, the health organizations' readiness to adopt the innovation and the wider national context should also be taken into consideration [17].

Although Singapore is a nation with technologically developed infrastructure, levels of comfort with video technologies and tech savviness vary considerably. Communication issues including hearing and language difficulties may be exacerbated when the consultation is not performed in person, especially for older adults. Therefore, it remains to be seen what the benefits and drawbacks of a video consultation might be for older adults with multimorbidity in the Singapore context.

While the use of video consultations is promising as an alternative mode of care, extant literature has demonstrated the relevance of sociodemographic factors in patients with multimorbidity. Multimorbidity is known to be more prevalent in socioeconomically disadvantaged groups [18-20]; this was also evident in a study conducted in Singapore [13]. People from less privileged households in Singapore were reportedly less likely to have internet access or personal computers, according to Singapore's Household Expenditure Survey 2017/2018 [21]. As such, the potential of video consultations for older adults with multimorbidity needs to take into consideration factors such as the digital divide leading to limited access among older adults, who tend to have lower levels of literacy and limited economic and social resources. While the present study acknowledges the ramifications of the digital divide, our current objectives are to pilot a video consultation workflow and identify challenges that even the more adept patients struggle with, as well as to identify whether there is a sizeable proportion of older adults with multimorbidity who are comfortable with video consultations. Being an IT (information technology)-related pilot project, we anticipate that some self-selection will occur, resulting in the patient population for

this study potentially being more IT-literate than the general population.

The goal of this pilot project is to explore the adoption and sustainability of video consultations in order to arrive at a better understanding as to how the current health care system can be improved to ensure levels of care for patients can be maintained through this trying time. We also propose to use the findings acquired from the study as a precursor to further studies that will inform the future implementation of video consultation with family physicians for older adults with multimorbidity in the primary care setting in Singapore.

Objectives

The objectives of this study are as follows:

1. At the micro-level (individual technology users): to study how patients are seen, heard and their needs are met in a safe manner; to explore patients' and physicians' acceptance, communication issues and logistical demands, thereby elucidating the features of an optimal video consultation
2. At the meso-level (organizational processes and systems): to understand and explore the social, technical, financial, and logistical support or lack thereof from the organization, thereby elucidating the requirements for introducing, sustaining, and scaling up of video consultations
3. At the macro-level (national policy and wider context): to understand the current regulatory, legal, professional, sociocultural, political, or policy context, in order to alert key stakeholders to the potential barriers and challenges of video consultation as a regular health care service model in the post–COVID-19 phase.

Research Questions

Our research questions are as follows:

1. What features characterize an optimal video consultation and how does the experience differ from an in-person consultation?
2. On an organizational level, what are the factors that affect the implementation of video consultations?
3. What is the national-level context of implementing video consultations as a regular health care service model option in the post–COVID-19 new normal?

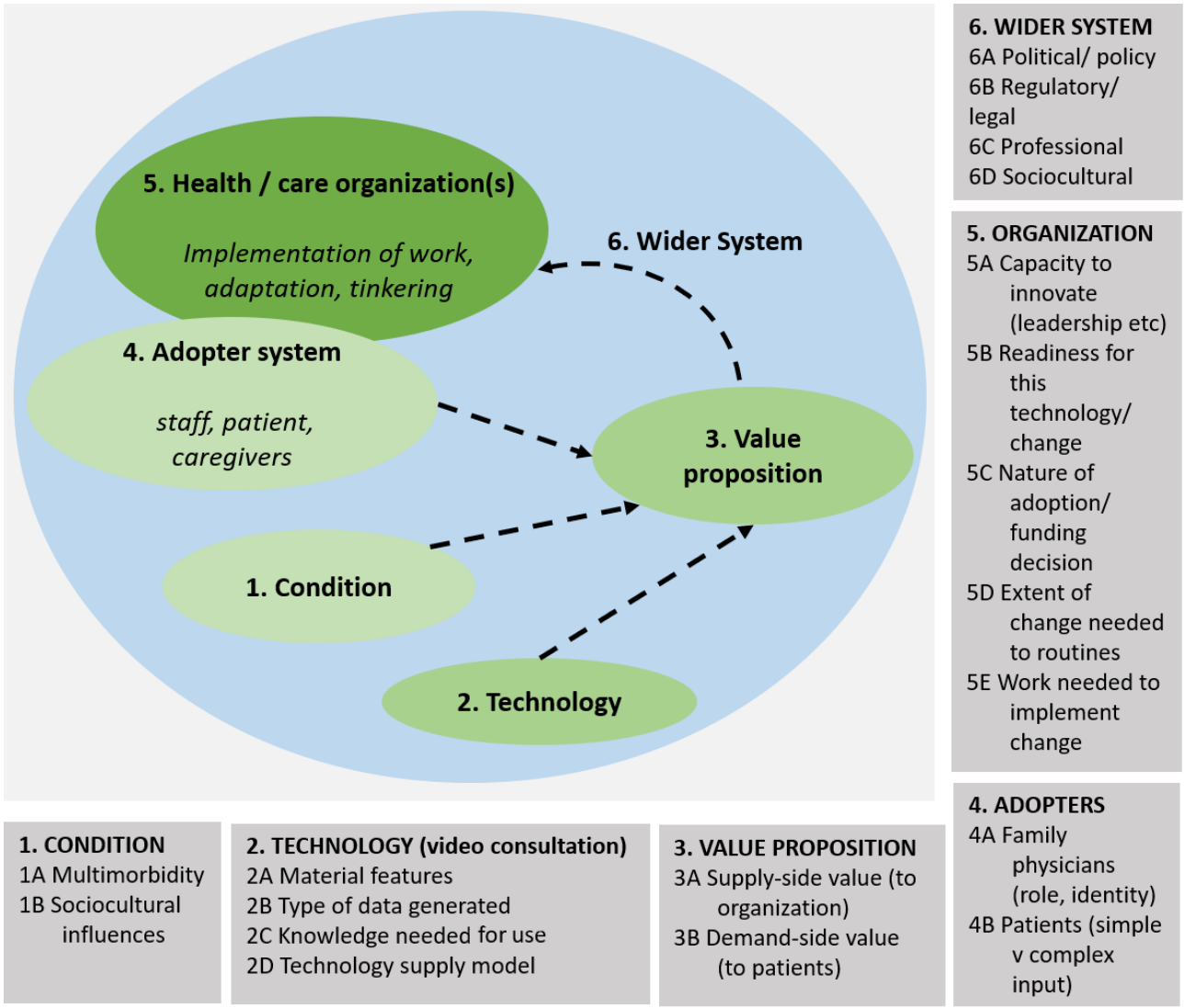
Methods

Study Design and Conceptual Framework

This is a predominantly qualitative descriptive study for understanding the perspectives of various stakeholders (patients, family physicians, organizational implementers/leaders, and organizational/national policymakers) on video consultation for community-dwelling older adults with multimorbidity in a public primary health care setting in Singapore.

Six domains from the nonadoption, abandonment, scale-up, spread, and sustainability (NASSS) technology implementation framework [17] will be adopted to guide our study design and analysis (Figure 1). The domains are the health condition, the technology, the value proposition to patients, the adopter system (family physician and patient), the health care organization (including attention to implementation and adaptation), and the wider system (related political, regulatory, legal, professional, and sociocultural factors). We propose to use the framework prospectively and in real time to explore the challenges of introducing and implementing video consultations to support a new health care model.

Figure 1. The NASSS (nonadoption, abandonment, scale-up, spread, and sustainability) framework (adapted from Greenhalgh et al [17]).



Setting

All provision of health care services in Singapore is based on the fee-for-service model with various forms of subsidies available for those in need. The government often finetunes the subsidy policies to regulate "the supply and prices of health care services in the country" to keep public sector health care costs in check. However, private medical care is largely subject to market forces.

Singaporeans not empaneled to any specific practice and are free to choose the providers within the government or private health care delivery system. The public primary health care services are provided through an island-wide network of 20 outpatient polyclinics, which provide subsidized primary care including primary medical treatment, preventive health care, and health education. In addition, there are up to 1700 clinics run by private general practitioners. For this study, recruitment will be based at NHGP, which consist of six polyclinics located in the northern and central parts of Singapore.

Sampling and Recruitment of Participants

Purposive sampling will be used to obtain views from four participant groups for this study: patients, family physicians, organizational implementers/leaders, and organizational/national policymakers. The patient group will include older adults aged 60 years and above with multimorbidity (at least three chronic conditions) being managed by the polyclinic who have undergone at least one video consultation. The family physician group will include family physicians who have conducted at least two video consultations. The organizational implementers/leaders will include members of the senior management team, family physician leaders, or operational staff of NHGP involved in the pilot video consultation project. Lastly, the organizational/national policymakers will include office holders from NHGP and relevant statutory boards or government departments.

Potential patient participants will be approached when they visit the clinic for their laboratory tests. Routinely, an in-person consultation will follow one week after their laboratory tests. Patients who are eligible and comfortable to convert their impending in-person visit to video consultation will be referred to a research team member after their laboratory tests. Written informed consent will then be obtained from patients by a research team member in clinic after explaining the study and providing ample time for them to ponder and decide. A

convenient time for an individual in-depth interview will be arranged within a week after the scheduled video consultation. All nonpatient participants will be sent an email invitation with information on the study. Written informed consent for nonpatient participants will be obtained by a study team member at their workplace. All study participants will be informed that the interviews (family physicians and organizational implementers/leaders) or focus group discussions (organizational/national policymakers) will be conducted using an institution-approved secure video conferencing platform and recorded using a digital audio recorder.

An estimated maximum number of 60 participants will be recruited: 20 patients (aged ≥60 years with at least three chronic conditions), 15 family physicians, 15 organizational implementers/leaders, and 10 organizational/national policymakers. The recruitment of participants may end earlier if the interview data have reached thematic saturation.

Data Collection

Individual in-depth interviews and focus group discussions will be conducted by research team members who have experience in qualitative research. Each interview and discussion is expected to last up to 40 minutes and 90 minutes, respectively. They will be conducted via the institution-approved secure Zoom platform [22,23]. The Zoom platform as a tool to conduct video interviews allows for physical distancing to be maintained so that the research project can be conducted during the COVID-19 pandemic period. The topic guides are developed from the NASSS and complexity assessment tool (CAT) framework. They include questions on the micro-level (patients and physicians), the meso-level (organizational implementers/leaders), and the macro-level (organizational/national policymakers) [24].

Questions at the micro-level will pertain to patients' and physicians' experiences of the video consultation (acceptability, communication needs, safety, and related logistics). At the meso-level, questions put to organizational implementers/leaders will relate to discovering what factors and processes within the organization contribute to or hinder the successful execution of video consultations. Finally, questions at the macro-level put to organizational/national policymakers will seek to grasp the relevant regulatory, legal, professional, and sociocultural context in which the innovation is implemented, to better understand what challenges may lie ahead if video consultations become a regular service model nationwide. We will be collecting demographic information from patients, including questions on household type, people they live with, and level of IT literacy. We will also engage the family physicians in structured reflective journaling, where they will be asked to provide reflections on their video consultation experiences. This will occur at three different time points (at the beginning of their involvement in the study, midway through the study period, and at the end of the study), allowing the study team members to understand how their views change over the course of initiating and conducting video consultations.

Data Analysis

The interviews and focus group discussions will be transcribed verbatim. Another data source will include the reflective journals of the family physicians. Inductive thematic analysis will be carried out by at least two investigators trained in qualitative methodology [25]. They will be working independently initially and develop preliminary coding structures for organizing the data thematically. Coding would be done in two phases—an initial phase and a focused selective phase. Once the coding scheme has been refined, relationships among categories will be explored to facilitate raising the analytical level from categorical to thematic in order to make meaningful interpretations of the data. All disagreements will be resolved by consulting the larger research team. NVivo version 12 Plus (QSR International) will be used to help organize the data.

Rigor

Credibility will be achieved through obtaining data from all stakeholders and investigator triangulation [26]. We aim to achieve transferability by providing a clear description of the participants, settings, and research process [27]. Dependability will be maintained by keeping field notes and recording all analytic decisions. Finally, we aspire to achieve confirmability by applying data triangulation and researcher reflexivity [26].

Ethics and Confidentiality

We have obtained ethics approval from the National Healthcare Group Domain Specific Review Board (reference #2020/00760). Study team members will ensure that the necessary precautions are taken to ensure that privacy and confidentiality are maintained, such as using institution-approved secure Zoom accounts that are password-protected and accessible by study team members only.

Results

This project received funding from the Geriatric Education and Research Institute under the COVID-19 grant. At the time of writing, no participants have been formally recruited, but clinicians have been contacted and invited to take part in the study. Literature review is ongoing for researchers to stay updated on the state of the field in telemedicine research. Given that this study is qualitative and exploratory, it would be precipitous to anticipate our findings in detail. However, we expect a diversity of opinions both within and between the patient, physician, organizational implementer/leaders, and policymaker groups. The patient and physician groups are likely to show a range of opinions that spans from enthusiasm to reluctance, although the specific reasons for these will need to be elucidated. Organizational implementers/leaders are likely to discuss operational and logistical demands, and their impact on the operation of the whole organization, while we expect policymakers to help us frame the views within a larger overarching context. It is precisely this detail and the divergence in opinions among different stakeholders that will enable us to grasp what challenges lie ahead for the eventual successful implementation and large-scale adoption of video consultation as part of routine care for older adults with multimorbidity.

Discussion

This qualitative study is intended to understand how video consultation can benefit both older adults with multimorbidity and family physicians in Singapore. This is the first study looking into using video consultation in public primary health care in the country.

The most recent NHS England long-term plan mandates the availability of video consultations in the next 5 years [28]. Comparing video consultations to telephone consultations, it has been shown to have a better rapport to facilitate understanding through nonverbal communication [28]. Video consultations have been found to support patients with chronic conditions and prevent unnecessary admissions to long-term institutional care [29]. In Canada, they have made possible an interprofessional model of practice involving hospital specialists, a social worker, a pharmacist, a home care community coordinator, and other allied health professionals who allow older patients with complex multimorbidity to be managed within the community [30]. Jiwa et al [31] reported that Australian general practitioners who were favorably inclined toward video consultations were more likely to work in larger practices and be more established professionally. Approximately one-third of them were positive about video consultations, one-third were ambivalent, and one-third were against them.

The COVID-19 crisis has led to the introduction of video consultations in Singapore's public primary health care setting. If found to be appropriate for future use, this study will offer practical guidance on maximizing the adoption of this consultation model for desired clinical outcomes and user acceptance.

Before scaling and spreading video consultations in primary care, all stakeholders should be involved in further studies, which will look at proof of concept for clinical outcomes, patient suitability, safety, and minimization of technical issues by referencing qualitative findings from this study; and proof of value for the cost-effectiveness of the model of care. Finally, for the implementation and scaling phases of video consultations, clinical process re-engineering is likely to be necessary to create the clinical, quality educational, business, logistic, and organizational systems necessary to support implementation of video consultations on an enterprise scale.

As mentioned above, the digital divide is a reality in Singapore despite its affluence and high levels of general literacy and technological literacy. Subsequent phases looking into full-scale implementation will certainly need to examine the practicability and desirability of making video consultations available to all sociodemographic sectors, providing extra IT support, taking into account a lower level of technological access and literacy among the elderly in economically less-advantaged areas. This future phase will need to examine the specific role video consultations can play in future health care models, whether in supplementing routine consultations or enabling doctors to connect with patients with mobility issues, for example. The present study thus represents only an initial step toward a much larger initiative involving the role of video consultations within the health care system in primary care.

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Authors' Contributions

ESL and YYD initiated and conceptualized the study. ESL and SYT refined the application for funding to GERI with inputs from YYD, PSSL, EALC, GM, and HLK. ESL and PSSL led the protocol writing with inputs from all other authors. All authors have checked and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer Review Report from the Geriatric Education and Research Institute.
[PDF File (Adobe PDF File), 80 KB - resprot_v9i10e22679_app1.pdf]

References

1. Miller EA. Telemedicine and doctor-patient communication: a theoretical framework for evaluation. J Telemed Telecare 2002;8(6):311-318. [doi: 10.1258/135763302320939185] [Medline: 12537917]
2. Host BK, Turner AW, Muir J. Real-time teleophthalmology video consultation: an analysis of patient satisfaction in rural Western Australia. Clin Exp Optom 2018 Jan;101(1):129-134 [FREE Full text] [doi: 10.1111/cxo.12535] [Medline: 28436157]

3. Johansson AM, Lindberg I, Söderberg S. Healthcare personnel's experiences using video consultation in primary healthcare in rural areas. Prim Health Care Res Dev 2017 Jan;18(1):73-83. [doi: 10.1017/S1463423616000347] [Medline: 27640522]
4. Johansson AM, Söderberg S, Lindberg I. Views of residents of rural areas on accessibility to specialist care through videoconference. Technol Health Care 2014;22(1):147-155. [doi: 10.3233/THC-140776] [Medline: 24561880]
5. Campos C, Caudevilla E, Alesanco A, Lasierra N, Martinez O, Fernández J, et al. Setting up a telemedicine service for remote real-time video-EEG consultation in La Rioja (Spain). Int J Med Inform 2012 Jun;81(6):404-414. [doi: 10.1016/j.ijmedinf.2012.01.006] [Medline: 22326706]
6. Bradford NK, Armfield NR, Young J, Smith AC. Paediatric palliative care by video consultation at home: a cost minimisation analysis. BMC Health Serv Res 2014 Jul 28;14:328 [FREE Full text] [doi: 10.1186/1472-6963-14-328] [Medline: 25069399]
7. Middleton-Green L, Gadoud A, Norris B, Sargeant A, Nair S, Wilson L, et al. 'A Friend in the Corner': supporting people at home in the last year of life via telephone and video consultation-an evaluation. BMJ Support Palliat Care 2019 Dec;9(4):e26. [doi: 10.1136/bmjspcare-2015-001016] [Medline: 26850118]
8. Fang JL, Collura CA, Johnson RV, Asay GF, Carey WA, Derleth DP, et al. Emergency Video Telemedicine Consultation for Newborn Resuscitations: The Mayo Clinic Experience. Mayo Clin Proc 2016 Dec;91(12):1735-1743. [doi: 10.1016/j.mayocp.2016.08.006] [Medline: 27887680]
9. Casey F, Brown D, Craig BG, Rogers J, Mulholland HC. Diagnosis of neonatal congenital heart defects by remote consultation using a low-cost telemedicine link. J Telemed Telecare 1996;2(3):165-169. [doi: 10.1258/1357633961930004] [Medline: 9375052]
10. Nandra K, Koenig G, DelMastro A, Mishler EA, Hollander JE, Yeo CJ. Telehealth provides a comprehensive approach to the surgical patient. Am J Surg 2019 Sep;218(3):476-479. [doi: 10.1016/j.amjsurg.2018.09.020] [Medline: 30253859]
11. Lai L. Coronavirus: Surge in patients choosing to see docs via telemedicine. The Straits Times. 2020 Feb 13. URL: https://www.straitstimes.com/singapore/surge-in-patients-choosing-to-see-docs-via-telemedicine [accessed 2020-09-02]
12. Han GY. Technology to help foreign workers in dorms monitor health amid Covid-19 pandemic: Josephine Teo. The Strait Times. 2020 May 10. URL: https://www.straitstimes.com/singapore/technology-to-help-foreign-workers-in-dorms-monitor-health-josephine-teo [accessed 2020-09-02]
13. Low LL, Kwan YH, Ko MSM, Yeam CT, Lee VSY, Tan WB, et al. Epidemiologic Characteristics of Multimorbidity and Sociodemographic Factors Associated With Multimorbidity in a Rapidly Aging Asian Country. JAMA Netw Open 2019 Nov 01;2(11):e1915245 [FREE Full text] [doi: 10.1001/jamanetworkopen.2019.15245] [Medline: 31722030]
14. Support measures for seniors during COVID-19. Ministry of Health Singapore. 2020 May 8. URL: https://www.moh.gov.sg/news-highlights/details/support-measures-for-seniors-during-covid-19 [accessed 2020-09-02]
15. Lim C. Doctor Anywhere, WhiteCoat, Doctor World… Can Telemedicine Apps Save Us Money? MoneySmart. 2020 Mar 1. URL: https://blog3.moneysmart.sg/healthcare/doctor-anywhere-telemedicine-apps/ [accessed 2020-09-02]
16. Licensing Experimentation and Adaptation Programme (LEAP) - A MOH regulatory sandbox. Ministry of Health Singapore. URL: https://www.moh.gov.sg/home/our-healthcare-system/licensing-experimentation-and-adaptation-programme-(leap)---a-moh-regulatory-sandbox [accessed 2020-09-03]
17. Greenhalgh T, Wherton J, Papoutsi C, Lynch J, Hughes G, A'Court C, et al. Beyond Adoption: A New Framework for Theorizing and Evaluating Nonadoption, Abandonment, and Challenges to the Scale-Up, Spread, and Sustainability of Health and Care Technologies. J Med Internet Res 2017 Nov 01;19(11):e367 [FREE Full text] [doi: 10.2196/jmir.8775] [Medline: 29092808]
18. McLean G, Gunn J, Wyke S, Guthrie B, Watt GCM, Blane DN, et al. The influence of socioeconomic deprivation on multimorbidity at different ages: a cross-sectional study. Br J Gen Pract 2014 Jul;64(624):e440-e447. [doi: 10.3399/bjgp14X680545] [Medline: 24982497]
19. Aminisani N, Stephens C, Allen J, Alpass F, Shamshirgaran SM. Socio-demographic and lifestyle factors associated with multimorbidity in New Zealand. Epidemiol Health 2020;42:e2020001 [FREE Full text] [doi: 10.4178/epih.e2020001] [Medline: 32028546]
20. Thavorn K, Maxwell CJ, Gruneir A, Bronskill SE, Bai Y, Koné Pefoyo AJ, et al. Effect of socio-demographic factors on the association between multimorbidity and healthcare costs: a population-based, retrospective cohort study. BMJ Open 2017 Oct 06;7(10):e017264. [doi: 10.1136/bmjopen-2017-017264] [Medline: 28988178]
21. Report on the Household Expenditure Survey 2017/2018. 2019. URL: https://www.singstat.gov.sg/-/media/files/publications/households/hes201718.pdf [accessed 2020-10-31]
22. Archibald MM, Ambagtsheer RC, Casey MG, Lawless M. Using Zoom Videoconferencing for Qualitative Data Collection: Perceptions and Experiences of Researchers and Participants. International Journal of Qualitative Methods 2019 Sep 11;18:160940691987459. [doi: 10.1177/1609406919874596]
23. Zoom Video Conferencing Platform. URL: https://www.zoom.us/ [accessed 2020-09-02]
24. Greenhalgh T, Maylor H, Shaw S, Wherton J, Papoutsi C, Betton V, et al. The NASSS-CAT Tools for Understanding, Guiding, Monitoring, and Researching Technology Implementation Projects in Health and Social Care: Protocol for an Evaluation Study in Real-World Settings. JMIR Res Protoc 2020 May 13;9(5):e16861 [FREE Full text] [doi: 10.2196/16861] [Medline: 32401224]

25. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology 2006 Jan;3(2):77-101. [doi: 10.1191/1478088706qp063oa]
26. Lincoln YS, Guba EG, Pilotta JJ. Naturalistic inquiry. International Journal of Intercultural Relations 1985 Jan;9(4):438-439. [doi: 10.1016/0147-1767(85)90062-8]
27. Creswell JW, Poth CN. Qualitative Inquiry and Research Design: Choosing Among Five Approaches. 3rd Edition. SAGE Publications: Thousands Oak, CA; 2013.
28. Hammersley V, Donaghy E, Parker R, McNeilly H, Atherton H, Bikker A, et al. Comparing the content and quality of video, telephone, and face-to-face consultations: a non-randomised, quasi-experimental, exploratory study in UK primary care. Br J Gen Pract 2019 Sep;69(686):e595-e604. [doi: 10.3399/bjgp19X704573] [Medline: 31262846]
29. Darkins A, Ryan P, Kobb R, Foster L, Edmonson E, Wakefield B, et al. Care Coordination/Home Telehealth: the systematic implementation of health informatics, home telehealth, and disease management to support the care of veteran patients with chronic conditions. Telemed J E Health 2008 Dec;14(10):1118-1126. [doi: 10.1089/tmj.2008.0021] [Medline: 19119835]
30. Pariser P, Pham TT, Brown JB, Stewart M, Charles J. Connecting People With Multimorbidity to Interprofessional Teams Using Telemedicine. Ann Fam Med 2019 Aug 12;17(Suppl 1):S57-S62. [doi: 10.1370/afm.2379] [Medline: 31405877]
31. Jiwa M, Meng X. Video consultation use by Australian general practitioners: video vignette study. J Med Internet Res 2013 Jun 19;15(6):e117 [FREE Full text] [doi: 10.2196/jmir.2638] [Medline: 23782753]

Abbreviations

CAT: complexity assessment tool
GERI: Geriatric Education and Research Institute
IT: information technology
NASSS: nonadoption, abandonment, scale-up, spread, and sustainability
NHGP: National Healthcare Group Polyclinics

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Proposal

Determinants of Medical Practice Variation Among Primary Care Physicians: Protocol for a Three Phase Study

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Abstract

Background: One of the greatest challenges of modern health systems is the choice and use of resources needed to diagnose and treat patients. Medical practice variation (MPV) is a broad term which entails the differences between health care providers inclusive of both the overuse and underuse. In this paper, we describe a 3-phase research protocol examining MPV in primary care.

Objective: We aim to identify the potential targets for behavioral modification interventions to reduce the variation in practice patterns and thus improve health care, decrease costs, and prevent disparities in care.

Methods: The first phase will delineate the variation in primary care practice over a wide range of services and long follow-up period (2003-2017), the second will examine the 3 determinants of variation (ie, patient, physician, and clinic characteristics), and attempt to derive the unexplained variance. In the third phase, we will assess a novel component that might contribute to the previously unexplained variance - the physicians' personal behavioral characteristics (such as risk aversion, fear of malpractice, stress from uncertainty, empathy, and burnout).

Results: This work was supported by the research grant from Israel National Institute for Health Policy Research (Grant No. 2014/134). Soroka University Medical Center Institutional Ethics Committee has approved the updated version of the study protocol (SOR-14-0063) in February 2019. All relevant data for phases 1 and 2, including patient, physician, and clinic, were collected from the Clalit Health Services data set in 2019 and are currently being analyzed. The evaluation of the individual physician characteristics (eg, risk aversion) by the face-to-face questionnaires was started on 2018 and remains in progress. We intend to publish the results during 2020-2021.

Conclusions: Based on the results of our study, we aim to propose a list of potential targets for focused behavioral intervention. Identifying new targets for such an intervention can potentially lead to a decrease in the unwarranted variation in the medical practice. We suggest that such an intervention will result in optimization of the health system, improvement of health outcomes, reduction of disparities in care and savings in cost.

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KEYWORDS

medical practice variation; variation determinants; primary care physicians; personal behavioral characteristics

Introduction

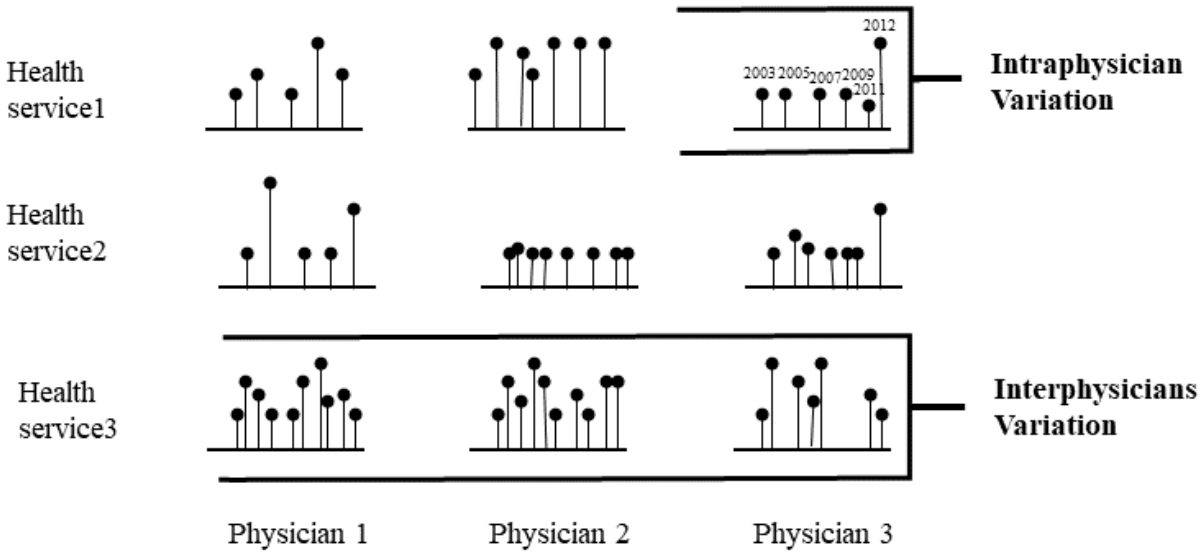
Background

Health care spending worldwide continues to increase and now accounts for approximately 17% of the gross domestic product in the United States, 9.8% in the Organisation for Economic Co-operation and Development (OECD) countries, and 7.5% in Israel [1]. Most experts consider the level of health care spending in the United States unsustainable [2]. Health economists identify unnecessary diagnostic and screening tests as a primary driver of this spending [2-5]. Moreover, many studies have shown that overuse neither benefits health care nor health outcomes [6-9] and may have adverse effects [10], leading to more unnecessary tests and treatment [11]. Major attempts to prevent the overuse of health services (HSs) include the British Medical Journal series *Too Much Medicine* [12], established in 2002, and *Choosing Wisely* campaigns [13], established in 2012. Increasing interest in this area is also reflected by the growing number of books, literature, and articles in the mainstream media [14].

Medical Practice Variation

In this study we chose to investigate medical practice variation (MPV), coined by the Dartmouth research group [15,16]. While MPV is based on a relative comparison between providers (Figure 1), overuse and underuse definitions call for a comparison between the individual provider practice and standard of care (absolute comparison) based on a "gold standard" or guideline recommendations [16,17]. Both overuse and underuse (eg, patients not receiving optimal care and resources used inefficiently) have negative consequences [14] and can contribute to MPV [15]. MPV is associated with poorer health outcomes, increased costs, disparities in care, and burden on medical systems [14,17-21]. Adopting the policy aimed to reduce variation is a central theme of quality management that has begun with industrial production and was recently adopted in medicine practice [19,22,23].

Figure 1. Two types of variation.



Not all MPV has pernicious effects. One should distinguish between unwarranted and warranted MPV. Warranted MPV reflects patient-centered care as it takes into account patient differences such as clinical or patient-preference differences [20,24]. Unwarranted MPV is caused by many factors such as variable access to resources or differing physician opinions and preferences [15,16]. In our study, we try to focus on factors contributing to the unwarranted MPV.

MPV Determinants

MPV causes can be divided into 3 main domains: patient characteristics, health care system characteristics, and physician characteristics [25,26]. Existing research suggests that variation is mainly attributable to patient characteristics, rather than to physician, or clinic [27-31]. Patient-related factors frequently studied in primary care [32] included age [33,34], type and severity of illness [33-35], socioeconomic status [36-39], ethnicity/race [40-42], and expectations of treatment effect [34,35,43,44]. Clinic factors included size [38,39,45,46], workload [46-48], funding method [49], services availability [35,50,51], services cost [52,53], and rural/urban location [15,34,54-56].

Factors related to the primary care physicians can be divided into demographic/professional and psychological characteristics. Demographic/professional characteristics include age, gender [33,42,46,47,57,58], specialty [38,58], area of expertise [36,47,57,59], and years of practice [33,46,58,60,61]. The psychological characteristics are discussed further on in the manuscript.

Unexplained Variance

It appears that the major part of the variation is unexplained [31,62,63], that is, there are more influential factors that were not adequately estimated and researched so far [64], such as system-level and physician-level psychological characteristics. Assessing the extent of the variance that can be explained by the physicians' psychological characteristics is essential because it will allow us to develop behavior modification tools that might help in reducing MPV [25]. Targeted interventions that address these variables might successfully optimize test ordering. The physician psychological characteristics include personality [65], attitudes [66], or behavior [67].

There is no generally agreed upon definition of personality, yet it is defined as person's stable feelings, thoughts, and behavioral patterns [68]. The Big Five dimensions of personality are openness, conscientiousness, extraversion, agreeableness, and neuroticism [69]. Attitude refers to one's opinions, beliefs, and feelings about aspects of his/her work environment. Two job attitudes have the greatest potential to influence how people behave at work: job satisfaction (feelings people have toward their job) and organizational commitment (the emotional attachment people have toward the company they work for) [68].

Compared with personality and attitudes, behavior is less abstract and more measurable, objective, and quantified and also it encompasses the other variables as it is a derivative of them [67,70]. Therefore we chose to focus on the physicians' behavior characteristics. Four types of behaviors have been extensively studied in the organizational behavior literature: job performance, organizational citizenship behaviors, absenteeism, and turnover [68]. Our research, which studies the referral rates of the physicians, is related to the job performance behavior. Job performance refers to the success that one accomplishes in the tasks listed in his/her job description. Factors related to a physician's job performance and medical decision making are the way s/he is treated at work, cognitive shortcuts (heuristics), the level of stress experienced at work, work attitudes to risks, and emotion [68,70].

Personal Behavioral Characteristics

Personal behavioral characteristics studied to date with respect to unwarranted variation included risk attitudes [58,71-74], adherence to treatment guidelines [50,75-78], empathy [79], and fear of malpractice [80]. We believe that the comprehensive approach where we will investigate the effect of risk aversion, stress due to uncertainty, fear of malpractice, empathy, and burnout will bring a higher level of inference as each can be reliably measured and may uniquely and independently account for significant MPV.

Risk Aversion

Risk aversion is the tendency to minimize risk by choosing known options with more certain, but less beneficial, expected outcomes [81]. A risk averse physician, for example, might refer a patient for tests with an unclear, yet not urgent clinical presentation, despite the potential increase in cost and detrimental effect of unnecessary test. MPV studies show that longer cardiopulmonary resuscitation [74], higher use of laboratory services [71,72,82,83], more referrals [58,74], and higher admission rate to an intensive care unit [84] are associated with higher risk aversion. None to date, however, have examined the proportion of variance in the decision making that can be explained by risk aversion level.

We believe that the increased understanding of the mechanisms of risk-taking and risk-aversion behavior (eg, reward sensitivity, impulsiveness, and social anxiety) may suggest ways in which intervention programs can be designed and administered to be sensitive to individual differences between the physicians [85].

Stress From Uncertainty

Uncertainty is common among physicians who must make decisions based on incomplete and imperfect data, with unpredictable patient responses to testing and treatment [86]. Primary care physicians experience more uncertainty than specialists due to the breadth and complexity of scope, generalist orientation, focus on continuity, and psychosocial factors [87]. Previous research has shown that physician uncertainty is associated with MPV [32,87,88], yet again the extent to which it explains variance in the practice patterns has not been studied.

Fear of Malpractice Claims

Defensive medicine is defined as the ordering of tests, procedures, and patient visits for the purpose of averting malpractice [89]. A nationwide study of Israeli physicians concluded that defensive medicine is prevalent, mostly resulting in unnecessary tests, referrals to consultants, and hospitalizations [90]. Primary care physicians have historically experienced low rates of malpractice claims, attributed to the high regard for them in their communities, low numbers of invasive procedures, and mutual trust and communication developing with patients over time. In the most recent Medscape Malpractice report [91], primary care was not on the list of the top 10 specialties for lawsuits. However, recent years have seen an increase in the incidence of the malpractice claims in primary care [92]. Therefore, estimating the contribution of malpractice to MPV may be important as it may influence the physicians' practice patterns and thus the variation between them.

Burnout

Burnout is increasing among general physicians [93] and associated with self-reported errors among primary care physicians and longer consultations [94]. However, it has neither been associated with overuse nor examined as a determinant of MPV. We assume that physicians with higher levels of burnout may have less variation in their HS utilizations and may be overused. This is because their discretion is consistently influenced by their mood and lack of motivation than by their patients' medical needs.

Empathy

It has been shown that perceptions of patient needs, feelings, and primary care physicians' ability to recognize emotions affect how they order tests [95]. For instance, physicians rated higher for empathy had a greater preference for intubation, ordered more laboratory tests, and performed cardiopulmonary resuscitation for longer periods [79]. Yet, it has not been proved as a determinant of MPV.

Why Primary Care?

While most MPV research has focused on secondary and tertiary care in health regions and hospitals [15], this study examines MPV across primary care physicians. Primary care accounts for 14% of all health care spending on average across OECD countries with patient–physician consultations accounting for the majority (55% in the United States; 90% in the UK) [96]. Determining what accounts for MPV in primary care can help to develop targeted approaches for preventing unnecessary tests and treatment, better care coordination, cost containment, and improved health outcomes.

Israel's Health System

In 2019, Israel was ranked the 10th healthiest country in the world by Bloomberg rankings, out of 169 countries [97]. The National Health Insurance Law of 1995 mandates all citizens resident in the country to join 1 of the 4 official not-for-profit health maintenance organizations, which are prohibited by law from denying any Israeli resident a membership [98]. The study is placed in the Southern District of Israel, the Negev, and includes physicians and patients of the Clalit Health Services health maintenance organizations, the largest health insuring organization in Israel (4.5 million insurees). Clalit Health Services is the largest health care provider in the area, covering approximately 70% of a population of 730,000 residents in the Negev.

Health Services

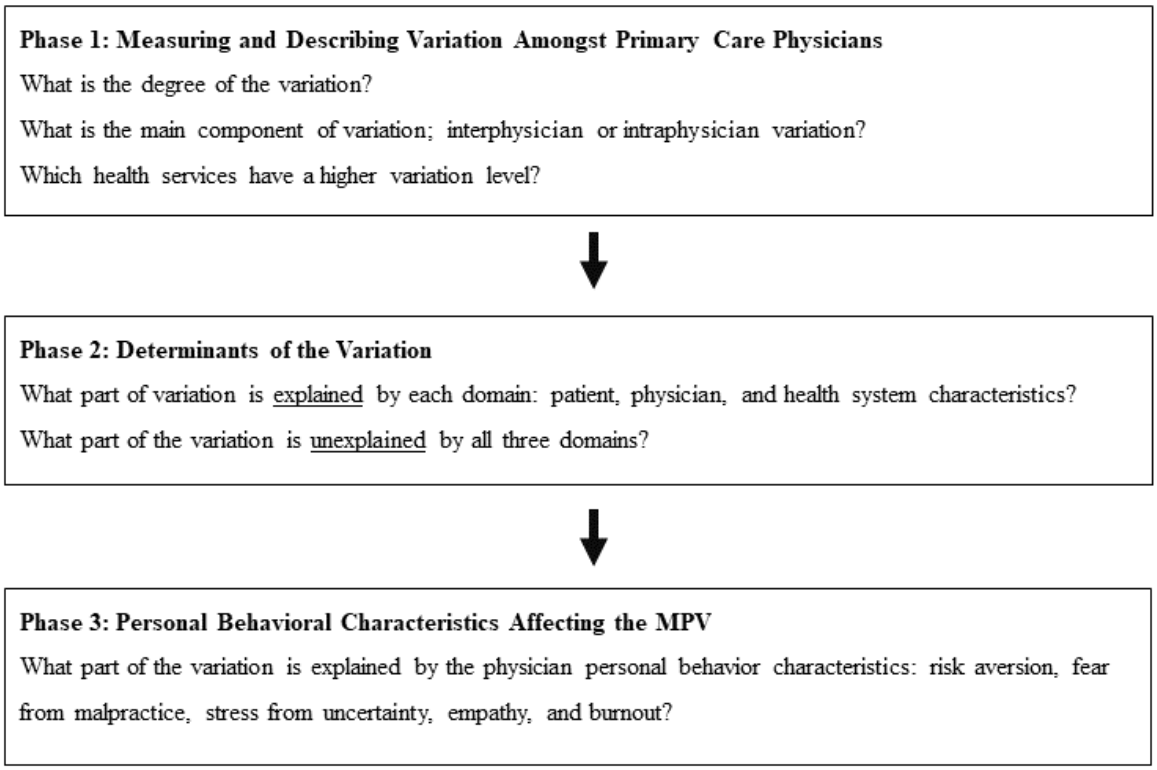
In this study we aimed to analyze HSs in the primary care in situations where the physician has the freedom of action to decide whether to utilize them [99], that is, clinical scenarios with discretionary decisions [100]. For instance, referring a patient with ST-elevation myocardial infarction to the hospital is not a discretionary decision as the physician's findings reflect an undoubtable urgent condition of myocardial infarction which can be cured in a catheterization room. But ordering a thyroid-stimulating hormone (TSH) test for a patient with generalized weakness is discretionary, because weakness is a nonspecific symptom which can be caused by many factors such as an infection, anemia, inflammation. For these discretionary HSs, different choices carry different benefits and risks and therefore we believe that physicians will differ in the decisions [101,102], based on their knowledge, experience, beliefs, and thoughts. We hypothesize that the derivative of these components, the physician personal behavioral patterns, can significantly influence the utilization of the services in this category. Therefore, we identified the 16 most frequently utilized HSs in primary care that can be discretionary.

- Four imaging tests: bone scans, computed tomography of the brain and spine, chest x-ray, magnetic resonance imaging;
- A composite of cardiac tests including Holter electrocardiography (ECG), echocardiogram, stress test, and transesophageal echocardiography;
- Six laboratory tests: vitamin B_{12}, vitamin D, TSH, hemoglobin, carcinoembryonic antigen, prostate-specific antigen;
- Three specialist consultation visits: rheumatology, pulmonary, and neurology;
- Two emergency department visits due to chest pain or back pain.

Objectives and Hypothesis

This paper describes a 3-phase research protocol (Figure 2) of MPV of primary care physicians across 16 HSs in the largest health care network in Southern Israel (Clalit Health Services) between 2003 and 2017.

Figure 2. Study flowchart - medical practice variation assessment.



The study's objectives are to (1) describe the variation of HSs referrals among primary care physicians; (2) derive the unexplained variance after the adjustment for patient, physician, and clinic characteristics; (3) assess the extent to which the personal behavioral characteristics of the primary care physicians contribute to the explanation of the unexplained variance; and (4) identify the potential targets for behavioral modification interventions to reduce the variation in practice patterns and thus improve health care, decrease costs, and prevent disparities in care.

We hypothesize that the physicians' personal behavioral characteristics such as risk aversion, stress due to uncertainty, fear of malpractice level of empathy, and burnout are affecting the decision-making process as demonstrated by the different levels of their HSs referrals.

Patient and Public Involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient-relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Methods

Study Phases

The first phase will delineate the variation in primary care practice over a wide range of services and long follow-up period, the second will examine the 3 determinants of variation (ie, patient, physician, and clinic characteristics) and attempt to derive the unexplained variance. In the third phase, we will assess a novel component that might contribute to the previously unexplained variance—the physicians' personal behavioral characteristics such as risk aversion, fear of malpractice, stress from uncertainty, empathy, and burnout.

Data Collection

Data will be collected from the computerized medical records of Clalit Health Services and will include (1) patient data (age, sex, marital status, residence type [urban, rural, or nomadic], number of annual visits by community physicians, background diseases, and socioeconomic status according to address); (2) primary care physician data (age, sex, years of active practice, area of expertise, specialty, country of birth, familial status, ethnicity, country where medical studies were completed, and number of insured patients in the physician's unit); (3) clinic data (number of insured patients per doctor, number of physicians per 1000 patients, number of annual visits, location [rural/urban]); (4) HS data (annual referral number per physician per clinic for bone scan, computed tomography, chest x-ray, magnetic resonance imaging, Holter ECG, echocardiogram, stress test, transesophageal echocardiography, vitamin B_{12} test, vitamin D test, TSH test, hemoglobin test, carcinoembryonic antigen test, prostate-specific antigen test; specialist consultation visits for rheumatology, pulmonary, and neurology; and emergency department visits due to chest pain and back pain).

The unit of analysis is physician/clinic/year. Each patient is assigned to 1 primary care physician and thus all data will be assigned annually to a physician per clinic. The HSs data will be extracted by numerical ID codes given for each HS.

Phase 1: Measuring and Describing Variation Among the Primary Care Across 16 HSs

In this initial phase of the research, we set out to identify MPV patterns by describing and comparing variation between HSs. Our first objective is to identify the main component of variation, that is, which variation is larger, between physicians or within the physician over time (interphysician vs. intraphysician variation). Additionally, we sought to identify which HSs have the highest variation and investigate their common characteristics.

The interphysician variation is the difference in utilization rates between physicians for a given HS, and the intraphysician or within-physician variation is the difference in practice pattern of an individual physician over the years. The difference between the 2 is illustrated in Figure 1. Most research to date examines variation in practice behavior between health care providers at one point in time, not within-physician variation over time. By delineating the 2 (between vs within), we can determine which accounts for a greater proportion of MPV (ie, relative importance of between- and within-physician variation) and what factors predict each. This information is germane to the policy makers, helping them determine where to direct efforts to reduce MPV. For instance, if within-physician variation accounts for a significant proportion of MPV, resources and efforts should be directed at fostering consistent physician clinical behavior over time. However, if between-physician variation is greater, efforts should be directed to assist overusing and underusing physicians to accommodate their utilization patterns to the appropriate level.

Statistical Analysis: Coefficient of Variation

Operational definitions and methods used to describe variation are diverse and inconsistent. Different authors have defined variation as absolute values [103,104]; rates [105,106]; ratios between tests [107,108] or 90th/10th percentiles [108,109]; and percentages of the overuse/underuse [96,110] or utilization [109,111] or inappropriate use [112]. We instead will measure variation using the coefficient of variation (COV), which is the ratio of the SD to the mean (SD/mean × 100). It represents the percent of the dispersion out of the central tendency, where higher values indicate larger difference between values (ie, higher variation). The COV is a standardized measurement; however, determining high variation for low-utilized HSs is considered overestimation [26], and therefore should be interpreted with caution.

The numerical levels (threshold) of COVs defining high versus low utilization differ across fields of science [113,114] and are not defined in MPV research literature [115]. Because it is a frequently used measure in the field of health policy research, there is a need for a consensus as to what represents high or low variation for each particular service [116].

To compare the utilization levels between physicians in each HS, we plan to calculate annual utilization rates per 1000 patients: ([utilization levels/total insured patients affiliated to the physician] × 1000 patients). Further, for each HS we will calculate between-physician COVs based on the averaged physicians' rates and within-physicians' COVs by the averaged individual physicians rates over the years of practice.

Correlation Between Variation and Utilization Levels

To identify potential MPV patterns, we will examine correlations between the averaged between- and within-physician variations and utilizations at the HSs level. For this analysis, we will use the Spearman test and chart the HSs' averaged utilizations and COVs to enable visual comparisons.

In conclusion for this phase, we intend to describe the MPV pattern among primary care physicians, identify the source of a greater variation component (between vs within), and the HSs with higher variation and higher utilization rates.

Phase 2: Determinants of the Variation

After describing the MPV patterns in primary care, we will then assess its determinants. The primary objective of the second phase is to estimate the extent to which each determinant explains the variation and to deduce the overall unexplained variance (Figure 2). In this stage we will collect a wide range of variables related to the domains, calculate the adjusted variance, and the proportional change in the variance (PCV) [117].

Statistical Analysis

PCV will be computed to determine the proportion of variance accounted for by each domain (patient, physician, clinic) across all HSs, using the following formula: PCV=(Vn1–Vn2)/Vn1. First, for each HS we will calculate the crude variance (Vn1), then, we will compute 3 regression models, each including covariates related to the domain. According to the models' predicted values, we will calculate the adjusted variance (Vn2), expecting a decrease from the crude variance. Then, for each HS we will calculate 3 PCVs, 1 for each domain, assessing the percent of the variance explained by each domain. The larger the PCV (ie, the larger the difference between crude and adjusted variances), the greater the variance explained by that domain. Consequently, we will determine which domain explains most of the variance across all HSs, and will be able to estimate the overall unexplained variance.

Prediction Model

As previously mentioned, we will perform regression model analysis to derive the adjusted variances for patient, physician, and clinic characteristics. We will utilize generalized linear negative binomial mixed models, the annual HSs utilizations as outcomes (nominator), and the annual insured patients per physician as the outcome's offset (denominator), and thus, defining the rates, the "count" variable of the negative binomial distribution. Physicians, clinics, and years (to account for secular and trajectory trends) will be defined as random effect clusters and patient, physician, and clinic characteristics will be included as fixed covariates separately. We will use "glmmTMB" R package (R Foundation for Statistical Computing), version 1.0.136 and IBM SPSS, version 24 for statistical analysis.

Phase 3: Personal Behavioral Characteristics Affecting the Variation

In this phase we will visit the clinics and ask the physicians to fill 5 short, validated research questionnaires measuring risk aversion, stress from uncertainty, fear from malpractice, empathy, and burnout [74,118]. We assume that these behavior characteristics are substantially stable [119,120] as well as the practice habits [121]. For instance, burnout [122] or stress from uncertainty is not a temporary emotion, but rather stable, as both are incurred by the properties of the specialty and the physician's capabilities and characteristics which tend to be fixed [122]. However, to be aligned with the most accurate and updated behaviors and practice habits, we chose in phase 3 to include physicians who worked also during 2017 (approximately 180) as we started to interview them in 2018. Furthermore, we will exclude physicians who worked starting from 2017, as the within-physician variation cannot be assessed for them. To increase the response rate, we plan to conduct face-to-face sessions during which the physicians will be asked to complete the questionnaires. We expect to achieve a response rate of more than 75%.

Questionnaires Scales

The risk-taking scale is a validated subset of the Jackson Personality Index that measures general risk-taking behavior in emergency physicians [89,123,124] and has 6 items, each rated on a 6-point Likert scale. Possible scores range from 6 to 36, and higher scores correspond to increased risk-taking [125,126]. The stress due to uncertainty is a validated psychometric tool, with a Cronbach alpha of .90 [127], that measures physician's stress due to uncertainty in patient care. It has 13 items, each rated on a 6-point Likert scale. Possible scores range from 13 to 78, with higher scores corresponding to higher stress due to uncertainty. The Malpractice Fear Scale is a validated scale, with a Cronbach alpha of .88 [93] that measures fear of malpractice in primary care and emergency physicians [58,123,128,129]. It has 6 items, each rated on a 5-point Likert scale, while possible scores range from 5 to 30, with higher scores corresponding to increased fear of malpractice. Empathy will be assessed by the Jefferson Scale of Physician Empathy, which consists of 20 items, with each rated on a 7-point Likert scale. Higher sum-scores indicate higher levels of empathy. The scale has been validated by explorative factor analysis and test–retest reliability [130]. Burnout will be assessed by the Maslach Burnout Inventory Human-Services-Survey [131], which has been used in more than 90% of empirical studies on burnout globally [132]. The Maslach Burnout Inventory – Human Services Survey consists of 22 items scored on a 7-point Likert scale constituting 3 subscales: (1) emotional exhaustion (9 items); (2) depersonalization (5 items); and (3) personal accomplishment (8 items). Burnout is defined as either a high score on the emotional exhaustion subscale or a high score on the depersonalization subscale or a low score on the personal accomplishment scale [131].

Statistical Analysis

During the analytic phase we will first compare the patient case mix and clinic and demographic characteristics between respondents and nonrespondents. This will allow us to estimate the degree of the potential bias in the analysis of the practice patterns. Then, we will assess the extent to which personal behavioral characteristics (ie, risk aversion, stress due to uncertainty, fear of malpractice, empathy, and burnout) contribute to the explanation of the unexplained variance defined in the previous phase, using the PCV approach. We hypothesize that high rates of HSs referrals will be associated with high levels of risk aversion, stress due to uncertainty, fear of malpractice, empathy, and burnout.

Ethics Approval and Consent to Participate

The study was approved by the Soroka University Medical Center Institutional Ethics Committee (0063-14-SOR). The consent to participate was written as part of the questionnaires.

Availability of Data and Material

The data sets that will be used or analyzed during this study will be available following local Ethics Committee approval.

Results

This work is supported by the research grant from Israel National Institute for Health Policy Research (2014/134). The funding agency has no input on the study design or execution. Our study protocol has undergone peer review by the funding body.

Soroka University Medical Center Institutional Ethics Committee has approved the updated version of the study protocol (SOR-14-0063) named "Determinants of Medical Practice Variation among Primary Care Physicians," in February 2019. The approval is valid until March 2021 and can be extended by request.

All the data for phase 1 (assessment of the cured variation) and phase 2 (derivation of the adjusted variation) including patient, physician, and clinic data were collected from the Clalit Health Services data set in 2019 and are currently being analyzed. The evaluation of the physicians' personal behavioral characteristics by the face-to-face questionnaires (phase 3) was started in 2018 and remains in progress. We intend to publish the results during 2020-2021.

Discussion

Overview

This study will allow us to approach the challenge of the targeted MPV reduction policies by answering a number of questions: What is the degree of the variation and what services have higher variation rates? Which variation is larger: between the physicians or within the physicians over time? What part of the variation cannot be explained by the patient case mix, clinic characteristics, or professional characteristics of the physician? Can physician personal behavioral characteristics explain part of the variation?

Risks and Limitations

Our current study focuses on the variation in the practice patterns, yet we cannot infer the clinical appropriateness of the

HSs used. In more general terms we will be not able to deduce what physician is practicing "good" medicine—the one who sends patients to a lot of tests or the one who sends few. Yet, because MPVs have been previously shown to be associated with poorer health outcomes [14,17-19,21], we believe that focusing on the measurement and dissection of the variation itself can contribute to the development of the approaches to reduce the MPV.

Another major limitation of the variation research in medicine is that acceptable values for variation are not defined. Therefore, we will be able only to have a relative comparison identifying factors associated with a higher variation (eg, physician characteristics, specific services).

Furthermore, in some circumstances the utilization of the HSs we are assessing can be considered not discretionary; for example, emergency department visits due to ECG presenting ST elevations in the primary care clinic, vitamin B_{12} laboratory tests for macrocytic anemia, or chest X-rays for chest injuries. However, the inclusion of these events decreases the variation and thus results in the bias toward zero (null hypothesis).

Moreover, our study precludes system-level factors such as resource constraints, process, workflow issues, funding, services accessibility. This is because we chose to focus on the physician level, not the system level. Therefore, we are only including patients and physicians belonging to 1 health care network (Clalit Health Services), thereby controlling for some of the system-level variation. However, it is possible that the variation between health care networks in the public health system in Israel is limited as the law controls their services' provision and accessibility, and thus reduces disparities in care. These health care networks are not-for-profit and are prohibited by law from denying any Israeli resident a membership. Yet, between regions in Israel there is a variation in the mentioned factors and therefore our findings can be generalized onto other regions and countries only after accounting for the patterns of this region.

At the final stage of our research we aim to identify behavioral characteristics associated with a higher variation by applying validated questionnaires. Physicians' attitudes as assessed by the abstract questionnaires may not fully represent their action in real-life clinical practice. Future research should aim at developing more reliable tools for assessing behavioral components of physicians practice.

The conventional risk of questionnaire-based research is a low response rate. To address this concern, we schedule face-to-face sessions with each one of the physicians enrolled into the study.

Outcomes of the Research Program

We expect to analyze a total of 3 million patient years and 6.5 million test utilizations across 16 diverse HSs, referred by 250 physicians in 170 clinics, over 15 years of practice. The size and comprehensiveness of the data will provide a good reassurance for the robustness and generalizability of the research program.

Focusing on the physician personal behavioral characteristics as a major contributing factor to the variation is essential, because it may allow us to identify what are the likely sources of unwarranted variation that can be redressed. We believe that most of the variation explained by patient or clinic characteristics is generally reasonable (eg, greater use by ill and older patients) [20]. However, variation stemming from the physician personal behavior characteristics might be unwarranted and can be reduced without negatively affecting patient care.

Based on the results of our study, we aim to propose a list of potential targets for focused behavioral intervention. The research of behavioral interventions designed for physicians is limited, and describes only a handful of strategies. The most common approaches focusing on changing the practice habits include clinical decision support, shared decision making, pay-for-performance, and insurer restrictions [133]. We believe that identifying new targets for such an intervention during the digital health era can potentially lead to a decrease in the unwarranted variation in the medical practice and thus to the improvement of health outcomes, reduction of disparities in care, and cost savings.

Acknowledgments

This work was supported by the research grant from Israel National Institute for Health Policy Research (Grant No. 2014/134). The funding agency has no input on the study design or execution. Our study protocol has not undergone peer review by the funding body.

Authors' Contributions

SS made substantial contributions to the design of the work and writing; SC and ED made substantial contributions to the conception and revision of the draft; VN and ME made substantial contributions to the design, substantively revised the work, and approved it.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review reports.
[PDF File (Adobe PDF File), 195 KB - resprot_v9i10e18673_app1.pdf]

References

1. OECD. Health Resources/Health Spending/OECD Data. 2019. URL: http://data.oecd.org/healthres/health-spending.htm [accessed 2020-09-02]
2. Maurer D, Stephens M, Reamy B, Crownover B, Crawford P, Chang T. Family physicians' knowledge of commonly overused treatments and tests. J Am Board Fam Med 2014;27(5):699-703 [FREE Full text] [doi: 10.3122/jabfm.2014.05.140003] [Medline: 25201940]
3. Iglehart JK. Health insurers and medical-imaging policy--a work in progress. N Engl J Med 2009 Mar 05;360(10):1030-1037. [doi: 10.1056/NEJMhpr0808703] [Medline: 19264694]
4. Lang K, Huang H, Lee DW, Federico V, Menzin J. National trends in advanced outpatient diagnostic imaging utilization: an analysis of the medical expenditure panel survey, 2000-2009. BMC Med Imaging 2013 Nov 26;13:40 [FREE Full text] [doi: 10.1186/1471-2342-13-40] [Medline: 24279724]
5. Smith-Bindman R, Miglioretti DL, Johnson E, Lee C, Feigelson HS, Flynn M, et al. Use of diagnostic imaging studies and associated radiation exposure for patients enrolled in large integrated health care systems, 1996-2010. JAMA 2012 Jun 13;307(22):2400-2409 [FREE Full text] [doi: 10.1001/jama.2012.5960] [Medline: 22692172]
6. Lehnert BE, Bree RL. Analysis of appropriateness of outpatient CT and MRI referred from primary care clinics at an academic medical center: how critical is the need for improved decision support? J Am Coll Radiol 2010 Mar;7(3):192-197. [doi: 10.1016/j.jacr.2009.11.010] [Medline: 20193924]
7. Chou R, Fu R, Carrino JA, Deyo RA. Imaging strategies for low-back pain: systematic review and meta-analysis. Lancet 2009 Feb 07;373(9662):463-472. [doi: 10.1016/S0140-6736(09)60172-0] [Medline: 19200918]
8. Fisher ES, Wennberg DE, Stukel TA, Gottlieb DJ, Lucas FL, Pinder EL. The implications of regional variations in Medicare spending. Part 1: the content, quality, and accessibility of care. Ann Intern Med 2003 Feb 18;138(4):273-287. [doi: 10.7326/0003-4819-138-4-200302180-00006] [Medline: 12585825]
9. Fisher ES, Wennberg DE, Stukel TA, Gottlieb DJ, Lucas FL, Pinder EL. The implications of regional variations in Medicare spending. Part 2: health outcomes and satisfaction with care. Ann Intern Med 2003 Feb 18;138(4):288-298. [doi: 10.7326/0003-4819-138-4-200302180-00007] [Medline: 12585826]
10. Starfield B, Shi L, Grover A, Macinko J. The effects of specialist supply on populations' health: assessing the evidence. Health Aff (Millwood) 2005 Jun;Suppl Web Exclusives:W5-97. [doi: 10.1377/hlthaff.w5.97] [Medline: 15769797]
11. Qaseem A, Alguire P, Dallas P, Feinberg LE, Fitzgerald FT, Horwitch C, et al. Appropriate use of screening and diagnostic tests to foster high-value, cost-conscious care. Ann Intern Med 2012 Jan 17;156(2):147-149. [doi: 10.7326/0003-4819-156-2-201201170-00011] [Medline: 22250146]
12. 2020. URL: https://www.bmj.com/too-much-medicine [accessed 2019-05-01]
13. 2020. URL: http://www.choosingwisely.org/ [accessed 2019-05-01]
14. Duddy C, Wong G. Explaining variations in test ordering in primary care: protocol for a realist review. BMJ Open 2018 Sep 12;8(9):e023117 [FREE Full text] [doi: 10.1136/bmjopen-2018-023117] [Medline: 30209159]
15. Corallo AN, Croxford R, Goodman DC, Bryan EL, Srivastava D, Stukel TA. A systematic review of medical practice variation in OECD countries. Health Policy 2014 Jan;114(1):5-14. [doi: 10.1016/j.healthpol.2013.08.002] [Medline: 24054709]
16. Goodman DC, Goodman AA. Medical care epidemiology and unwarranted variation: the Israeli case. Isr J Health Policy Res 2017 Feb 20;6(1). [doi: 10.1186/s13584-017-0135-6]
17. Krumholz HM. Variations in health care, patient preferences, and high-quality decision making. JAMA 2013 Jul 10;310(2):151-152 [FREE Full text] [doi: 10.1001/jama.2013.7835] [Medline: 23839747]
18. John H. The Role of Clinical Variation in Medical Practice. Clinical Variation in Your Medical Organization?. 2020. URL: https://www.healthcatalyst.com/role-clinical-variation-medical-practice
19. Berwick DM. Controlling variation in health care: a consultation from Walter Shewhart. Med Care 1991 Dec;29(12):1212-1225. [doi: 10.1097/00005650-199112000-00004] [Medline: 1745079]
20. Mercuri M, Gafni A. Examining the role of the physician as a source of variation: Are physician-related variations necessarily unwarranted? J Eval Clin Pract 2018 Feb;24(1):145-151. [doi: 10.1111/jep.12770] [Medline: 28556526]
21. KaiserFamFound. Disparities in Health and Health Care: Five Key Questions and Answers: @KaiserFamFound; 2018. URL: https://www.kff.org/disparities-policy/issue-brief/disparities-in-health-and-health-care-five-key-questions-and-answers/ [accessed 2019-05-01] [WebCite Cache ID https://www.kff.org/disparities-policy/issue-brief/disparities-in-health-and-health-care-five-key-questions-and-answers/]
22. Mullan F. Wrestling With Variation: An Interview With Jack Wennberg. Health Affairs 2004 Jan;23(Suppl2):VAR-73-VAR-80. [doi: 10.1377/hlthaff.var.73]
23. Fung V, Schmittdiel JA, Fireman B, Meer A, Thomas S, Smider N, et al. Meaningful variation in performance: a systematic literature review. Med Care 2010 Feb;48(2):140-148. [doi: 10.1097/MLR.0b013e3181bd4dc3] [Medline: 20057334]
24. Mercuri M, Gafni A. Medical practice variations: what the literature tells us (or does not) about what are warranted and unwarranted variations. J Eval Clin Pract 2011 Aug;17(4):671-677. [doi: 10.1111/j.1365-2753.2011.01689.x] [Medline: 21501341]

25. Sood R, Sood A, Ghosh AK. Non-evidence-based variables affecting physicians' test-ordering tendencies: a systematic review. Neth J Med 2007 May;65(5):167-177 [FREE Full text] [Medline: 17519512]
26. O'Sullivan JW, Stevens S, Oke J, Hobbs FDR, Salisbury C, Little P, et al. Practice variation in the use of tests in UK primary care: a retrospective analysis of 16 million tests performed over 3.3 million patient years in 2015/16. BMC Med 2018 Dec 20;16(1). [doi: 10.1186/s12916-018-1217-1]
27. Orueta JF, García-Alvarez A, Grandes G, Nuño-Solinís R. The Origin of Variation in Primary Care Process and Outcome Indicators: Patients, Professionals, Centers, and Health Districts. Medicine (Baltimore) 2015 Aug;94(31):e1314 [FREE Full text] [doi: 10.1097/MD.0000000000001314] [Medline: 26252315]
28. Singh S, Lin Y, Kuo Y, Nattinger AB, Goodwin JS. Variation in the risk of readmission among hospitals: the relative contribution of patient, hospital and inpatient provider characteristics. J Gen Intern Med 2014 Apr;29(4):572-578 [FREE Full text] [doi: 10.1007/s11606-013-2723-7] [Medline: 24307260]
29. Beaulieu M, Haggerty J, Tousignant P, Barnsley J, Hogg W, Geneau R, et al. Characteristics of primary care practices associated with high quality of care. CMAJ 2013 Sep 03;185(12):E590-E596 [FREE Full text] [doi: 10.1503/cmaj.121802] [Medline: 23877669]
30. Sándor J, Nagy A, Jenei T, Földvári A, Szabó E, Csenteri O, et al. Influence of patient characteristics on preventive service delivery and general practitioners' preventive performance indicators: A study in patients with hypertension or diabetes mellitus from Hungary. European Journal of General Practice 2018 Aug 02;24(1):183-191. [doi: 10.1080/13814788.2018.1491545]
31. Davis P, Gribben B, Lay-Yee R, Scott A. How much variation in clinical activity is there between general practitioners? A multi-level analysis of decision-making in primary care. J Health Serv Res Policy 2002 Oct;7(4):202-208. [doi: 10.1258/135581902320432723] [Medline: 12425779]
32. Davis P, Gribben B, Scott A, Lay-Yee R. The. Soc Sci Med 2000 Feb;50(3):407-418. [doi: 10.1016/s0277-9536(99)00299-3] [Medline: 10626764]
33. Tan A, Zhou J, Kuo Y, Goodwin JS. Variation among Primary Care Physicians in the Use of Imaging for Older Patients with Acute Low Back Pain. J Gen Intern Med 2016 Feb;31(2):156-163 [FREE Full text] [doi: 10.1007/s11606-015-3475-3] [Medline: 26215847]
34. Langley GR, MacLellan AM, Sutherland HJ, Till JE. Effect of nonmedical factors on family physicians' decisions about referral for consultation. CMAJ 1992 Sep 01;147(5):659-666 [FREE Full text] [Medline: 1521211]
35. Christensen B, Sørensen HT, Mabeck CE. Differences in referral rates from general practice. Fam Pract 1989 Mar;6(1):19-22. [doi: 10.1093/fampra/6.1.19] [Medline: 2714538]
36. Epstein AM, McNeil BJ. Physician characteristics and organizational factors influencing use of ambulatory tests. Med Decis Making 1985;5(4):401-415. [doi: 10.1177/0272989X8500500402] [Medline: 3916109]
37. Hartley RM, Charlton JR, Harris CM, Jarman B. Influence of patient characteristics on test ordering in general practice. Br Med J (Clin Res Ed) 1984 Sep 22;289(6447):735-738 [FREE Full text] [doi: 10.1136/bmj.289.6447.735] [Medline: 6434064]
38. Pham HH, Landon BE, Reschovsky JD, Wu B, Schrag D. Rapidity and modality of imaging for acute low back pain in elderly patients. Arch Intern Med 2009 May 25;169(10):972-981 [FREE Full text] [doi: 10.1001/archinternmed.2009.78] [Medline: 19468091]
39. Hawkey CJ, Cullen DJ, Greenwood DC, Wilson JV, Logan RF. Prescribing of nonsteroidal anti-inflammatory drugs in general practice: determinants and consequences. Aliment Pharmacol Ther 1997 Apr;11(2):293-298 [FREE Full text] [doi: 10.1046/j.1365-2036.1997.150326000.x] [Medline: 9146765]
40. Kressin NR, Lin M. Race/ethnicity, and Americans' perceptions and experiences of over- and under-use of care: a cross-sectional study. BMC Health Serv Res 2015 Oct 01;15:443 [FREE Full text] [doi: 10.1186/s12913-015-1106-7] [Medline: 26428620]
41. Kressin NR, Groeneveld PW. Race/Ethnicity and overuse of care: a systematic review. Milbank Q 2015 Mar;93(1):112-138 [FREE Full text] [doi: 10.1111/1468-0009.12107] [Medline: 25752352]
42. Wagner AC, Hann M, Ashcroft DM. Influence of population and general practice characteristics on prescribing of minor tranquilisers in primary care. Pharm Pract (Granada) 2010 Jul;8(3):193-200 [FREE Full text] [doi: 10.4321/s1886-36552010000300007] [Medline: 25126140]
43. Britten N, Ukoumunne O. The influence of patients' hopes of receiving a prescription on doctors' perceptions and the decision to prescribe: a questionnaire survey. BMJ 1997 Dec 06;315(7121):1506-1510 [FREE Full text] [doi: 10.1136/bmj.315.7121.1506] [Medline: 9420493]
44. Haggerty J, Tudiver F, Brown JB, Herbert C, Ciampi A, Guibert R. Patients' anxiety and expectations: how they influence family physicians' decisions to order cancer screening tests. Can Fam Physician 2005 Dec;51:1658-1659 [FREE Full text] [Medline: 16926946]
45. McCarthy M, Wilson-Davis K, McGavock H. Relationship between the number of partners in a general practice and the number of different drugs prescribed by that practice. Br J Gen Pract 1992 Jan;42(354):10-12 [FREE Full text] [Medline: 1586524]

46. Davidson W, Molloy DW, Somers G, Bédard M. Relation between physician characteristics and prescribing for elderly people in New Brunswick. CMAJ 1994 Mar 15;150(6):917-921 [FREE Full text] [Medline: 8131124]
47. Haikio JP, Linden K, Kvist M. Outcomes of referrals from general practice. Scand J Prim Health Care 1995 Dec;13(4):287-293. [doi: 10.3109/02813439508996777] [Medline: 8693214]
48. Healey AT, Yule BF, Reid JP. Variations in general practice prescribing costs and implications for budget setting. Health Econ 1994;3(1):47-56. [doi: 10.1002/hec.4730030107] [Medline: 8167799]
49. Wilson RP, Hatcher J, Barton S, Walley T. Influences of practice characteristics on prescribing in fundholding and non-fundholding general practices: an observational study. BMJ 1996 Sep 07;313(7057):595-599 [FREE Full text] [doi: 10.1136/bmj.313.7057.595] [Medline: 8806250]
50. Filan PM, Inder TE, Anderson PJ, Doyle LW, Hunt RW. Monitoring the neonatal brain: a survey of current practice among Australian and New Zealand neonatologists. J Paediatr Child Health 2007;43(7-8):557-559. [doi: 10.1111/j.1440-1754.2007.01136.x] [Medline: 17635686]
51. Lysdahl KB, Børretzen I. Geographical variation in radiological services: a nationwide survey. BMC Health Serv Res 2007 Feb 15;7:21 [FREE Full text] [doi: 10.1186/1472-6963-7-21] [Medline: 17302970]
52. Hart J, Salman H, Bergman M, Neuman V, Rudniki C, Gilenberg D, et al. Do drug costs affect physicians' prescription decisions? J Intern Med 1997 May;241(5):415-420 [FREE Full text] [doi: 10.1046/j.1365-2796.1997.137143000.x] [Medline: 9183310]
53. Weiss MC, Fitzpatrick R, Scott DK, Goldacre MJ. Pressures on the general practitioner and decisions to prescribe. Fam Pract 1996 Oct;13(5):432-438. [doi: 10.1093/fampra/13.5.432] [Medline: 8902511]
54. Holm M, Olesen F. Factors affecting prescription of psychotropic drugs in general practice. Scand J Prim Health Care 1988 Sep;6(3):169-173. [doi: 10.3109/02813438809009311] [Medline: 3222588]
55. McDonald JT, Sherman A. Determinants of mammography use in rural and urban regions of Canada. Can J Rural Med 2010;15(2):52-60. [Medline: 20350446]
56. Niemann T, Lous J, Thorsgaard N, Nielsen TT. Regional variations in the use of diagnostic coronary angiography. A one-year population-based study of all diagnostic coronary angiographies performed in a rural and an urban Danish county. Scand Cardiovasc J 2000 Jun;34(3):286-292. [doi: 10.1080/713783124] [Medline: 10935776]
57. Tan A, Kuo Y, Elting LS, Goodwin JS. Refining physician quality indicators for screening mammography in older women: distinguishing appropriate use from overuse. J Am Geriatr Soc 2013 Mar;61(3):380-387 [FREE Full text] [doi: 10.1111/jgs.12151] [Medline: 23452077]
58. Franks P, Williams GC, Zwanziger J, Mooney C, Sorbero M. Why do physicians vary so widely in their referral rates? J Gen Intern Med 2000 Mar;15(3):163-168 [FREE Full text] [doi: 10.1046/j.1525-1497.2000.04079.x] [Medline: 10718896]
59. Vehviläinen AT, Kumpusalo EA, Voutilainen SO, Takala JK. Does the doctors' professional experience reduce referral rates? Evidence from the Finnish referral study. Scand J Prim Health Care 1996 Mar;14(1):13-20. [doi: 10.3109/02813439608997063] [Medline: 8725089]
60. Mehrotra A, Reid RO, Adams JL, Friedberg MW, McGlynn EA, Hussey PS. Physicians with the least experience have higher cost profiles than do physicians with the most experience. Health Aff (Millwood) 2012 Nov;31(11):2453-2463 [FREE Full text] [doi: 10.1377/hlthaff.2011.0252] [Medline: 23129676]
61. Choudhry NK, Fletcher RH, Soumerai SB. Systematic review: the relationship between clinical experience and quality of health care. Ann Intern Med 2005 Feb 15;142(4):260-273. [doi: 10.7326/0003-4819-142-4-200502150-00008] [Medline: 15710959]
62. Seymour CW, Iwashyna TJ, Ehlenbach WJ, Wunsch H, Cooke CR. Hospital-level variation in the use of intensive care. Health Serv Res 2012 Oct;47(5):2060-2080 [FREE Full text] [doi: 10.1111/j.1475-6773.2012.01402.x] [Medline: 22985033]
63. Hofer TP, Hayward RA, Greenfield S, Wagner EH, Kaplan SH, Manning WG. The unreliability of individual physician. JAMA 1999 Jun 09;281(22):2098-2105. [doi: 10.1001/jama.281.22.2098] [Medline: 10367820]
64. Korenstein D. Medical Overuse as a Physician Cognitive Error: Looking Under the Hood. JAMA Intern Med 2019 Jan 01;179(1):26-27. [doi: 10.1001/jamainternmed.2018.5136] [Medline: 30508015]
65. Duberstein PR, Chapman BP, Epstein RM, McCollumn KR, Kravitz RL. Physician personality characteristics and inquiry about mood symptoms in primary care. J Gen Intern Med 2008 Nov;23(11):1791-1795 [FREE Full text] [doi: 10.1007/s11606-008-0780-0] [Medline: 18780127]
66. Morgan S, Morgan A, Kerr R, Tapley A, Magin P. Test ordering by GP trainees: Effects of an educational intervention on attitudes and intended practice. Can Fam Physician 2016 Sep;62(9):733-741 [FREE Full text] [Medline: 27629671]
67. Meidani Z, Mousavi GA, Kheirkhah D, Benar N, Maleki MR, Sharifi M, et al. Going beyond audit and feedback: towards behaviour-based interventions to change physician laboratory test ordering behaviour. J R Coll Physicians Edinb 2017 Dec;47(4):339-344. [doi: 10.4997/JRCPE.2017.407] [Medline: 29537404]
68. Mason CT. Berrin Erdogan. Management Principles. 2012. URL: https://2012books.lardbucket.org/pdfs/management-principles-v1.0.pdf [accessed 2019-05-01] [WebCite Cache ID https://2012books.lardbucket.org/pdfs/management-principles-v1.0.pdf]
69. Goldberg LR. An alternative. J Pers Soc Psychol 1990 Dec;59(6):1216-1229. [doi: 10.1037//0022-3514.59.6.1216] [Medline: 2283588]

70. Nelson-Piercy C, Vlaev I, Harris K, Fischer-Betz R. What factors could influence physicians' management of women of childbearing age with chronic inflammatory disease? A systematic review of behavioural determinants of clinical inertia. BMC Health Serv Res 2019 Nov 21;19(1):863 [FREE Full text] [doi: 10.1186/s12913-019-4693-x] [Medline: 31752837]
71. Holtgrave DR, Lawler F, Spann SJ. Physicians' risk attitudes, laboratory usage, and referral decisions: the case of an academic family practice center. Med Decis Making 1991;11(2):125-130. [doi: 10.1177/0272989X9101100210] [Medline: 1865781]
72. Nightingale SD. Risk preference and laboratory use. Med Decis Making 1987;7(3):168-172. [doi: 10.1177/0272989X8700700307] [Medline: 3613916]
73. Nightingale SD, Grant M. Risk Preference and Decision Making in Critical Care Situations. Chest 1988 Apr;93(4):684-687. [doi: 10.1378/chest.93.4.684]
74. Pedersen AF, Carlsen AH, Vedsted P. Association of GPs' risk attitudes, level of empathy, and burnout status with PSA testing in primary care. Br J Gen Pract 2015 Dec;65(641):e845-e851 [FREE Full text] [doi: 10.3399/bjgp15X687649] [Medline: 26541183]
75. Santora LM, Mahoney MC, Lawvere S, Englert JJ, Symons AB, Mirand AL. Breast cancer screening beliefs by practice location. BMC Public Health 2003 Feb 04;3:9 [FREE Full text] [doi: 10.1186/1471-2458-3-9] [Medline: 12646070]
76. Symons AB, Mahoney MC, Englert J, Mirand AL. Variations in approaches to breast cancer screening among primary care physicians. J Cancer Educ 2002;17(4):205-210. [doi: 10.1080/08858190209528839] [Medline: 12556057]
77. Bipat S, van Leeuwen MS, Ijzermans JNM, Bossuyt PMM, Greve J, Stoker J. Imaging and treatment of patients with colorectal liver metastases in the Netherlands: a survey. Neth J Med 2006 May;64(5):147-151 [FREE Full text] [Medline: 16702613]
78. Saigal CS, Pashos CL, Henning JM, Litwin MS. Variations in use of imaging in a national sample of men with early-stage prostate cancer. Urology 2002 Mar;59(3):400-404. [doi: 10.1016/s0090-4295(01)01543-6] [Medline: 11880080]
79. Nightingale SD, Yarnold PR, Greenberg MS. Sympathy, empathy, and physician resource utilization. J Gen Intern Med 1991;6(5):420-423. [Medline: 1744756]
80. Cascade PN, Webster EW, Kazerooni EA. Ineffective use of radiology: the hidden cost. AJR Am J Roentgenol 1998 Mar;170(3):561-564. [doi: 10.2214/ajr.170.3.9490931] [Medline: 9490931]
81. Oussedik E, Anderson MS, Feldman SR. Risk versus benefit or risk versus risk: Risk aversion in the medical decision making process. J Dermatolog Treat 2017 Feb;28(1):1-2. [doi: 10.1080/09546634.2017.1290575] [Medline: 28201943]
82. Nightingale SD. Risk preference and laboratory test selection. J Gen Intern Med 1987;2(1):25-28. [doi: 10.1007/BF02596246] [Medline: 3806268]
83. Zaat JO, van Eijk JT. General practitioners' uncertainty, risk preference, and use of laboratory tests. Med Care 1992 Sep;30(9):846-854. [doi: 10.1097/00005650-199209000-00008] [Medline: 1518316]
84. Nightingale SD. Risk preference and admitting rates of emergency room physicians. Med Care 1988 Jan;26(1):84-87. [doi: 10.1097/00005650-198801000-00009] [Medline: 3336247]
85. Reniers RLEP, Murphy L, Lin A, Bartolomé SP, Wood SJ. Risk Perception and Risk-Taking Behaviour during Adolescence: The Influence of Personality and Gender. PLoS One 2016;11(4):e0153842 [FREE Full text] [doi: 10.1371/journal.pone.0153842] [Medline: 27100081]
86. Simpkin AL, Schwartzstein RM. Tolerating Uncertainty - The Next Medical Revolution? N Engl J Med 2016 Nov 03;375(18):1713-1715. [doi: 10.1056/NEJMp1606402] [Medline: 27806221]
87. Evans L, Trotter DRM. Epistemology and uncertainty in primary care: an exploratory study. Fam Med 2009 May;41(5):319-326 [FREE Full text] [Medline: 19418279]
88. Ghosh AK. Dealing with medical uncertainty: a physician's perspective. Minn Med 2004 Oct;87(10):48-51. [Medline: 15559102]
89. Katz DA, Williams GC, Brown RL, Aufderheide TP, Bogner M, Rahko PS, et al. Emergency physicians' fear of malpractice in evaluating patients with possible acute cardiac ischemia. Ann Emerg Med 2005 Dec;46(6):525-533. [doi: 10.1016/j.annemergmed.2005.04.016] [Medline: 16308068]
90. Asher E, Greenberg-Dotan S, Halevy J, Glick S, Reuveni H. Defensive Medicine in Israel – A Nationwide Survey. PLoS ONE 2012 Aug 16;7(8):e42613. [doi: 10.1371/journal.pone.0042613]
91. Byrne G. MedScape. Nursing Standard 2015 Aug 19;29(51):29-29. [doi: 10.7748/ns.29.51.29.s34]
92. Blackston JW, Bouldin MJ, Brown CA, Duddleston DN, Hicks GS, Holman HE. Malpractice risk prevention for primary care physicians. Am J Med Sci 2002 Oct;324(4):212-219. [doi: 10.1097/00000441-200210000-00008] [Medline: 12385494]
93. Arigoni F, Bovier PA, Sappino AP. Trend of burnout among Swiss doctors. Swiss Med Wkly 2010;140:w13070. [doi: 10.4414/smw.2010.13070] [Medline: 20809437]
94. Williams ES, Manwell LB, Konrad TR, Linzer M. The relationship of organizational culture, stress, satisfaction, and burnout with physician-reported error and suboptimal patient care: results from the MEMO study. Health Care Manage Rev 2007;32(3):203-212. [doi: 10.1097/01.HMR.0000281626.28363.59] [Medline: 17666991]
95. van der Weijden T, van Bokhoven MA, Dinant G, van Hasselt CM, Grol RPTM. Understanding laboratory testing in diagnostic uncertainty: a qualitative study in general practice. Br J Gen Pract 2002 Dec;52(485):974-980 [FREE Full text] [Medline: 12528582]

96. O'Sullivan JW, Albasri A, Nicholson BD, Perera R, Aronson JK, Roberts N, et al. Overtesting and undertesting in primary care: a systematic review and meta-analysis. BMJ Open 2018 Feb 11;8(2):e018557. [doi: 10.1136/bmjopen-2017-018557]
97. These Are the World?s Healthiest Nations 2019. Lee J Miller, Lu W. 2020. URL: https://www.bloomberg.com/news/articles/2019-02-24/spain-tops-italy-as-world-s-healthiest-nation-while-u-s-slips [accessed 2019-05-01] [WebCite Cache ID https://www.bloomberg.com/news/articles/2019-02-24/spain-tops-italy-as-world-s-healthiest-nation-while-u-s-slips]
98. Rosen B, Waitzberg R, Merkur S. Israel: Health System Review. Health Syst Transit 2015;17(6):1-212 [FREE Full text] [Medline: 27050102]
99. Sirovich B, Gallagher PM, Wennberg DE, Fisher ES. Discretionary decision making by primary care physicians and the cost of U.S. Health care. Health Aff (Millwood) 2008;27(3):813-823 [FREE Full text] [doi: 10.1377/hlthaff.27.3.813] [Medline: 18474975]
100. Glasson J. Essential vs Discretionary Health Care in System Reform-Reply. JAMA 1995 Mar 22;273(12):919. [doi: 10.1001/jama.1995.03520360032027]
101. Kuo RN, Lai C, Yeh Y, Lai M. Discretionary decisions and disparities in receiving drug-eluting stents under a universal healthcare system: A population-based study. PLoS ONE 2017 Jun 8;12(6):e0179127. [doi: 10.1371/journal.pone.0179127]
102. Pierre L Yong, Robert S Saunders, LeighAnne Olsen. The Healthcare Imperative: Lowering Costs and Improving Outcomes. The National Academies Collection: Reports funded by National Institutes of Health 2010. [doi: 10.17226/12750] [Medline: 21595114]
103. Verstappen WHJM, ter Riet G, Dubois WI, Winkens R, Grol RPTM, van der Weijden T. Variation in test ordering behaviour of GPs: professional or context-related factors? Fam Pract 2004 Aug;21(4):387-395. [doi: 10.1093/fampra/cmh408] [Medline: 15249527]
104. Sá L, Teixeira ASC, Tavares F, Costa-Santos C, Couto L, Costa-Pereira A, et al. Diagnostic and laboratory test ordering in Northern Portuguese Primary Health Care: a cross-sectional study. BMJ Open 2017 Nov 15;7(11):e018509. [doi: 10.1136/bmjopen-2017-018509]
105. Busby J, Schroeder K, Woltersdorf W, Sterne JAC, Ben-Shlomo Y, Hay A, et al. Temporal growth and geographic variation in the use of laboratory tests by NHS general practices: using routine data to identify research priorities. Br J Gen Pract 2013 Apr;63(609):e256-e266 [FREE Full text] [doi: 10.3399/bjgp13X665224] [Medline: 23540482]
106. Selby J, Grumbach K, Quesenberry CP, Schmittdiel JA, Truman AF. Differences in resource use and costs of primary care in a large HMO according to physician specialty. Health Serv Res 1999 Jun;34(2):503-518 [FREE Full text] [Medline: 10357287]
107. Larsson AP, Palmer M, Hultén G, Tryding N. Large differences in laboratory utilisation between hospitals in Sweden. Clin Chem Lab Med 2000 May;38(5):383-389. [doi: 10.1515/CCLM.2000.056] [Medline: 10952220]
108. Lin DC, Straseski JA, Schmidt RL, The Thyroid Benchmarking Group. Multi-Center Benchmark Study Reveals Significant Variation in Thyroid Testing in United States. Thyroid 2017 Oct 01;27(10). [doi: 10.1089/thy.2017.0190] [Medline: 28679353]
109. Taroni F, Siass R, Traversa G, Raschetti R, Menniti-Ippolito F, Maggini M, et al. The nature, content and interpractice variation of general practice: A regional study in Italy. Eur J Epidemiol 1990 Sep;6(3):313-318. [doi: 10.1007/bf00150439]
110. Zhi M, Ding EL, Theisen-Toupal J, Whelan J, Arnaout R. The Landscape of Inappropriate Laboratory Testing: A 15-Year Meta-Analysis. PLoS ONE 2013 Nov 15;8(11):e78962. [doi: 10.1371/journal.pone.0078962]
111. Romain S, Schillaci MA. Childhood immunization: Availability of primary care providers in Ontario. Can Fam Physician 2009 Nov;55(11):1104-1105.e4 [FREE Full text] [Medline: 19910599]
112. Chami N, Simons JE, Sweetman A, Don-Wauchope AC. Rates of inappropriate laboratory test utilization in Ontario. Clin Biochem 2017 Oct;50(15):822-827. [doi: 10.1016/j.clinbiochem.2017.05.004] [Medline: 28483406]
113. Kwanchai A, Gomez AAG. Statistical Procedures for Agricultural Research. Second Edition. New York: John Wiley and Sons Inc; 1984.
114. Semenova VA, Schiffer J, Steward-Clark E, Soroka S, Schmidt DS, Brawner MM, et al. Validation and long term performance characteristics of a quantitative enzyme linked immunosorbent assay (ELISA) for human anti-PA IgG. J Immunol Methods 2012 Feb 28;376(1-2):97-107. [doi: 10.1016/j.jim.2011.12.002] [Medline: 22197974]
115. Nguyen LT, Guo M, Hemmelgarn B, Quan H, Clement F, Sajobi T, et al. Evaluating practice variance among family physicians to identify targets for laboratory utilization management. Clin Chim Acta 2019 Oct;497:1-5. [doi: 10.1016/j.cca.2019.06.017] [Medline: 31228416]
116. 2020. URL: https://www.oecd.org/health/geographic-variations-in-health-care-9789264216594-en.htm
117. Merlo J, Chaix B, Yang M, Lynch J, Råstam L. A brief conceptual tutorial of multilevel analysis in social epidemiology: linking the statistical concept of clustering to the idea of contextual phenomenon. J Epidemiol Community Health 2005 Jun;59(6):443-449 [FREE Full text] [doi: 10.1136/jech.2004.023473] [Medline: 15911637]
118. Melnick ER, O'Brien EGJ, Kovalerchik O, Fleischman W, Venkatesh AK, Taylor RA. The Association Between Physician Empathy and Variation in Imaging Use. Acad Emerg Med 2016 Aug;23(8):895-904 [FREE Full text] [doi: 10.1111/acem.13017] [Medline: 27343485]
119. Harris MA, Brett CE, Johnson W, Deary IJ. Personality stability from age 14 to age 77 years. Psychol Aging 2016 Dec;31(8):862-874 [FREE Full text] [doi: 10.1037/pag0000133] [Medline: 27929341]

120. Leon GR, Gillum B, Gillum R, Gouze M. Personality stability and change over a 30-year period--middle age to old age. J Consult Clin Psychol 1979 Jun;47(3):517-524. [doi: 10.1037//0022-006x.47.3.517] [Medline: 528720]
121. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. JAMA 1999 Oct 20;282(15):1458-1465. [Medline: 10535437]
122. Schaufeli W, Gerard H. Maassen, Arnold B. Bakker. Stability and change in burnout: A 10 - year follow - up study among primary care physicians. Journal of Occupational and Organizational Psychology 2011;Volume84(Issue2):248-267. [doi: 10.1111/j.2044-8325.2010.02013]
123. Pines JM, Hollander JE, Isserman JA, Chen EH, Dean AJ, Shofer FS, et al. The association between physician risk tolerance and imaging use in abdominal pain. Am J Emerg Med 2009 Jun;27(5):552-557. [doi: 10.1016/j.ajem.2008.04.031] [Medline: 19497460]
124. Pines JM, Isserman JA, Szyld D, Dean AJ, McCusker CM, Hollander JE. The effect of physician risk tolerance and the presence of an observation unit on decision making for ED patients with chest pain. Am J Emerg Med 2010 Sep;28(7):771-779. [doi: 10.1016/j.ajem.2009.03.019] [Medline: 20837253]
125. Pearson SD, Goldman L, Orav EJ, Guadagnoli E, Garcia TB, Johnson PA, et al. Triage decisions for emergency department patients with chest pain: do physicians' risk attitudes make the difference? J Gen Intern Med 1995 Oct;10(10):557-564. [doi: 10.1007/BF02640365] [Medline: 8576772]
126. Jackson D. Jackson personality inventory manual. Goshen NRPP 1975.
127. Gerrity MS, DeVellis RF, Earp JA. Physicians' reactions to uncertainty in patient care. A new measure and new insights. Med Care 1990 Aug;28(8):724-736. [doi: 10.1097/00005650-199008000-00005] [Medline: 2385142]
128. Fiscella K, Franks P, Zwanziger J, Mooney C, Sorbero M, Williams GC. Risk aversion and costs: a comparison of family physicians and general internists. J Fam Pract 2000 Jan;49(1):12-17. [Medline: 10691394]
129. Wong AC, Kowalenko T, Roahen-Harrison S, Smith B, Maio RF, Stanley RM. A survey of emergency physicians' fear of malpractice and its association with the decision to order computed tomography scans for children with minor head trauma. Pediatr Emerg Care 2011 Mar;27(3):182-185. [doi: 10.1097/PEC.0b013e31820d64f7] [Medline: 21346679]
130. Hojat M, Gonnella JS, Nasca TJ, Mangione S, Vergare M, Magee M. Physician empathy: definition, components, measurement, and relationship to gender and specialty. Am J Psychiatry 2002 Sep;159(9):1563-1569. [doi: 10.1176/appi.ajp.159.9.1563] [Medline: 12202278]
131. Maslach CJ, Susan E. Jackson, Michael Leiter. Leiter MP . Maslach burnout inventory manualrd edn. Palo Alto, CA: Consulting Psychologists Press, Inc;; 1996:3.
132. Kristensen TB, Villadsen E, Christensen K. The Copenhagen burnout inventory: a new tool for the assessment of burnout. Work and Stress 2005;19(3):192-207 [FREE Full text] [doi: 10.1037/t62096-000]
133. Colla CH, Mainor AJ, Hargreaves C, Sequist T, Morden N. Interventions Aimed at Reducing Use of Low-Value Health Services: A Systematic Review. Med Care Res Rev 2017 Oct;74(5):507-550. [doi: 10.1177/1077558716656970] [Medline: 27402662]

Abbreviations

CHS: Clalit Health services
HS: health service
MPV: medical practice variation
TSH: thyroid-stimulating hormone

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Protocol

Investigation of Cardiovascular Health and Risk Factors Among the Diverse and Contemporary Population in London (the TOGETHER Study): Protocol for Linking Longitudinal Medical Records

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Abstract

Background: Global trends in cardiovascular disease (CVD) exhibit considerable interregional and interethnic differences, which in turn affect long-term CVD risk across diverse populations. An in-depth understanding of the interplay between ethnicity, socioeconomic status, and CVD risk factors and mortality in a contemporaneous population is crucial to informing health policy and resource allocation aimed at mitigating long-term CVD risk. Generating bespoke large-scale and reliable data with sufficient numbers of events is expensive and time-consuming but can be circumvented through utilization and linkage of data routinely collected in electronic health records (EHR).

Objective: We aimed to characterize the burden of CVD risk factors across different ethnicities, age groups, and socioeconomic groups, and study CVD incidence and mortality by EHR linkage in London.

Methods: The proposed study will initially be a cross-sectional observational study unfolding into prospective CVD ascertainment through longitudinal follow-up involving linked data. The government-funded National Health System (NHS) Health Check program provides an opportunity for the systematic collation of CVD risk factors on a large scale. NHS Health Check data on approximately 200,000 individuals will be extracted from consenting general practices across London that use the Egton Medical Information Systems (EMIS) EHR software. Data will be analyzed using appropriate statistical techniques to (1) determine the cross-sectional burden of CVD risk factors and their prospective association with CVD outcomes, (2) validate existing prediction tools in diverse populations, and (3) develop bespoke risk prediction tools across diverse ethnic groups.

Results: Enrollment began in January 2019 and is ongoing with initial results to be published mid-2021.

Conclusions: There is an urgent need for more real-life population health studies based on analyses of routine health data available in EHRs. Findings from our study will help quantify, on a large scale, the contemporaneous burden of CVD risk factors by geography and ethnicity in a large multiethnic urban population. Such detailed understanding (especially interethnic and sociodemographic variations) of the burden of CVD risk and its determinants, including heredity, environment, diet, lifestyle, and socioeconomic factors, in a large population sample, will enable the development of tailored and dynamic (continuously learning from new data) risk prediction tools for diverse ethnic groups, and thereby enable the personalized provision of prevention strategies and care. We anticipate that this systematic approach of linking routinely collected data from EHRs to study CVD can be conducted in other settings as EHRs are being implemented worldwide.

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KEYWORDS

electronic health records; cardiovascular health; cardiovascular risk factors

Introduction

Background

Globally, cardiovascular disease (CVD) is a leading cause of disability and premature mortality, with the number of deaths attributable to CVD rising from 12.3 to 17.3 million between 1990 and 2013 [1]. Furthermore, projections indicate that CVD will remain the leading cause of mortality worldwide for decades [2]. Notwithstanding the public health importance of CVD and its risk factors, the use of proven preventative strategies to mitigate risk is far from satisfactory due to a multitude of factors including complex intra- and interregional distribution of the determinants of CVD [1,3]. For instance, deaths attributable to different types of CVD vary between China and the United Kingdom. This variation may, in part, reflect the prevalence of different underlying risk factors such as hypertension and diabetes [4]. Thus, with regions around the world undergoing major epidemiological transitions, a population strategy aimed at reducing the burden of classical risk factors can have a major impact on CVD risk reduction [5].

Population Prevention Strategy in England

In England, the National Health Service (NHS) established a population-based Health Check program in 2009 to provide a systematic assessment and management of CVD risk for adults. Individuals aged 40-74 years without pre-existing CVD, diabetes, or hypertension are invited for a five-yearly check-up to identify and to receive advice and treatment for their risk of having a CVD event [6]. Commissioned by local authorities and delivered primarily through primary care practices, henceforth referred to as general practices (GP), this program aims to prevent around 2000 deaths and 9500 nonfatal myocardial infarctions (MI) and strokes annually [7,8]. As a free service for all eligible individuals, this program has the potential to reduce health inequalities associated with CVD [7,8], assuming equitable uptake and universal coverage. Available data suggest that between 2011-12, NHS Health Check coverage in east London was quite high at 73% (compared to national coverage of 30%). Of those that attended the screening, over a third belonged to ethnic minority groups such as south Asians and Black African/Caribbeans [9-13]. While modification of individual risk factors (eg, blood pressure) has generally been shown to be associated with improved health outcomes (eg, lower incidence of ischaemic stroke), favorable changes in risk factor distribution at a societal level have also contributed to overall improvements in community health [14]. For example, in 1989, in Poland, the increased accessibility and consumption of fruits and vegetables through the opening of markets resulted in a reduction in CVD mortality [15]. By contrast, Japanese migrants, who adopted the diet and lifestyle of the United States (US) population, relative to those who retained their original dietary patterns, had a higher prevalence of CVD [16]. Given the variation in ethnic-specific diet and lifestyle habits, and given genetic differences across population groups around the world, there is currently an unmet need to understand the complex relationship between ethnicity and factors as diverse as heredity, environment, diet, lifestyle, and socioeconomic factors (and their mutual interaction) in determining the burden, distribution, and temporal trends in both CVD risk factors and clinical CVD outcomes and cause-specific death.

Dietary exposures determine nutritional status, which may, in turn, impact CVD outcomes. As nutritional status is a key intermediary in the development of CVD, health services need to measure nutritional status as well as associated dietary exposures in order to guide appropriate preventative measures, particularly in multiethnic populations in primary care. The National Diet and Nutrition Survey (NDNS) and components of the National Survey of Health and Development (NSHD) have been developed to assess dietary exposure patterns, nutritional status, and associated social as well as biological factors within a sample of UK populations [17-19]. However, to date, no systematic attempts have been made to harness these data to boost or complement information gleaned from population-based studies investigating ethnic-specific CVD risk factor burden or risk [20].

Calculation of CVD Risk

The risk of CVD in an asymptomatic individual is based on risk factor data collected by their primary care physician to produce a numerical estimate. Traditional risk scores, such as those derived from the Framingham risk equation, have potential limitations, primarily because they were derived from a cohort of predominantly White individuals in the United States [21,22].

Moreover, they do not make allowances for factors such as socioeconomic status, resulting in systematic over- or underestimation of CVD risk based on the population studied [21,22]. With the emergence of obesity and diabetes as key global cardiovascular risk factors [22], the QRISK2 CVD risk calculator was developed and calibrated, enabling adjustments for more contemporary risk factors in the United Kingdom [22,23]. Despite these considerations, the representation of ethnic minorities in the cohort used to derive QRISK2 was approximately 1% for South Asians and 0.5% for Afro-Caribbean individuals, with the likelihood of underestimation of 10-year CVD event risk in these population groups [21].

Furthermore, QRISK prediction models contain imputations due to missing data. While established statistical methods are often used, considerations such as imputing cholesterol values to individuals without vascular disease could lead to weakened associations between cholesterol and CVD [24], as was observed in the first iteration of QRISK where about 80% of cholesterol measures were imputed. Hence, additional validation of QRISK2 in a contemporaneous multiethnic population with more systematic approaches to the collation of exposures than previously possible would be beneficial [21].

These systems need to be interoperable to enable a systematic analysis of routine healthcare data collected in electronic health records (EHRs). However, over 100 commercial EHR vendors are operating within the NHS across primary, secondary, and tertiary sectors [25]. While organizations are beginning to link data from different EHR systems, there is still fragmentation and absence of vital data as, for example, GPs serving multiethnic populations are not providing their data. Moreover, given that establishing bespoke prospective studies on CVD prevention can be prohibitively expensive, using real-life routinely collected data from EHRs and subsequent linkage of these datasets across different sectors can provide invaluable systematic approaches to conducting research.

We developed the following study specific objectives:

1. To robustly quantify and characterize, across diverse ethnic groups and sociodemographic groups, the burden of CVD risk factors among NHS Health Check attendees in a diverse population in London.
2. To prospectively study the incidence of CVD within this population by EHR linkage.
3. To validate existing CVD risk prediction algorithms and to develop novel, bespoke algorithms for CVD risk prediction among diverse multiethnic population groups.
4. To characterize dietary exposures and nutritional status as well as their associations with CVD outcomes, using data from index assessment methods that mirror or correlate well with those used in national surveillance.

Methods

Study Design and Setting

We propose to conduct a large-scale, cross-sectional observational study of NHS Health Check attendees in London with additional virtual longitudinal follow-up established via electronic health record linkage of their primary (NHS Health Check) and secondary care (hospital) data over 10 years starting in 2009. One of the major providers of EHR software to GP practices is Egton Medical Information Systems (EMIS). GPs utilizing this EHR will be eligible to participate. Figure 1 illustrates the number of individuals belonging to ethnic minority groups within London. Such a high prevalence of diverse ethnic groups in London, relative to other areas in England, coupled with high utilization of the EMIS system (Figure 2), lends itself naturally to London as the ideal backdrop for our proposed investigation.

Figure 1. Data from 2011, showing ethnic minority populations across the regions of England [26].

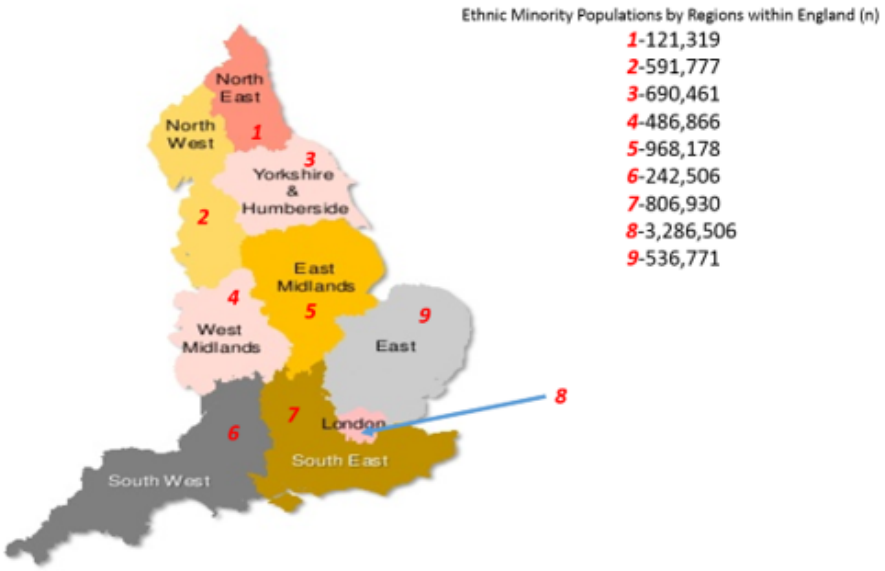
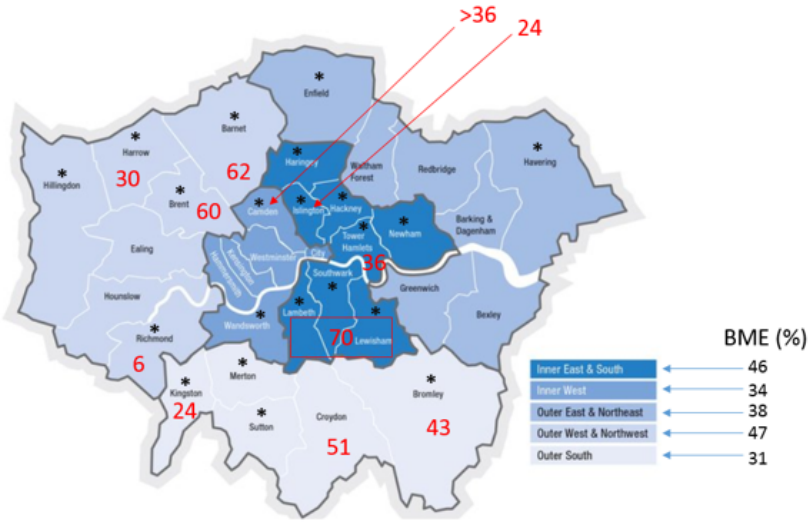


Figure 2. Map of London showing the number of GP practices utilizing the EMIS system (red), boroughs utilizing EMIS (asterisk), and proportion of Black and Minority Ethnic (BME) by region [26-36].



Recruitment

GP practices using EMIS Web clinical systems across London will be invited to provide practice-wide consent to participating in the study by way of sharing pseudonymized data on individuals undergoing NHS Health Checks within their practices between 2009 and 2018. GP practices across London are being informed of the study and recruited through liaising with clinical research networks through information letters and Clinical Commissioning Group meetings. Data will be remotely extracted centrally by EMIS using Read codes.

Data Collection and Linkage

Our study, designed as a population-based registry at the outset, will collect, alongside NHS Health Check data, additional demographic variables and prescription information to help build a large and robust repository of primary care data on residents of London undergoing NHS Health Check from 2009 onwards in GP practices.

All individuals seeking healthcare in the United Kingdom are assigned a unique identifier (ie, their NHS number). This number allows the allocation of any subsequent data collected to the individual's record and enables linkage with diverse data sources. For instance, the Office for National Statistics and Hospital Episode Statistics databases maintain records on mortality and clinical outcomes of individuals utilizing secondary healthcare services, respectively. Data from these sources can be linked through NHS numbers to the NHS Health Check data to provide a comprehensive and contemporary database on CVD risk factors (predictor variables) and outcomes across different ethnic groups. Other data sources recording clinical CVD outcomes such as the Myocardial Infarction National Audit Project and the National Institute of Cardiovascular Outcomes Research will also be harnessed to provide additional details relevant to this study.

This process of data sharing and linking, while protecting an individual's confidentiality, is possible due to pseudonymization and will be conducted by EMIS and a third party organization familiar with bespoke linkage. Using Open Pseudonymiser Software, EMIS will create a pseudonymized version of NHS numbers for individuals who meet the inclusion criteria. The data will be encrypted with a project-specific key. By using this encrypted key, an external organization will be able to link the NHS Health Check data with outcomes data through a similar pseudonymization process and a Global Unique Identifier (GUID). The research team will only have access to completely linked anonymized data as the linkage of NHS Health Check data with outcomes data will not contain the GUID.

Sample Size

Although data are not available for 2009-2011, of the invited population for NHS Health Check in 2016-17, 51.6% and 49.9% were residing in London and the rest of England, respectively [27]. In 2015, EMIS utilization in GP clinics was approximately 55%. Therefore, if 50% of all NHS Health Check attendees visit GP clinics utilizing the EMIS system, then it can be assumed that 587,273 individuals in London are eligible for consideration in this study between 2011 and 2017 [28,29]. Due to a lack of visibility of the true number of GP practices using a particular system, Figure 2 highlights that the majority of the areas in London do utilize the EMIS system, and, therefore, we anticipate that the intended sample size will be met.

To develop novel risk prediction tools for population groups, we anticipate that data will be available on approximately 200,000 individuals across London between 2011 and 2017. During 2009-13, of those with a recorded ethnic group, uptake of the NHS Health Check across England was greatest amongst South Asians (19.2%), Black Caribbeans (19.6%), Black Africans (15.7%), and Chinese (15.3%). Attendance was 16.9% in all other recorded ethnic groups and 17.4% in white Caucasians. Extrapolating the current rate of CVD incidence (2.4%) for people aged below 79 years in England on our estimated study sample of 200,000, we expect to encounter 15,000 CVD events giving 100% power to observe relative risks as modest as 1.2-1.5 [23]. Within population subgroups, the power to detect overall association is expected to range from 49% to 100% [38,39]. Given the large Black and minority ethnic

(BME) population in London and considering the above numbers, we estimate that our study sample will be highly representative of a diverse cohort [38,39].

Predictor and Outcome Variables

Cardiovascular risk factors (predictor variables) used to calculate QRISK2 include age, sex, ethnicity, index of multiple deprivations, smoking status, diabetes status, family history of CVD, chronic kidney disease (stage 4 or 5), atrial fibrillation, hypertension treatment, rheumatoid arthritis, lipids, blood pressure, and BMI. EMIS will also extract prescription data. CVD outcomes will include fatal and nonfatal coronary heart disease, fatal and nonfatal stroke, heart failure, all CVD-related hospitalizations (including those for revascularization), and all-cause mortality.

Harmonization and Cleaning of Data

Since the data for our study will be extracted at a single source (EMIS), this is likely to obviate the need for harmonizing, although we will undertake detailed quality checks (both at baseline and on follow-up) and undertake data cleaning, where necessary.

Statistical Analyses

By using appropriate statistical tests to perform univariate comparisons, the collected data will be initially analyzed to explore the cross-sectional characteristics of this population. Skewed data will be transformed to an approximately normal distribution, with the calculation of Pearson correlation coefficients and partial correlation coefficients for relevant factors of interest.

Cross-sectional associations of baseline risk factors will be studied with adjustments for appropriate confounders using logistic regression analyses. Prospective associations between individual risk factors and CVD outcomes will be evaluated using Kaplan-Meier survival curves and further quantified by fitting Cox proportional hazards regression models with multivariable adjustments. Where possible, associations will be studied after making allowances for the time-varying effects of both exposures and potential confounders. Detailed analyses of the associations will be conducted in prespecified subgroups of participants (including, but not restricted to, age, sex, conventional risk factors, and ethnicity). Established methods of calibration (Hosmer-Lemeshow), discrimination (C or D statistic), and reclassification (net reclassification index, integrated discrimination improvement) will be used to study the predictive ability of individual risk factors on CVD outcomes, with prespecified analyses involving multiple ethnic groups to enable direct, head-to-head comparisons of any differences.

Additional analyses will be conducted to quantify the impact of factors such as access to healthcare and utilization rates (of NHS Health Checks), prescription rates and medication compliance, and patterns of healthy behavior on CVD risk (both overall and, where possible, within subgroups). Standardized rates of prescription drug use will be calculated to investigate the extent of correlation between the present use of cardiovascular medication and cardiovascular risk. Variations in prescription patterns of CVD prevention and risk factor control, discontinuation of prescribed medication(s), and adverse effects to prescription medications from various therapeutic categories such as anti-hypertensive agents, lipid-lowering drugs (statins), and antidiabetic medication will be further assessed for their impact on CVD as time-dependent covariates in Cox regression models. Physical measurements within the NHS Health Check program will be obtained by the GP practices according to standard operating procedures, anticipating minimum inter-observer variability. Analyses to explore potential sources of heterogeneity concerning physical measurements (besides other characteristics) will also be conducted.

New and existing risk prediction models will be compared in terms of their ability to predict the onset of CVD across diverse population groups to develop improved risk prediction tools for primary prevention of CVD using outcomes data up to 2020. The resulting CVD risk algorithm will be calibrated by further analyses of CVD outcomes data of these patients through to 2027.

Results

The study is ongoing with enrollment underway since January 2019. Recruitment ended in January 2020, with extraction and linkage completed by March 2020. We expect the initial results for NHS Checks conducted between 2009 and 2018 and linked to Hospital Episode Statistics and Office for National Statistics to be published in mid-2021. This research has been supported by an unrestricted investigator-initiated research grant from Regeneron Pharmaceuticals to Imperial College London in 2015.

Ethical Considerations

The study protocol underwent an external peer review before the ethics submission. This study has received a favorable ethics opinion by the East Scotland Research Ethics Committee (Ref: 17-ES-0104), Health Research Authority, and adopted by the clinical research network portfolio in November 2018.

Discussion

Nationally delivered, the NHS Health Check program has the potential for universal outreach in the United Kingdom. However, differences in uptake of this program may lead to inadvertent and undesirable health inequalities (for instance, those already more likely to engage with the health care benefiting from increased contact while many who are less likely to engage with healthcare not availing themselves of this opportunity). However, it is unclear whether (and to what extent) ethnic differences at a population level drive such disparities, and whether targeting specific sociodemographic subgroups within the population might help mitigate CVD risk.

The complex interplay and variations of individual risk factors with wider determinants between and within regions and population groups reinforce the need for a detailed understanding of different cultural, socioeconomic, and epidemiological contexts for developing tailored population strategies.

Given its ethnic diversity (and a population of 8 million representing around 270 nationalities), London provides the ideal backdrop for studying CVD risk factor burden in all the permutations mentioned above. It has been estimated that the proportion of BME groups in London is 41% (10% in the rest of England). Moreover, a report commissioned by the King's Fund found greater health inequalities in London than in the rest of England [13]. For instance, although CVD death rates are reported to be higher in the North than in the South of England, 10 of the 33 London boroughs are currently experiencing above-national-average mortality [26-28,30-37]. These factors highlight the need for a more in-depth understanding of the determinants of CVD risk based on ethnicity and other key demographic variables, which could then pave the way for more effective societal interventions.

Thus, the aim of our study, using NHS Health Check data in London, is to understand the burden of CVD risk factors and to eventually validate/develop ethnic-specific CVD risk prediction tools to inform public health policy and guidelines which could lead to improvements in overall health outcomes and reduction in healthcare costs.

Ethnic diversity in England in general, and London in particular, has hitherto not been systematically captured in large-scale studies creating uncertainty in the existing guidelines on CVD risk prevention. QRISK2 score has been shown to underpredict CVD risk in population groups such as South Asians, in part reflecting low representation of the ethnic groups in the cohorts to derive sufficient information to inform risk prediction tools adequately [40,41]. This disparity may be attributed to the low participation of GP practices in London who, based on the location of these populations, are likely to treat the greatest number of BME groups relative to the rest of England. Thus, in certain ethnic groups, there may be a missed opportunity to mitigate CVD risk as they are at greater risk of CVD but have a systematic under-estimation/-representation of risk. Given that EHR data in many GP practices within London have not been utilized for investigating CVD across the multiethnic population they serve, there is a unique opportunity to recruit these practices to share their EHR data and link with other EHR sources to create a registry of varied population groups.

Moreover, the data from this study could help develop bespoke risk prediction models across diverse ethnic groups that can be embedded into the existing GP EHR systems. Following the development of such models, individuals of diverse ethnicities could potentially be reclassified into higher- or lower-than-predicted CVD risk categories, thereby enabling more tailored approaches to prevention or intervention. By contrast, if conventional risk factors were found not to be associated with discernible differences in CVD risk across various ethnic groups, then our findings will have the potential to influence future research aimed at addressing alternative (and hitherto unexplored) risk factors (such as genetic variation or dietary factors) contributing to excess CVD risk in ethnic minorities. Further offshoots from the TOGETHER research program will not only be able to address some of the novel hypotheses regarding ethnic variation in CVD risk but also serve as a platform for pragmatic randomized controlled trials to explore, for example, various emerging health technologies. One such approach could be leveraging the use of mobile phones/smartphones and applications (apps) to modify risk factors [41] and then identify the key elements to effective and sustainable approaches for reducing the risk of CVD [42]. Furthermore, there could be an opportunity to leverage the derived dataset to perform machine learning techniques, which could be potentially incorporated into creating digital health interventions [43].

As CVD burden varies between population groups and by regions, our study has the potential to investigate the expression of this disease and the contemporary risk factors in a large multiethnic cohort. Thus, our research can be considered a contemporary Framingham study on a large scale. Combining a real-life observational approach with the potential for yearly updates from the EHRs will offer new insights and understanding of the burden of risk factors for re-calibration of the variables used to derive risk prediction tools and dynamic improvement of risk prediction algorithms. Longitudinal follow-up will help quantify the incidence of CVD and, therefore, the derivation of population attributable risk (PAR) [44]. The ability to predict the impact of removing a particular risk factor in specific population groups and the risk of developing subsequent CVD is imperative for service provision and evaluating current public health strategies for CVD risk reduction. Thus, given its sample size, our study will have sufficient power to investigate CVD risk factor burden across diverse ethnicities among NHS Health Check attendees enabling further refinement of guidelines and will therefore have the potential to improve the overall public health of England in the foreseeable future.

The proposed analyses are in keeping with statistical analyses conducted in other similar large-scale population-based studies [45-47]. As the NHS Health Check program collects simple lifestyle-related data, a proportion of the population from this study will be investigated using the NDNS database to derive a more detailed understanding of the impact of nutritional determinants on CVD [48-50]. As this study aims to provide current estimates of CVD risk factor burden in a very large sample of ethnically diverse individuals in London (and following successful linkage with outcomes databases, estimates of association), we believe that this project surpasses every other contemporary study in terms of both its scale as well as representativeness (from an ethnic perspective). While our estimates of association and risk prediction derived from this cohort of CVD-free individuals (at baseline) may be similar to those already obtained from studies conducted in predominantly Western populations, these estimates will nevertheless be significantly refined across diverse ethnicities given the power and precision afforded by the study.

Despite the development of evidence-based guidelines and tools by the NHS, opportunities to reduce CVD mortality and morbidity are still being missed. Premature mortality and high healthcare costs associated with CVD underscore the need for a more detailed investigation into CVD risk across multiple ethnic groups since residual CVD risk remains a major challenge for health systems around the world. With the identification of more than 200 risk factors [51], determining the specific risk factors in population groups is imperative. Therefore, with this

study examining an ethnically diverse and contemporary population in London, the findings will have the potential to be applied to other (hitherto under-investigated) ethnicities, and towns and cities around the world that have considerable population diversity. Finally, the systematic approach of linking data from different sources can be utilized by other health systems that have implemented EHRs.

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Conflicts of Interest

KD, MW, DC, NM, JC, SR, AM, SRS declare no conflicts of interest. KK reports Member of Independent Scientific Advisory Group for Emergencies (SAGE), SAHF Trustee, ARC East Midlands Director, Centre for BME Director. KKR reports personal fees for consultancy from AbbVie, Amgen, AstraZeneca, Sanofi, Regeneron, Merck Sharp & Dohme, Pfizer, Resverlogix, Akcea, Boehringer Ingelheim, Novo Nordisk, Takeda, Kowa, Algorithm, Cipla, Cerenis, Dr Reddys, Lilly, Zuellig Pharma, Bayer, Daiichi Sankyo, The Medicines Company, and Esperion, and research grant support from Pfizer, Amgen, Sanofi, Regeneron, and Merck Sharp & Dohme.

References

1. Roth GA, Huffman MD, Moran AE, Feigin V, Mensah GA, Naghavi M, et al. Global and regional patterns in cardiovascular mortality from 1990 to 2013. Circulation 2015 Oct 27;132(17):1667-1678. [doi: 10.1161/CIRCULATIONAHA.114.008720] [Medline: 26503749]
2. Kelly B, Fuster V. Promoting cardiovascular health in the developing world a critical challenge to achieve global health. In: editors. Washington DC, USA: National Academies Press; 2010:a.
3. Yusuf S, Wood D, Ralston J, Reddy KS. The World Heart Federation's vision for worldwide cardiovascular disease prevention. Lancet 2015 Jul 25;386(9991):399-402. [doi: 10.1016/S0140-6736(15)60265-3] [Medline: 25892680]
4. Neal B, Chapman N, Patel A. Managing the global burden of cardiovascular disease. European Heart Journal Supplements 2002;4(suppl_F):2-6.
5. Deaton C, Froelicher ES, Wu LH, Ho C, Shishani K, Jaarsma T. The global burden of cardiovascular disease. Eur J of Cardiovasc Nurs 2011;10(2 suppl):S5-13.
6. Dalton ARH, Bottle A, Okoro C, Majeed A, Millett C. Uptake of the NHS Health Checks programme in a deprived, culturally diverse setting: cross-sectional study. J Public Health (Oxf) 2011 Sep;33(3):422-429. [doi: 10.1093/pubmed/fdr034] [Medline: 21546385]
7. Robson J, Dostal I, Sheikh A, Eldridge S, Madurasinghe V, Griffiths C, et al. The NHS Health Check in England: an evaluation of the first 4 years. BMJ Open 2016 Jan 13;6(1):e008840 [FREE Full text] [doi: 10.1136/bmjopen-2015-008840] [Medline: 26762161]
8. Forster AS, Burgess C, McDermott L, Wright AJ, Dodhia H, Conner M, et al. Enhanced invitation methods to increase uptake of NHS health checks: study protocol for a randomized controlled trial. Trials 2014 Aug 30;15:342 [FREE Full text] [doi: 10.1186/1745-6215-15-342] [Medline: 25174568]
9. Robson J, Dostal I, Madurasinghe V, Sheikh A, Hull S, Boomla K, et al. NHS Health Check comorbidity and management: an observational matched study in primary care. Br J Gen Pract 2017 Feb;67(655):e86-e93 [FREE Full text] [doi: 10.3399/bjgp16X688837] [Medline: 27993901]
10. Chang KCM, Soljak M, Lee JT, Woringer M, Johnston D, Khunti K, et al. Coverage of a national cardiovascular risk assessment and management programme (NHS Health Check): Retrospective database study. Prev Med 2015 Sep;78:1-8. [doi: 10.1016/j.ypmed.2015.05.022] [Medline: 26051202]
11. Asaria P, Fortunato L, Fecht D, Tzoulaki I, Abellan JJ, Hambly P, et al. Trends and inequalities in cardiovascular disease mortality across 7932 English electoral wards, 1982-2006: Bayesian spatial analysis. Int J Epidemiol 2012 Dec;41(6):1737-49; discussion 1750 [FREE Full text] [doi: 10.1093/ije/dys151] [Medline: 23129720]
12. Artac M, Dalton ARH, Babu H, Bates S, Millett C, Majeed A. Primary care and population factors associated with NHS Health Check coverage: a national cross-sectional study. J Public Health (Oxf) 2013 Sep;35(3):431-439. [doi: 10.1093/pubmed/fdt069] [Medline: 23881962]
13. Raleigh V, Tian Y, Goodwin N, Dixon A, Thompson J, Millett C, et al. General practice in London Supporting improvements in quality. London: The King's Fund.: The King's Fund URL: https://www.kingsfund.org.uk/sites/default/files/field/field_publication_file/general-practice-in-london-dec12.pdf [accessed 2019-10-01]
14. Chow CK, Lock K, Teo K, Subramanian SV, McKee M, Yusuf S. Environmental and societal influences acting on cardiovascular risk factors and disease at a population level: a review. Int J Epidemiol 2009 Dec;38(6):1580-1594 [FREE Full text] [doi: 10.1093/ije/dyn258] [Medline: 19261658]

15. Zatonski WA, McMichael AJ, Powles JW. Ecological study of reasons for sharp decline in mortality from ischaemic heart disease in Poland since 1991. BMJ 1998 Apr 04;316(7137):1047-1051. [doi: 10.1136/bmj.316.7137.1047] [Medline: 9552904]
16. Marmot MG, Syme SL. Acculturation and coronary heart disease in Japanese-Americans. Am J Epidemiol 1976 Sep;104(3):225-247. [doi: 10.1093/oxfordjournals.aje.a112296] [Medline: 961690]
17. Wells JC, Sawaya AL, Wibaek R, Mwangome M, Poullas MS, Yajnik CS, et al. The double burden of malnutrition: aetiological pathways and consequences for health. Lancet 2020 Jan 04;395(10217):75-88. [doi: 10.1016/S0140-6736(19)32472-9] [Medline: 31852605]
18. Frayn K. Diet, Nutrition and Emerging Risk Factors. In: Stanner S, Coe S, editors. Diet, Nutrition and Emerging Risk Factors. New Jersey: John Wiley & Sons; 2018:978-971.
19. Maddock J, Ziauddeen N, Ambrosini GL, Wong A, Hardy R, Ray S. Adherence to a Dietary Approaches to Stop Hypertension (DASH)-type diet over the life course and associated vascular function: a study based on the MRC 1946 British birth cohort. Br J Nutr 2018 Mar;119(5):581-589 [FREE Full text] [doi: 10.1017/S0007114517003877] [Medline: 29508688]
20. Public HE. National Diet and Nutrition Survey. Years 1 to 9 of the Rolling Programme (2008/ 2009;2016 [FREE Full text]
21. Tillin T, Hughes AD, Whincup P, Mayet J, Sattar N, McKeigue PM, SABRE Study Group. Ethnicity and prediction of cardiovascular disease: performance of QRISK2 and Framingham scores in a U.K. tri-ethnic prospective cohort study (SABRE--Southall And Brent REvisited). Heart 2014 Jan;100(1):60-67 [FREE Full text] [doi: 10.1136/heartjnl-2013-304474] [Medline: 24186564]
22. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Minhas R, Sheikh A, et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. BMJ 2008 Jun 28;336(7659):1475-1482. [doi: 10.1136/bmj.39609.449676.25] [Medline: 18573856]
23. Volmink JA, Newton JN, Hicks NR, Sleight P, Fowler GH, Neil HA. Coronary event and case fatality rates in an English population: results of the Oxford myocardial infarction incidence study. The Oxford Myocardial Infarction Incidence Study Group. Heart 1998 Jul;80(1):40-44 [FREE Full text] [doi: 10.1136/hrt.80.1.40] [Medline: 9764057]
24. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, May M, Brindle P. Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. BMJ 2007 Jul 21;335(7611):136. [doi: 10.1136/bmj.39261.471806.55] [Medline: 17615182]
25. Parliamentary Office of Science and Technology. URL: https://researchbriefings.parliament.uk/ResearchBriefing/Summary/POST-PN-0519#fullreport [accessed 2019-10-01]
26. Public HEP. Fingertips. phe. URL: https://fingertips.phe.org.uk/profile/cardiovascular/data#page/0/gid/1938133108/pat/46/par/E39000018/ati/153/are/E38000004/iid/273/age/1/sex/4 [accessed 2019-10-01]
27. Trust for London 2018. URL: http://www.londonspovertyprofile.org.uk/indicators/topics/11-services/gp-services-by-borough/ [accessed 2019-10-01]
28. Lewisham Clinical Commissioning Group. URL: http://www.lewishamccg.nhs.uk/about-us/Who-we-are/Governing%20Body%20papers/Lewisham%20CCG%20Governing%20Body%20meeting%2014%20January%202016.pdf [accessed 2019-10-01]
29. Public HEF. phe. org. URL: https://fingertips.phe.org.uk/profile/nhs-health-check-detailed/data#page/0/gid/1938132726/pat/6/par/E12000007/ati/102/are/E09000002 [accessed 2019-10-01]
30. Trust for London. London's geography and population. 2019. URL: https://www.trustforlondon.org.uk/data/londons-geography/
31. Public HEP. Fingertips. phe. URL: https://fingertips.phe.org.uk/profile/cardiovascular/data#page/0/gid/1938133108/pat/46/par/E39000018/ati/153/are/E38000004/iid/273/age/1/sex/4 [accessed 2019-10-01]
32. Healthwatch Camden. GP practices in Camden: a study of variation 2015. 2019. URL: http://www.healthwatchcamden.co.uk/sites/default/files/gp_report_-_final_december_2015_distributed.pdf
33. Barnet Clinical Commissioning Group. URL: http://www.barnetccg.nhs.uk/Downloads/boardpapers/20160526/Paper%2015.0%20BCCG%20Governing%20Body%20May%202016%20PCS.pdf [accessed 2019-10-01]
34. Richmond Clinical Commissioning Group. 2019. URL: http://www.richmondccg.nhs.uk/PCCC%202016/18-10-2016/20161018%20PCCC%20papers%20combined.pdf
35. London Borough of Bromley. URL: http://cds.bromley.gov.uk/documents/s50017580/CS14021%20PROMISE%20Programme.pdf [accessed 2019-10-01]
36. Digital Healthcare Strategy 2015-2020. Croydon Clinical Commissioning Group. 2019. URL: http://www.croydonccg.nhs.uk/news-publications/publications/Documents/Digital%20Healthcare%20Strategy%20(Dec%202015).pdf
37. Croydon Clinical Commissioning Group. URL: http://www.islingtonccg.nhs.uk/Downloads/CCG/BoardPapers/20130306/App%206.4%20GP%20IT%20Update.pdf [accessed 2019-10-01]
38. Emerging Risk Factors Collaboration, Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, et al. Major lipids, apolipoproteins, and risk of vascular disease. JAMA 2009 Nov 11;302(18):1993-2000 [FREE Full text] [doi: 10.1001/jama.2009.1619] [Medline: 19903920]
39. Danesh J, Wheeler JG, Hirschfield GM. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med 2004;350:1387-1397. [Medline: 15070788]

40. George J, Mathur R, Shah AD, Pujades-Rodriguez M, Denaxas S, Smeeth L, et al. Ethnicity and the first diagnosis of a wide range of cardiovascular diseases: Associations in a linked electronic health record cohort of 1 million patients. PLoS One 2017;12(6):e0178945. [doi: 10.1371/journal.pone.0178945] [Medline: 28598987]
41. Woringer M. , Dharmayat, K., Greenfield, G., Bottle, A. Ray, K 2019; American Heart Association?s Cholesterol CarePlan as a Smartphone-Delivered Web App for Patients Prescribed Cholesterol-Lowering Medication. [Medline: 30679150]
42. Volker N. , Davey, R., Cochrane, T., Williams, L. Clancy, T 2014; Improving the Prevention of Cardiovascular Disease in Primary Health Care. [Medline: 25008232]
43. Triantafyllidis AK, Tsanas A. Applications of Machine Learning in Real-Life Digital Health Interventions: Review of the Literature. J Med Internet Res 2019 Apr 05;21(4):e12286. [doi: 10.2196/12286] [Medline: 30950797]
44. Macera CA, Powell KE. Population attributable risk: implications of physical activity dose. Med Sci Sports Exerc 2001;33(6):S635-S639. [Medline: 11427788]
45. Langer RD, White E, Lewis CE, Kotchen JM, Hendrix SL, Trevisan M. The Women's Health Initiative Observational Study: baseline characteristics of participants and reliability of baseline measures. Ann Epidemiol 2003 Oct;13(9 Suppl):S107-S121. [doi: 10.1016/s1047-2797(03)00047-4] [Medline: 14575943]
46. Anderson G, Cummings S, Freedman L. Design of the Women's Health Initiative clinical trial and observational study. Control Clin Trials 1998;19(1):61-109. [Medline: 9492970]
47. Emerging Risk Factors Collaboration, Danesh J, Erqou S, Walker M, Thompson SG, Tipping R, et al. The Emerging Risk Factors Collaboration: analysis of individual data on lipid, inflammatory and other markers in over 1.1 million participants in 104 prospective studies of cardiovascular diseases. Eur J Epidemiol 2007;22(12):839-869. [doi: 10.1007/s10654-007-9165-7] [Medline: 17876711]
48. Almoosawi S, Cole D, Nicholson S. Biomarkers of diabetes risk in the National Diet and Nutrition Survey rolling programme (2008?2011). J Epidemiol Community Health 2014;68(1):51-56. [Medline: 24052516]
49. Ashwell M, Gibson S. Waist to height ratio is a simple and effective obesity screening tool for cardiovascular risk factors: Analysis of data from the British National Diet And Nutrition Survey of adults aged 19-64 years. Obes Facts 2009;2(2):97-103. [doi: 10.1159/000203363] [Medline: 20054212]
50. Woodside JV, Young IS, McKinley MC. Fruit and vegetable intake and risk of cardiovascular disease. Proc Nutr Soc 2013 Nov;72(4):399-406. [doi: 10.1017/S0029665113003029] [Medline: 24050503]
51. Hobbs FDR. Cardiovascular disease: different strategies for primary and secondary prevention? Heart 2004 Oct;90(10):1217-1223 [FREE Full text] [doi: 10.1136/hrt.2003.027680] [Medline: 15367530]

Abbreviations

BME: Black and Minority Ethnic
CVD: cardiovascular disease
EMIS: Egton Medical Information Systems
GP: general practice
GUID: global unique identifier
MI: myocardial infarction
NDNS: National Diet and Nutrition Survey
NHS: National Health Service
NSHD: National Survey of Health and Development

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Protocol

Microwave Breast Imaging Using Rotational Bistatic Impulse Radar for the Detection of Breast Cancer: Protocol for a Prospective Diagnostic Study

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Abstract

Background: Mammography is the standard examination for breast cancer screening; however, it is associated with pain and exposure to ionizing radiation. Microwave breast imaging is a less invasive method for breast cancer surveillance. A bistatic impulse radar–based breast cancer detector has recently been developed.

Objective: This study aims to present a protocol for evaluating the diagnostic accuracy of the novel microwave breast imaging device.

Methods: This is a prospective diagnostic study. A total of 120 participants were recruited before treatment administration and divided into 2 cohorts: 100 patients diagnosed with breast cancer and 20 participants with benign breast tumors. The detector will be directly placed on each breast, while the participant is in supine position, without a coupling medium. Confocal images will be created based on the analyzed data, and the presence of breast tumors will be assessed. The primary endpoint will be the diagnostic accuracy, sensitivity, and specificity of the detector for breast cancer and benign tumors. The secondary endpoint will be the safety and detectability of each molecular subtype of breast cancer. For an exploratory endpoint, the influence of breast density and tumor size on tumor detection will be investigated.

Results: Recruitment began in November 2018 and was completed by March 2020. We anticipate the preliminary results to be available by summer 2021.

Conclusions: This study will provide insights on the diagnostic accuracy of microwave breast imaging using a rotational bistatic impulse radar. The collected data will improve the diagnostic algorithm of microwave imaging and lead to enhanced device performance.

Trial Registration: Japan Registry of Clinical Trials jRCTs062180005; https://jrct.niph.go.jp/en-latest-detail/jRCTs062180005

International Registered Report Identifier (IRRID): DERR1-10.2196/17524

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KEYWORDS

breast cancer; microwave imaging; diagnostic accuracy; screening; ultra-wideband radar

Introduction

Background

The incidence of breast cancer is increasing, and the breast is the leading cancer location for women both worldwide and in Japan [1,2]. Mammography has been demonstrated to be effective in reducing breast cancer mortality and has become a standard screening method [3]. However, the screening rate of breast cancer varies greatly across countries; in Japan, it was 42.3% in 2016, which is lower than that in other developed countries [4,5]. The reasons for this lower rate of breast cancer screening could be the experience of pain by compression and exposure to ionizing radiation in mammography [6,7]. Therefore, painless and radiation exposure–free methodologies are required for the screening of breast cancer. In addition, mammography relies on the contrast in the X-ray attenuation coefficient between a normal mammary gland and malignant tissue, which can be as small as 1:1.1 [8]. This low contrast leads to lower sensitivity of mammography screening, particularly in dense breast tissue [6,7,9,10].

Microwave Breast Imaging

Microwave breast imaging has developed significantly in the recent years [10,11]. The physical basis for microwave breast imaging consists of the difference in dielectric properties between the normal breast and cancerous tissues. The normal breast primarily consists of adipose tissue (low dielectric properties) with dispersed distributions of mammary glands (higher dielectric properties). Cancer tissue has greater dielectric properties at a frequency of 0.5GHz-50 GHz. A high contrast between healthy and cancerous tissues has been previously reported [12-17]. Among microwave breast imaging systems, the radar-based technology that uses time of flight of the impulse radio ultra-wideband (IR-UWB) signal is widely applied due to the simplicity and robustness of calculation [18-23]. This approach can calculate the amount of scattered electromagnetic energy at any spatial position to reconstruct an energy map of the object. The radar-based imaging method was developed in 1998, and it is referred to as confocal microwave imaging [18,19]. Synthetic focusing was performed under the assumption that the dielectric constant of breast was homogeneous. The electromagnetic signals scattered from the target location were calculated based on the signal path between the transmitter and receiver antennas and the average propagation speed of microwave radiation. This method reconstructs an energy map, which shows the qualitative position of the highest intensity of the confocal image of the scattered signals. In addition, the bistatic radar system, which allows different aspects of a target to be visualized, can deliver more information than the monostatic systems [24-29].

Some microwave breast imaging systems have already been evaluated in clinical settings. The largest cohort studies have been conducted with 86 and 223 patients using the Multistatic Array Processing for Radiowave Image Acquisition (MARIA) system [26,30]. Results indicated that the sensitivity of breast cancer detection was 74%-75%. Studies using other systems have also been conducted, and the results from 150 females with abnormal mammograms indicated a mean increase in the image contrast of 150%-200% between abnormal and normal breast tissues [31-33]. However, these conventional prototypes use vector network analyzers, resulting in heavy instrumentation and high cost. Although some groups have developed compact microwave imaging systems [27-29,34,35], these systems are yet to be applied in clinical settings.

Preliminary Work

We developed a prototype handheld bistatic radar–based system using complementary metal–oxide–semiconductor (CMOS)-integrated circuits [36-41]. In a clinical pilot study, this system showed a 100% sensitivity in 5 patients with breast cancer [42]. Information on specificity and causes of false positives using this microwave imaging technology has not yet been clarified. Therefore, we aim to determine the diagnostic performance of our in-house bistatic radar–based detector with patients with breast cancer or those with benign breast tumors.

Purpose

This study has 3 major goals. It aims to assess the sensitivity and specificity of the system in screening for breast cancer, assess the sensitivity and specificity of the system screening for benign tumors, and investigate the impact of tumor biology based on the measured results.

Methods

Study Design

This study is a single-center, single-arm, prospective diagnostic study on women with breast tumors and will be performed as a specified clinical trial under the Japanese law on clinical research (the Clinical Trials Act). Women with breast cancer or benign breast tumors as diagnosed by conventional examinations were recruited for this purpose. An examination using the handheld bistatic radar–based breast imaging system will be performed before any treatment. The flowchart and time schedule for this study are shown in Figure 1 and Table 1, respectively.

Figure 1. Study flowchart.

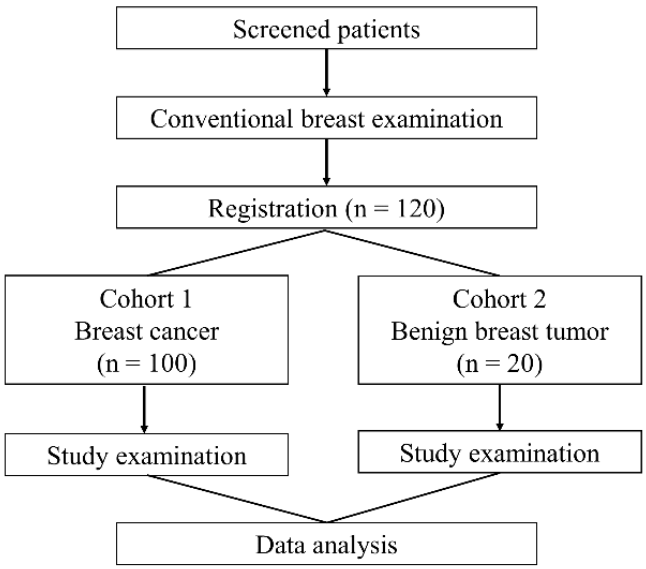


Table 1. Time schedule of the study.

Procedure	Baseline	Enrollment (week 0)	Intervention and assessment (week 0 to week 8)
Clinical breast imaging[a]	✓		
Pathological examination	✓		
Informed consent		✓	
Confirmation of eligibility criteria		✓	
Study examination			✓
Safety			✓

[a]Conducted by mammography, breast ultrasonography, contrast-enhanced breast magnetic resonance imaging, or fluorodeoxyglucose positron emission tomography.

The Certified Review Board of the Hiroshima University Hospital approved this study (CRB6180006) on October 3, 2018 (version 1). All procedures will be in accordance with the Japanese law (the Clinical Trials Act), the Declaration of Helsinki, and comparable ethical standards. This study is covered by clinical research insurance, and compensation is provided. Written informed consents will be obtained from all study participants.

Study Population

Participants were recruited from the Hiroshima University Hospital and were classified into 2 groups: cohort 1, comprising 100 women with histologically diagnosed breast cancer; and cohort 2, comprising 20 women with histologically or radiologically diagnosed benign breast tumors.

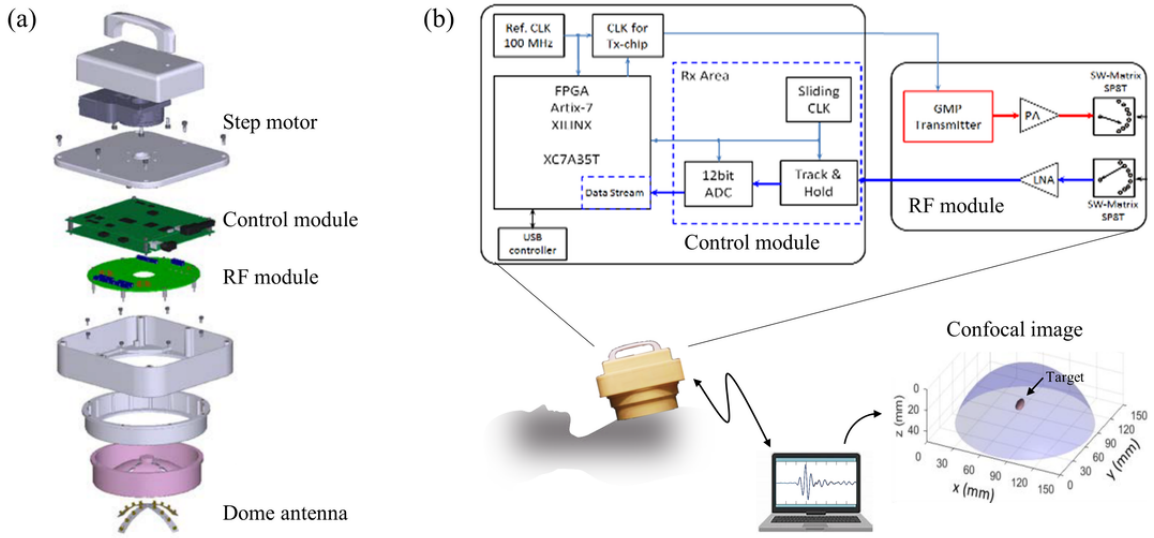
The inclusion criteria included (1) female patients older than 20 years; (2) those with histologically confirmed breast cancer (only for cohort 1); (3) those with confirmed breast tumor by 1 or more arbitrary imaging examinations, such as mammography, breast ultrasonography, contrast-enhanced breast magnetic resonance imaging, or fluorodeoxyglucose positron emission tomography; and (4) those who provide a written informed consent. The exclusion criteria included (1) history of chemotherapy or radiotherapy within 6 months prior to registration; (2) hypersensitivity to the acrylonitrile butadiene styrene (ABS) plastic resin; (3) presence of a pacemaker; or (4) a physician's decision. Participant examination will be discontinued and their data will be removed in case of withdrawal of consent, ineligibility, inability to participate in the study due to disease progression or complications, death, induction of treatment before the study, or any other exclusion criterion deemed necessary by the investigators. Benign breast tumors will be diagnosed by the Breast Imaging Reporting and Data System (BI-RADS) (ultrasound category 2 or less), fine-needle aspiration, or core needle biopsy. The radiological images will be read by 2 experienced radiologists.

Study Examination

Measurements and weight of the handheld detector are 19.1 × 17.7 × 18.8 cm and 2 kg, respectively. It consists of a handle, step motor, control module, radio frequency module, and dome

antenna array. The structure of the detector is depicted in Figure 2A. The system is composed of CMOS-integrated circuits that enable the generation and transmission of Gaussian monocycle pulse (GMP) trains and the control of the combination of a 4 × 4 cross-shaped dome antenna array, using a single-pole 8-throw switching matrix (SP8T-SW). The dome antenna array consists of 16 elements, and each antenna element is composed of a square slot set in a ground plane on 1 side of a Duroid RT 6010 substrate. The center frequency and the bandwidth of the ultra-wideband antenna are 6 GHz and 6.7 GHz, respectively. The dome shell is composed of ABS to hold the antennae in place. The dome antenna will be placed on each breast without any coupling liquid with the participant in a supine position and held by hand or supported by a stand to keep the device stationary. A transmitter antenna array emits GMP signals with the pulse duration of 160 picoseconds at a repetition frequency of 100 MHz to illuminate the breast tumor, and a receiver antenna receives the reflected signal. The antenna array rotates in 9 steps from 0° to 360° using a step motor. A single inspection can yield 40 sets of data with 2048 measurement points acquired within 5 minutes for each breast. The received signals are converted from analog to digital via a 12-bit analog-to-digital converter, and a confocal image is constructed (Figure 2B).

Figure 2. Structure of the microwave breast tumor detector. ADC: analog-to-digital converter; CLK: clock; FPGA: field-programmable gate array; GMP: Gaussian monocycle pulse; LNA: low noise amplifier; PA: power amplifier; Ref. CLK: reference clock; RF: radio frequency; RX: receiver; SP8T: single-pole 8-throw; SW: switching; TX: transmitter.



Study Endpoints

The primary endpoint is the detection sensitivity and specificity for breast cancer or benign breast tumors by the screening system. Contralateral healthy breasts will also be measured in this study, and the diagnostic accuracy will be calculated on a per-breast basis. The secondary endpoints are sensitivity for breast cancer detection according to the different molecular subtypes, sensitivity for benign breast tumors according to histology, and feasibility of the examination. The biology of breast cancer will be pathologically evaluated by surgery or using collected biopsy specimens. For exploratory purposes, the influence of tumor size and breast density on the detectability of breast tumor will also be investigated.

Sample Size Calculation

Sample size calculations were based on the sensitivity of breast cancer detection and the significance of breast cancer screening. The expected sensitivity was set at 80% with reference to the sensitivity of the Japanese mammography screening [43]. The required sample size was 171 breasts according to a width of the 95% CI being set to 0.12 at one-sided α=.05. Therefore, a sample size of 100 women (200 breasts) in cohort 1 was proposed.

Data Security and Analysis

Data will be entered directly in a database and kept in a secure network computer in a locked office at the Hiroshima University. All information will be uniquely anonymized. The operational process of this study will be subject to annual monitoring, and no audit is required. The occurrence of serious adverse events will be reported to the Certified Review Board of the Hiroshima University Hospital or the Ministry of Health, Labor and Welfare of Japan. Raw data from measurements will be analyzed using customized software that was independently developed to control the operation of the detector. Statistical analysis will be performed using the R statistical software (R Foundation for Statistical Computing) environment.

Results

Recruitment began in November 2018 and was completed by March 2020. We expect to submit the results for publication by summer 2021.

Discussion

Overview

Some microwave breast imaging systems have been previously developed and clinically investigated [11]. Of these, 2 systems were considered in clinical studies with large cohorts and suggested their potential utility in the clinical settings [30,32]. These studies focused solely on sensitivity, but the diagnostic accuracy (including specificity) of these systems has not been reported. To the best of our knowledge, this study is the first of its kind that focuses on both sensitivity and specificity of a microwave breast imaging system on a per-breast basis.

Our imaging system has several advantages in addition to the general features of microwave imaging. First, it is an easy-to-operate system, where an operator simply places the device in close contact with a breast and presses a start switch. No special training is required for the examinations, and the system is not affected by differences of technical skills of its operators. Second, this system places compact integrating antennae, excitation and acquisition hardware, and signal routing in a single unit. The high portability will provide a significant benefit for remote inspection [44]. Additionally, this compact system can be used repeatedly at low cost and is useful for monitoring applications. The advantages of this system make it suitable for breast cancer screening, although concerns regarding the production of mechanical heat and influence on pacemakers need to be assessed. In the prestage experiment, the temperature of the device after 30 minutes of operation was 30 degrees, and thus the burn risk was minimal. In addition, this study will exclude individuals with a pacemaker. Therefore, the risk associated with this study is low. Data obtained in this study will be helpful for future system improvements. This study will also provide important information on factors that lead to the false positives in breast lesions and differentiation between benign and malignant lesions.

Limitations

This study targets breast tumor cases. The diagnostic accuracy of this screening system cannot be evaluated on a per-person basis in clinical settings. In addition, the data analysts will be blind to whether breast tumors are on the left or right because of the influence of the interpretation of the test data.

Conclusions

We expect that this study will demonstrate the clinically meaningful diagnostic accuracy of the bistatic IR-UWB radar–based breast imaging system. We also hope that this study will propose a novel methodology for breast cancer screening and contribute to improvements in the current technical equipment.

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Conflicts of Interest

None declared.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA A Cancer J Clin 2019 Jan 08;69(1):7-34 [FREE Full text] [doi: 10.3322/caac.21551] [Medline: 30620402]
2. Hori M, Matsuda T, Shibata A, Katanoda K, Sobue T, Nishimoto H, Japan Cancer Surveillance Research Group. Cancer incidence and incidence rates in Japan in 2009: a study of 32 population-based cancer registries for the Monitoring of Cancer Incidence in Japan (MCIJ) project. Jpn J Clin Oncol 2015 Sep;45(9):884-891. [doi: 10.1093/jjco/hyv088] [Medline: 26142437]
3. Nelson H, Cantor A, Humphrey L, Fu R, Pappas M, Daeges M, et al. Screening for Breast Cancer: A Systematic Review to Update the 2009 U.S. Preventive Services Task Force Recommendation. Rockville (MD): Agency for Healthcare Research and Quality (US); Jan 2016.
4. OECD Health Statistics 2018. URL: https://stats.oecd.org/index.aspx?DataSetCode=HEALTH_STAT [accessed 2019-08-21]
5. Foundation for Promotion of Cancer Research. Cancer statistics in Japan 2018. URL: https://ganjoho.jp/data/reg_stat/statistics/brochure/2018/cancer_statistics_2018.pdf [accessed 2019-08-21]
6. Nelson HD, Pappas M, Cantor A, Griffin J, Daeges M, Humphrey L. Harms of Breast Cancer Screening: Systematic Review to Update the 2009 U.S. Preventive Services Task Force Recommendation. Ann Intern Med 2016 Feb 16;164(4):256-267 [FREE Full text] [doi: 10.7326/M15-0970] [Medline: 26756737]

7. Hamashima C, Japanese Research Group for the Development of Breast Cancer Screening Guidelines, Hamashima C, Hattori M, Honjo S, Kasahara Y, Japanese Research Group for the Development of Breast Cancer Screening Guidelines. The Japanese Guidelines for Breast Cancer Screening. Jpn J Clin Oncol 2016 May;46(5):482-492. [doi: 10.1093/jjco/hyw008] [Medline: 27207993]
8. Johns PC, Yaffe MJ. X-ray characterisation of normal and neoplastic breast tissues. Phys Med Biol 1987 Jun;32(6):675-695. [doi: 10.1088/0031-9155/32/6/002] [Medline: 3039542]
9. Boyd NF, Guo H, Martin LJ, Sun L, Stone J, Fishell E, et al. Mammographic density and the risk and detection of breast cancer. N Engl J Med 2007 Jan 18;356(3):227-236. [doi: 10.1056/NEJMoa062790] [Medline: 17229950]
10. Modiri A, Goudreau S, Rahimi A, Kiasaleh K. Review of breast screening: Toward clinical realization of microwave imaging. Med Phys 2017 Dec;44(12):e446-e458. [doi: 10.1002/mp.12611] [Medline: 28976568]
11. O'Loughlin D, O'Halloran M, Moloney BM, Glavin M, Jones E, Elahi MA. Microwave Breast Imaging: Clinical Advances and Remaining Challenges. IEEE Trans Biomed Eng 2018 Nov;65(11):2580-2590. [doi: 10.1109/TBME.2018.2809541] [Medline: 29993488]
12. Sugitani T, Kubota S, Kuroki S, Sogo K, Arihiro K, Okada M, et al. Complex permittivities of breast tumor tissues obtained from cancer surgeries. Appl. Phys. Lett 2014 Jun 27;104(25):253702. [doi: 10.1063/1.4885087]
13. Lazebnik M, McCartney L, Popovic D, Watkins CB, Lindstrom MJ, Harter J, et al. A large-scale study of the ultrawideband microwave dielectric properties of normal breast tissue obtained from reduction surgeries. Phys Med Biol 2007 May 21;52(10):2637-2656. [doi: 10.1088/0031-9155/52/10/001] [Medline: 17473342]
14. Lazebnik M, Popovic D, McCartney L, Watkins CB, Lindstrom MJ, Harter J, et al. A large-scale study of the ultrawideband microwave dielectric properties of normal, benign and malignant breast tissues obtained from cancer surgeries. Phys Med Biol 2007 Oct 21;52(20):6093-6115. [doi: 10.1088/0031-9155/52/20/002] [Medline: 17921574]
15. Martellosio A, Pasian M, Bozzi M, Perregrini L, Mazzanti A, Svelto F, et al. Dielectric Properties Characterization From 0.5 to 50 GHz of Breast Cancer Tissues. IEEE Trans Microw Theory Tech 2017 Mar;65(3):998-1011. [doi: 10.1109/tmtt.2016.2631162]
16. England TS, Sharples NA. Dielectric Properties of the Human Body in the Microwave Region of the Spectrum. Nature 1949 Mar;163(4143):487-488. [doi: 10.1038/163487b0] [Medline: 18115108]
17. Surowiec AJ, Stuchly SS, Barr JB, Swarup A. Dielectric properties of breast carcinoma and the surrounding tissues. IEEE Trans Biomed Eng 1988 Apr;35(4):257-263. [doi: 10.1109/10.1374] [Medline: 2834285]
18. Hagness SC, Taflove A, Bridges JE. Two-dimensional FDTD analysis of a pulsed microwave confocal system for breast cancer detection: fixed-focus and antenna-array sensors. IEEE Trans Biomed Eng 1998 Dec;45(12):1470-1479. [doi: 10.1109/10.730440] [Medline: 9835195]
19. Fear EC, Li X, Hagness SC, Stuchly MA. Confocal microwave imaging for breast cancer detection: localization of tumors in three dimensions. IEEE Trans Biomed Eng 2002 Aug;49(8):812-822. [doi: 10.1109/TBME.2002.800759] [Medline: 12148820]
20. Xu Li, Bond E, Van Veen B, Hagness S. An overview of ultra-wideband microwave imaging via space-time beamforming for early-stage breast-cancer detection. IEEE Antennas Propag. Mag 2005 Feb;47(1):19-34. [doi: 10.1109/map.2005.1436217]
21. Lim HB, Nhung NT, Li EP, Thang ND. Confocal microwave imaging for breast cancer detection: delay-multiply-and-sum image reconstruction algorithm. IEEE Trans Biomed Eng 2008 Jun;55(6):1697-1704. [doi: 10.1109/tbme.2008.919716] [Medline: 18714833]
22. Gibbins D, Klemm M, Craddock I, Leendertz J, Preece A, Benjamin R. A Comparison of a Wide-Slot and a Stacked Patch Antenna for the Purpose of Breast Cancer Detection. IEEE Trans. Antennas Propagat 2010 Mar;58(3):665-674. [doi: 10.1109/tap.2009.2039296]
23. Byrne D, Sarafianou M, Craddock IJ. Compound Radar Approach for Breast Imaging. IEEE Trans Biomed. Eng 2017 Jan;64(1):40-51. [doi: 10.1109/TBME.2016.2536703] [Medline: 26955012]
24. Klemm M, Craddock IJ, Leendertz JA, Preece A, Benjamin R. Radar-Based Breast Cancer Detection Using a Hemispherical Antenna Array—Experimental Results. IEEE Trans Antennas Propag 2009 Jun;57(6):1692-1704. [doi: 10.1109/tap.2009.2019856]
25. Klemm M, Leendertz JA, Gibbins D, Craddock IJ, Preece A, Benjamin R. Microwave Radar-Based Differential Breast Cancer Imaging: Imaging in Homogeneous Breast Phantoms and Low Contrast Scenarios. IEEE Trans Antennas Propag 2010 Jul;58(7):2337-2344. [doi: 10.1109/tap.2010.2048860]
26. Preece AW, Craddock I, Shere M, Jones L, Winton HL. MARIA M4: clinical evaluation of a prototype ultrawideband radar scanner for breast cancer detection. J Med Imaging (Bellingham) 2016 Jul;3(3):033502 [FREE Full text] [doi: 10.1117/1.JMI.3.3.033502] [Medline: 27446970]
27. Porter E, Coates M, Popović M. An Early Clinical Study of Time-Domain Microwave Radar for Breast Health Monitoring. IEEE Trans Biomed Eng 2016 Mar;63(3):530-539. [doi: 10.1109/TBME.2015.2465867] [Medline: 26259214]
28. Porter E, Bahrami H, Santorelli A, Gosselin B, Rusch LA, Popovic M. A Wearable Microwave Antenna Array for Time-Domain Breast Tumor Screening. IEEE Trans Med Imaging 2016 Jun;35(6):1501-1509. [doi: 10.1109/TMI.2016.2518489] [Medline: 26780788]

29. Santorelli A, Porter E, Kang E, Piske T, Popovic M, Schwartz JD. A Time-Domain Microwave System for Breast Cancer Detection Using a Flexible Circuit Board. IEEE Trans. Instrum. Meas 2015 Nov;64(11):2986-2994. [doi: 10.1109/tim.2015.2440565]
30. Massey H, Ridley N, Lyburn I, Jones L, Taylor S, Schoenleber-Lewis M, et al. Radio-wave detection of breast cancer in the symptomatic clinic: a multi-centre study. 2017 Jul Presented at: International Cambridge Conference on Breast Cancer Imaging; Jul 2017; Cambridge, UK.
31. Poplack SP, Paulsen KD, Hartov A, Meaney PM, Pogue BW, Tosteson TD, et al. Electromagnetic breast imaging: average tissue property values in women with negative clinical findings. Radiology 2004 May;231(2):571-580. [doi: 10.1148/radiol.2312030606] [Medline: 15128998]
32. Poplack SP, Tosteson TD, Wells WA, Pogue BW, Meaney PM, Hartov A, et al. Electromagnetic breast imaging: results of a pilot study in women with abnormal mammograms. Radiology 2007 May;243(2):350-359. [doi: 10.1148/radiol.2432060286] [Medline: 17400760]
33. Meaney PM, Fanning MW, Raynolds T, Fox CJ, Fang Q, Kogel CA, et al. Initial clinical experience with microwave breast imaging in women with normal mammography. Acad Radiol 2007 Feb;14(2):207-218 [FREE Full text] [doi: 10.1016/j.acra.2006.10.016] [Medline: 17236994]
34. Mobashsher AT, Mahmoud A, Abbosh AM. Portable Wideband Microwave Imaging System for Intracranial Hemorrhage Detection Using Improved Back-projection Algorithm with Model of Effective Head Permittivity. Sci Rep 2016 Feb 04;6:20459 [FREE Full text] [doi: 10.1038/srep20459] [Medline: 26842761]
35. Bassi M, Caruso M, Khan MS, Bevilacqua A, Capobianco A, Neviani A. An Integrated Microwave Imaging Radar With Planar Antennas for Breast Cancer Detection. IEEE Trans Microw Theory Tech 2013 May;61(5):2108-2118. [doi: 10.1109/tmtt.2013.2247052]
36. Sugitani T, Kubota S, Toya A, Xiao X, Kikkawa T. A Compact 4 × 4 Planar UWB Antenna Array for 3-D Breast Cancer Detection. Antennas Wireless Propag Lett 2013 Dec;12:733-736. [doi: 10.1109/lawp.2013.2270933]
37. Sugitani T, Kubota S, Hafiz M, Xiao X, Kikkawa T. Three-dimensional confocal imaging for breast cancer detection using CMOS Gaussian monocycle pulse transmitter and 4 × 4 ultra wideband antenna array with impedance matching layer. Jpn J Appl Phys 2014 Mar 05;53(4S):04EL03. [doi: 10.7567/jjap.53.04el03]
38. Kubota S, Toya A, Sugitani T, Kikkawa T. 5-Gb/s and 10-GHz Center-Frequency Gaussian Monocycle Pulse Transmission Using 65-nm Logic CMOS With On-Chip Dipole Antenna and High-κ Interposer. IEEE Trans Compon Packag Manufact Technol 2014 Jul;4(7):1193-1200. [doi: 10.1109/tcpmt.2014.2320497]
39. Song H, Kono H, Seo Y, Azhari A, Somei J, Suematsu E, et al. A radar-based breast cancer detection system using CMOS integrated circuits. IEEE Access 2015;3:2111-2121. [doi: 10.1109/access.2015.2496101]
40. Azhari A, Sugitani T, Xiao X, Kikkawa T. DC–17-GHz CMOS single-pole-eight-throw switching matrix for radar-based image detection. Jpn J Appl Phys 2016 Nov 17;55(12):127301. [doi: 10.7567/jjap.55.127301]
41. Song H, Azhari A, Xiao X, Suematsu E, Watanabe H, Kikkawa T. Microwave Imaging Using CMOS Integrated Circuits with Rotating 4 × 4 Antenna Array on a Breast Phantom. Int J Antennas Propag 2017;2017:1-13. [doi: 10.1155/2017/6757048]
42. Sasada S, Masumoto N, Song H, Kajitani K, Emi A, Kadoya T, et al. Portable impulse-radar detector for breast cancer: a pilot study. J Med Imaging (Bellingham) 2018 Apr;5(2):025502 [FREE Full text] [doi: 10.1117/1.JMI.5.2.025502] [Medline: 29900185]
43. Ohuchi N, Suzuki A, Sobue T, Kawai M, Yamamoto S, Zheng Y, et al. Sensitivity and specificity of mammography and adjunctive ultrasonography to screen for breast cancer in the Japan Strategic Anti-cancer Randomized Trial (J-START): a randomised controlled trial. Lancet 2016 Jan 23;387(10016):341-348. [doi: 10.1016/S0140-6736(15)00774-6] [Medline: 26547101]
44. Leung J, McKenzie S, Martin J, McLaughlin D. Effect of rurality on screening for breast cancer: a systematic review and meta-analysis comparing mammography. Rural Remote Health 2014;14(2):2730 [FREE Full text] [Medline: 24953122]

Abbreviations

ABS: acrylonitrile butadiene styrene
BI-RADS: Breast Imaging Reporting and Data System
CMOS: complementary metal–oxide–semiconductor
GMP: Gaussian monocycle pulse
IR-UWB: impulse radio ultra-wideband
MARIA: Multistatic Array Processing for Radiowave Image Acquisition
SP8T-SW: single-pole 8-throw switching matrix

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Protocol

Comparing Web-Based Platforms for Promoting HIV Self-Testing and Pre-Exposure Prophylaxis Uptake in High-Risk Men Who Have Sex With Men: Protocol for a Longitudinal Cohort Study

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Abstract

Background: The majority of those living with HIV in the United States are men who have sex with men (MSM), and young, minority MSM account for more new HIV infections than any other group. HIV transmission can be reduced through detection and early treatment initiation or by starting pre-exposure prophylaxis (PrEP), but rates of testing are lower than recommended among MSM, and PrEP uptake has been slow. Although promoting HIV testing and PrEP uptake by placing advertisements on web-based platforms — such as social media websites and dating apps — is a promising approach for promoting HIV testing and PrEP, the relative effectiveness of HIV prevention advertising on common web-based platforms is underexamined.

Objective: This study aims to evaluate the relative effectiveness of advertisements placed on 3 types of web-based platforms (social media websites, dating apps, and informational websites) for promoting HIV self-testing and PrEP uptake.

Methods: Advertisements will be placed on social media websites (Facebook, Instagram, and Twitter), dating apps (Grindr, Jack'd, and Hornet), and informational search websites (Google, Yahoo, and Bing) to recruit approximately 400 young (18-30 years old), minority (Black or Latino) MSM at elevated risk of HIV exposure. Recruitment will occur in 3 waves, with each wave running advertisements on 1 website from each type of platform. The number of participants per platform is not prespecified, and recruitment in each wave will occur until approximately 133 HIV self-tests are ordered. Participants will complete a baseline survey assessing risk behavior, substance use, psychological readiness to test, and attitudes and then receive an electronic code to order a free home-based HIV self-test kit. Two follow-ups are planned to assess HIV self-test results and PrEP uptake.

Results: Recruitment was completed in July 2020.

Conclusions: Findings may improve our understanding of how the platform users' receptivity to test for HIV differs across web-based platforms and thus may assist in facilitating web-based HIV prevention campaigns.

Trial Registration: ClinicalTrials.gov NCT04155502; https://clinicaltrials.gov/ct2/show/NCT04155502

International Registered Report Identifier (IRRID): DERR1-10.2196/20417

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KEYWORDS

HIV; HIV self-testing; men who have sex with men; web-based platforms; online advertising; social media; dating apps; informational search websites

Introduction

Despite accounting for a small fraction of the US population (6%), men who have sex with men (MSM) account for the majority (61%) of those infected with human HIV in the United States and experience the largest burden (69%) of new infections [1-3]. More than 30% of new infections occur in young (under 35 years of age) MSM who identify as Black or Hispanic/Latino [3]. Most new HIV infections are the result of male-to-male sexual contact [2], but other behaviors elevate risk of HIV transmission. For example, substance use is prevalent among young MSM [4], and use of substances, particularly alcohol and amphetamines, is associated with not using a condom, a key risk factor for transmission of HIV infection [5-7].

Although minority MSM are not more likely to engage in risky sexual behavior than other MSM [8,9], Black and Hispanic/Latino MSM are disproportionately affected by societal factors — such as discrimination, lack of social support, and financial barriers — that are associated with problematic substance use and elevated HIV risk behavior [10,11]. Among minority MSM, experiences of racism are associated with greater likelihood of stimulant and polydrug use in the past 6 months [12]. Relative to other MSM, Black MSM have lower levels of social support that may drive higher rates of substance dependence and transactional sex [13], which further increase the risk of HIV transmission. In addition, some young Black and Latino MSM use social media websites and dating apps to exchange sex for money or drugs [14]. Cultural variables are also associated with elevated HIV risk behavior. For example, among Latino MSM, greater endorsement of cultural beliefs about gender and sexuality is related to HIV risk behaviors, such as unprotected anal intercourse [15,16]. Similarly, perceptions of imbalanced masculinity within partner dyads can create imbalanced partner dynamics among young Black MSM that negatively impact condom use [17].

HIV testing and treatment initiation can reduce the transmission of infection by 95% [18]. Approximately 1.1 million people in the United States are living with an HIV infection, and 14% (1 in 7) of those people are unaware they are infected [19]. Although the Centers for Disease Control and Prevention (CDC) recommends HIV testing at least every 6 months for those at elevated risk of HIV transmission [19], only 85% of internet-using MSM have been tested for HIV infection, and only 58% had been tested in the last year [20]. Younger MSM (<30 years old) are moderately more likely to never have been tested for HIV [19,20], and common barriers to HIV testing, such as not having insurance or transportation to a testing place, are reported more by younger MSM [21,22]. Substance use is also associated with decreased odds of recent HIV testing and increased likelihood of unknown HIV infection [23,24], suggesting an unmet need for HIV testing promotion, particularly among younger MSM and those who use substances.

HIV transmission rates can also be reduced with pre-exposure prophylaxis (PrEP). PrEP is the combination of 2 antiviral drugs in the form of a pill that, when taken, regularly prevents new infections. Randomized controlled trials in high-risk populations have shown that infection rates with PrEP use drop dramatically, to as low as 0% (eg, [25]). PrEP is only available by prescription, and the CDC recommends prescribing PrEP to all adults with substantial risk for HIV infection [26]. Nevertheless, PrEP awareness [27] and, most importantly, uptake have been slow, especially among young Black and Hispanic/Latino MSM [28,29]. Among young MSM, concerns about stigma from medical providers and concerns about paying for PrEP were significantly associated with reduced likelihood of PrEP use, even though PrEP assistance programs are available to help those who do not have health insurance that covers PrEP [30].

Using online approaches to promote HIV testing and PrEP uptake is a promising avenue for HIV prevention. Nearly 7 of 10 Americans use social media to connect with one another, engage with news content, share information, and entertain themselves [31]. Compared to all other age groups, regardless of sexual preference, those between 18 and 30 years of age comprise the group that is most likely to be active and engaged in daily social media use [32]. Among MSM, 97% use social media [33], and previous studies have used social media websites (eg, Facebook) for a range of HIV prevention efforts [34,35]. Young MSM also frequently use dating apps like Grindr to connect with new sex partners [32]. Researchers have also used dating apps to promote HIV prevention, such as by distributing HIV self-testing kits [36]. Social media websites and dating apps target health promotion advertising based on user demographics and behavior, while informational search websites (eg, Google, Bing, and Yahoo) focus on advertising to users by integrating data from what is privately typed into search bars. MSM may privately search for HIV prevention-related materials, even if they do not publicly post content about personal HIV prevention interests to social media websites. Trends in search data from informational search websites predict new diagnoses of sexually transmitted infections, including HIV, at the community level [37,38]. Although different in nature from social media websites, informational search websites also represent a highly promising additional avenue for outreach. Little is known, however, about the relative effectiveness of different web-based platforms (ie, social media websites, informational search websites, and dating apps) in promoting HIV testing and PrEP use.

In addition, key factors that differentiate or moderate web-based platform users' receptivity to HIV testing are less understood. For example, although substance use is associated with lower rates of HIV testing among MSM, how substance use impacts the likelihood of HIV self-testing when MSM are recruited online is underexamined. This study seeks to address those questions by evaluating the effectiveness of online campaigns

promoting HIV self-testing on different types of web-based platforms: social media websites (Facebook, Instagram, Twitter), dating apps (Grindr, Jack'd, Hornet), and informational search websites (Google, Bing, Yahoo). Factors that moderate platform users' testing receptivity across web-based platforms will also be examined.

The primary objective of this study is to compare HIV self-testing uptake among users of the 3 different types of web-based platforms. Secondary aims will seek to evaluate differences in PrEP uptake, as well as the impact of key moderator variables — problematic substance use and psychological readiness to test — on HIV testing and PrEP uptake. Other secondary aims include determining the efficiency of the different platform types for promoting HIV testing and PrEP uptake and evaluating the impact of perceptions and attitudes on HIV testing and PrEP uptake.

Methods

Study Design

This will be a longitudinal cohort study recruiting participants from 3 types of web-based platforms: social media websites, dating apps, and informational websites. The study team will develop a culturally appropriate, community-tested study advertisement for use on the social media websites and dating apps and will develop a list of keywords for advertising on informational search websites. The study advertisement will be placed on each platform, and similar campaigns will be employed across all 3 web-based platforms with the same money budgeted for advertising.

Recruitment will occur in 3 waves. In each wave, the advertisement will be placed on 1 social media website, 1 dating app, and 1 informational search website (see Table 1), for a total of 3 social media websites, dating apps, and informational search websites. To address the possibility of history effects occurring across waves, the study team selected a social media website, a dating app, and an informational search website to include in each wave. There will not be a prespecified number of participants recruited per platform/website (social media websites, informational search websites, or dating apps). Instead, recruitment in each wave will continue until approximately 133 self-test kits are ordered from across the 3 websites in that wave. Advertising in each wave will be scheduled to run for 30 calendar days. This duration was selected to optimize the advertisement placement given the advertising budget for each website. If at least 133 self-test kits are not ordered by the end of 30 calendar days, recruitment may be extended across all 3 websites to obtain the 133 self-test kit orders.

Table 1. HIV self-test study recruitment waves and web-based platforms.

Recruitment wave	Informational search website	Social media website	Dating app
1	Google	Facebook	Grindr
2	Bing	Instagram	Jack'd
3	Yahoo	Twitter	Hornet

Upon clicking the study advertisement, users will land on the study informational page in Qualtrics 2020 software [39], where they will receive information about the study and undergo eligibility screening. An electronic study information sheet describing study procedures, participant rights, and potential risks and benefits will be provided to eligible users to review and download. The consent form will include information on what information the websites will be able to access and how the study team will ensure participants' confidentiality, with identifiable information stored separately from responses. Participants will consent to participate by clicking an "Agree" button and proceed to identity verification. If users are ineligible or decline to participate in the study, they will be redirected to a website with information about HIV and sexually transmitted disease prevention, PrEP, and HIV testing locations.

After consenting, participants will be asked to login to their Facebook account within Qualtrics via single sign-on (SSO) to verify their identity and reduce duplicate participation. The information obtained by the study team from the SSO feature is described in the consent form, and private data are stored securely. The SSO requires participants to have a Facebook account and may prevent or deter some people from participating [40], but this requirement was deemed to be important for preventing duplicate participation and test kit orders, given that the study procedures are entirely remote. After logging into Facebook, participants will continue in Qualtrics to complete the baseline assessment. Once the baseline assessment has been completed, study staff will verify that the Facebook account is active (ie, has a photo and >10 friends) and that the participation is not a duplicate (ie, name, contact information, and Facebook account do not match any enrolled participants). If the participation is not a duplicate, site staff will email an electronic code for the participant to order 1 free HIV self-test kit. Duplicate participations will not receive a self-test kit code, gift card, or invitation to participate in follow-ups. Each eligible individual enrolled in the study can only order 1 HIV self-test kit. The study team will send approximately 400 coupon codes redeemable for free OraQuick Home HIV self-test kits [41] to eligible participants. The OraQuick Home HIV test kit is a Federal Drug Administration–approved self-test kit for home use that detects HIV antibodies in oral fluid in approximately 20 minutes. The kit is commercially available in pharmacies and online. The test kit includes a pretest counseling pamphlet and access to OraSure customer support by website and phone. In-home self-test kits have high acceptability among MSM [42], and prior research has found the OraQuick test kit to be easy to use [36].

We will follow up with each participant at 2 intervals, 14 days and 60 days after baseline, to evaluate our study objectives. Each participant will receive a US $25 electronic gift card upon completion of each evaluation (baseline, 14-day follow-up, and 60-day follow-up) for a maximum total of US $75.

Study Population

The study aims to recruit approximately 400 MSM (or an appropriate number of participants until approximately 400 HIV self-test kits have been ordered) aged 18-30 years, inclusive, who are at increased risk of HIV exposure or infection and who use social media websites, dating apps, or informational search websites. Participants will have to self-report being Latino and/or Black/African American men (including multiracial and multiethnic members of these groups) and report high-risk sexual behavior with men (such as both condomless anal sex in the past 90 days and more than 1 sexual partner in the past 90 days). Participants must report not currently being on PrEP, not having taken PrEP in the past 6 months, and not having been tested for HIV in at least the past 3 months.

Study Sites

Web-Based Platforms and Websites

Recruitment for this study will occur online through blast advertisements placed on 1 of 3 types of web-based platforms: social media websites, dating apps, and informational search websites. We selected 9 websites (3 of each platform type) that are popular among the study population (MSM aged 18-30 years old) and allow us to place location-targeted advertisements. Although some websites offer additional targeting options (eg, LGBTQ interests), no additional targeting was specified to keep conditions similar across platforms. During each wave, we will allocate approximately US $1100 weekly for advertising on each website.

For social media websites, we selected Facebook, Instagram, and Twitter. Facebook is a social networking website accessible through a dedicated smartphone app or a web browser. Of US adults aged 18-29 years, 81% own and use a Facebook account [32]. Facebook has been frequently used in many studies as a means for recruitment and prevention message dissemination [32,43]. Our team has previously used Facebook to recruit and retain MSM for 12 months [44,45]. Instagram is a photo-sharing social networking app that can be accessed by a smartphone app or web browser. As of June 2018, Instagram reported more than 1 billion monthly active users worldwide, mostly younger users below the age of 35 years [46]. In a recent study among focus groups of Black college students, participants indicated Instagram was one of their preferred social networks, underscoring the increased popularity and usage of these websites for young people (18-29 years of age) and non-Hispanic Black people [35]. Twitter is a news and social networking service accessible by web browser and a dedicated app. There are over 69 million Twitter users in the United States, and an average 36% of Americans aged 18-29 years use Twitter [47].

Grindr, Jack'd, and Hornet were selected as dating apps. Grindr, which is accessible only via its dedicated smartphone app, is the largest social networking app for gay, bisexual ("bi"), transgender ("trans"), and queer people [48]. Multiple studies have used Grindr as a platform to reach and recruit study participants (eg, [49,50]). Our team has used Grindr for advertising and has reached nearly 12,000 unique users, which resulted in 334 HIV self-test kit orders [49]. Jack'd is a location-based mobile app for gay and bisexual men to meet other men. The app has a global network of 1.2 million users. Nearly 80% of its users are under 24 years of age, while 30% of its users are Black, and 20% are multiracial or Latino [51]. Hornet is accessible via smartphone app and a web-based platform. It has nearly 3 million users in the United States, and its most active users are gay men aged 18-34 years. In the United States, 16% of Hornet users are Latinos, and 9% are African Americans [52].

Google, Bing, and Yahoo were selected as the informational search websites for this study. These internet search engines are accessible from personal computers or handheld devices. Google received approximately 92% of search visits in the United States as of 2019 [53,54]. Bing received 3.9% of search visits, and Yahoo received approximately 3% of search visits [53,54].

The study team identified relevant topics and generated a list of keywords for the informational search websites, which were then tested with Google Trends to identify additional keywords and remove less relevant or unpopular words and phrases. Textbox 1 shows the final list of keywords used on the informational search websites. We developed potential advertisements, which were then modified through feedback with the study team and pilot testing. We pilot tested 2 advertisements using Facebook's A/B testing, and Figure 1 shows the advertisement selected for use on the study platforms. The same image and text were used in all advertising placed on social media websites and dating apps.

Textbox 1. HIV self-test study keywords for informational search websites. Keywords and informational website searches were not case sensitive. Expansions of abbreviations shown in parentheses are included for clarity and were not included among the keywords.

- HIV
- HIV symptoms
- Signs of HIV
- HIV AIDS
- Home HIV test
- Free HIV testing
- HIV positive
- How do you get HIV
- HIV test
- Free STD (sexually transmitted disease) testing
- Where to get HIV test
- PrEP (preexposure prophylaxis) HIV
- PrEP
- Preexposure prophylaxis
- Prevent HIV
- Prevent AIDS
- Truvada, Descovy
- AIDS HIV
- HIV and AIDS
- How do you get tested for HIV
- HIV negative
- Test for HIV
- HIV at home blood test
- At home early HIV test
- Over the counter at home HIV test kit
- AIDS and HIV
- Which HIV home test kit has FDA (Federal Drug Administration) approval
- Where to buy HIV home test kit
- Where to get HIV home test kit
- When to use HIV home test kit
- When to take HIV home test
- What is HIV home test kit
- HIV home test kit in stores
- Where to buy HIV test
- Where to do an HIV test
- Where to get an HIV test
- Where to get a free HIV test
- What is HIV home test
- Home test kit for HIV
- Home test kit for STD
- Where to get preexposure prophylaxis
- When to get preexposure prophylaxis

- When to get an HIV test
- HIV test without blood
- HIV test near me
- HIV test near me free
- HIV test nearby
- What HIV test can provide immediate results
- When HIV test can be done
- HIV test for free
- HIV test to buy
- HIV test to order
- HIV test at home
- HIV test with saliva
- HIV test with
- HIV test with swab
- FDA approved HIV home test
- Where to buy HIV home test kit
- Where to get HIV home test kit
- When to use HIV home test kit
- When to take HIV home test kit
- HIV home test near me
- HIV test home testing kits
- What is HIV home test kit
- Will PrEP prevent HIV

Figure 1. HIV self-test study advertisement developed by the study team for social media websites and dating apps.

As part of systems testing, we ran a version of the advertisement that linked to Qualtrics on 6 of the 9 study websites (testing of the dating apps was precluded by the limited budget). That testing allowed us to revise our participant tracking system and selected website metrics. We also modified our informational search website keywords based on recommendations from the

Google Ads Search Engine Optimization feature, which utilizes user search data to assist with keyword development.

Geographical Study Areas

We will place advertisements in the District of Columbia (D.C.) and 8 states: Florida, Georgia, Louisiana, Maryland, Mississippi, Nevada, South Carolina, and Texas. These areas were selected because they have high rates of new HIV infections (≥17 per 100,000 [2]), sufficient coverage for confirmatory testing (gettested.org [55]), and at least one organization that provides PrEP in the area (PrEPmenow [56]) to facilitate uptake of PrEP among study participants (see Multimedia Appendix 1 for details).

Study Assessments and Data Collection

The study assessments and time points are shown in Table 2 (see Multimedia Appendix 2 for copy of study assessments). Participants will complete the self-administered baseline assessment online via Qualtrics after electronically consenting and logging into Facebook SSO. As part of baseline, they will provide demographic and contact information, and then participants will report sexual risk behaviors using a subset of questions from the Rapid HIV Behavioral Assessment [57] and social media activity [44]. Recent substance use will be reported using a subset of the Tobacco, Alcohol, Prescription medications, and other Substance use (TAPS) tool [58] that will assess past 3-month use of alcohol, cannabis, cocaine and amphetamines, heroin, prescription drugs, and other illicit substances (eg, 3,4-methylenedioxy-methamphetamine, psilocybin, alkyl nitrites, lysergic acid diethylamide, gamma-hydroxybutyrate, ketamine). Participants will also answer a single-item Transtheoretical Model of Health Behavior Change question assessing readiness to test for HIV [59], a 1-question item extracted from the HIV Testing Questions - CDC that evaluates reasons for not testing for HIV [60], and the Medical Mistrust Inventory [61]. Additional measures will assess attitudes toward HIV testing [62], attitudes toward HIV treatment [63], HIV-related stigma [64], and sexual delay discounting [65], which assesses the participant's likelihood of waiting for access to a condom. At the 14-day follow-up, participants will be emailed a link to a Qualtrics survey. Participants will report their self-test kit use and optionally upload a picture of their test result in the survey. If a participant elects to upload a photo, the study team will confirm the self-reported result using the manufacturer's instructions [21]. If participants report a negative test result, they will be asked if they visited a PrEP provider, if they started PrEP, their opinions about PrEP, and facilitators and barriers [66]. If participants report a preliminary positive on the HIV self-test, they will be asked whether they visited an HIV treatment provider. At the 60-day follow-up, all participants will be asked to respond to study evaluation questions. If participants reported not testing or not starting PrEP at the 14-day follow-up, they will be asked those questions again. Although not part of study data collection, additional outreach attempts will be conducted by email and phone for those with positive or indeterminate test results to encourage confirmatory testing and linkage to care.

Table 2. HIV self-test study schedule of study assessments.

Measure	Baseline	14–day follow-up	60–day follow-up
Social Media Activity [44]	X[a]		
Rapid HIV Behavioral Assessment [57]	X		
Tobacco, Alcohol, Prescription medications, and other Substance use (TAPS) Tool [58]	X		
The Transtheoretical Model of Health Behavior Change (State of Change): HIV Testing [59]	X		
Attitudes Toward HIV Testing [62]	X		
Reasons for Not Testing for HIV [60]	X		
Attitudes Toward HIV Treatment [63]	X		
HIV-Related Stigma [64]	X		
Medical Mistrust Inventory [61]	X		
Sexual Delay Discounting [65]	X		
HIV Self-Test Result		X	*[b]
PrEP[c] Uptake Facilitators & Barriers [66]		X	*
PrEP Opinions		X	*
Study Evaluation Questions			X

[a]X: assessed.

[b]*: assessed if not reported at 14-day follow-up.

[c]PrEP: preexposure prophylaxis.

Additional data will be collected from websites and online services. Each recruitment website will provide advertising metrics (eg, cost, impressions, clicks), and the advertisement placed on each platform will link to a separate Qualtrics screening and baseline survey to track from which platform participants were recruited. Reports on HIV self-test kit orders

will be obtained directly from OraSure, allowing objective measurement in addition to the self-report data collected during follow-ups.

Outcome Measures

The primary outcome is the number of HIV self-test kits ordered per day through each type of online platform (social media websites, informational search websites, dating apps) during the time each wave is operational. This will be measured by the number of HIV self-test kits ordered through the OraSure website by the type of online platform. This outcome was specified as a rate because of the expectation that different waves may be open for recruitment for different periods. Secondary outcomes include the number of participants who started PrEP and the number of participants who tested positive for HIV. Secondary outcomes will also assess whether those with more complex substance use history and severity — as measured using the validated categories of the TAPS [58] — will be less likely to order an HIV self-test kit and less likely to uptake PrEP. Similarly, we will examine whether those closer to the "action" (ie, Determination) stage for HIV testing will be more likely to be recruited through informational sites and will be more likely to order an HIV home self-test kit and start PrEP [59]. Other measures will characterize the sample or be assessed as potential moderators of HIV testing and PrEP uptake outcomes: attitudes toward HIV testing and treatment, HIV-related stigma, medical mistrust, sexual delay discounting, and PrEP facilitators and barriers. The amount of money spent per test kit ordered per promotion type, including all the costs of the intervention (advertisement, test kit), will be compared to determine the most efficient web-based platform for advertisements related to promotion of HIV home self-test kits and PrEP uptake.

Sample Size Justification

The relative effectiveness of the 3 platform types will be evaluated by comparing the rates of test kit orders. The study will recruit a sufficient number of MSM who actively use social media websites, dating apps, and informational search websites to obtain approximately 400 test kit orders. The sample size justification involved investigating power for selected data aspects and estimating platform rates and their confidence intervals by specifying different effect sizes. The simulations assumed that each wave would be open for recruitment until at least 133 test kits were ordered across all 3 websites in that wave. The time each wave was open for enrollment was used as an offset in the Poisson regression model implemented in the simulations. The covariates in this Poisson model included wave, type of platform, and the interaction between the two. Power was investigated for data aspects such as for the test of the null hypothesis that the rates for the 3 dating apps can be pooled and for the test of the null hypothesis that the pooled rates (ie, across waves) of social media websites and dating apps are the same. Regarding the estimation of the rate for the dating app Grindr, the results showed that if the true Grindr rate is 40 kits per 2 weeks, the majority (at least 80%) of the 95% CIs for the Grindr rate will lie within 31 and 62 kits. If the true Grindr value is 10 kits per 2 weeks, the 95% CI will probably lie between 4 and 19. For the test of whether the rates of the 3 dating app websites can be pooled, we expect at least 80% power if the range of the rates exceeds 12 kits per 2 weeks. For the test of whether the pooled rates of social media websites and dating apps are the same, there is at least 80% power if the absolute difference is 8 kits per 2 weeks.

Statistical Analysis

The platforms and their implementation are provided in Table 1. There are 3 rows corresponding to the 3 waves and 3 columns corresponding to the 3 types of promotional platforms. For each wave, the number of kits ordered from each website will be expressed as a daily rate (ie, number of kits ordered in that website divided by days to recruit 133 test kit orders). All kits ordered while the wave is actively recruiting will be included in the primary outcome analysis. It is hypothesized that the rate of kit orders will vary across platforms. The primary outcome analysis will be conducted using a Poisson regression model with wave recruitment time as an offset. The model will adjust for wave, type of website, and their interaction. A similar model will be used for the PrEP uptake secondary outcome. The additional secondary and exploratory analyses will be conducted using univariate tests and descriptive statistics such as counts, percentages, and 95% CIs.

Results

The protocol and informed consent document were reviewed and approved by the University of California, Los Angeles Institutional Review Board. We started recruitment in January 2020, and recruitment was expected to take up to 9 months. Recruitment was completed in July 2020. Follow-up data collection was completed in September 2020.

Discussion

This study seeks to evaluate the effectiveness of an online campaign promoting HIV self-testing on different types of web-based platforms: social media websites, dating apps, and informational search websites. The platforms' relative effectiveness for promoting HIV self-testing will be determined by their rates of HIV test kit orders. The order rate for each platform may reflect the number of users, the number of high-risk users, and whether the users of that platform are likely to order a kit. For example, targeted analyses may demonstrate differences between the platforms in terms of their ability to reach a larger number of eligible participants quickly, as measured by a higher click volume, versus their ability to appeal to individuals that are more likely to ultimately order a test kit, as measured by a higher proportion of successful clicks. Secondary outcomes will include the number of participants who started PrEP, the number who tested positive for HIV, how these key outcomes are impacted by variables such as substance use, and the efficiency of the online platforms types for promoting HIV testing and PrEP uptake.

This study has implications for future research and public health promotion. Although previous studies have used dating and social media websites to promote HIV testing, to our knowledge, this is the first study to include informational search websites in an evaluation of online HIV prevention efforts. Findings may

contribute to our understanding of the receptivity of users from these different types of platforms to obtain HIV prevention services. Further, public health funds are limited, so it is important to study the relative costs of different approaches for promoting health behavior, including HIV testing and PrEP uptake. Another piece of critical information to understand is the drivers and moderators of online users' HIV testing and PrEP uptake. For example, results may inform how substance use affects HIV self-testing when MSM are recruited online. Understanding these and other factors impacting an individual's receptiveness to test could assist in maximizing the impact of prevention campaigns through these popular online platforms.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Table showing criteria for selection of geographical study areas.
[DOCX File , 23 KB - resprot_v9i10e20417_app1.docx]

Multimedia Appendix 2
Human Immunodeficiency Virus self-test study assessments.
[DOCX File , 81 KB - resprot_v9i10e20417_app2.docx]

References

1. Rosenberg ES, Grey JA, Sanchez TH, Sullivan PS. Rates of Prevalent HIV Infection, Prevalent Diagnoses, and New Diagnoses Among Men Who Have Sex With Men in US States, Metropolitan Statistical Areas, and Counties, 2012-2013. JMIR Public Health Surveill 2016 May 17;2(1):e22 [FREE Full text] [doi: 10.2196/publichealth.5684] [Medline: 27244769]
2. Centers for Disease Control and Prevention. HIV Surveillance Report: Diagnoses of HIV Infection in the United States and Dependent Areas, 2018 (updated). 2018. URL: https://www.cdc.gov/hiv/statistics/overview/index.html [accessed 2020-09-12]
3. Centers for Disease Control and Prevention. NCHHSTP AtlasPlus. 2019. URL: https://www.cdc.gov/nchhstp/atlas/index.htm [accessed 2020-05-11]
4. Lelutiu-Weinberger C, Pachankis JE, Golub SA, Walker JJ, Bamonte AJ, Parsons JT. Age cohort differences in the effects of gay-related stigma, anxiety and identification with the gay community on sexual risk and substance use. AIDS Behav 2013 Jan 30;17(1):340-349 [FREE Full text] [doi: 10.1007/s10461-011-0070-4] [Medline: 22038078]
5. Lacefield K, Negy C, Schrader RM, Kuhlman C. Comparing Psychosocial Correlates of Condomless Anal Sex in HIV-Diagnosed and HIV-Nondiagnosed Men Who Have Sex with Men: A Series of Meta-Analyses of Studies from 1993-2013. LGBT Health 2015 Sep;2(3):200-220. [doi: 10.1089/lgbt.2014.0069] [Medline: 26788669]
6. Koblin BA, Murrill C, Camacho M, Xu G, Liu K, Raj-Singh S, et al. Amphetamine use and sexual risk among men who have sex with men: results from the National HIV Behavioral Surveillance study--New York City. Subst Use Misuse 2007 Jul 03;42(10):1613-1628. [doi: 10.1080/10826080701212519] [Medline: 17918031]
7. Bourne A, Weatherburn P. Substance use among men who have sex with men: patterns, motivations, impacts and intervention development need. Sex Transm Infect 2017 Aug 11;93(5):342-346. [doi: 10.1136/sextrans-2016-052674] [Medline: 28400466]
8. Holloway IW, Pulsipher CA, Gibbs J, Barman-Adhikari A, Rice E. Network Influences on the Sexual Risk Behaviors of Gay, Bisexual and Other Men Who Have Sex with Men Using Geosocial Networking Applications. AIDS Behav 2015 Jun 9;19 Suppl 2(S2):112-122 [FREE Full text] [doi: 10.1007/s10461-014-0989-3] [Medline: 25572832]
9. Millett GA, Peterson JL, Wolitski RJ, Stall R. Greater risk for HIV infection of black men who have sex with men: a critical literature review. Am J Public Health 2006 Jun;96(6):1007-1019. [doi: 10.2105/AJPH.2005.066720] [Medline: 16670223]
10. Ayala G, Bingham T, Kim J, Wheeler DP, Millett GA. Modeling the Impact of Social Discrimination and Financial Hardship on the Sexual Risk of HIV Among Latino and Black Men Who Have Sex With Men. Am J Public Health 2012 May;102(S2):S242-S249. [doi: 10.2105/ajph.2011.300641] [Medline: PMC3477911]

11. Buttram ME, Kurtz SP. A mixed methods study of health and social disparities among substance-using African American/Black men who have sex with men. J Racial Ethn Health Disparities 2015 Mar 15;2(1):1-10 [FREE Full text] [doi: 10.1007/s40615-014-0042-2] [Medline: 25960944]
12. Paul JP, Boylan R, Gregorich S, Ayala G, Choi K. Substance use and experienced stigmatization among ethnic minority men who have sex with men in the United States. J Ethn Subst Abuse 2014 Nov 14;13(4):430-447 [FREE Full text] [doi: 10.1080/15332640.2014.958640] [Medline: 25397640]
13. Buttram ME, Kurtz SP, Surratt HL. Substance use and sexual risk mediated by social support among Black men. J Community Health 2013 Feb 1;38(1):62-69 [FREE Full text] [doi: 10.1007/s10900-012-9582-8] [Medline: 22752575]
14. Patel VV, Masyukova M, Sutton D, Horvath KJ. Social Media Use and HIV-Related Risk Behaviors in Young Black and Latino Gay and Bi Men and Transgender Individuals in New York City: Implications for Online Interventions. J Urban Health 2016 Apr;93(2):388-399 [FREE Full text] [doi: 10.1007/s11524-016-0025-1] [Medline: 26936854]
15. Lo SC, Reisen CA, Poppen PJ, Bianchi FT, Zea MC. Cultural beliefs, partner characteristics, communication, and sexual risk among Latino MSM. AIDS Behav 2011 Apr 21;15(3):613-620 [FREE Full text] [doi: 10.1007/s10461-010-9760-6] [Medline: 20652629]
16. Jarama SL, Kennamer JD, Poppen PJ, Hendricks M, Bradford J. Psychosocial, behavioral, and cultural predictors of sexual risk for HIV infection among Latino men who have sex with men. AIDS Behav 2005 Dec 3;9(4):513-523. [doi: 10.1007/s10461-005-9022-1] [Medline: 16328712]
17. Fields EL, Bogart LM, Smith KC, Malebranche DJ, Ellen J, Schuster MA. HIV risk and perceptions of masculinity among young black men who have sex with men. J Adolesc Health 2012 Mar;50(3):296-303 [FREE Full text] [doi: 10.1016/j.jadohealth.2011.07.007] [Medline: 22325136]
18. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, HPTN 052 Study Team. Antiretroviral Therapy for the Prevention of HIV-1 Transmission. N Engl J Med 2016 Sep 01;375(9):830-839 [FREE Full text] [doi: 10.1056/NEJMoa1600693] [Medline: 27424812]
19. US Department of Health and Human Services. Overview: Data & Trends: U.S. Statistics. HIV.gov. URL: https://www.hiv.gov/hiv-basics/overview/data-and-trends/statistics [accessed 2020-03-03]
20. Noble M, Jones AM, Bowles K, DiNenno EA, Tregear SJ. HIV Testing Among Internet-Using MSM in the United States: Systematic Review. AIDS Behav 2017 Feb 6;21(2):561-575 [FREE Full text] [doi: 10.1007/s10461-016-1506-7] [Medline: 27498198]
21. Margolis AD, Joseph H, Belcher L, Hirshfield S, Chiasson MA. 'Never testing for HIV' among men who have sex with men recruited from a sexual networking website, United States. AIDS Behav 2012 Jan 29;16(1):23-29. [doi: 10.1007/s10461-011-9883-4] [Medline: 21279431]
22. Mackellar DA, Hou S, Whalen CC, Samuelsen K, Sanchez T, Smith A, WHBS Study Group. Reasons for not HIV testing, testing intentions, and potential use of an over-the-counter rapid HIV test in an internet sample of men who have sex with men who have never tested for HIV. Sex Transm Dis 2011 May;38(5):419-428. [doi: 10.1097/OLQ.0b013e31820369dd] [Medline: 21183863]
23. Carrico AW, Storholm ED, Flentje A, Arnold EA, Pollack LM, Neilands TB, et al. Spirituality/religiosity, substance use, and HIV testing among young black men who have sex with men. Drug Alcohol Depend 2017 May 01;174:106-112 [FREE Full text] [doi: 10.1016/j.drugalcdep.2017.01.024] [Medline: 28319751]
24. Morgan E, Khanna AS, Skaathun B, Michaels S, Young L, Duvoisin R, et al. Marijuana Use Among Young Black Men Who Have Sex With Men and the HIV Care Continuum: Findings From the uConnect Cohort. Subst Use Misuse 2016 Nov 09;51(13):1751-1759 [FREE Full text] [doi: 10.1080/10826084.2016.1197265] [Medline: 27556866]
25. Volk JE, Marcus JL, Phengrasamy T, Blechinger D, Nguyen DP, Follansbee S, et al. No New HIV Infections With Increasing Use of HIV Preexposure Prophylaxis in a Clinical Practice Setting. Clin Infect Dis 2015 Nov 15;61(10):1601-1603 [FREE Full text] [doi: 10.1093/cid/civ778] [Medline: 26334052]
26. Centers for Disease Control and Prevention. Preexposure Prophylaxis for the Prevention of HIV Infection in the United States – 2017 Update Clinical Practice Guideline. 2017. URL: https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf [accessed 2020-09-12]
27. Eaton LA, Driffin DD, Bauermeister J, Smith H, Conway-Washington C. Minimal Awareness and Stalled Uptake of Pre-Exposure Prophylaxis (PrEP) Among at Risk, HIV-Negative, Black Men Who Have Sex with Men. AIDS Patient Care STDS 2015 Aug;29(8):423-429 [FREE Full text] [doi: 10.1089/apc.2014.0303] [Medline: 26083143]
28. Huang YA, Zhu W, Smith DK, Harris N, Hoover KW. HIV Preexposure Prophylaxis, by Race and Ethnicity - United States, 2014-2016. MMWR Morb Mortal Wkly Rep 2018 Oct 19;67(41):1147-1150 [FREE Full text] [doi: 10.15585/mmwr.mm6741a3] [Medline: 30335734]
29. Snowden J, Chen Y, McFarland W, Raymond H. Prevalence and characteristics of users of pre-exposure prophylaxis (PrEP) among men who have sex with men, San Francisco, 2014 in a cross-sectional survey: implications for disparities. Sex Transm Infect 2017 Feb;93(1):52-55 [FREE Full text] [doi: 10.1136/sextrans-2015-052382] [Medline: 27356041]
30. Jaiswal J, Griffin M, Singer SN, Greene RE, Acosta ILZ, Kaudeyr SK, et al. Structural Barriers to Pre-exposure Prophylaxis Use Among Young Sexual Minority Men: The P18 Cohort Study. Curr HIV Res 2018;16(3):237-249. [doi: 10.2174/1570162X16666180730144455] [Medline: 30062970]

31. Pew Research Center. Social media fact sheet: Demographics of social media users and adoption in the United States. 2019 Jun 12. URL: https://www.pewresearch.org/internet/fact-sheet/social-media/ [accessed 2019-11-13]
32. Smith A, Anderson M. Social media use in 2018. Pew Research Center. 2018 Mar 01. URL: https://www.pewresearch.org/internet/2018/03/01/social-media-use-in-2018/ [accessed 2019-11-12]
33. Community Marketing & Insights. 13th Annual LGBTQ Community Survey USA Summary Report. 2019 Jul. URL: https://www.communitymarketinginc.com/documents/temp/CMI-13th_LGBTQ_Community_Survey_US_Profile.pdf [accessed 2020-09-12]
34. Rhodes SD, McCoy TP, Tanner AE, Stowers J, Bachmann LH, Nguyen AL, et al. Using Social Media to Increase HIV Testing Among Gay and Bisexual Men, Other Men Who Have Sex With Men, and Transgender Persons: Outcomes From a Randomized Community Trial. Clin Infect Dis 2016 Jun 01;62(11):1450-1453 [FREE Full text] [doi: 10.1093/cid/ciw127] [Medline: 26980878]
35. Jones J, Carter B, Wilkerson R, Kramer C. Attitudes toward HIV testing, awareness of HIV campaigns, and using social networking sites to deliver HIV testing messages in the age of social media: a qualitative study of young black men. Health Educ Res 2019 Feb 01;34(1):15-26. [doi: 10.1093/her/cyy044] [Medline: 30508106]
36. Huang E, Marlin RW, Young SD, Medline A, Klausner JD. Using Grindr, a Smartphone Social-Networking Application, to Increase HIV Self-Testing Among Black and Latino Men Who Have Sex With Men in Los Angeles, 2014. AIDS Educ Prev 2016 Aug;28(4):341-350 [FREE Full text] [doi: 10.1521/aeap.2016.28.4.341] [Medline: 27427928]
37. Young SD, Torrone EA, Urata J, Aral SO. Using Search Engine Data as a Tool to Predict Syphilis. Epidemiology 2018 Jul;29(4):574-578. [doi: 10.1097/EDE.0000000000000836] [Medline: 29864105]
38. Young SD, Zhang Q. Using search engine big data for predicting new HIV diagnoses. PLoS One 2018 Jul 12;13(7):e0199527 [FREE Full text] [doi: 10.1371/journal.pone.0199527] [Medline: 30001360]
39. Version March 2020. Qualtrics. URL: https://www.qualtrics.com/ [accessed 2020-09-12]
40. Bauer L, Bravo-Lillo C, Fragkaki E, Melicher W. A Comparison of Users' Perceptions of and Willingness to Use Google, Facebook, and Google+ Single-Sign-On Functionality. 2013 Presented at: 20th ACM Conference on Computer and Communications Security; November 4-8, 2013; Berlin, Germany. [doi: 10.1145/2517881.2517886]
41. OraQuick: In-Home HIV Test. URL: http://www.oraquick.com/What-is-OraQuick/OraQuick-In-Home-HIV-Test [accessed 2020-09-12]
42. Raymond HF, Bingham T, McFarland W. Locating unrecognized HIV infections among men who have sex with men: San Francisco and Los Angeles. AIDS Educ Prev 2008 Oct;20(5):408-419. [doi: 10.1521/aeap.2008.20.5.408] [Medline: 18956982]
43. Pedersen ER, Kurz J. Using Facebook for Health-related Research Study Recruitment and Program Delivery. Curr Opin Psychol 2016 May;9:38-43 [FREE Full text] [doi: 10.1016/j.copsyc.2015.09.011] [Medline: 26726313]
44. Young SD, Cumberland WG, Nianogo R, Menacho LA, Galea JT, Coates T. The HOPE social media intervention for global HIV prevention in Peru: a cluster randomised controlled trial. Lancet HIV 2015 Jan;2(1):e27-e32 [FREE Full text] [doi: 10.1016/S2352-3018(14)00006-X] [Medline: 26236767]
45. Young SD. Social media technologies for HIV prevention study retention among minority men who have sex with men (MSM). AIDS Behav 2014 Sep 6;18(9):1625-1629 [FREE Full text] [doi: 10.1007/s10461-013-0604-z] [Medline: 24062015]
46. Clement J. Instagram - Statistics & Facts. Statista. 2020 May 14. URL: https://www.statista.com/topics/1882/instagram/ [accessed 2020-09-12]
47. Omnicore. Twitter by the Numbers: Stats, Demographics & Fun Facts. 2020 Feb 10. URL: https://www.omnicoreagency.com/twitter-statistics/ [accessed 2020-03-03]
48. About us. Grindr. 2020. URL: https://www.grindr.com/about/ [accessed 2020-09-12]
49. Rosengren AL, Huang E, Daniels J, Young SD, Marlin RW, Klausner JD. Feasibility of using Grindr to distribute HIV self-test kits to men who have sex with men in Los Angeles, California. Sex Health 2016 May 23 [FREE Full text] [doi: 10.1071/SH15236] [Medline: 27209076]
50. Gibbs JJ, Rice E. The Social Context of Depression Symptomology in Sexual Minority Male Youth: Determinants of Depression in a Sample of Grindr Users. J Homosex 2016 Aug 21;63(2):278-299. [doi: 10.1080/00918369.2015.1083773] [Medline: 26295497]
51. Contact us: Advertise. Jack'd. 2020. URL: https://www.jackd.com/en/contact [accessed 2020-09-12]
52. Hornet Review. DatingScout. 2020. URL: https://www.datingscout.com/lgbt/hornet/review [accessed 2020-09-12]
53. Statista. Distribution of total and mobile organic search visits in the United States as of 1st quarter 2020, by engine. 2020. URL: https://www.statista.com/statistics/625554/mobile-share-of-us-organic-search-engine-visits/ [accessed 2020-09-12]
54. Merkle. Digital marketing report. 2020. URL: https://www.merkleinc.com/thought-leadership/digital-marketing-report?utm_source=email&utm_medium=email&utm_campaign=2019_DMR_Q4 [accessed 2020-09-12]
55. Find a PrEP provider. PleasePrEPme.org. URL: https://www.pleaseprepme.org/find-a-provider [accessed 2020-09-12]
56. Centers for Disease Control and Prevention. GetTested: National HIV, STD, and Heptatitis Testing. 2020. URL: https://gettested.cdc.gov/ [accessed 2020-09-12]

57. Gallagher KM, Denning PD, Allen DR, Nakashima AK, Sullivan PS. Use of rapid behavioral assessments to determine the prevalence of HIV risk behaviors in high-risk populations. Public Health Rep 2007;122 Suppl 1:56-62 [FREE Full text] [doi: 10.1177/00333549071220S109] [Medline: 17354528]
58. McNeely J, Wu L, Subramaniam G, Sharma G, Cathers LA, Svikis D, et al. Performance of the Tobacco, Alcohol, Prescription Medication, and Other Substance Use (TAPS) Tool for Substance Use Screening in Primary Care Patients. Ann Intern Med 2016 Nov 15;165(10):690-699 [FREE Full text] [doi: 10.7326/M16-0317] [Medline: 27595276]
59. Prochaska JO, Redding CA, Harlow LL, Rossi JS, Velicer WF. The transtheoretical model of change and HIV prevention: a review. Health Educ Q 1994 Sep 04;21(4):471-486. [doi: 10.1177/109019819402100410] [Medline: 7843978]
60. U.S. Centers for Disease Control HIV/STD Behavioral Surveillance Working Group. Core Measure for HIV/STD Risk Behavior and Prevention: Questionnaire-Based Measurement for Surveys and Other Data Systems. UCLA Center for HIV Identification, Prevention and Treatment Services. 2001. URL: http://chipts.ucla.edu/resources/download-info/hiv-testing-questions-cdc-chtq/ [accessed 2020-09-12]
61. LaVeist T, Isaac L, Williams K. Mistrust of health care organizations is associated with underutilization of health services. Health Serv Res 2009 Dec;44(6):2093-2105 [FREE Full text] [doi: 10.1111/j.1475-6773.2009.01017.x] [Medline: 19732170]
62. Kalichman SC, Simbayi LC. HIV testing attitudes, AIDS stigma, and voluntary HIV counselling and testing in a black township in Cape Town, South Africa. Sex Transm Infect 2003 Dec 01;79(6):442-447 [FREE Full text] [doi: 10.1136/sti.79.6.442] [Medline: 14663117]
63. Stolte IG, Dukers NH, Geskus RB, Coutinho RA, de Wit JBF. Homosexual men change to risky sex when perceiving less threat of HIV/AIDS since availability of highly active antiretroviral therapy: a longitudinal study. AIDS 2004 Jan 23;18(2):303-309. [doi: 10.1097/00002030-200401230-00021] [Medline: 15075549]
64. EKOS Research Associates Inc. 2012 HIV/AIDS Attitudinal Tracking Survey: Final Report. Public Health Agency of Canada. 2012 Oct. URL: https://www.catie.ca/ga-pdf.php?file=sites/default/files/2012-HIV-AIDS-attitudinal-tracking-survey-final-report.pdf [accessed 2020-09-12]
65. Johnson MW, Bruner NR. The Sexual Discounting Task: HIV risk behavior and the discounting of delayed sexual rewards in cocaine dependence. Drug Alcohol Depend 2012 Jun 01;123(1-3):15-21 [FREE Full text] [doi: 10.1016/j.drugalcdep.2011.09.032] [Medline: 22055012]
66. Golub SA, Gamarel KE, Rendina HJ, Surace A, Lelutiu-Weinberger CL. From efficacy to effectiveness: facilitators and barriers to PrEP acceptability and motivations for adherence among MSM and transgender women in New York City. AIDS Patient Care STDS 2013 Apr;27(4):248-254 [FREE Full text] [doi: 10.1089/apc.2012.0419] [Medline: 23565928]

Abbreviations

CDC: Centers for Disease Control and Prevention
FDA: Federal Drug Administration
MSM: men who have sex with men
NIDA: National Institute on Drug Abuse
PrEP: pre-exposure prophylaxis
SSO: single sign-on
STD: sexually transmitted disease
TAPS: Tobacco, Alcohol, Prescription medications, and other Substance use

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Protocol

The Kidney Score Platform for Patient and Clinician Awareness, Communication, and Management of Kidney Disease: Protocol for a Mixed Methods Study

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Abstract

Background: Patient awareness, clinician detection, and management of chronic kidney disease remain suboptimal, despite clinical practice guidelines and diverse education programs.

Objective: This protocol describes a study to develop and investigate the impact of the National Kidney Foundation Kidney Score Platform on chronic kidney disease awareness, communication, and management, by leveraging the Behavior Change Wheel, an implementation science framework that helps identify behavioral intervention targets and functions that address barriers to behavior change.

Methods: We interviewed 20 patients with chronic kidney disease and 11 clinicians to identify patient and clinician behaviors suitable for intervention and barriers to behavior change (eg, limited awareness of chronic kidney disease clinical practice guidelines within primary care settings, limited data analytics to highlight chronic kidney disease care gaps, asymptomatic nature of chronic kidney disease in conjunction with patient reliance on primary care clinicians to determine risk and order kidney testing). Leveraging the Behavior Change Wheel, the Kidney Score Platform was developed with a patient-facing online Risk Calculator and a clinician-facing Clinical Practice Toolkit. The Risk Calculator utilizes risk predictive analytics to provide interactive health information tailored to an individual's chronic kidney disease risk and health status. The Clinical Practice Toolkit assists clinicians in discussing chronic kidney disease with individuals at risk for and with kidney disease and in managing their patient population with chronic kidney disease. The Kidney Score Platform will be tested in 2 Veterans Affairs primary health care settings using a pre–post study design. Outcomes will include changes in patient self-efficacy for chronic kidney disease management (primary outcome), quality of communication with clinicians about chronic kidney disease, and practitioners' knowledge of chronic kidney disease guidelines. Process outcomes will identify usability and adoption of different elements of the Kidney Score Platform using qualitative and quantitative methods.

Results: As of September 2020, usability studies are underway with veterans and clinicians to refine the patient-facing components of the Kidney Score Platform before study initiation. Results and subsequent changes to the Kidney Score Platform will be published at a later date. The study is expected to be completed by December 2021.

Conclusions: Results of this study will be used to inform integration of the Kidney Score Platform within primary care settings so that it can serve as a central component of the National Kidney Foundation public awareness campaign to educate, engage, and empower individuals at risk for and living with chronic kidney disease.

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KEYWORDS

chronic kidney disease; CKD; awareness; implementation science; behavioral change wheel, RE-AIM

Introduction

Chronic kidney disease affects 37 million Americans [1]. Chronic kidney disease progression can ultimately lead to kidney failure, a life-threatening illness that, even with dialysis treatment, confers a death rate worse than most cancers and significantly reduces quality of life [2]. Additionally, chronic kidney disease is a disease multiplier that often occurs with diabetes or hypertension and increases the risk of emergency department visits, hospitalizations, and cardiovascular events [3]. Total Medicare spending for beneficiaries with chronic kidney disease and kidney failure was over $120 billion in 2017, of which over $35.9 billion was spent to manage or treat kidney failure, a condition that can often be prevented with optimal chronic kidney disease management [2].

Chronic kidney disease is usually asymptomatic. Optimal management slows the progression of kidney disease and reduces cardiovascular events [4,5]. Individuals cannot readily know their disease status or risk without clinician recognition of risk, testing, detection, and communication [6]. Previous studies [7,8] show that clinician detection and communication about kidney disease are suboptimal. Importantly, clinician diagnosis of chronic kidney disease is associated with increased delivery of evidence-based care, as well as increased patient awareness of their kidney disease [9-11]. As many as half of patients with advanced chronic kidney disease are unaware that they have chronic kidney disease, including those with laboratory manifestations of their kidney disease [12]. Patient awareness of chronic kidney disease, including the knowledge of having a kidney problem and the perceived risk of developing kidney disease, as well as the ability to affect their kidney health, is necessary for patients to participate in shared decision making about their kidney health and to apply management recommendations to improve outcomes [13]. Existing education programs, awareness campaigns, and clinical practice guidelines, including those from the National Kidney Foundation's (NKF) Kidney Disease Outcomes Quality Initiative and the Veterans Affairs and Department of Defense Clinical Practice Guidelines for the Management of Chronic Kidney Disease, have minimally improved chronic kidney disease awareness in the United States and veteran populations, respectively [14,15].

Among the population served by Veterans Affairs (VA), 1 in 6 has chronic kidney disease. It is the fourth most diagnosed disease within the Department of Veteran Affairs, and over 13,000 veterans develop end-stage renal disease each year [16]. Diagnosis within the VA is low, with only 39% of veterans with chronic kidney disease stages 3-4 appropriately identified with International Classification of Diseases diagnostic codes in 2011 [7]. A roundtable discussion during the Kidney Innovation Summit hosted by the VA Center for Innovation and the American Society of Nephrology highlighted the need for a paradigm shift in education and awareness by addressing gaps in communication between "what is said, what is heard, and what the patient understands" and educating clinicians on how to meaningfully engage with patients at different stages of kidney health. This investigation is a significant incremental contribution to the Advancing American Kidney Health Initiative's aim 1 of 3 to reduce the number of Americans developing end-stage renal disease by 25% by 2030 [17].

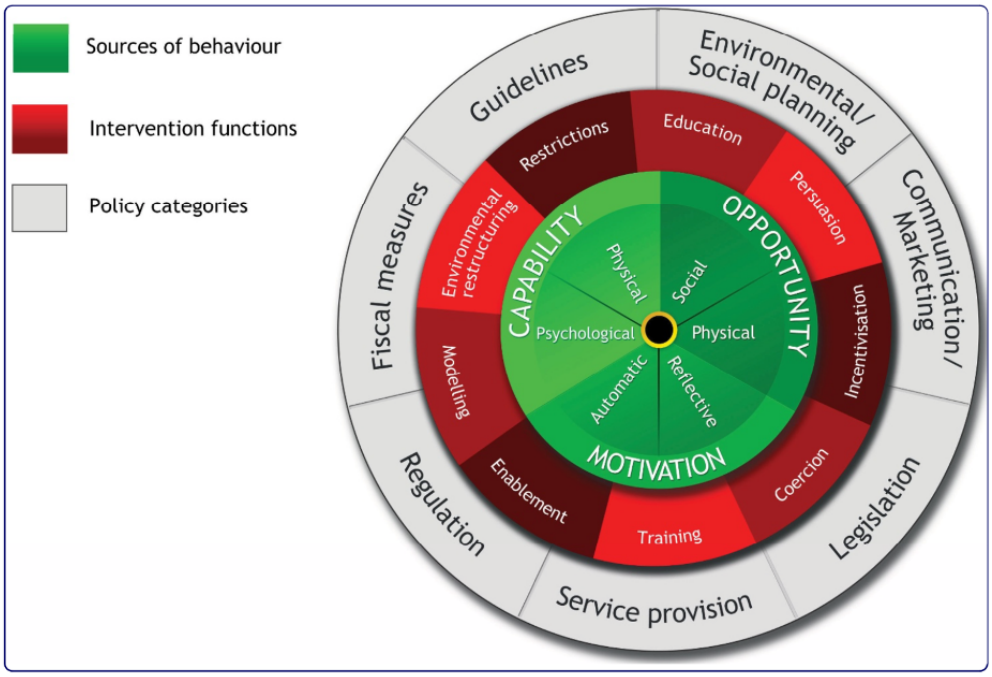
Implementation science frameworks, which take into account multiple interacting domains and processes that factor into successful program implementation, can help assure that the aforementioned gaps in chronic kidney disease awareness and education are addressed with interventions that are feasible and generalizable in real-world setting [18]. Consistent with these principles, the National Kidney Foundation developed the Kidney Score Platform to increase individual awareness and perceived risk of chronic kidney disease, thereby enhancing discussions about kidney disease between patients and clinicians. With this paper, we describe how we leveraged an implementation science framework to develop the Kidney Score Platform and propose to implement and evaluate its impact on veteran understanding and engagement with chronic kidney disease care as well as clinician self-efficacy for identifying and discussing chronic kidney disease with their patients.

Methods

Behavior Change Wheel

We selected the Behavior Change Wheel [19] as a framework for the development of the Kidney Score Platform. This framework was developed from a synthesis of 19 other frameworks of behavior change and incorporates 3 layers to guide intervention development and deployment (Figure 1) [19]. The first layer uses the Capability, Opportunity, Motivation, Behavior (COM-B) model to identify barriers, enablers, and sources of behaviors that serve as potential intervention targets. The second layer of the wheel identifies 9 intervention functions that could be leveraged by the Kidney Score Platform to address the enablers and barriers to behavior change identified in the first layer. The third layer offers 7 policy options that can be deployed to support the testing and subsequent use of the Kidney Score Platform.

Figure 1. The behavior change wheel from reference Michie and colleagues [19].



The Kidney Score Platform

From June 2016 to September 2016, the NKF conducted in-depth interviews with 20 nondialysis-requiring chronic kidney disease patients and 11 clinician experts in chronic kidney disease care including nephrologists and primary care practitioners (Multimedia Appendix 1). These interviews identified information that patients found most useful at various stages of their chronic kidney disease journey and provided insight into the type of information that clinicians conveyed to patients at those stages. Data from both clinician and patient audiences also identified barriers and enablers to behavior change that were categorized according to the COM-B model. Examples of patient barriers included the asymptomatic nature of disease, reliance on primary care clinicians to determine risk and order testing, and inadequate kidney-focused clinical workforce (ie, primary care clinicians, chronic kidney disease certified nutritionists, and nephrologists) (capability); underdiagnosis of chronic kidney disease in primary care and limited public awareness of chronic kidney disease (opportunity); and limited kidney literacy and low patient activation (motivation). Patient enablers included access to patient portals containing laboratory findings, availability of chronic kidney disease care planning, and care coordination (capability); availability of online chronic kidney disease patient education and access to chronic kidney disease care management tools (opportunity); and participation in chronic kidney disease peer mentoring programs and availability of self-management programs for chronic kidney disease (motivation).

Examples of clinician barriers were limited awareness of chronic kidney disease clinical practice guidelines, challenges in modifying organizational workflows for diabetes and hypertension, no financial incentives for chronic kidney disease recognition (capability); limited availability of chronic kidney disease training in medical school and absence of formal chronic kidney disease awareness campaigns (opportunity); low prioritization of chronic kidney disease by health care organizations and by health care payers; and limited data analytics to highlight chronic kidney disease care gaps (motivation). Clinician enablers included chronic kidney disease clinical decision support in the electronic health record, performance measures for chronic kidney disease testing, and risk adjustment strategies for chronic kidney disease diagnosis and severity (capability); systemic quality improvement focused on chronic kidney disease care processes and inclusion of chronic kidney disease interventions in risk factor education (ie, hypertension) (opportunity); and use of practice facilitation teams to improve chronic kidney disease care and use of registries to demonstrate opportunities in chronic kidney disease care (motivation).

Kidney Score Platform Online Interface (for Patients)

Based on the aforementioned behavior change targets, the NKF's multidisciplinary team of experts in web technology design, user interface development, information architecture, adult learning, and patient education partnered with experts in kidney care, patient education, and app design to develop the Kidney Score Platform online interface. Using the Behavior Change Wheel intervention functions education, persuasion, and enablement, the interface was designed to improve awareness and understanding about kidney disease among people at risk for and living with chronic kidney disease (Table 1).

Table 1. Elements of the Kidney Score Platform informed by the 3 layers of the Behavior Change Wheel framework to directly address patient and clinician barriers and facilitators of behavior change for chronic kidney disease awareness, communication, and management.

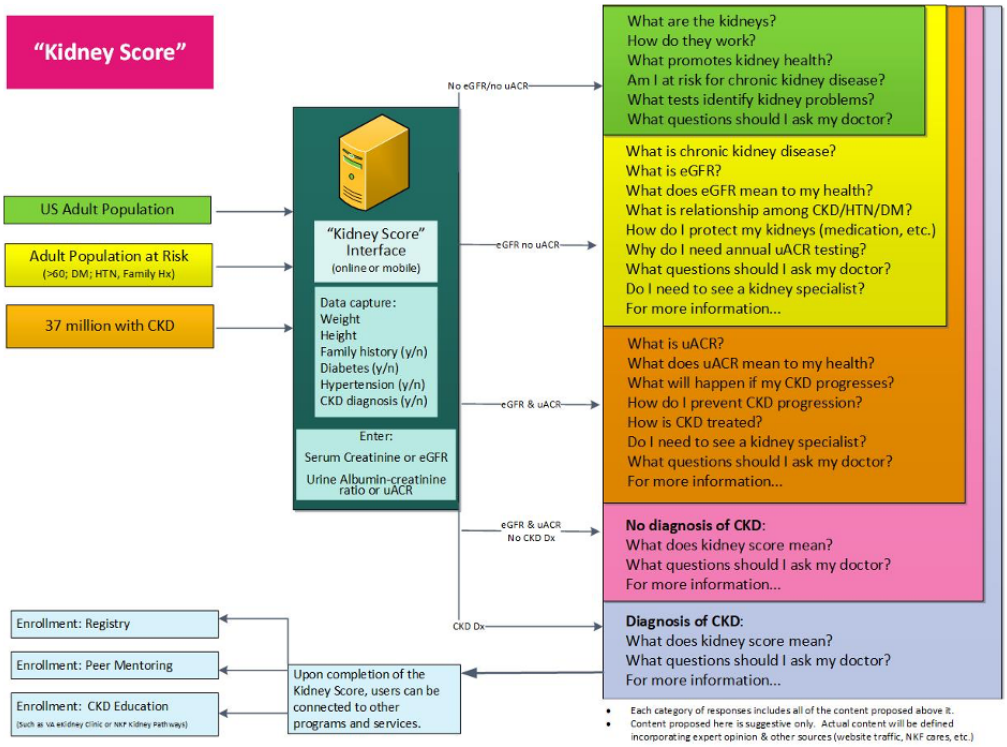
Elements	Behavior change		Behaviour Change Wheel		
	Barriers	Facilitators	Behavior sources	Intervention functions	Policy categories
Patient-facing					
Risk online interface					
	Asymptomatic nature	Patient portals with laboratory data	Capability	Education	Communication/ marketing
	Limited public awareness	Online education	Opportunity	Education	Communication/ marketing
	Underdiagnosis	Access to management tools	Opportunity	Persuasion	Regulation
	Limited health literacy; low patient activation	Existing self-management programs	Motivation	Enablement	Regulation
Clinician-facing					
Practice assessment	Suboptimal awareness of clinical practice guidelines	Quality improvement focused on chronic kidney disease	Opportunity	Persuasion	Regulation; communication/ marketing
CKDinform 2.0	Absence of formal awareness campaigns	Linkage of chronic kidney disease with risk factor education	Opportunity	Education	Guidelines
AHRQ REALM-SF[a]	Poor knowledge about health literacy	Validated tools to quickly assess health literacy	Motivation	Education	Regulation
Teach-back video	Limited training in medical school	Linkage of chronic kidney disease with risk factor education	Capability	Modeling	Communication/ marketing; Regulation
Change Package	Challenges in modifying workflows for diabetes and hypertension	Clinical decision support in the electronic health record	Capability	Enablement	Service provision

[a]AHRQ REALM-SF: Agency for Healthcare Research and Quality Rapid Estimate of Adult Literacy in Medicine—Short Form.

The 3 other policy categories described in the Behavior Change Wheel that will not be applied to the evaluate the Kidney Score Platform are fiscal, legislation, and social planning.

The free online interface utilizes a rule engine and risk predictive analytics to provide interactive health information tailored to the individual's chronic kidney disease risk and health status. After entering risk factor information as well as laboratory findings in the Kidney Score Platform's online interface, end users receive educational programming tailored to their current clinical status and risk for chronic kidney disease development or progression. Information is organized into context-specific easily digestible snippets, an approach aligned with the growing body of health education on how interactive content and tools such as apps, online health assessments, calculators, games, and quizzes can significantly affect comprehension, attitudes, self-efficacy, and health-related behavior change (Figure 2) [20-22]. The Kidney Score Platform Online interface blends the two of the most frequently accessed areas on the NKF website [23] (which receive over 19 million unique visitors per year)—the chronic kidney disease Risk Stratification Tool (Heat Map) and the patient-directed A to Z Guide—into a single tailored learning experience about kidney health. Topics span the spectrum of information from risk factors for chronic kidney disease to the benefit of medical nutrition therapy, fitness, weight control, and informed decision making for medical management of chronic kidney disease.

Figure 2. Design of the Kidney Score Platform online interface, which utilizes a rule engine and risk predictive analytics to provide interactive health information tailored to the individual's chronic kidney disease risk and health status. CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; DM: diabetes; HTN: hypertension; uACR: urine albumin-creatinine ratio.



Clinical Practice Toolkit (for Clinician Teams)

Clinician-identified barriers and enablers for optimal discussions about chronic kidney disease informed the creation of the Kidney Score Platform's Clinical Practice Toolkit. Leveraging the Behavior Change Wheel intervention functions of education, persuasion, enablement, and modeling, the toolkit assists clinicians in discussing chronic kidney disease with individuals at risk of and those living with chronic kidney disease who may have different health literacy levels (Table 1). The toolkit includes elements that help identify patient populations at risk for and with chronic kidney disease, online continuing medical education about kidney disease detection and management, a tool that can be applied in clinical practice to assess patient health literacy for education tailoring, teach-back videos that model discussions about chronic kidney disease concepts, and quality improvement interventions that can be implemented at the clinic level to improve identification of patients at risk or living with chronic kidney disease.

Practice assessment is an algorithm that extracts chronic kidney disease-related data from the electronic medical record to assist clinical practices in identifying (1) patients at risk for chronic kidney disease who have not been tested for kidney disease; (2) patients with underlying undiagnosed chronic kidney disease based on laboratory testing; (3) patients with chronic kidney disease who could benefit from improved understanding of chronic kidney disease and the choices for medical management of chronic kidney disease.

CKDinform 2.0 is an online continuing education activity based on Kidney Disease Outcomes Quality Initiative clinical practice guidelines that review chronic kidney disease testing, detection, and care [24].

The *Rapid Estimate of Adult Literacy in Medicine—Short Form* (REALM-SF) is a validated 7-item word recognition test that provides clinicians with a quick assessment of a patient's health literacy and capacity to understand health information [25].

Teach-back videos provide examples for practitioners of how to utilize the Kidney Score Platform online tool to communicate with individuals at risk for or living with chronic kidney disease. These short videos, featuring an expert clinician investigator and an individual living with chronic kidney disease, provide several examples of the teach-back method being utilized to assess patient comprehension of chronic kidney disease–related concepts (ie, understanding the importance of kidney health, medical nutrition therapy for chronic kidney disease, and importance of avoiding certain over-the-counter medications) including instructions conveyed during the office visit about medication safety use.

Change Package is a free publicly available online compendium of tools or actionable process improvements that clinicians in primary care settings can implement to integrate Kidney Score Platform chronic kidney disease education and related interventions into their practice workflow [26]. By including process improvements that can be rapidly tested, the Change Package can help practices to deploy systems that efficiently and effectively support patients with chronic kidney disease. It was developed in collaboration with the Centers for Disease Control and Prevention Million Hearts initiative based on the foundation of their Hypertension Change Package [27].

Study Design

The policy strategies from the Behavior Change Wheel that enable and support the testing and use of the Kidney Score Platform include communication/marketing, regulation,

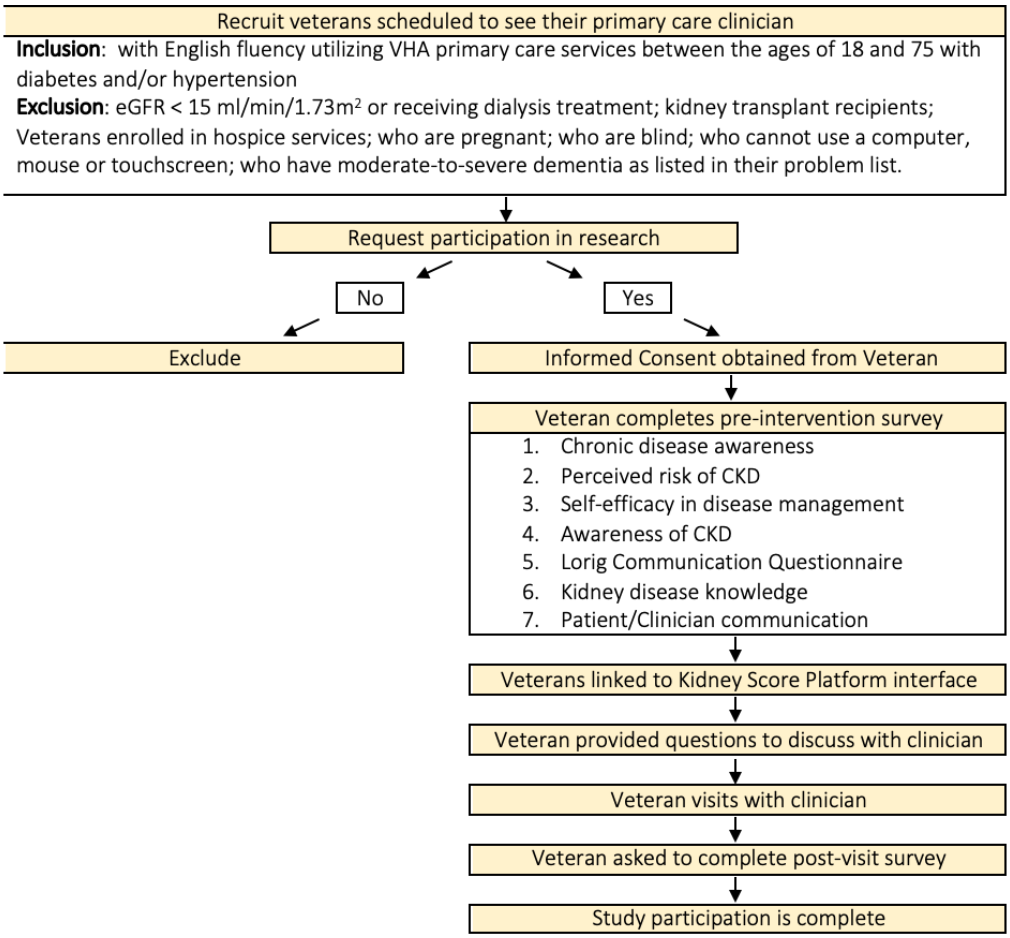
guidelines, and service provision (Table 1). These are embedded in the pre–post study design that will test the impact of the Kidney Score Platform on patient self-efficacy for chronic kidney disease management within the primary health care settings of 2 VA medical centers: VA New York Harbor Healthcare System and VA Connecticut Healthcare System. This study has been approved by the Institutional Review Boards of the VA Connecticut Healthcare System (#02290) and VA New York Harbor Healthcare System (#01705) and any modifications to the study protocol will be communicated to them for review before implementation.

Intervention

Veterans will interact with the Kidney Score Platform online interface individually while awaiting their clinical encounter via tablets or laptops (communication/marketing). As depicted in Figure 3, veterans who have consented to participate in the study will complete an online preassessment survey before exposure to the Kidney Score Platform's Online Interface. Participants will then engage with the online interface for 5-20 minutes before their clinician visit. This interaction can occur at home for a telehealth visit or in the waiting room for an in-person visit. If requested, Kidney Score Platform will offer participants a copy of questions to ask their clinician about their kidney health, tailored to their chronic kidney disease risk, determined by the Kidney Score Platform's embedded rules engine. These questions aim to further reinforce important chronic kidney disease topics and foster meaningful patient-professional conversations (regulation). Within a week after the clinical encounter, veterans will be asked to complete a brief survey (electronically or by phone) to assess the impact of the Kidney Score Platform on their understanding of chronic kidney disease and the quality of their conversation with their practitioner about kidney health. The Kidney Score Platform is intended to serve as an adjunct to clinical care; there will be no restrictions on concomitant care interventions delivered during or after the clinical visit.

Prior to veteran recruitment, we will offer the accompanying clinical practice toolkit to primary care teams (service provision). Practitioners will be encouraged (but not mandated) to utilize the clinical practice tools, particularly completing CKDinform 2.0 and watching the chronic kidney disease teach-back video (communication/marketing). These tools will prepare practitioners for conversations with veterans as well as reinforce chronic kidney disease clinical practice guidelines on detection, patient education, and intervention (regulation, guidelines). Pre and postsurveys will be conducted to assess the impact of the clinical practice toolkit on practitioners' perception of chronic kidney disease, chronic kidney disease knowledge, and important topics for chronic kidney disease patient education.

Figure 3. Process flow for Kidney Score study. CKD: Chronic Kidney Disease; eGFR: estimated glomerular filtration rate; VHA: Veteran's Health Administration.



Study Population Criteria

Veterans with and at risk for chronic kidney disease and their primary care clinical teams represent the target population. English-speaking veterans utilizing VA primary care services between the ages of 18 and 75 with diabetes or hypertension as defined in the electronic health record will be eligible for this study. Exclusion criteria include an estimated glomerular filtration rate <15 mL/min/1.73m^2 from recent laboratory tests in the medical record or those receiving dialysis treatment, as the Kidney Score Platform is not geared toward individuals with severe chronic kidney disease. Kidney transplant recipients will also be excluded, as their care is delivered predominantly in the subspecialty care setting rather than the primary care setting. We will also exclude veterans enrolled in hospice services, as chronic kidney disease awareness and self-management are less important for this population. Other exclusions include pregnancy, vision impairment, and severe dementia, identified by the problem list in the electronic health record or during the consent process. All primary care clinicians working as part of a Patient Aligned Care Team (PACT) in participating VA Medical Centers will be eligible for participation in the study.

Recruitment

Veterans work collaboratively with their PACT multidisciplinary team members to meet their health care needs. PACTs often include clinicians, nurses, medical assistants, social workers, and pharmacists, among other allied health professionals. The study team will work with each PACT team's care coordination staff to identify veterans who meet the inclusion criteria with appointments during the intervention's phase. Collaborating with primary care champions at each site, the project team will explore variations in recruitment process based on the site's resources, clinical flow, and use of telehealth for care delivery due to the COVID-19 pandemic.

Recruitment of clinicians from each PACT team will occur during a presentation of the project, during which the research team can answer questions. Clinical champions from each participating VA have been engaged in project co-design and will help ensure adequate and diverse clinician participation.

Consent

A member of the project team will describe the innovation and its goals and purpose to eligible veterans. Individuals that can correctly explain the project protocol and answer simple teach-back questions (in part to assess for dementia) will be asked to provide consent. Eligible providers will also be asked to provide consent to participate after they hear about the project and its goals.

Data Collection and Outcomes

Sociodemographic Data

Sociodemographic data (age, gender, race/ethnicity), co-morbid conditions (diabetes, hypertension, cardiovascular disease), and baseline laboratory data (serum creatinine, proteinuria, or albuminuria), will be collected from all consenting participants from the electronic health record, including participants who do not complete surveys for primary outcome collection (see below). All individually identifiable data will remain within the VA data system. Practitioner sociodemographic data (age, gender, race/ethnicity), role, panel size or practitioner caseload, and years of experience will be self-reported.

Behavior and Attitude Outcomes

The primary outcome is change in self-efficacy for chronic kidney disease management, measured by the Patient Activation Measure [28]. We will also examine changes in self-reported communication with practitioners about chronic kidney disease and ability of veterans to describe the tests used to detect chronic kidney disease. Validated instruments will be used [29,30], deployed via secure online surveys linked to the Kidney Score Platform's online interface to maximize data quality and security. We will also assess the impact of the Clinical Practice Toolkit on practitioners' perception of chronic kidney disease, chronic kidney disease knowledge, and important topics for chronic kidney disease patient education (Table 2).

Table 2. Patient and clinician behavior outcomes.

Outcome	Method of ascertainment
Change in patient self-efficacy for disease self-management	Patient Activation Measure [28]
Change in patient perceived risk of chronic kidney disease and chronic kidney disease awareness	Boulware questionnaire [31]
Change in patient comfort communicating with providers	Stanford communication instrument [29]
Change in clinician perception of and actual chronic kidney disease knowledge	Knowledge survey

Process Measures

Using the Reach Evaluation-Adoption Implementation and Maintenance (RE-AIM) framework for program evaluation [32], we will conduct process evaluation of the Kidney Score's online platform and accompanying Clinical Practice Toolkit, across and within VA partnering sites. We will examine (1) reach to intended target audiences (veterans most at risk for chronic kidney disease, PACT team members); (2) effectiveness of the Kidney Score among veterans and practitioners, including usability of the online interface; (3) adoption of the Kidney Score and toolkit by primary care teams across and within partnering VA Medical Centers and (4) implementation consistency, costs, and adaptations made during deployment and delivery (Table 3).

Table 3. Process outcomes for implementation analysis, based on the RE-AIM framework [32].

RE-AIM[a] dimension	Outcome	Method of assessment
Reach (representativeness of participants)	1. Number of eligible patients who consent	VAMC[b] clinic lists; electronic health record data; description of PACT[c] teams
	2. Demographic and clinical characteristics of subjects who enroll/do not enroll	
	3. Demographic characteristics of participating clinicians	
Effectiveness (adherence and engagement)	1. Usability of the Kidney Score Platform online interface	Screen sharing and observation
	2. Percentage of patients who request a copy of discussion questions for their provider	
	3. Percentage of at-risk patients with urine albumin-creatinine ratio testing	Electronic health record data
	4. Percentage of patients with chronic kidney disease with diagnosis on problem list	
	5. Percentage of patients with proteinuria prescribed angiotensin converting enzyme inhibitor/angiotensin receptor blocker	
	6. Percentage of patients referred to nephrology	
Adoption	1. Are providers satisfied with integration with clinic work flow?	Formative evaluation with PACT team members and Quality Improvement team leaders
Implementation	1. Is each component delivered as intended? (fidelity)	
	2. What components of the intervention were customized to each VAMC?	
	3. How much VAMC personnel time is required to deploy the clinical practice toolkit?	

[a]RE-AIM: Reach Evaluation-Adoption Implementation and Maintenance.

[b]VAMC: Veteran Affairs Medical Center.

[c]PACT: Patient Aligned Care Team.

Sample Size Considerations

The study is powered to detect changes in Patient Activation Measure (PAM) score, a validated measure of an individual's knowledge, skill, and confidence in managing one's health [28]. Data from prior self-management intervention studies have demonstrated a change in PAM score SD of 14.5. Using two-tailed paired *t* test calculations, we would need to enroll 103 veterans to engage with the Kidney Score Platform and complete the pre and postsurveys to detect a 4-point clinically meaningful change in the PAM, assuming that the PAM would not change among individuals not exposed to Kidney Score Platform [33]. Accounting for a conservative 20% dropout, we need to recruit 124 veterans. In previous studies [30] related to chronic kidney disease education in primary care, 67% of eligible patients agreed to participate. Preliminary data suggest that there are >1200 eligible veterans for our project in each medical center PACT program.

Data Analysis

Impact of the Kidney Score Platform on change in participant PAM scores (primary outcome) will be conducted with linear mixed models, adjusting for age, gender, diabetes status, kidney disease severity, and clinic site. Additional analyses will look for effect modification by clinician knowledge of chronic kidney disease. Similar methods will be used to assess secondary outcomes: self-reported communication with practitioners about chronic kidney disease and ability of veterans to describe the tests used to detect chronic kidney disease.

Results

As of September 2020, usability studies are underway with veterans and clinicians to refine the patient-facing components of the Kidney Score Platform before study initiation. Results and subsequent changes to the Kidney Score Platform will be published at a later date. The study is expected to be completed by December 2021.

Discussion

This paper illustrates a theory-informed and evidence-based approach to developing and testing an intervention to enhance communication about kidney disease among patients and health care professionals. To develop all of the elements of the Kidney Score Platform, we leveraged the Behavior Change Wheel framework to directly target behaviors that were identified as barriers to optimal chronic kidney disease awareness and communication during preparatory interviews, using evidence-based intervention functions [19]. To test The Kidney Score Platform's impact, we partnered with VA leaders to identify the policy categories from the Behavior Change Wheel that could be employed at the organizational level to support its implementation. We are now poised to test the Kidney Score Platform's efficacy and effectiveness on increasing an individual's self-efficacy and activation to decrease chronic kidney disease risk and a primary care team's ability to manage chronic kidney disease and communicate about kidney disease.

While several chronic kidney disease education programs and awareness campaigns exist across the United States, there are limited examples in the literature of how theoretical frameworks

can be leveraged to develop and test interventions to enhance kidney-related communication among clinicians and patients and improve self-efficacy and overall health among individuals with kidney disease. To our knowledge, this is one of the few chronic kidney disease awareness interventions developed and proposed to be tested according to an individual behavioral change theory (ie, Behavior Change Wheel). Theory-informed interventions are more likely to be effective than interventions not based on theory, though a formal study is required to test whether the slow deliberate process (such as that used to develop the Kidney Score Platform) leads to greater effectiveness within the context of health care delivery.

Results of the anticipated study examining the impact of Kidney Score Platform on patients and clinician chronic kidney disease awareness and communication will be shared with participants and will used to refine the different elements of the platform and their integration within primary care settings including new care delivery workflows, such as telehealth. Study results will be most applicable to care delivery in VA administration settings involving in-person and phone or video visits. While this is one limitation to this study, we anticipate that the Kidney Score Platform's impact on awareness, self-efficacy, educational, and communication outcomes among veterans and their clinicians will be generalizable to other settings and novel care delivery mechanisms. If so, the robust process by which the Kidney Score Platform was developed can serve as a model for the creation and implementation of other innovations that focus on behavior change as a means of enhancing kidney health. The refined Kidney Score Platform that will emerge from this study has the potential to significantly impact the lives of the approximately 37 million US adults affected by chronic kidney disease, as it will serve as a central component of the NKF's national public awareness initiative to educate, engage, and empower individuals at risk for and living with chronic kidney disease.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Kidney Score Platform design interview probe.
[DOCX File , 24 KB - resprot_v9i10e22024_app1.docx]

References

1. Chronic kidney disease in the United States. Centers for Disease Control and Prevention. 2019. URL: https:/www.cdc.gov/kidneydisease/publications-resources/2019-national-facts.html [accessed 2020-09-28]
2. 2018 USRDS annual data report: epidemiology of kidney disease in the United States. United States Renal Data System. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2018. URL: https://www.usrds.org/annual-data-report/previous-adrs/ [accessed 2020-09-28]
3. Go A, Chertow G, Fan D, McCulloch C, Hsu C. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. ACC Current Journal Review 2004 Dec;13(12):1296-1305. [doi: 10.1016/j.accreview.2004.11.016]
4. Sarnak MJ, Greene T, Wang X, Beck G, Kusek JW, Collins AJ, et al. The effect of a lower target blood pressure on the progression of kidney disease: long-term follow-up of the modification of diet in renal disease study. Ann Intern Med 2005 Mar 01;142(5):342-351. [doi: 10.7326/0003-4819-142-5-200503010-00009] [Medline: 15738453]
5. Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis 2014 May;63(5):713-735. [doi: 10.1053/j.ajkd.2014.01.416] [Medline: 24647050]
6. Vassalotti JA, Centor R, Turner BJ, Greer RC, Choi M, Sequist TD, National Kidney Foundation Kidney Disease Outcomes Quality Initiative. Practical approach to detection and management of chronic kidney disease for the primary care clinician. Am J Med 2016 Feb;129(2):153-162.e7 [FREE Full text] [doi: 10.1016/j.amjmed.2015.08.025] [Medline: 26391748]
7. Plantinga LC, Tuot DS, Powe NR. Awareness of chronic kidney disease among patients and providers. Adv Chronic Kidney Dis 2010 May;17(3):225-236 [FREE Full text] [doi: 10.1053/j.ackd.2010.03.002] [Medline: 20439091]
8. Greer RC, Cooper LA, Crews DC, Powe NR, Boulware LE. Quality of patient-physician discussions about CKD in primary care: a cross-sectional study. Am J Kidney Dis 2011 Apr;57(4):583-591 [FREE Full text] [doi: 10.1053/j.ajkd.2010.08.027] [Medline: 21131116]
9. Rothberg MB, Kehoe ED, Courtemanche AL, Kenosi T, Pekow PS, Brennan MJ, et al. Recognition and management of chronic kidney disease in an elderly ambulatory population. J Gen Intern Med 2008 Aug 29;23(8):1125-1130 [FREE Full text] [doi: 10.1007/s11606-008-0607-z] [Medline: 18443883]
10. Allen AS, Forman JP, Orav EJ, Bates DW, Denker BM, Sequist TD. Primary care management of chronic kidney disease. J Gen Intern Med 2011 Apr 5;26(4):386-392 [FREE Full text] [doi: 10.1007/s11606-010-1523-6] [Medline: 20922494]

11. Szczech LA, Stewart RC, Su H, DeLoskey RJ, Astor BC, Fox CH, et al. Primary care detection of chronic kidney disease in adults with type-2 diabetes: the ADD-CKD Study (awareness, detection and drug therapy in type 2 diabetes and chronic kidney disease). PLoS One 2014 Nov 26;9(11):e110535 [FREE Full text] [doi: 10.1371/journal.pone.0110535] [Medline: 25427285]
12. Tuot DS, Plantinga LC, Hsu C, Jordan R, Burrows NR, Hedgeman E, et al. Chronic kidney disease awareness among individuals with clinical markers of kidney dysfunction. CJASN 2011 Jul 22;6(8):1838-1844. [doi: 10.2215/cjn.00730111]
13. Bodenheimer T, Lorig K, Holman H, Grumbach K. Patient self-management of chronic disease in primary care. JAMA 2002 Nov 20;288(19):2469-2475. [doi: 10.1001/jama.288.19.2469] [Medline: 12435261]
14. Plantinga LC, Boulware LE, Coresh J, Stevens LA, Miller ER, Saran R, et al. Patient awareness of chronic kidney disease: trends and predictors. Arch Intern Med 2008 Nov 10;168(20):2268-2275 [FREE Full text] [doi: 10.1001/archinte.168.20.2268] [Medline: 19001205]
15. Management of chronic kidney disease. VA/DoD Clinical Practice Guidelines. URL: https://www.healthquality.va.gov/guidelines/CD/ckd/ [accessed 2020-09-01]
16. Chronic kidney disease surveillance system. Centers for Disease Control and Prevention. URL: http://www.cdc.gov/ckd [accessed 2020-09-01]
17. Azar A. Advancing American Kidney Health. U.S. Department of Health and Human Services. 2019. URL: https://www.asn-online.org/policy/webdocs/AdvancingAmericanKidneyHealth-1.pdf [accessed 2020-09-28]
18. Glasgow R, Chambers D. Developing robust, sustainable, implementation systems using rigorous, rapid and relevant science. Clin Transl Sci 2012 Feb;5(1):48-55 [FREE Full text] [doi: 10.1111/j.1752-8062.2011.00383.x] [Medline: 22376257]
19. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. Implement Sci 2011 Apr 23;6(1):42 [FREE Full text] [doi: 10.1186/1748-5908-6-42] [Medline: 21513547]
20. Diamantidis CJ, Becker S. Health information technology (IT) to improve the care of patients with chronic kidney disease (CKD). BMC Nephrol 2014 Jan 09;15(1):7 [FREE Full text] [doi: 10.1186/1471-2369-15-7] [Medline: 24405907]
21. Baranowski T, Buday R, Thompson DI, Baranowski J. Playing for real: video games and stories for health-related behavior change. Am J Prev Med 2008 Jan;34(1):74-82 [FREE Full text] [doi: 10.1016/j.amepre.2007.09.027] [Medline: 18083454]
22. Stout P, Villegas J, Kim H. Enhancing learning through use of interactive tools on health-related websites. Health Educ Res 2001 Dec;16(6):721-733. [doi: 10.1093/her/16.6.721] [Medline: 11780710]
23. Are you the 33%? National Kidney Foundation. URL: https://www.kidney.org [accessed 2020-09-01]
24. CKDinform 2.0: chronic kidney disease in primary care: implementation best practices to improve outcomes. National Kidney Foundation. URL: https://education.kidney.org/ckdi2enduring [accessed 2020-09-01]
25. Agency for Health care Research and Quality. Health Literacy Measurement Tools (Revised). URL: http://www.ahrq.gov/professionals/quality-patient-safety/quality-resources/tools/literacy/index.html [accessed 2020-09-01]
26. Chronic kidney disease change package. National Kidney Foundation. URL: https://www.kidney.org/contents/chronic-kidney-disease-change-package [accessed 2020-09-01]
27. Hypertension control change package for clinicians. Centers for Disease Control and Prevention. 2015. URL: https://millionhearts.hhs.gov/files/HTN_Change_Package.pdf [accessed 2020-09-28]
28. Hibbard JH, Mahoney ER, Stockard J, Tusler M. Development and testing of a short form of the patient activation measure. Health Serv Res 2005 Dec;40(6 Pt 1):1918-1930 [FREE Full text] [doi: 10.1111/j.1475-6773.2005.00438.x] [Medline: 16336556]
29. Lorig K, Stewart A, Ritter P, Gonzalez V, Laurant D, Lynch J. Outcome Measures for Health Education and Other Health Care Interventions. Thousand Oaks, CA: Sage Publications; 1996.
30. Tuot DS, Zhu Y, Velasquez A, Espinoza J, Mendez CD, Banerjee T, et al. Variation in patients' awareness of CKD according to how they are asked. Clin J Am Soc Nephrol 2016 Sep 07;11(9):1566-1573. [doi: 10.2215/CJN.00490116] [Medline: 27340288]
31. Boulware LE, Carson KA, Troll MU, Powe NR, Cooper LA. Perceived susceptibility to chronic kidney disease among high-risk patients seen in primary care practices. J Gen Intern Med 2009 Oct 27;24(10):1123-1129 [FREE Full text] [doi: 10.1007/s11606-009-1086-6] [Medline: 19711135]
32. Glasgow RE, Klesges LM, Dzewaltowski DA, Estabrooks PA, Vogt TM. Evaluating the impact of health promotion programs: using the RE-AIM framework to form summary measures for decision making involving complex issues. Health Educ Res 2006 Oct 15;21(5):688-694. [doi: 10.1093/her/cyl081] [Medline: 16945984]
33. Hibbard JH, Greene J, Tusler M. Improving the outcomes of disease management by tailoring care to the patient's level of activation. Am J Manag Care 2009 Jun;15(6):353-360 [FREE Full text] [Medline: 19514801]

Abbreviations

COM-B: capability, opportunity, motiviation – behavior
NKF: National Kidney Foundation
PACT: Patient Aligned Care Teams

PAM: Patient Activation Measure
RE-AIM: Reach Evaluation-Adoption Implementation and Maintenance
VA: Veterans Affairs

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Protocol

Understanding the Uptake of Big Data in Health Care: Protocol for a Multinational Mixed-Methods Study

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Abstract

Background: Despite the high potential of big data, their applications in health care face many organizational, social, financial, and regulatory challenges. The societal dimensions of big data are underrepresented in much medical research. Little is known about integrating big data applications in the corporate routines of hospitals and other care providers. Equally little is understood about embedding big data applications in daily work practices and how they lead to actual improvements for health care actors, such as patients, care professionals, care providers, information technology companies, payers, and the society.

Objective: This planned study aims to provide an integrated analysis of big data applications, focusing on the interrelations among concrete big data experiments, organizational routines, and relevant systemic and societal dimensions. To understand the similarities and differences between interactions in various contexts, the study covers 12 big data pilot projects in eight European countries, each with its own health care system. Workshops will be held with stakeholders to discuss the findings, our recommendations, and the implementation. Dissemination is supported by visual representations developed to share the knowledge gained.

Methods: This study will utilize a mixed-methods approach that combines performance measurements, interviews, document analysis, and cocreation workshops. Analysis will be structured around the following four key dimensions: performance, embedding, legitimation, and value creation. Data and their interrelations across the dimensions will be synthesized per application and per country.

Results: The study was funded in August 2017. Data collection started in April 2018 and will continue until September 2021. The multidisciplinary focus of this study enables us to combine insights from several social sciences (health policy analysis, business administration, innovation studies, organization studies, ethics, and health services research) to advance a holistic understanding of big data value realization. The multinational character enables comparative analysis across the following eight European countries: Austria, France, Germany, Ireland, the Netherlands, Spain, Sweden, and the United Kingdom. Given that national and organizational contexts change over time, it will not be possible to isolate the factors and actors that explain the implementation of big data applications. The visual representations developed for dissemination purposes will help to reduce complexity and clarify the relations between the various dimensions.

Conclusions: This study will develop an integrated approach to big data applications that considers the interrelations among concrete big data experiments, organizational routines, and relevant systemic and societal dimensions.

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KEYWORDS

big data; performance; business modeling; regulation; implementation; innovation; social sciences; legitimacy; governmental regulation; balance score card; ethics

Introduction

Background

The potential of big data in health care is well-recognized in the literature [1-4]. Big data are heterogeneous, complex, and derived from many sources, for example, primary and secondary electronic medical records, laboratory data, prescriptions, imaging data, patient monitors, and telemedicine. Big data can be captured by mobile apps, real-time location tracking, and urban registries [1]. Patients, citizens, and other stakeholders can collect big data, sometimes for other purposes than health care. The framework often used to describe big data is "3V," which refers to the volume of data, variety of sources and types of data, and velocity of the analysis [5-7]. Other authors have added "veracity" (referring to credibility and "error-free" analytics of big data) and "value" (referring to the impact of big data usage on competitive advantage and performance) to the 3V framework [8-10].

In health care, big data have been described as "encompassing high volume, high variety biological, clinical, environmental, and lifestyle information collected from single individuals to large cohorts, in relation to their health and wellness status, at one or several time points" [11]. With big data *analytics*, routinely generated and collected health care data can be reused for quality improvement (eg, quality registries, benchmarking, and guideline development) [1], population management (eg, early detection of diseases and accessibility), or improved decision making (eg, treatment and cost reduction) [4]. Examples of big data analytics in health care are machine learning, deep learning, image analytics, prediction algorithms, and real-time event detection [4].

In medicine, research has focused on the technical dimensions of big data, that is, how algorithms work and what is technically accomplished with data, and the societal dimensions are underrepresented in medical research literature. Including societal dimensions is important as big data use in health care faces many organizational, social, financial, and regulatory challenges [10,11]. Moreover, organizations have to deal with ethical dilemmas and public outcry [12]. Research on big data technologies and applications in health care should be studied not only as a set of techniques for data extraction, analysis, and reuse, but also as a set of ideas and understandings of its use [13]. Thus, big data research should include the societal dimensions [10-13]. While new analytical techniques may hold significant promise, embedding them sustainably in organizational routines requires more than technical feasibility. It also depends upon "sense-making work" in order to enhance professional acceptability [14]. Similarly, while big data technologies might be legally acceptable, public concerns regarding ethical acceptability can create issues [15]. This protocol therefore outlines an integral research approach that sets out to understand the underlying patterns connected to the societal, business, legal, ethical, political, and organizational change issues surrounding big data applications in health care [10,11].

Limited research in health care has tried to provide an integrated analysis of big data pilots in varying organizational and social contexts. Most papers in this field describe an empirical study of a small-scale pilot, sometimes showing the results of big data analysis [16,17]. For instance, information technology (IT) literature (in health care and beyond) mostly describes promising applications that are yet to be developed [18,19]. In addition, most studies have a specific focus. Business administration literature describes the business value of big data [20] or shows how it can enhance organizational performance [21,22]. The literature in philosophy and ethics centers on theoretical discussions that only occasionally draw on rigorously analyzed empirical examples [15,23]. Importantly, studies in the field of health services research focus on legal frameworks and principles, but often neglect how such frameworks and principles become embedded in organizational practices [24,25]. Hence, little is known about how promising big data pilot projects get integrated in the organizational work practices of care providers or how they get embedded in the daily routines of health care professionals and actually improve health care for all the actors concerned (eg, patients, health care professionals, health care organizations, IT companies, payers, and the society) [26].

A recent systematic literature review revealed that in order to advance our understanding of big data value realization, research should move beyond pilot levels and examine how work practices, organizational models, and stakeholder interests interact with big data technology practices [12]. Few studies provide this integrated analysis of the interaction among the development of concrete pilots, the organizations in which they take place, and the health care systems of which they are a part. Wang et al [27], for instance, developed an integrated transformation model that seeks to investigate causal relationships among big data analytics capability, IT-enabled transformation practices, benefit dimensions, and business values. The authors sought to understand how big data analytics capability transforms organizational practices, thereby generating potential benefits. Cohen et al [28] linked the major legal, policy, and ethical issues raised by predictive analytics to the life cycle phases of predictive analytics models. Heitmueller et al [29] explored questions that policy makers should consider when developing public policy for big data usage in health care. Their approach distinguishes the following three broad categories of barriers: normative barriers (including cultural and ethical norms), market failures, and technocratic barriers (related to technological issues and government processes and regulations). Such studies offer important advances toward an integrated understanding of big data technologies and embedding them in organizations and societies.

In this research protocol, we outline our research approach that aims to add to the body of knowledge on embedding big data applications and technologies in organizations and societies. Applying a mixed-methods approach, our protocol describes how we plan to conduct a detailed multidisciplinary analysis of the interactions among concrete big data applications, organizational routines, and relevant systemic and societal dimensions. We will study how 12 big data applications (developed in pilot projects within a European Union–funded consortium of which we are also a part) strive to become embedded in (1) the daily routines of health care professionals and health care organizations; (2) stakeholder networks in health care organizations with varying infrastructures, policies, routines, and opportunities; and (3) the broader societal context. The overall research question is as follows: How do big data applications and technologies become embedded (or fail to become embedded) in the daily practice of health care professionals, in the health care organization, and in the society at large?

Research Aim and Approach

This protocol describes research that will be conducted within the context of a broad consortium that is experimenting with 12 big data pilot projects covering the following three themes: population health and chronic disease management, oncology, and industrialization of health care services [30]. The research will aim to understand how big data applications become embedded in the daily practice of professionals (or fail to do so), in the health care organization (why or why not), and in the society at large. To study the interrelations between the applications to be developed in the pilots and the organizational and societal contexts in which they are situated, we will use the Nicolini dual "zooming in-zooming out" approach because "practices are always immersed in a thick texture of interconnections" [31]. We will zoom in to allow different aspects to come to the fore and zoom out to facilitate investigation of the interrelations among concrete big data applications, organizational routines, and relevant systemic and societal dimensions.

To position our work, it is important to note that we will not only study single pilots and their individual contexts, but also feed our insights back into the pilots during the course of the projects. While the idea of transferring gained knowledge in oral and written forms to a pilot shares affinities with action research, our approach differs in two aspects. First, action research traditionally includes *multiple* feedback loops, which not only provide feedback on practical problems but also on any incorporated changes to practice that result from this feedback [32,33]. In contrast, our study focuses on developing knowledge and providing feedback to the pilots, but not on the consequent implementation of this feedback. Second, action research usually focuses on enabling transformative change through a simultaneous process of taking action and doing research, often through a participatory process involving practice members as coresearchers [33]. Instead, our study gives targeted feedback to the pilot, without involving coresearchers in the way action research does. Rather than conducting action research, our study adopts the approach of "situated intervention" by Zuiderent-Jerak [34]. This approach argues that intervention and knowledge production are not opposites, but can be productively combined. Situated intervention builds on the idea that the intervention is not just about practice improvement, but is simultaneously a generative mode of knowledge production. Thus, through commuting between the pilot practices, cocreation workshops with the pilot team members, and theory building beyond the individual pilots, we aim to *both* improve practice via actionable insights and produce new knowledge [35].

We will collect data through a range of carefully aligned studies. We investigate from various disciplinary perspectives how the stakeholders in the 12 pilot projects work toward the performance, embedding, legitimation, and value creation of their big data applications (these dimensions are described below). These pilots all concern innovative uses of big data in health care, but have different purposes and deal with various illnesses and treatments in several contexts (eight European countries with different health care systems). To this end, our study combines methods from many of the social sciences, including health policy analysis, business administration, innovation studies, organization studies, ethics, and health services research. To clarify, this means that our research will not use the big data collected in the 12 pilot projects, but will study how these pilot projects work on dimensions of performance, embedding, legitimation, and value creation.

A multidisciplinary approach is advisable for empirical studies of big data value realization focusing on several dimensions of analysis [12,36]. We will synthesize the data and compare countries to explore similarities and differences in how big data applications become embedded (or not) nationally. To capture the interrelations among individual big data applications, organizational routines, and relevant systemic and societal dimensions, we have selected "performance," "value creation," "embedding," and "legitimation" as key theoretical heuristics. For each of these concepts, we have developed a particular research question (Table 1). In line with our aim to combine study practices and provide feedback, we will visualize the results of each question in easily accessible ways.

Table 1. Key concepts and visualization.

Heuristic	Methods	Research question
Performance	Cocreation workshops to develop KPIs[a] and biannual performance measurements	How does the uptake of big data applications affect health care performance in terms of patient satisfaction, process outcomes, patient outcomes, and financial outcomes?
Embedding	Document analysis, semistructured interviews, focus groups, and follow-up interviews	What underlying mechanisms can explain how big data applications do or do not become embedded in organizational routines?
Legitimation	Document analysis and semistructured interviews	What are the major country-specific facilitators and barriers for the legal, moral, and societal legitimacy of big data applications in health care?
Value creation	Cocreation workshops to develop business models	Which stakeholder group captures which kind(s) of value from big data applications; through which activities, partners, and resources is the value generated; and how can big data applications sustainably be financed?

[a]KPIs: key performance indicators.

Performance fits the multidimensional character of public sector organizations [37,38]. The notion of multidimensionality is a central tenet of the distinction between financial and nonfinancial performance, as well as between processes and outputs/outcomes [39]. Following this design, we distinguish patient satisfaction, process outcomes, patient outcomes, and financial outcomes in an adjusted version of the balanced scorecard [40]. Patient satisfaction is defined as the perceptions and experiences of patients with health care delivery and the results thereof. Process outcomes refer to the activities undertaken in health care delivery (eg, hospitalization and visits to the specialist). Patient outcomes are defined as the effects of care on patients' health status (eg, mortality rates). Financial outcomes are the monetary implications for individuals, organizations, and the society. The associated research question is as follows: How does the uptake of big data applications affect health care performance in terms of patient satisfaction, process outcomes, patient outcomes, and financial outcomes?

The concept of *embedding* refers to the dynamic processes that lead the big data applications developed in the pilots to become integrated (or not) in the daily work practices of health care professionals, organizations, and societies. Based on insights from normalization process theory, we focus on the following four dimensions of embedding: sense-making work (actors' interpretations of what the application can add to work processes), relational work (actors' efforts in building a community of practice around the application), operational work (the work of actors involved in establishing new task divisions), and appraisal work (formal and informal assessments conducted by actors to assess the value of the application) [14,41]. Through these four dimensions, we aim to develop insights into the underlying mechanisms of embedding. The associated research question is as follows: What underlying mechanisms can explain how big data applications do or do not become embedded in organizational routines?

We conceptualize *legitimacy* as containing legal, societal, and moral dimensions [42]. The legal dimension refers to whether the big data application complies with formal legislation and official regulations. New regulations (or national policies) can be expected to affect (possibly limit) the opportunities available to the pilots (eg, the EU General Data Protection Regulation [GPDR] legislation could have major consequences for pilots working with international technology development partners). The legal dimension is less straightforward than it appears, as regulations are often diverse and might conflict in practice. Most often legislation trails new technological developments, creating a large gray area in which the application of a regulation can be interpreted in various ways [15]. The societal dimension addresses national policies and the social acceptability of big data. Since regulation is shaped by and embedded in cultural and social practices and policies, these constitute another dimension of legitimacy. The moral dimension focuses on the ethical discussions about big data in different countries. Informal societal aspects (eg, societal perspectives on the sharing of health data, ways in which big data are represented in popular media, and the ethical framing of the debate) can be expected to have consequences for the ways big data applications are developed and legitimized. The associated research question is as follows: What are the major country-specific facilitators and barriers for the legal, moral, and societal legitimacy of big data applications in health care?

The concept of *value creation* relates to the impact of big data applications in terms of both benefits (qualitative or quantitative) and costs for stakeholders (ie, anyone who affects or is affected by the application) [43]. As different stakeholders in the health care system have different perspectives on value [44], the dimensions of value focus on the value needs of the various stakeholders. Value dimensions are broader in scope and thus different from performance dimensions. Moreover, each health care system has its own unique stakeholder network. As such, stakeholder evaluation and participation in the development process will have a distinct inward impact on the success of big data applications in each health care system. We will focus on the value needs of the following various stakeholders usually associated with health care systems: patients, health care organizations and providers, IT companies, vendors, insurers, and the society. The business modeling process suggested by Osterwalder et al can be used to capture, understand, and evaluate the value creation process [45]. Therefore, we will use a business model framework adapted for big data applications

in health care to better understand the influence of such applications on the development and implementation of various activities within a health care system. The associated research question is as follows: Which stakeholder group captures which kind(s) of value from each big data application; through which activities, partners, and resources is the value generated; and through which models of cost coverage can big data applications be sustainably financed in different health care systems?

Methods

Our study base is multidisciplinary to incorporate the many dimensions of big data applications and their mutual interrelations [13,30,36]. The design combines qualitative and quantitative research methods stemming from several social sciences, including health policy analysis, business administration, innovation studies, organization studies, ethics, and health services research [14,15,39,44]. Various researchers with backgrounds in these fields are collaborating in a team that is embedded in the bigger European Union–funded consortium.

The *performance* of big data applications [30] will be monitored over time with pilot-specific key performance indicators (KPIs). It is important that the pilot teams develop their own KPIs with researchers, because these teams possess specific knowledge required to capture the changes in their performance. The KPIs should reflect the multidimensionality of performance underlying this study (patient satisfaction, process outcomes, patient outcomes, and financial outcomes) [46]. We will organize workshops for the 12 pilot teams in order to select KPIs and tailor these to the patient cohort, particular big data application, and aim of the pilot. KPIs will be included in the set if the pilot team and our research group consider them relevant, given the context and availability of reliable data. For the set of relevant and feasible KPIs, data will be collected periodically to allow comparison of performance over time. KPIs are based on various data sources used in the pilots (eg, administrative hospital data, electronic medical records, and registries from regional health ministries). For each pilot, there will be a baseline measurement referring to the period before implementation of the big data application. Following the baseline measurement, data will be collected every 6 months during and after the implementation of the big data application, unless this timing is not feasible or meaningful for the type of pilot.

Since prior literature advocates using dashboards to organize KPIs in a health care setting [eg 47], we will bundle KPIs into dashboards, with visualization per performance dimension to provide feedback to the pilot teams. This visualized feedback will allow both researchers and pilot team members to monitor performance within and across pilots. The information on the KPI dashboards will be discussed periodically with pilot teams to understand performance improvements and obtain insights into the facilitating or hindering factors. At the end of the study period, we will perform a comparative analysis across and within pilots to assess whether or by how much performance has improved during and after the implementation of the big data application. Wherever possible and in close collaboration with the pilots, the comparative analysis will relate to a granular unit of analysis (eg, individual patient level).

To study *embedding*, data are needed from various health care systems, because how rules and regulations are set depends on different actors in the various health care systems [48]. Relevant data to study organizational embedding processes include key contextual documents, such as policy documents from national government and intermediary bodies. At the organizational level, we will analyze organizational strategy documents and conduct semistructured interviews to provide insights into how the different actors and factors involved in setting the pilot influence the embedding of the big data applications in organizational routines. Causal loop diagrams can be used to identify underlying feedback mechanisms that facilitate or hinder these embedding processes [48,49]. Causal loop diagrams derive from a tradition of systems thinking in organizational studies [50] and social sciences [51].

We will study the embedding of big data applications in the following three different health care systems: the Dutch regulated market-based system, Sweden's decentralized system, and Austria's national health service. We will perform face-to-face semistructured interviews with pilot members, key organizational actors, and expert informants. The pilot team members will help to identify the respondents who best understand their specific big data pilot and context. At the start of each interview, we will obtain documented consent to record the interview. All recorded interviews will be transcribed verbatim. We will also conduct a document analysis. During the course of the study, pilot team members will collect relevant documents (eg, minutes, policy documents, and relevant emails). The interview material and documents will be qualitatively coded (open, thematic, and axial coding) and analyzed in order to select the 10 to 20 most important factors for a causal model [48,49]. Researchers will draw an initial causal model to explain the hurdles that need to be overcome to structurally embed the big data application in organizational routines, taking country-specific contextual elements into consideration. This initial causal model will be member-checked at a workshop with the pilot team members. After 6 months, we will conduct follow-up interviews with the same respondents to gain new insights into the embedding process. If necessary, we will adapt the causal models to incorporate new developments. We will discuss these new developments for member-checking purposes at the periodic consortium meetings.

Building again on our approach to combine research and intervention [34], the discussions triggered by the causal models will serve as a way to transfer our findings back to the pilot team members, allowing them to use the developed insights in the underlying patterns and mechanisms that hinder or facilitate embedding of big data applications. Specifically, pilot teams could use such insights to improve the embedding process of their big data application.

Legitimacy includes legal, societal, and moral dimensions. Previous research by Custers et al [52] identified the following six themes: (1) awareness and trust, (2) government policies for personal data protection, (3) applicable laws and regulations, and (4) their implementation, (5) supervision, and (6)

enforcement. Rumbold and Pierscionek [53] compared seven European countries to identify regulatory barriers for restrictions on using health data for research and included both formal legislation and informal social/cultural norms and routines as aspects of informal legitimacy.

We will study the following three aspects of legitimacy: legal (legislation and regulations), societal (social and cultural norms), and moral legitimacy (ethical dimensions and informal norms). Besides conducting document analysis and semistructured expert interviews, we will perform desktop research to analyze policy documents, news articles, scientific papers, presentations, and gray literature for each of the eight countries. We will search for policy strategies on big data or related terms (artificial intelligence and digital health), news articles on big data application in health care, and presentations on the topic given by domain experts. The documents will be qualitatively coded (open, thematic, and axial coding) and analyzed in order to increase our understanding of various country-specific elements, such as the organization of the national health system, concrete examples of media discussions or debates about big data, and specific legislation. We will also conduct 20 semistructured interviews in person or over Skype (Microsoft Corp) per country (n=160) with (1) health care professionals and management; (2) ethical/legal experts; (3) technology/IT developers and data scientists; (4) patient representatives and prominent actors in public/societal debate; and (5) policy makers and other experts. To identify relevant experts in each country, we will build on the knowledge and relationships of the consortium partners, who have an expert network in their country. Other respondents will be identified via document analysis and the snowballing method. At the start of each interview, we will obtain documented consent to record the interview. The topic list will be informed by document analysis and core theoretical concepts from the report by Custers et al [52]. The transcripts of the interviews will be qualitatively coded (open, thematic, and axial coding) and analyzed to develop a detailed understanding of the three dimensions of legitimacy for health-related big data in each country [54].

We will share the results of our aggregated analysis with pilot partners using infographics to visualize the core dimensions of legitimacy for each country, producing insights into the national facilitators and barriers for the uptake of big data applications. Building on our approach to combine research and intervention, the infographics can also be used by pilot partners to support their implementation activities.

We will study *value creation* through cocreation workshops with pilot team members. At these workshops, the researchers will guide team members in developing a business model canvas to gain an understanding of how their big data applications can be made financially sustainable beyond the pilot stage [55]. The business model canvas enables identification of key activities, key resources, required partners, investment and operational costs, (economic) outcomes, and main beneficiaries, as well as the added value of big data for each pilot [56]. The business model canvas will be discussed and refined at periodic meetings. We will collect observational data about the process of business model development, as well as the various versions of the business models as design artifacts. We will analyze the designed business model canvases across the pilots to understand how big data applications impact value creation for various stakeholders across countries and diseases. We will compare business model canvases across the pilots to identify a limited number of business model types for sustainable value creation based on big data applications in health care. The aim is to understand the business prospects of big data in the various national health care systems and under which conditions the business model could be sustainable and add value for patients, providers, payers, and the society.

Results

The study was funded in August 2017. Data collection started in April 2018 and will continue until September 2021. This combined research approach is likely to lead to the following expected results. First, a set of pilot-specific KPIs and corresponding dashboards to monitor progress. Second, three causal loop diagrams that visualize the underlying patterns and mechanisms that hinder or facilitate embedding of big data applications into broader organizational routines. Third, infographics to visualize the core dimensions of legitimacy for each country, producing insights into the national facilitators and barriers for the uptake of big data applications. Fourth, business model canvases per project to provide insights of value creation.

All our anonymized data will be stored in a secure online environment (BlackBerry Workspace) available to researchers and pilot team leaders only. The study has been approved by the ethics board of Erasmus Medical Center (MEC-2018-056) and the ethics review board of Erasmus University (EA18-01). The review board of Erasmus University checked if we are GDPR compliant. Written informed consent for all participants (including respondents of the interviews, and focus group and workshop participants) will be obtained, and member checks for all interviews will be applied.

Discussion

Need for an Integrated Sociotechnical Approach

To evaluate whether big data applications can be embedded in health care systems and provide value for patients, providers, payers, and the society, we need an integrated sociotechnical approach that considers not only concrete experiments but also organizational routines, as well as systemic and societal dimensions. Only then will we be able to develop crucial insights into the interdependencies among big data projects, organizations, and systems required to support providers and payers in their investment decisions and policymakers in shaping their policy goals, ethical questions, and regulations for big data.

Limitations

Our study is focused on the context of the uptake of big data, concentrating on embedding big data applications and technologies in organizations and societies. However, one could question if health care is already in the embedding phase or still in the phase of understanding how and when to use big data applications, especially by small pilots [57].

Dissemination of Findings

Our work will be disseminated at conferences and workshops, and published in professional (trade) journals, on electronic media, and in a series of research articles in peer-reviewed journals. We will arrange a series of workshops, inviting stakeholders from the various pilot projects and experts to discuss the contents and the implications of our findings. Dissemination will focus on developing graphic visualizations, as these help to reduce complexity and capture the relations between the dimensions. We will use dashboards to visualize performance over time as measured by jointly developed KPIs.

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Authors' Contributions

AW and AdB conceptualized the study on which this protocol is based. RW wrote the first draft of the manuscript. RW, VS, SS, HvE, EvR, AdB, and AW participated in revising and approving the final manuscript.

Conflicts of Interest

None declared.

References

1. Raghupathi W, Raghupathi V. Big data analytics in healthcare: promise and potential. Health Inf Sci Syst 2014 Feb 7;2(1):3 [FREE Full text] [doi: 10.1186/2047-2501-2-3] [Medline: 25825667]
2. Bates DW, Saria S, Ohno-Machado L, Shah A, Escobar G. Big data in health care: using analytics to identify and manage high-risk and high-cost patients. Health Aff (Millwood) 2014 Jul;33(7):1123-1131. [doi: 10.1377/hlthaff.2014.0041] [Medline: 25006137]
3. Wang Y, Kung L, Byrd TA. Big data analytics: Understanding its capabilities and potential benefits for healthcare organizations. Technological Forecasting and Social Change 2018 Jan;126:3-13. [doi: 10.1016/j.techfore.2015.12.019]
4. Kruse CS, Goswamy R, Raval Y, Marawi S. Challenges and Opportunities of Big Data in Health Care: A Systematic Review. JMIR Med Inform 2016 Nov 21;4(4):e38 [FREE Full text] [doi: 10.2196/medinform.5359] [Medline: 27872036]
5. Chen H, Chiang R, Storey V. Business Intelligence and Analytics: From Big Data to Big Impact. MIS Quarterly 2012;36(4):1165. [doi: 10.2307/41703503]
6. Kwon O, Lee N, Shin B. Data quality management, data usage experience and acquisition intention of big data analytics. International Journal of Information Management 2014 Jun;34(3):387-394. [doi: 10.1016/j.ijinfomgt.2014.02.002]
7. MacRae J, Darlow B, McBain L, Jones O, Stubbe M, Turner N, et al. Accessing primary care Big Data: the development of a software algorithm to explore the rich content of consultation records. BMJ Open 2015 Aug 21;5(8):e008160. [doi: 10.1136/bmjopen-2015-008160] [Medline: 26297364]
8. Grover V, Chiang RH, Liang T, Zhang D. Creating Strategic Business Value from Big Data Analytics: A Research Framework. Journal of Management Information Systems 2018 May 15;35(2):388-423. [doi: 10.1080/07421222.2018.1451951]
9. Reimer A, Madigan E. Veracity in big data: How good is good enough. Health Informatics J 2019 Dec;25(4):1290-1298. [doi: 10.1177/1460458217744369] [Medline: 29388495]
10. Kankanhalli A, Hahn J, Tan S, Gao G. Big data and analytics in healthcare: Introduction to the special section. Inf Syst Front 2016 Mar 9;18(2):233-235. [doi: 10.1007/s10796-016-9641-2]
11. Auffray C, Balling R, Barroso I, Bencze L, Benson M, Bergeron J, et al. Making sense of big data in health research: Towards an EU action plan. Genome Med 2016 Jun 23;8(1):71 [FREE Full text] [doi: 10.1186/s13073-016-0323-y] [Medline: 27338147]
12. Günther WA, Rezazade Mehrizi MH, Huysman M, Feldberg F. Debating big data: A literature review on realizing value from big data. The Journal of Strategic Information Systems 2017 Sep;26(3):191-209. [doi: 10.1016/j.jsis.2017.07.003]
13. boyd D, Crawford K. Critical Questions for Big Data. 2012 Jun;15(5):662-679. [doi: 10.1080/1369118x.2012.678878]
14. May CR, Mair F, Finch T, MacFarlane A, Dowrick C, Treweek S, et al. Development of a theory of implementation and integration: Normalization Process Theory. Implement Sci 2009 May 21;4(1):29 [FREE Full text] [doi: 10.1186/1748-5908-4-29] [Medline: 19460163]
15. Mittelstadt BD, Floridi L. The Ethics of Big Data: Current and Foreseeable Issues in Biomedical Contexts. Sci Eng Ethics 2016 Apr 23;22(2):303-341. [doi: 10.1007/s11948-015-9652-2] [Medline: 26002496]
16. Yao Q, Tian Y, Li P, Tian L, Qian Y, Li J. Design and development of a medical big data processing system based on Hadoop. J Med Syst 2015 Mar 10;39(3):23. [doi: 10.1007/s10916-015-0220-8] [Medline: 25666927]

17. Zolfaghar K, Meadem N, Teredesai A, Basu Roy S, Chin S, Muckian B. Big data solutions for predicting risk-of-readmission for congestive heart failure patients. 2013 Oct Presented at: IEEE International Conference On Big Data; 2013; Silicon Valley, CA, USA p. 64-71. [doi: 10.1109/BigData.2013.6691760]
18. Ali A, Qadir J, Rasool RU, Sathiaseelan A, Zwitter A, Crowcroft J. Big data for development: applications and techniques. Big Data Anal 2016 Jul 1;1(1). [doi: 10.1186/s41044-016-0002-4]
19. Weil AR. Big data in health: a new era for research and patient care. Health Aff (Millwood) 2014 Jul;33(7):1110-1110. [doi: 10.1377/hlthaff.2014.0689] [Medline: 25006134]
20. Wang Y, Hajli N. Exploring the path to big data analytics success in healthcare. Journal of Business Research 2017 Jan;70:287-299. [doi: 10.1016/j.jbusres.2016.08.002]
21. Akter S, Wamba SF, Gunasekaran A, Dubey R, Childe SJ. How to improve firm performance using big data analytics capability and business strategy alignment? International Journal of Production Economics 2016 Dec;182:113-131. [doi: 10.1016/j.ijpe.2016.08.018]
22. Ji-fan Ren S, Fosso Wamba S, Akter S, Dubey R, Childe SJ. Modelling quality dynamics, business value and firm performance in a big data analytics environment. International Journal of Production Research 2016 Mar 04;55(17):5011-5026. [doi: 10.1080/00207543.2016.1154209]
23. Crawford K, Gray M, Miltner K. Critiquing Big Data: Politics, Ethics, Epistemology. International Journal of Communications - Special Section Introduction 2014;8:1663-1672.
24. Mendelson D, Mendelson D. Legal protections for personal health information in the age of Big Data – a proposal for regulatory framework. Ethics, Medicine and Public Health 2017 Jan;3(1):37-55. [doi: 10.1016/j.jemep.2017.02.005]
25. Mostert M, Bredenoord AL, Biesaart MC, van Delden JJ. Big Data in medical research and EU data protection law: challenges to the consent or anonymise approach. Eur J Hum Genet 2016 Jul 11;24(7):956-960 [FREE Full text] [doi: 10.1038/ejhg.2015.239] [Medline: 26554881]
26. Abbasi A, Sarker S, Chiang R. Big Data Research in Information Systems: Toward an Inclusive Research Agenda. JAIS 2016 Feb;17(2):I-XXXII. [doi: 10.17705/1jais.00423]
27. Wang Y, Kung L, Wang WY, Cegielski CG. An integrated big data analytics-enabled transformation model: Application to health care. 2018 Jan;55(1):64-79. [doi: 10.1016/j.im.2017.04.001]
28. Cohen IG, Amarasingham R, Shah A, Xie B, Lo B. The legal and ethical concerns that arise from using complex predictive analytics in health care. Health Aff (Millwood) 2014 Jul;33(7):1139-1147. [doi: 10.1377/hlthaff.2014.0048] [Medline: 25006139]
29. Heitmueller A, Henderson S, Warburton W, Elmagarmid A, Pentland A, Darzi A. Developing public policy to advance the use of big data in health care. Health Aff (Millwood) 2014 Sep;33(9):1523-1530. [doi: 10.1377/hlthaff.2014.0771] [Medline: 25201656]
30. Bigmedilytics. URL: https://www.bigmedilytics.eu/ [accessed 2020-09-30]
31. Nicolini D. Zooming In and Out: Studying Practices by Switching Theoretical Lenses and Trailing Connections. Organization Studies 2010 Jan 14;30(12):1391-1418. [doi: 10.1177/0170840609349875]
32. Coughlan P, Coghlan D. Action research for operations management. 2002 Feb;22(2):220-240. [doi: 10.1108/01443570210417515]
33. Bradbury H, editor. The SAGE Handbook of Action Research. Los Angeles: SAGE Publications Ltd; 2015.
34. Zuiderent-Jerak T. Situated Intervention: Sociological Experiments in Health Care. Cambridge: MIT; 2015.
35. Antonacopoulou EP. Impact and Scholarship: Unlearning and Practising to Co-create Actionable Knowledge. Management Learning 2009 Aug 27;40(4):421-430. [doi: 10.1177/1350507609336708]
36. Markus M, Topi H. Big Data, Big Decisions for Science, Society, and Business: Report on a Research Agenda Setting Workshop. ACM Digital Library. 2015. URL: http://dl.acm.org/citation.cfm?id=2849516 [accessed 2019-10-18]
37. Djellal F, Gallouj F. The productivity challenge in services: measurement and strategic perspectives. The Service Industries Journal 2013 Feb;33(3-4):282-299. [doi: 10.1080/02642069.2013.747519]
38. Van Elten H, Van der Kolk B, Sülz S. Do Different Uses of Performance Measurement Systems Yield Different Outcomes? Evidence from Dutch Hospitals. Health Care Management Review 2019 (forthcoming). [doi: 10.1097/hmr.0000000000000261]
39. Bos A, Boselie P, Trappenburg M. Financial performance, employee well-being, and client well-being in for-profit and not-for-profit nursing homes. Health Care Management Review 2017;42(4):352-368. [doi: 10.1097/hmr.0000000000000121]
40. Kaplan R, Norton D. The balanced scorecard: Measures that drive performance. Harvard Business Review 1992;70:71-80.
41. Murray E, Treweek S, Pope C, MacFarlane A, Ballini L, Dowrick C, et al. Normalisation process theory: a framework for developing, evaluating and implementing complex interventions. BMC Med 2010 Oct 20;8(1):63 [FREE Full text] [doi: 10.1186/1741-7015-8-63] [Medline: 20961442]
42. Suchman MC. Managing Legitimacy: Strategic and Institutional Approaches. AMR 1995 Jul;20(3):571-610. [doi: 10.5465/amr.1995.9508080331]
43. van Limburg M, van Gemert-Pijnen JE, Nijland N, Ossebaard HC, Hendrix RM, Seydel ER. Why business modeling is crucial in the development of eHealth technologies. J Med Internet Res 2011 Dec 28;13(4):e124 [FREE Full text] [doi: 10.2196/jmir.1674] [Medline: 22204896]

44. Prada G. Value-based procurement: Canada's healthcare imperative. Healthc Manage Forum 2016 Jul 08;29(4):162-164. [doi: 10.1177/0840470416646119] [Medline: 27278137]
45. Osterwalder A, Pigneur Y. Business Model Generation: A Handbook for Visionaries, Game Changers, and Challengers. Hoboken, New Jersey: John Wiley & Sons, Inc; 2010.
46. Fernando SM, Neilipovitz D, Sarti AJ, Rosenberg E, Ishaq R, Thornton M, et al. Monitoring intensive care unit performance-impact of a novel individualised performance scorecard in critical care medicine: a mixed-methods study protocol. BMJ Open 2018 Jan 21;8(1):e019165. [doi: 10.1136/bmjopen-2017-019165] [Medline: 29358441]
47. Chong CA, Nguyen GC, Wilcox ME. Trends in Canadian hospital standardised mortality ratios and palliative care coding 2004-2010: a retrospective database analysis. BMJ Open 2012 Nov 05;2(6):e001729. [doi: 10.1136/bmjopen-2012-001729] [Medline: 23131397]
48. Vermaak H. Working Interactively with Causal Loop Diagrams: Intervention Choices and Paradoxes in Practical Applications. In: Boonstra J, de Caluwé L, editors. Intervening and Changing: Looking for Meaning in Interactions. Chichester, West Sussex, England: John Wiley & Sons Ltd; 2007:175-194.
49. Anderson V, Johnson L. Systems Thinking Basics: From Concepts to Causal Loops. Cambridge, Massachusetts: Pegasus Communications, Inc; 1997.
50. Senge P, Kleiner A, Roberts C, Ross R, Smith B. The Fifth Discipline Fieldbook: Strategies and Tools for Building a Learning Organization. New York, New York: Doubleday; 1994.
51. Blalock J. Causal Models in the Social Sciences. New York: Routledge; 2017.
52. Custers B, Dechesne F, Sears AM, Tani T, van der Hof S. A comparison of data protection legislation and policies across the EU. 2018 Apr;34(2):234-243. [doi: 10.1016/j.clsr.2017.09.001]
53. Rumbold JM, Pierscionek BK. A critique of the regulation of data science in healthcare research in the European Union. BMC Med Ethics 2017 Apr 08;18(1):27 [FREE Full text] [doi: 10.1186/s12910-017-0184-y] [Medline: 28388916]
54. Mortelmans D. Handboek kwalitatieve onderzoeksmethoden. Leuven: Acco; 2013.
55. Muhtaroğlu F, Demir S, Obalı M, Girgin C. Business model canvas perspective on big data applications. 2013 Presented at: IEEE International Conference On Big Data; 2013; Silicon Valley, CA p. 32-37. [doi: 10.1109/bigdata.2013.6691684]
56. Joyce A, Paquin RL. The triple layered business model canvas: A tool to design more sustainable business models. Journal of Cleaner Production 2016 Nov;135:1474-1486. [doi: 10.1016/j.jclepro.2016.06.067]
57. Iliashenko O, Bikkulova Z, Dubgorn A. Opportunities and challenges of artificial intelligence in healthcare. E3S Web Conf 2019 Aug 09;110:02028. [doi: 10.1051/e3sconf/201911002028]

Abbreviations

GPDR: General Data Protection Regulation
IT: information technology
KPI: key performance indicator

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Protocol

A Biological Age Model Designed for Health Promotion Interventions: Protocol for an Interdisciplinary Study for Model Development

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Abstract

Background: Actions to improve healthy aging and delay morbidity are crucial, given the global aging population. We believe that biological age estimation can help promote the health of the general population. Biological age reflects the heterogeneity in functional status and vulnerability to disease that chronological age cannot. Thus, biological age assessment is a tool that provides an intuitively meaningful outcome for the general population, and as such, facilitates our understanding of the extent to which lifestyle can increase health span.

Objective: This interdisciplinary study intends to develop a biological age model and explore its usefulness.

Methods: The model development comprised three consecutive phases: (1) conducting a cross-sectional study to gather candidate biomarkers from 100 individuals representing normal healthy aging people (the derivation cohort); (2) estimating the biological age using principal component analysis; and (3) testing the clinical use of the model in a validation cohort of overweight adults attending a lifestyle intervention course.

Results: We completed the data collection and analysis of the cross-sectional study, and the initial results of the principal component analysis are ready. Interpretation and refinement of the model is ongoing. Recruitment to the validation cohort is forthcoming. We expect the results to be published by December 2021.

Conclusions: We expect the biological age model to be a useful indicator of disease risk and metabolic risk, and further research should focus on validating the model on a larger scale.

Trial Registration: ClinicalTrials.gov NCT03680768, https://clinicaltrials.gov/ct2/show/NCT03680768 (Phase 1 study); NCT04279366 https://clinicaltrials.gov/ct2/show/NCT04279366 (Phase 3 study).

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KEYWORDS

biological age; health promotion; protocol; healthy aging; principal component analysis

Introduction

Healthy aging is of paramount importance when considering the trajectory of future aging populations [1,2]. Healthy aging refers to a healthy aging phenotype constituting a course of aging with high autonomy, no major chronic diseases, high quality of life, and an extended health span [3,4]. Following a healthy lifestyle earlier in life (eg, consuming alcohol moderately, not smoking, maintaining a healthy diet, and conducting regular physical activity) improves the chances of healthy aging [5,6]. Unfortunately, the steady increase in the prevalence of overweight and obesity in parallel with insufficient physical activity threatens healthy aging and emphasizes the need for effective health promotion of the general population [7-9].

Development of health literacy is a key element to promote a healthy lifestyle in the general population [10]. Applying various forms of health screenings, such as health risk assessment and health checks, is one way to track health status and thereby enable people to make qualified health decisions before diseases are manifested or progress. However, while knowledge is an important factor, it may not, by itself, motivate a change in lifestyle behavior. Health screenings often include measurements of well-established risk factors such as blood cholesterol, fasting blood glucose, and waist circumference. Although some people can understand the risk connected with these risk factors, they may be unaware of the extent to which their lifestyle affects their capability of maintaining youthful vigor and delaying morbidity to an older age. Such awareness might be pivotal and motivate changes in health behavior. Biological age plays a key role in this respect. We suggest that being “older” than stated on one’s birth certificate readily translates into disease and mortality risks, and is thus effective as health literacy to improve people’s lifestyles. In addition, we propose that biological age can be used as an outcome measure to quantify the overall placement of an individual on the healthy aging trajectory and their susceptibility to disease, which are useful in the context of primary and secondary health promotion interventions.

Unlike chronological age, biological age assesses the heterogeneity in functional metabolic status and vulnerability to disease. The increase in chronological age is uniform, whereas biological age can increase more rapidly for some and slower for others. This is due to nonmodifiable factors, such as genetics, and modifiable factors, such as lifestyle (smoking, diet, physical activity, etc) [11,12]. Biological age has been studied since the 1960s [13,14]. Much research has been directed toward finding the best biomarkers of aging [15,16] as well as the optimal method to estimate biological age [17,18]. Studies have shown that biological age can predict mortality better than chronological age and incidence of age-related diseases such as cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) [18,19]. These results were obtained from large cross-sectional data and were derived statistically. Moreover, these studies rarely investigated the clinical use of the model in health promotion interventions.

This study aims to develop a biological age model that can distinguish between healthy and unhealthy aging among individuals with the same chronological age and sex, and investigate its clinical applicability. We apply acknowledged mathematical methodology to estimate biological age; use a combination of commonly used biological age modelling biomarkers that are minimally invasive, represent healthy aging [20], and denote the processes that change with age [15]; and explore their usefulness.

Methods

Overview

When developing a biological age model, it is optimal to combine knowledge of integrative physiology and health technology. Thus, our approach is interdisciplinary and involves expertise in human physiology, healthy aging, prediction modeling, and human data science.

This study protocol comprises three consecutive phases: (1) conducting a cross-sectional study to gather indicators from 100 individuals representing normal healthy aging (the derivation cohort); (2) defining a novel biological age model and estimating biological age using principal component analysis; and (3) investigating the clinical use of the model in a validation cohort of overweight adults attending a lifestyle intervention course.

Phase 1: Derivation Cohort

Study Design

We recruited 100 healthy individuals equally distributed in sex and evenly spread out within the age range of 18-65 years. It is difficult to distinguish normal aging from pathological aging because physiological and functional decrements (or pathological changes) at the outset of a disease occurs as part of the normal aging process. Considering this, we excluded individuals with a history of previous or current CVD, and using medicine to reduce blood pressure, cholesterol, or glucose levels. Pregnancy is marked by physiological dynamics and is very different from the nonpregnant state (eg, the blood volume increases in the former) [21]. Thus, pregnant women or women who breastfeed were excluded from participation. In addition, people with conditions that would prevent them from enduring the cycle exercise and strength tests (eg, knee osteoarthritis) were also excluded. The study was approved by the Regional Ethics Committee, Copenhagen, Denmark (H-18031350) and was performed in accordance with the Helsinki Declaration. The study was recorded as a clinical trial (NCT03680768).

Candidate Biological Age Model Biomarkers

Eligible women and men arrived at the laboratory for a 2-hour examination after fasting overnight and abstaining from vigorous exercise in the prior 24 hours. The examination involved measuring 50 parameters to assess the health of the participants and collecting candidate biomarkers for the biological age model. Thus, the examination included measures of anthropometrics, physiological and metabolic health, and physical capacity as well as answering quality of life and daily physical activity questionnaires.

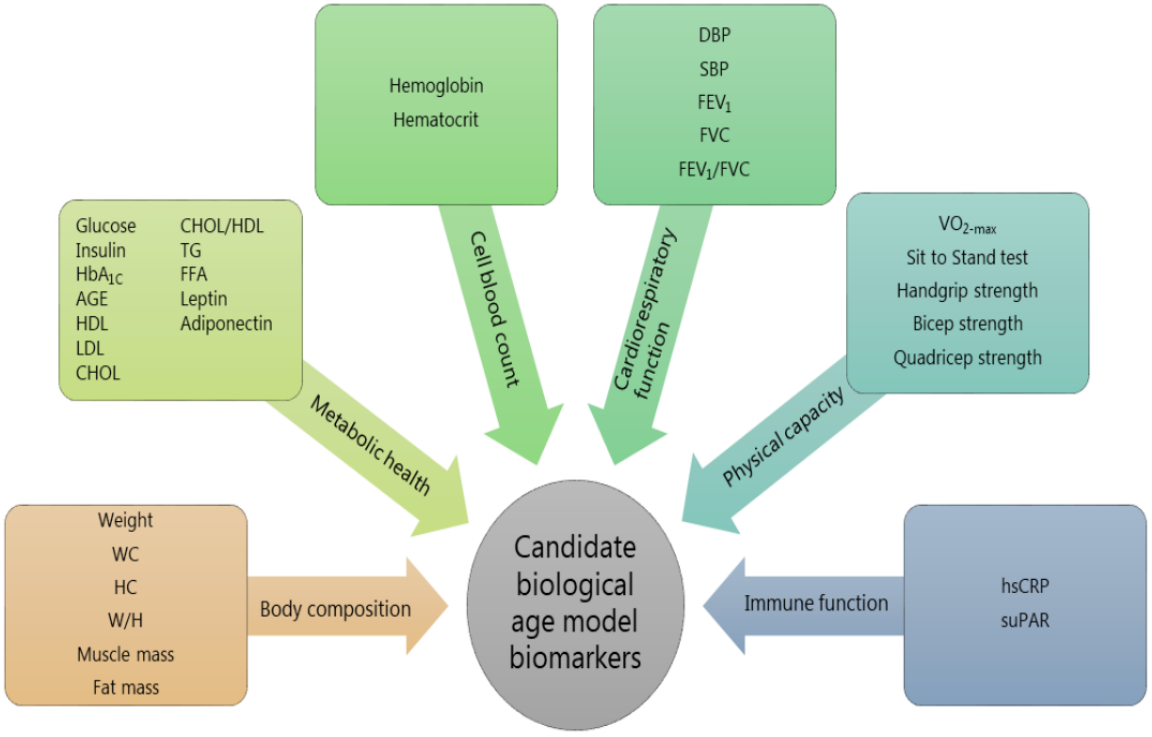
When selecting candidate biomarkers for the biological age model, we focused on variables that (1) characterize features

of the healthy aging phenotype [20], (2) are associated with aging and age-related diseases, (3) are affected by lifestyle, and (4) are possible to obtain in a variety of settings (ie, that are not limited to use in a research setting).

Due to the mathematical approach used to estimate biological age, binary/discrete variables (eg, quality of life and education level) were not considered for the biological age model although we recognize that some of these variables are important for assessing social and mental wellbeing in the healthy aging phenotype [3].

In total, 32 variables were selected as candidate biomarkers and categorized in the following 6 domains: (1) body composition, (2) metabolic health, (3) cell blood count, (4) cardiorespiratory function, (5) physical capacity, and (6) immune function (Figure 1).

Figure 1. Candidate biomarkers proposed for the BA model. Each square represents 1 of the 6 following domains: (1) Body composition, (2) metabolic health, (3) cell blood count, (4) cardiorespiratory function, (5) physical capacity, and (6) immune function. The candidate biomarkers for the BA model are listed within each domain. AGE: advanced glycation end products; CHOL: Total cholesterol; CHOL/HDL: HDL to CHOL ratio; DBP: Diastolic blood pressure; FEV_1: Forced expiratory volume within 1 second; FEV_1/FVC: FEV_1-FVC ratio; FFA: Free fatty acids; FVC: Forced vital capacity; Hb_{A1c}: Glycated hemoglobin; HC: Hip circumference; HDL: High-density lipoprotein; hsCRP: High-sensitive C-reactive protein; LDL: Low-density lipoprotein; SBP: Systolic blood pressure; TG: Triglycerides; suPAR: soluble urokinase Plasminogen Activator Receptor; VO_{2max}: Maximal oxygen uptake; WC: Waist circumference; W/H: waist to hip ratio.



Relevance of Domains

In this section, we outline the variables included as possible biomarkers for the biological age model. We describe the variables and explain their relevance in a model that assesses healthy aging.

Body Composition

Aging is associated with loss of muscle mass and strength (sarcopenia) and an increase in fat mass and central adiposity. Muscle mass has been reported to begin showing a negative association with age as early as 27 years [22], with the decline in strength exceeding that in muscle mass [23]. This characteristic is related to loss in muscle quality, gradual muscle denervation, loss of type 2 muscle fibers, reduced muscle capillary density, reduced oxidative capacity, and fat infiltration [24,25].

Excess fat mass, and especially fat distribution, are important risk factors for the development of CVD and T2DM. Waist circumference and hip to waist ratio are used as surrogate measures for central adiposity and visceral adipose tissue [26,27].

Metabolic Health

Aging and unhealthy lifestyle are associated with reduced glucose homeostasis [28]. Fasting blood glucose concentration, HbA_{1c}, and insulin sensitivity are markers of glucose homeostasis and are associated with incidence of CVD, T2DM, and mortality [20]. The prevalence of metabolic syndrome (a cluster of risk factors for T2DM and CVD) increases with age [29,30]. According to the International Diabetes Federation, the risk factors of metabolic syndrome are central obesity and any two of the following: raised triglyceride concentrations, reduced

high-density lipoprotein concentrations, raised blood pressure, and raised fasting plasma glucose concentration [31]. The increase in metabolic syndrome prevalence observed with aging is associated with the age-related redistribution of fat, particularly increased central adiposity. Low levels of adiponectin are induced by visceral fat accumulation, recognized as a risk factor for CVD and T2DM, and associated in an inverse correlation with insulin resistance [32,33]. Leptin regulates the appetite, and high levels of leptin induced by subcutaneous fat accumulation may indicate decreased leptin sensitivity in obese individuals [34]. Finally, high levels of free fatty acids associated with obesity contribute to the development of peripheral insulin resistance [35].

Advanced glycation end products (AGEs) are a result of the nonenzymatic reactions between sugars and amino groups such as proteins and lipids [36]. As some AGEs have typical fluorescence bands [37], skin autofluorescence can be used as a robust noninvasive biomarker of AGE accumulation in tissues [38]. AGEs accumulate with age in healthy individuals and have been observed to accumulate faster in people with diabetes and inflammatory diseases [39]. AGEs can predict the severity of complications in diabetes [40]. The inclusion of skin autofluorescence in the Finnish Diabetes Risk Score improved the ability to detect undiagnosed diabetes and reclassify people in the intermediate risk category [41].

Cell Blood Count

A decrease in blood hemoglobin with age and anemia in older people is associated with functional and cognitive impairment as well as mortality [42,43]. In addition, studies on biological age modelling often include hemoglobin and hematocrit as biomarkers of aging due to their correlation with age [18,44]. Therefore, we included hemoglobin and hematocrit as candidate variables for the biological age model despite the notion that anemia is not a physiological finding related to aging per se but is associated with nutrient-related iron deficiency or unexplained anemia [45].

Cardiorespiratory Function

Blood pressure is a biomarker of cardiovascular (CV) function and is one of the most important modifiable risk factors that strongly predicts CV morbidity and mortality [46]. High blood pressure is a common medical condition, and its prevalence increases with age [47]. As excess fat mass represents the major factor predisposing high blood pressure, lifestyle interventions targeting obesity (and smoking) are highly relevant [48]. Forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and the FEV_1-FVC ratio are biomarkers of dynamic lung function [49]. FEV_1 declines in a nonlinear manner with age, with the estimated decline of 25-30 mL/year starting at the age of 35-40 years and increasing up to 60 mL/year after the age of 70 years; however, the interindividual variability can be considerable [49].

Physical Capacity

A main indicator of physical activity and cardiorespiratory fitness is maximal oxygen uptake (VO_{2max}). Functional independence is dependent on VO_{2max} [50], and its association with mortality and morbidity of noncommunicable diseases is well established [5]. Aging is associated with a decline in VO_{2max} (about 6.2%/decade) [51], primarily due to a reduction in maximal cardiac output and, secondly, due to a reduced oxygen extraction capacity at the muscle level (maximal arteriovenous oxygen difference) [52,53]. Importantly, the decline in VO_{2max} is decelerated in trained compared to sedentary subjects [54]. Finally, physical inactivity accelerates secondary aging by reduction in VO_{2max}, skeletal muscle strength, and bone mineral density [55]. A Norwegian study found that sedentary time increased by 4.4 and 3.2 min/day for women and men, respectively from the age of 65 years, concomitant with a decrease in both low and moderate to vigorous physical activity [56]. Handgrip strength is a robust measure of overall strength, which correlates with mortality and declines in a linear manner with age (0.34 and 0.65 kg/year for women and men, respectively) [57,58]. Knee extension and elbow flexion are associated with functional independence and health. They are important for daily activities and have been used in previous epidemiological health investigations [59,60]. The sit to stand test is part of the “Short Physical Performance Battery” [61], which assesses lower extremity function and predicts disability in older age [59,62].

Immune Function

Adipose tissue is an endocrine organ and a major regulator of inflammation [63]. Excess adipose tissue is an important contributor to the elevated C-reactive protein (CRP) concentrations observed in obese people [64] and is related to the production of interleukin 6 (IL-6) and its stimulation of hepatic CRP production [65]. Chronically elevated levels of pro-inflammatory markers such as IL-6 and tumor necrosis factor-α are also key features of the aging phenotype defined as “inflammaging” [66]. Chronic low-grade inflammation (LGI) is thought to be part of the T2DM [67], CVD [68], cancer [69], and Alzheimer disease [70] pathophysiologies. CRP is considered a gold standard biomarker of low-grade inflammation and chronic inflammation. Recently, soluble urokinase plasminogen activator receptor (suPAR) was proposed as a biomarker of inflammation and was shown to predict T2DM, CVD, and cancer independently of CRP [71]. Plasma suPAR concentration increases with aging and unhealthy lifestyles (eg, unhealthy dieting and smoking) [71,72].

Measurements and Procedure

The examination was conducted in the order described below. Arterial blood pressure was measured in triplicate in the supine position using an automatic monitor (BoSo Medicus Control, BOSCH + SOHN GmbH). Venous blood samples were obtained for measuring concentrations of total cholesterol, high- and low-density lipoproteins, triglycerides, glucose, insulin, adiponectin, glycated hemoglobin (HbA_{1c}), hematocrit, hemoglobin, CRP, and suPAR. Body composition was assessed by dual-energy X-ray absorptiometry scanning and visceral fat measurements using the CoreScan software (Lunar Prodigy Advanced, Lunar). Body composition was also assessed by bio-impedance (MC-780MA, Tanita Corporation of America Inc), which is commonly used in clinical settings. Measures of waist and hip circumference were collected. A high-quality

portrait picture was taken for a subanalysis on perceived age. Skin autofluorescence was measured by an AGE Reader (DiagnOptics BV). Lung function was assessed in terms of FEV_1 and FVC (Vyntus SPIRO spirometer, Vyaire Medical). We tested three isometric strength measures. The first test involved measuring knee extension strength. The participant was made to sit on a table. The test was performed with one leg, with the knee in 90° flexion serving as the starting position while the thigh was stabilized against the table with a standard gait belt so that it could not be lifted during the test. A standardized belt stabilization configuration was used to position the dynamometer (microFET2, Hoggan Health Industries) against the back of the table leg using a flat attachment. This method has been validated against the "gold standard" isokinetic dynamometer [73]. The second test involved measuring handgrip strength. Keeping the arm by the side, the participant was asked to squeeze a handgrip dynamometer (Takei Digital Hand Grip Dynamometer, Takei Scientific Instruments Co, Ltd). The third test measured bicep strength. The participants were asked to keep both arms by the side and flex both elbows by 90° using a Takei TKK 5402 Digital Back Strength Dynamometer (Takei Scientific Instruments Co, Ltd, Tokyo). Participants performed a minimum of 3 test trials and continued until no increase in strength occurred. A graded exercise test (Quark PFT Ergo, Cosmed) was conducted to determine VO_{2max} with an electromagnetically braked cycle ergometer (Lode Excalibur, Groeningen). The exercise protocol consisted of 5 minutes of warm-up time at 50 and 100 W for females and males, respectively, followed by a 25 W increase in load every minute until voluntary exhaustion. Finally, the participants filled out the quality of life (SF-12v2 Health Survey) and Physical Activity Score (PAS 2.1) questionnaires [74], and their education level and smoking habits were recorded.

Phase 2: BA Estimation

Mathematical Approach

The three most common approaches to estimate biological age are (1) multiple linear regression (MLR) [14,75-78]; (2) principal component analysis (PCA) [19,44,79-82]; and (3) Klemera and Doubals' method (KDM) [83,84]. Each method has its own benefits and limitations and has been compared substantially in the literature [17,18,85]. The MLR method is considered the basic approach to estimate biological age but is criticized for over- and underestimating biological age at each end of the age spectrum and the risk of biomarker multicollinearity. The PCA method derives from MLR but uses the first principal component from the PCA to form the biological age equation. This reduces the over- and underestimation observed in the MLR method and resolves the risk of multicollinearity [79]. In comparison with the MLR and PCA approaches, the KDM is a comprehensive mathematical approach. The biological age estimation is based on minimizing the distance between *m* regression lines and *m* biomarker points within an *m*-dimensional space of all included biomarkers [83]. Although the biological age estimated by the KDM has been shown to predict mortality better than that estimated by MLR and PCA [18], the majority of the studies on biological age models using minimally invasive biomarkers (essential for the use of a biological age model in health promotion) have been conducted using PCA [86]. Therefore, we will use PCA in our model development. Doing so will also allow a wider comparison of our results against more data and the findings of prior studies that had applied this approach to their models, thus facilitating an evaluation of the external validity of our model.

PCA was originally proposed by Nakamura et al [79] to select the fewest possible physiological variables to estimate biological age. Biological age construction when applying PCA includes (1) selection of the variables using correlation analysis, redundancy assessment, and loss of informative value caused by internal consistency among the variables; (2) use of PCA to obtain the principal components; (3) application of the first principal component to develop the normalized biological age score; and (4) transformation of the normalized biological age score into biological age expressed in years so that it is comparable with the chronological age [79,86]. The mathematical and statistical analysis will be completed using SAS Enterprise Guide 7.1 and MATLAB R2018b.

Phase 3: Validation Cohort

Study Design

We intend to recruit overweight and obese subjects as obesity increases the risk of age-related diseases early in life. Thus, individuals with obesity are expected to deviate from the pathway of a healthy aging phenotype, resulting in a higher biological age compared to chronological age. Recruitment for the study will commence at a Danish folk high school conducting lifestyle interventions. We seek to recruit 80 overweight or obese adults (≥18 years) attending a 15-week lifestyle intervention course. Pregnancy, history of CVD, and using β-blockers are the exclusion criteria for participation in the study. The aim of the lifestyle intervention is an 8%-10% weight loss. Initial moderate weight loss induces improvements in most CV risk factors [87,88]. Therefore, this setting will allow us to explore the clinical relevance of the biological age model in assessing healthy aging. The intensive lifestyle intervention includes key features to achieve healthy aging and compress morbidity. Daily activities from 7 AM to 4 PM include supervised training (1-3 hour/day), class-based theoretical teaching focusing on changes to healthy behavior, and individual cognitive therapy. Participants are served healthy hypocaloric diets, individually prepared in accordance to an energy balance required for a normal BMI of 25 kg/m^2. For more information on the intensive lifestyle intervention, refer to the work of Dandanell et al [89].

Measurements and Procedure

The results from the PCA will determine the measures to be included in the protocol. The procedure will be similar to the one described in the Phase 1 study, with the exception that we will use the short version (4 generic items) of the International Physical Activity Questionnaire and a modified exercise protocol to assess VO_{2max}. To ensure that the exercise protocol elicits a valid VO_{2max}, warm up will be performed at 30 and 50 W for women and men, respectively, and thereafter increased by 20 and 25 W every minute until exhaustion for women and men, respectively. Biological age will be estimated at the beginning

and end of the course based on the results of the PCA. In addition, we will estimate the metabolic syndrome and Framingham risk score in the validation cohort [90,91]. Doing so will allow us to evaluate the response variation in biological age after an expected moderate weight loss and improved aerobic capacity, and we will compare these results with the changes observed in the existing validated health metrics used in health promotion and disease prevention (Framingham risk score and metabolic syndrome) [92,93]. Furthermore, we will (1) compare the biological age results in the healthy study population (the derivation cohort) with the overweight study population (the validation cohort) and (2) evaluate our biological age model against existing models to assess the feasibility of the former for health promotion.

Results

Phase 1

The derivation cohort consists of 51 women and 49 men. The distributions of their demographic and clinical characteristics are presented in Tables 1 and 2.

Table 1. Characteristics of study participants in the derivation cohort.

Variables	Women (n=51)	Men (n=49)
Age groups (years), n (%)		
18-23	7 (13.7)	6 (12.2)
24-29	7 (13.7)	6 (12.2)
30-35	6 (11.7)	7 (14.3)
36-41	6 (11.8)	6 (12.2)
42-47	6 (11.8)	6 (12.2)
48-53	6 (11.8)	6 (12.2)
54-59	7 (13.7)	6 (12.2)
60-65	6 (11.8)	6 (12.2)
BMI (kg/m^2), n (%)		
<25	33 (64.7)	27 (55.1)
≥25	13 (25.5)	21 (42.9)
≥30	5 (9.8)	1 (2.0)
HbA_{1c}[a] (mmol/mol), mean (SD)	32.3 (3.2)	33.4 (3.1)
Lung function - FEV_1/FVC (%), mean (SD)	79.4 (6.0)	79.1 (5.3)
Physical activity[b] (min/week), n (%)		
≥150	41 (80.4)	46 (93.9)
<150	10 (19.6)	3 (6.1)
Education[c] (years), n (%)		
<10[d]	0 (0.0)	3 (7.5)
10-12[e]	32 (69.6)	29 (72.5)
≥13[f]	14 (30.4)	8 (20)
Smoking status, n (%)		
Yes	3 (5.9)	3 (6.1)
No	48 (94.1)	46 (93.9)

[a]HbA_{1c}: Hemoglobin A_{1c}.

[b]Leisure-time spent on moderate (5 metabolic equivalents) and vigorous (6 metabolic equivalents) physical activity.

[c]Level of education was reported by 86.0% (86/100) of the total study population (46/100, 46.0% women; 40/100, 40.0% men).

[d]Lower secondary education.

[e]Upper secondary education.

[f]First- and second-stage tertiary education.

Table 2. Maximal oxygen consumption of study participants in the derivation cohort.

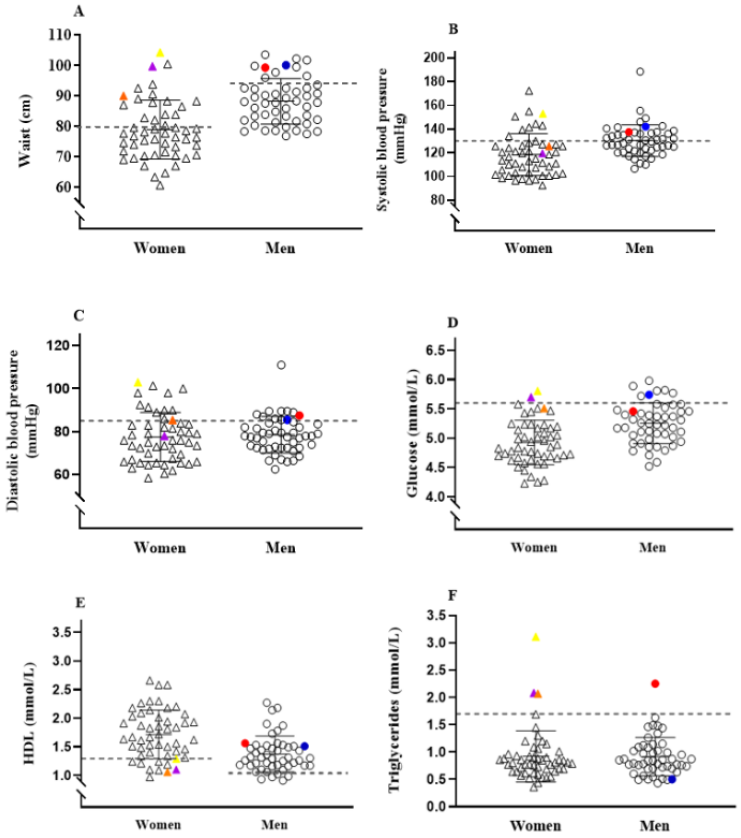
Age group (years)	VO_{2max}[a] (mL/min/kg), mean (SD)	
	Women (n=51)	Men (n=49)
18-23	36.9 (7.3)	45.2 (4.0)
24-29	37.4 (2.5)	44.8 (7.8)
30-35	37.7 (5.6)	47.9 (7.8)
36-41	36.0 (7.8)	43.2 (7.7)
42-47	39.7 (7.4)	47.1 (6.5)
48-53	29.8 (4.7)	42.7 (6.0)
54-59	30.1 (3.9)	39.7 (9.8)
60-65	31.8 (4.6)	40.1 (4.1)

[a]VO_{2max}: Maximal oxygen consumption.

The majority of the participants reported having an upper secondary education (eg, high school diploma; women: 32/46, 69.6%; men: 29/40, 72.5%). Very few within the cohort (6/100, 6% in total) smoked. Cardiorespiratory fitness (VO_{2max}) was moderate to high in women and men throughout the age range, the majority (women, 41/51, 80.4%; men, 46/49, 93.9%) adhering to the national recommendations of a minimum of 150 min/week of moderate to vigorous physical activity [94]. No indications of decreased lung function or T2DM were found.

Although free from diseases, we found variations in metabolic health when assessing the cohort in terms of metabolic syndrome. Metabolic syndrome was present in 3 women and 2 men. The distribution of risk factors related to metabolic syndrome are visualized in Figure 2. We used the definition provided by the International Diabetes Federation to assess metabolic syndrome [31].

Figure 2. Health profile in relation to metabolic syndrome variables. The triangles represent women, and the circles represent men. Three women (yellow, orange, and purple triangles) and two men (red and blue circles) fulfilled the criteria for metabolic syndrome. The solid lines represent the mean (SD) for each group. The dashed lines represent the cut-off criteria (values mentioned in the brackets that follow) for each variable in accordance with the definition provided by the International Diabetes Federation. A: Waist circumference in females (≥80 cm) and males (≥94 cm); B: Systolic blood pressure (≥130 mm Hg); C: Diastolic blood pressure (≥85 mm Hg); D: Fasting plasma glucose (≥5.6 mmol/L); E: High-density lipoprotein (HDL) for females (1.29 mmol/L) and males (1.03 mmol/L); F: Triglycerides (≥1.7 mmol/L).



Phase 2

Correlation analysis and principal component analysis have been performed. Interpretation of the model, including sensitivity analysis, internal consistency reliability, and model refinement, will follow.

Phase 3

This study has been approved by the Local Research Ethics Committee, Copenhagen, Denmark (H-19073643; Clinical Trial Number NCT04279366). We have established collaboration with the staff at the folk high school and recruitment for participation is forthcoming.

Discussion

Findings

The primary objective of this pilot study was to develop a biological age model that could be applied for health promotion of the general adult population, given its ability to distinguish healthy and unhealthy aging trajectories among individuals with the same chronological age and sex. Within this objective lies the practical limitation of including as few and minimally invasive biomarkers in the model as possible despite the complexity of aging. Therefore, to develop a reliable biological age model, it is essential to select biomarkers that accurately show significant change with age, reflect the aging status independent of disease, have high reproducibility, cover essential areas of human function, and are appropriate for in vivo studies of humans [15,79,95]. A limitation of this study is that this biological age model is designed to assess a healthy aging trajectory only on a physical level; the assessment of the cognitive aspects of maintaining functional independence for a socially active life, an important part of the healthy aging phenotype, are not included herein [4]. Another limitation is that while the biomarkers included in the proposed biological age model align with the phenotypic biomarkers of aging (eg, clinical measures such as grip strength and glucose concentration), the model overlooks the molecular-based biomarkers of aging (ie, DNA-related markers). Short telomere length is associated with risk of CVD, age-related decline in physical function, and mortality [96]. Furthermore, DNA methylation, a biomarker for biological age (DNAm age, also referred to as the "epigenetic clock"), predicts all-cause mortality independent of the classic risk factors (age, body mass index, smoking, etc) as well as frailty, self-related health, and chronological age [96]. While such models seem promising, the lack of feasibility regarding use in community-based interventions is the main reason for not including these biomarkers in our biological age model. We do, however, plan to validate the biological age model against telomere length at a later time, when data from the derivation cohort become available. Our secondary objective involves investigating the usefulness of the model. Validating the model against mortality and morbidity is preferable but beyond the scope of this study. Instead, we plan to validate the clinical use of the model in Phase 3 by comparing the change in biological age against that in already validated prediction metrics commonly used in health promotion (eg, the Framingham risk score and metabolic syndrome) in relation to a lifestyle intervention. As the validation cohort is not randomly assigned from the general population, there is a risk that it might represent a selected group whose physiological state is independent of behavioral factors (eg, diet and physical activity) and biased by genetics. Regardless, the change in biological age after an intensive lifestyle intervention can provide initial evidence about the potential of the biological age model for health promoting interventions.

Conclusions

We expect to find that the biological age model is a useful indicator of the risk of metabolic dysfunction and disease. Given future challenges, our expectation calls for further optimization of the model (eg, extending the sample size of the derivation cohort) and validation (by including hard endpoints such as mortality and morbidity).

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KH and JWH designed and conceptualized the study. KH, MF, and PH collected the data. KH and ABK analyzed the data. KH, ABK, K-ÅH, JWH, and HBDS interpreted the data. KH wrote the first draft, and FD, HBDS, ABK, and JWH revised the manuscript. All authors read and approved the final manuscript. This work was supported by the Copenhagen Center for Health Technology, the Center for Healthy Aging, and University College Copenhagen. The sponsors had no involvement in the study design, writing of the manuscript, and choice of publication.

Conflicts of Interest

None declared.

References

1. Harper S. Economic and social implications of aging societies. Science 2014 Oct 31;346(6209):587-591. [doi: 10.1126/science.1254405] [Medline: 25359967]
2. Petsko GA. A seat at the table. Genome Biol 2008;9(12):113 [FREE Full text] [doi: 10.1186/gb-2008-9-12-113] [Medline: 19144208]
3. Fuchs J, Scheidt-Nave C, Hinrichs T, Mergenthaler A, Stein J, Riedel-Heller S, et al. Indicators for healthy ageing--a debate. Int J Environ Res Public Health 2013 Dec 02;10(12):6630-6644 [FREE Full text] [doi: 10.3390/ijerph10126630] [Medline: 24317381]

4. Lara J, Godfrey A, Evans E, Heaven B, Brown LJ, Barron E, et al. Towards measurement of the Healthy Ageing Phenotype in lifestyle-based intervention studies. Maturitas 2013 Oct;76(2):189-199 [FREE Full text] [doi: 10.1016/j.maturitas.2013.07.007] [Medline: 23932426]
5. Blair S, Sallis R, Hutber A, Archer E. Exercise therapy - the public health message. Scand J Med Sci Sports 2012 Aug;22(4):e24-e28. [doi: 10.1111/j.1600-0838.2012.01462.x] [Medline: 22429265]
6. Loef M, Walach H. The combined effects of healthy lifestyle behaviors on all cause mortality: a systematic review and meta-analysis. Prev Med 2012 Sep;55(3):163-170. [doi: 10.1016/j.ypmed.2012.06.017] [Medline: 22735042]
7. Kohl HW, Craig CL, Lambert EV, Inoue S, Alkandari JR, Leetongin G, Lancet Physical Activity Series Working Group. The pandemic of physical inactivity: global action for public health. Lancet 2012 Jul 21;380(9838):294-305. [doi: 10.1016/S0140-6736(12)60898-8] [Medline: 22818941]
8. Sallis JF, Bull F, Guthold R, Heath GW, Inoue S, Kelly P, Lancet Physical Activity Series 2 Executive Committee. Progress in physical activity over the Olympic quadrennium. Lancet 2016 Sep 24;388(10051):1325-1336. [doi: 10.1016/S0140-6736(16)30581-5] [Medline: 27475270]
9. GBD 2015 Obesity Collaborators T, Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, et al. Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med 2017 Jul 06;377(1):13-27 [FREE Full text] [doi: 10.1056/NEJMoa1614362] [Medline: 28604169]
10. What is Health Promotion? World Health Organization. URL: https://www.who.int/features/qa/health-promotion/en/ [accessed 2020-10-05]
11. Lowsky D, Olshansky S, Bhattacharya J, Goldman D. Heterogeneity in healthy aging. J Gerontol A Biol Sci Med Sci 2014 Jun;69(6):640-649 [FREE Full text] [doi: 10.1093/gerona/glt162] [Medline: 24249734]
12. Goffaux J, Friesinger GC, Lambert W, Shroyer LW, Moritz TE, McCarthy M, et al. Biological age--a concept whose time has come: a preliminary study. South Med J 2005 Oct;98(10):985-993. [doi: 10.1097/01.smj.0000182178.22607.47] [Medline: 16295813]
13. Comfort A. Test-battery to measure ageing-rate in man. The Lancet 1969 Dec;294(7635):1411-1415. [doi: 10.1016/s0140-6736(69)90950-7]
14. Hollingsworth JW, Hashizume A, Jablon S. Correlations between tests of aging in Hiroshima subjects--an attempt to define "physiologic age". Yale J Biol Med 1965 Aug;38(1):11-26 [FREE Full text] [Medline: 5841151]
15. Crimmins E, Vasunilashorn S, Kim JK, Alley D. Biomarkers related to aging in human populations. Adv Clin Chem 2008;46:161-216 [FREE Full text] [doi: 10.1016/s0065-2423(08)00405-8] [Medline: 19004190]
16. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell 2013 Jun 06;153(6):1194-1217 [FREE Full text] [doi: 10.1016/j.cell.2013.05.039] [Medline: 23746838]
17. Jee H, Park J. Selection of an optimal set of biomarkers and comparative analyses of biological age estimation models in Korean females. Arch Gerontol Geriatr 2017;70:84-91. [doi: 10.1016/j.archger.2017.01.005] [Medline: 28110151]
18. Levine ME. Modeling the rate of senescence: can estimated biological age predict mortality more accurately than chronological age? J Gerontol A Biol Sci Med Sci 2013 Jun;68(6):667-674 [FREE Full text] [doi: 10.1093/gerona/gls233] [Medline: 23213031]
19. Kang YG, Suh E, Lee J, Kim DW, Cho KH, Bae C. Biological age as a health index for mortality and major age-related disease incidence in Koreans: National Health Insurance Service - Health screening 11-year follow-up study. Clin Interv Aging 2018;13:429-436 [FREE Full text] [doi: 10.2147/CIA.S157014] [Medline: 29593385]
20. Lara J, Cooper R, Nissan J, Ginty AT, Khaw K, Deary IJ, et al. A proposed panel of biomarkers of healthy ageing. BMC Med 2015 Sep 15;13:222 [FREE Full text] [doi: 10.1186/s12916-015-0470-9] [Medline: 26373927]
21. Blehar MC, Spong C, Grady C, Goldkind SF, Sahin L, Clayton JA. Enrolling pregnant women: issues in clinical research. Womens Health Issues 2013 Jan;23(1):e39-e45 [FREE Full text] [doi: 10.1016/j.whi.2012.10.003] [Medline: 23312713]
22. Silva AM, Shen W, Heo M, Gallagher D, Wang Z, Sardinha LB, et al. Ethnicity-related skeletal muscle differences across the lifespan. Am J Hum Biol 2010;22(1):76-82 [FREE Full text] [doi: 10.1002/ajhb.20956] [Medline: 19533617]
23. Narici MV, Maganaris CN, Reeves ND, Capodaglio P. Effect of aging on human muscle architecture. J Appl Physiol (1985) 2003 Dec;95(6):2229-2234. [doi: 10.1152/japplphysiol.00433.2003] [Medline: 12844499]
24. Mitchell WK, Williams J, Atherton P, Larvin M, Lund J, Narici M. Sarcopenia, dynapenia, and the impact of advancing age on human skeletal muscle size and strength; a quantitative review. Front Physiol 2012;3:260 [FREE Full text] [doi: 10.3389/fphys.2012.00260] [Medline: 22934016]
25. Delmonico MJ, Beck DT. The current understanding of sarcopenia: Emerging tools and interventional possibilities. Am J Lifestyle Med 2017;11(2):167-181 [FREE Full text] [doi: 10.1177/1559827615594343] [Medline: 30202329]
26. Wei M, Gaskill S, Haffner S, Stern M. Waist circumference as the best predictor of noninsulin dependent diabetes mellitus (NIDDM) compared to body mass index, waist/hip ratio and other anthropometric measurements in Mexican Americans--a 7-year prospective study. Obes Res 1997 Jan;5(1):16-23. [doi: 10.1002/j.1550-8528.1997.tb00278.x] [Medline: 9061711]
27. Huxley R, Mendis S, Zheleznyakov E, Reddy S, Chan J. Body mass index, waist circumference and waist:hip ratio as predictors of cardiovascular risk--a review of the literature. Eur J Clin Nutr 2010 Jan;64(1):16-22 [FREE Full text] [doi: 10.1038/ejcn.2009.68] [Medline: 19654593]

28. Brewer RA, Gibbs VK, Smith DL. Targeting glucose metabolism for healthy aging. Nutr Healthy Aging 2016 Oct 27;4(1):31-46 [FREE Full text] [doi: 10.3233/NHA-160007] [Medline: 28035340]
29. Hildrum B, Mykletun A, Hole T, Midthjell K, Dahl AA. Age-specific prevalence of the metabolic syndrome defined by the International Diabetes Federation and the National Cholesterol Education Program: the Norwegian HUNT 2 study. BMC Public Health 2007 Aug 29;7:220 [FREE Full text] [doi: 10.1186/1471-2458-7-220] [Medline: 17727697]
30. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA 2002 Jan 16;287(3):356-359. [doi: 10.1001/jama.287.3.356] [Medline: 11790215]
31. Alberti KGMM, Zimmet P, Shaw J. Metabolic syndrome--a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med 2006 May;23(5):469-480. [doi: 10.1111/j.1464-5491.2006.01858.x] [Medline: 16681555]
32. Matsuzawa Y. Establishment of a concept of visceral fat syndrome and discovery of adiponectin. Proc Jpn Acad Ser B Phys Biol Sci 2010;86(2):131-141 [FREE Full text] [doi: 10.2183/pjab.86.131] [Medline: 20154470]
33. Yadav A, Kataria MA, Saini V, Yadav A. Role of leptin and adiponectin in insulin resistance. Clin Chim Acta 2013 Feb 18;417:80-84. [doi: 10.1016/j.cca.2012.12.007] [Medline: 23266767]
34. Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med 1996 Feb 01;334(5):292-295. [doi: 10.1056/NEJM199602013340503] [Medline: 8532024]
35. Guilherme A, Virbasius JV, Puri V, Czech MP. Adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes. Nat Rev Mol Cell Biol 2008 May;9(5):367-377 [FREE Full text] [doi: 10.1038/nrm2391] [Medline: 18401346]
36. Isami F, West BJ, Nakajima S, Yamagishi S. Association of advanced glycation end products, evaluated by skin autofluorescence, with lifestyle habits in a general Japanese population. J Int Med Res 2018 Mar;46(3):1043-1051. [doi: 10.1177/0300060517736914] [Medline: 29322837]
37. Ulrich P, Cerami A. Protein glycation, diabetes, and aging. Recent Prog Horm Res 2001;56:1-21. [doi: 10.1210/rp.56.1.1] [Medline: 11237208]
38. Mulder DJ, Water TVD, Lutgers HL, Graaff R, Gans RO, Zijlstra F, et al. Skin autofluorescence, a novel marker for glycemic and oxidative stress-derived advanced glycation endproducts: an overview of current clinical studies, evidence, and limitations. Diabetes Technol Ther 2006 Oct;8(5):523-535. [doi: 10.1089/dia.2006.8.523] [Medline: 17037967]
39. Nowotny K, Jung T, Höhn A, Weber D, Grune T. Advanced glycation end products and oxidative stress in type 2 diabetes mellitus. Biomolecules 2015 Mar 16;5(1):194-222 [FREE Full text] [doi: 10.3390/biom5010194] [Medline: 25786107]
40. Monnier V, Sell D, Genuth S. Glycation products as markers and predictors of the progression of diabetic complications. Ann N Y Acad Sci 2005 Jun;1043:567-581. [doi: 10.1196/annals.1333.065] [Medline: 16037280]
41. Fokkens B, van Waateringe R, Mulder D, Wolffenbuttel B, Smit A. Skin autofluorescence improves the Finnish Diabetes Risk Score in the detection of diabetes in a large population-based cohort: The LifeLines Cohort Study. Diabetes Metab 2018 Nov;44(5):424-430 [FREE Full text] [doi: 10.1016/j.diabet.2017.09.002] [Medline: 29097003]
42. Zakai NA, Katz R, Hirsch C, Shlipak MG, Chaves PHM, Newman AB, et al. A prospective study of anemia status, hemoglobin concentration, and mortality in an elderly cohort: the Cardiovascular Health Study. Arch Intern Med 2005 Oct 24;165(19):2214-2220. [doi: 10.1001/archinte.165.19.2214] [Medline: 16246985]
43. Mahlknecht U, Kaiser S. Age-related changes in peripheral blood counts in humans. Exp Ther Med 2010 Nov;1(6):1019-1025 [FREE Full text] [doi: 10.3892/etm.2010.150] [Medline: 22993635]
44. Nakamura E, Miyao K. A method for identifying biomarkers of aging and constructing an index of biological age in humans. J Gerontol A Biol Sci Med Sci 2007 Oct;62(10):1096-1105. [doi: 10.1093/gerona/62.10.1096] [Medline: 17921421]
45. Röhrig G, Gütgemann I, Kolb G, Leischker A. Anemia in the aged is not ageing related: position paper on anemia in the aged by the “working group anemia” of the German Geriatric Society (DGG). Eur Geriatr Med 2018 Apr 9;9(3):395-397. [doi: 10.1007/s41999-018-0048-0]
46. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002 Dec 14;360(9349):1903-1913. [doi: 10.1016/s0140-6736(02)11911-8] [Medline: 12493255]
47. Egan BM, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of hypertension, 1988-2008. JAMA 2010 May 26;303(20):2043-2050. [doi: 10.1001/jama.2010.650] [Medline: 20501926]
48. Beilin LJ, Puddey IB, Burke V. Lifestyle and hypertension. Am J Hypertens 1999 Sep;12(9 Pt 1):934-945. [doi: 10.1016/s0895-7061(99)00057-6] [Medline: 10509554]
49. Sharma G, Goodwin J. Effect of aging on respiratory system physiology and immunology. Clin Interv Aging 2006;1(3):253-260 [FREE Full text] [doi: 10.2147/ciia.2006.1.3.253] [Medline: 18046878]
50. Shephard RJ. Maximal oxygen intake and independence in old age. Br J Sports Med 2009 May;43(5):342-346. [doi: 10.1136/bjsm.2007.044800] [Medline: 18403414]
51. Aspenes ST, Nilsen TIL, Skaug EA, Bertheussen GF, Ellingsen Ø, Vatten L, et al. Peak oxygen uptake and cardiovascular risk factors in 4631 healthy women and men. Med Sci Sports Exerc 2011 Aug;43(8):1465-1473. [doi: 10.1249/MSS.0b013e31820ca81c] [Medline: 21228724]

52. Stratton JR, Levy WC, Cerqueira MD, Schwartz RS, Abrass IB. Cardiovascular responses to exercise. Effects of aging and exercise training in healthy men. Circulation 1994 Apr;89(4):1648-1655. [doi: 10.1161/01.cir.89.4.1648] [Medline: 8149532]
53. Hossack KF, Bruce RA. Maximal cardiac function in sedentary normal men and women: comparison of age-related changes. J Appl Physiol Respir Environ Exerc Physiol 1982 Oct;53(4):799-804. [doi: 10.1152/jappl.1982.53.4.799] [Medline: 7153117]
54. Ogawa T, Spina RJ, Martin WH, Kohrt WM, Schechtman KB, Holloszy JO, et al. Effects of aging, sex, and physical training on cardiovascular responses to exercise. Circulation 1992 Aug;86(2):494-503. [doi: 10.1161/01.cir.86.2.494] [Medline: 1638717]
55. Booth FW, Laye MJ, Roberts MD. Lifetime sedentary living accelerates some aspects of secondary aging. J Appl Physiol (1985) 2011 Nov;111(5):1497-1504. [doi: 10.1152/japplphysiol.00420.2011] [Medline: 21836048]
56. Hansen BH, Kolle E, Dyrstad SM, Holme I, Anderssen SA. Accelerometer-determined physical activity in adults and older people. Med Sci Sports Exerc 2012 Feb;44(2):266-272. [doi: 10.1249/MSS.0b013e31822cb354] [Medline: 21796052]
57. Frederiksen H, Hjelmborg J, Mortensen J, McGue M, Vaupel JW, Christensen K. Age trajectories of grip strength: cross-sectional and longitudinal data among 8,342 Danes aged 46 to 102. Ann Epidemiol 2006 Jul;16(7):554-562. [doi: 10.1016/j.annepidem.2005.10.006] [Medline: 16406245]
58. Sillanpää E, Laakkonen EK, Vaara E, Rantanen T, Kovanen V, Sipilä S, et al. Biological clocks and physical functioning in monozygotic female twins. BMC Geriatr 2018 Apr 04;18(1):83 [FREE Full text] [doi: 10.1186/s12877-018-0775-6] [Medline: 29614968]
59. Eriksen L, Grønbæk M, Helge JW, Tolstrup JS, Curtis T. The Danish Health Examination Survey 2007-2008 (DANHES 2007-2008). Scand J Public Health 2011 Mar;39(2):203-211. [doi: 10.1177/1403494810393557] [Medline: 21257645]
60. Arnold CM, Warkentin KD, Chilibeck PD, Magnus CRA. The reliability and validity of handheld dynamometry for the measurement of lower-extremity muscle strength in older adults. J Strength Cond Res 2010 Mar;24(3):815-824. [doi: 10.1519/JSC.0b013e3181aa36b8] [Medline: 19661831]
61. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994 Mar;49(2):M85-M94. [doi: 10.1093/geronj/49.2.m85] [Medline: 8126356]
62. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. N Engl J Med 1995 Mar 02;332(9):556-561. [doi: 10.1056/NEJM199503023320902] [Medline: 7838189]
63. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. J Clin Endocrinol Metab 2004 Jun;89(6):2548-2556. [doi: 10.1210/jc.2004-0395] [Medline: 15181022]
64. Aronson D, Bartha P, Zinder O, Kerner A, Markiewicz W, Avizohar O, et al. Obesity is the major determinant of elevated C-reactive protein in subjects with the metabolic syndrome. Int J Obes Relat Metab Disord 2004 May;28(5):674-679. [doi: 10.1038/sj.ijo.0802609] [Medline: 14993913]
65. Heinrich P, Castell J, Andus T. Interleukin-6 and the acute phase response. Biochem J 1990 Feb 01;265(3):621-636. [doi: 10.1042/bj2650621] [Medline: 1689567]
66. Starr ME, Evers BM, Saito H. Age-associated increase in cytokine production during systemic inflammation: adipose tissue as a major source of IL-6. J Gerontol A Biol Sci Med Sci 2009 Jul;64(7):723-730 [FREE Full text] [doi: 10.1093/gerona/glp046] [Medline: 19377014]
67. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Invest 2006 Jul;116(7):1793-1801 [FREE Full text] [doi: 10.1172/JCI29069] [Medline: 16823477]
68. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005 Apr 21;352(16):1685-1695. [doi: 10.1056/NEJMra043430] [Medline: 15843671]
69. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet 2001 Feb 17;357(9255):539-545. [doi: 10.1016/S0140-6736(00)04046-0] [Medline: 11229684]
70. Heneka MT, O'Banion MK. Inflammatory processes in Alzheimer's disease. J Neuroimmunol 2007 Mar;184(1-2):69-91. [doi: 10.1016/j.jneuroim.2006.11.017] [Medline: 17222916]
71. Eugen-Olsen J, Andersen O, Linneberg A, Ladelund S, Hansen T, Langkilde A, et al. Circulating soluble urokinase plasminogen activator receptor predicts cancer, cardiovascular disease, diabetes and mortality in the general population. J Intern Med 2010 Sep;268(3):296-308. [doi: 10.1111/j.1365-2796.2010.02252.x] [Medline: 20561148]
72. Haupt TH, Kallemose T, Ladelund S, Rasmussen LJH, Thorball CW, Andersen O, et al. Risk Factors Associated with Serum Levels of the Inflammatory Biomarker Soluble Urokinase Plasminogen Activator Receptor in a General Population. Biomark Insights 2014 Dec 16;9:BMI.S19876. [doi: 10.4137/bmi.s19876]
73. Hansen E, McCartney C, Sweeney R, Palimenio M, Grindstaff T. Hand-held dynamometer positioning impacts discomfort during quadriceps strength testing: A validity and reliability study. Int J Sports Phys Ther 2015 Feb;10(1):62-68 [FREE Full text] [Medline: 25709864]
74. Aadahl M, Jørgensen T. Validation of a new self-report instrument for measuring physical activity. Med Sci Sports Exerc 2003 Jul;35(7):1196-1202. [doi: 10.1249/01.MSS.0000074446.02192.14] [Medline: 12840642]

75. Dubina T, Mints AYa, Zhuk E. Biological age and its estimation. III. Introduction of a correction to the multiple regression model of biological age in cross-sectional and longitudinal studies. Exp Gerontol 1984;19(2):133-143. [doi: 10.1016/0531-5565(84)90016-0] [Medline: 6610563]
76. Dubina T, Dyundikova V, Zhuk E. Biological age and its estimation. II. Assessment of biological age of albino rats by multiple regression analysis. Exp Gerontol 1983;18(1):5-18. [doi: 10.1016/0531-5565(83)90046-3] [Medline: 6873212]
77. Bae C, Kang YG, Kim S, Cho C, Kang HC, Yu BY, et al. Development of models for predicting biological age (BA) with physical, biochemical, and hormonal parameters. Arch Gerontol Geriatr 2008;47(2):253-265. [doi: 10.1016/j.archger.2007.08.009] [Medline: 17889950]
78. Bae C, Kang YG, Piao M, Cho B, Cho KH, Park YK, et al. Models for estimating the biological age of five organs using clinical biomarkers that are commonly measured in clinical practice settings. Maturitas 2013 Jul;75(3):253-260. [doi: 10.1016/j.maturitas.2013.04.008] [Medline: 23642770]
79. Nakamura E, Miyao K, Ozeki T. Assessment of biological age by principal component analysis. Mech Ageing Dev 1988 Dec;46(1-3):1-18. [doi: 10.1016/0047-6374(88)90109-1] [Medline: 3226152]
80. Zhang W, Bai X, Sun X, Cai G, Bai X, Zhu S, et al. Construction of an integral formula of biological age for a healthy Chinese population using principle component analysis. J Nutr Health Aging 2014;18(2):137-142. [doi: 10.1007/s12603-013-0345-8] [Medline: 24522464]
81. Zhang W, Jia L, Cai G, Shao F, Lin H, Liu Z, et al. Model construction for biological age based on a cross-sectional study of a healthy Chinese Han population. J Nutr Health Aging 2017;21(10):1233-1239. [doi: 10.1007/s12603-017-0874-7] [Medline: 29188884]
82. Park J, Cho B, Kwon H, Lee C. Developing a biological age assessment equation using principal component analysis and clinical biomarkers of aging in Korean men. Arch Gerontol Geriatr 2009;49(1):7-12. [doi: 10.1016/j.archger.2008.04.003] [Medline: 18597867]
83. Klemera P, Doubal S. A new approach to the concept and computation of biological age. Mech Ageing Dev 2006 Mar;127(3):240-248. [doi: 10.1016/j.mad.2005.10.004] [Medline: 16318865]
84. Mitnitski A, Howlett SE, Rockwood K. Heterogeneity of human aging and its assessment. J Gerontol A Biol Sci Med Sci 2017 Jul 01;72(7):877-884 [FREE Full text] [doi: 10.1093/gerona/glw089] [Medline: 27216811]
85. Cho IH, Park KS, Lim CJ. An empirical comparative study on biological age estimation algorithms with an application of Work Ability Index (WAI). Mech Ageing Dev 2010 Feb;131(2):69-78. [doi: 10.1016/j.mad.2009.12.001] [Medline: 20005245]
86. Jia L, Zhang W, Chen X. Common methods of biological age estimation. Clin Interv Aging 2017;12:759-772 [FREE Full text] [doi: 10.2147/CIA.S134921] [Medline: 28546743]
87. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002 Feb 07;346(6):393-403 [FREE Full text] [doi: 10.1056/NEJMoa012512] [Medline: 11832527]
88. Pasanisi F, Contaldo F, de Simone G, Mancini M. Benefits of sustained moderate weight loss in obesity. Nutr Metab Cardiovasc Dis 2001 Dec;11(6):401-406. [Medline: 12055705]
89. Dandanell S, Skovborg C, Præst CB, Kristensen K, Nielsen M, Lionett S, et al. Maintaining a clinical weight loss after intensive lifestyle intervention is the key to cardiometabolic health. Obes Res Clin Pract 2017;11(4):489-498. [doi: 10.1016/j.orcp.2016.09.009] [Medline: 27720417]
90. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. Stroke 1991 Mar;22(3):312-318. [doi: 10.1161/01.str.22.3.312] [Medline: 2003301]
91. Reaven GM. Role of insulin resistance in human disease (syndrome X): an expanded definition. Annu Rev Med 1993;44:121-131. [doi: 10.1146/annurev.me.44.020193.001005] [Medline: 8476236]
92. Sundström J, Risérus U, Byberg L, Zethelius B, Lithell H, Lind L. Clinical value of the metabolic syndrome for long term prediction of total and cardiovascular mortality: prospective, population based cohort study. BMJ 2006 Apr 15;332(7546):878-882 [FREE Full text] [doi: 10.1136/bmj.38766.624097.1F] [Medline: 16510492]
93. Jahangiry L, Farhangi MA, Rezaei F. Framingham risk score for estimation of 10-years of cardiovascular diseases risk in patients with metabolic syndrome. J Health Popul Nutr 2017 Nov 13;36(1):36 [FREE Full text] [doi: 10.1186/s41043-017-0114-0] [Medline: 29132438]
94. World Health Organization. Physical Activity and Adults Fact Sheet. Global Strategy on Diet, Physical Activity and Health. URL: https://www.who.int/dietphysicalactivity/factsheet_adults/en/ [accessed 2020-10-05]
95. Baker GT, Sprott RL. Biomarkers of aging. Exp Gerontol 1988;23(4-5):223-239. [doi: 10.1016/0531-5565(88)90025-3] [Medline: 3058488]
96. Jylhävä J, Pedersen NL, Hägg S. Biological age predictors. EBioMedicine 2017 Jul;21:29-36 [FREE Full text] [doi: 10.1016/j.ebiom.2017.03.046] [Medline: 28396265]

Abbreviations

AGEs: advanced glycation end products

CV: cardiovascular
CVD: cardiovascular disease
CRP: C-reactive protein
FEV_1: forced expiratory volume in 1 second
FVC: forced vital capacity
Hb_{A1c}: glycated hemoglobin
IL-6: interleukin 6
KDM: Klemera and Doubals' method
MLR: multiple linear regression
PAS: physical activity score
PCA: principal component analysis
suPAR: soluble urokinase Plasminogen Activator Receptor
T2DM: type 2 diabetes mellitus
VO_{2max}: maximal oxygen uptake

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Protocol

Harmonized One Health Trans-Species and Community Surveillance for Tackling Antibacterial Resistance in India: Protocol for a Mixed Methods Study

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Abstract

Background: India has the largest burden of drug-resistant organisms compared with other countries around the world, including multiresistant and extremely drug-resistant tuberculosis and resistant Gram-negative and Gram-positive bacteria. Antibiotic resistant bacteria are found in all living hosts and in the environment and move between hosts and ecosystems. An intricate interplay of infections, exposure to antibiotics, and disinfectants at individual and community levels among humans, animals, birds, and fishes triggers evolution and spread of resistance. The *One Health* framework proposes addressing antibiotic resistance as a complex multidisciplinary problem. However, the evidence base in the Indian context is limited.

Objective: This multisectoral, trans-species surveillance project aims to document the infection and resistance patterns of 7 resistant-priority bacteria and the risk factors for resistance following the One Health framework and geospatial epidemiology.

Methods: This hospital- and community-based surveillance adopts a cross-sectional design with mixed methodology (quantitative, qualitative, and spatial) data collection. This study is being conducted at 6 microbiology laboratories and communities in Khurda district, Odisha, India. The laboratory surveillance collects data on bacteria isolates from different hosts and their resistance patterns. The hosts for infection surveillance include humans, animals (livestock, food chain, and pet animals), birds (poultry), and freshwater fishes (not crustaceans). For eligible patients, animals, birds and fishes, detailed data from their households or farms on health care seeking (for animals, birds and fishes, the illness, and care seeking of the caretakers), antibiotic use, disinfection practices, and neighborhood exposure to infection risks will be collected. Antibiotic prescription and use patterns at hospitals and clinics, and therapeutic and nontherapeutic antibiotic and disinfectant use in farms will also be collected. Interviews with key informants from animal breeding, agriculture, and food processing will explore the perceptions, attitudes, and practices related

to antibiotic use. The data analysis will follow quantitative (descriptive and analytical), qualitative, and geospatial epidemiology principles.

Results: The study was funded in May 2019 and approved by Institute Ethics Committees in March 2019. The data collection started in September 2019 and shall continue till March 2021. As of June 2020, data for 56 humans, 30 animals and birds, and fishes from 10 ponds have been collected. Data analysis is yet to be done.

Conclusions: This study will inform about the bacterial infection and resistance epidemiology among different hosts, the risk factors for infection, and resistance transmission. In addition, it will identify the potential triggers and levers for further exploration and action.

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KEYWORDS

bacterial infection; antibiotics resistance; sentinel surveillance; drug prescriptions; One Health; India

Introduction

The last century has witnessed a significant reduction in infectious disease mortality and morbidity with the use of antimicrobials. Antimicrobial resistance (AMR), especially antibiotic resistance (ABR), poses a major threat to clinical medicine and public health. The development of new antimicrobials and antibiotics is becoming increasingly difficult and is unable to match the pace of emergence of resistance. It is estimated that AMR-attributable deaths shall rise from 700,000 in 2014 to 10 million by 2050, with US $100 trillion lost output [1]. India is the top contributor toward global morbidity and mortality. India also carries the largest burden of drug-resistant organisms worldwide, including multiresistant and extremely drug-resistant mycobacteria and resistant Gram-negative and Gram-positive bacteria. In India, approximately 60,000 newborns die from resistant bacterial infections [2]. It is projected that over 2 million Indians will die because of AMR by 2050 [3]. Infection with methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-sensitive *S aureus* (MSSA) increased the risk of death by 5.6 times and 2.7 times, respectively [4]. The attributable risk of death with MRSA was double that of MSSA by 90 days [4]. Infection with resistant *Escherichia coli* and *S aureus* increased mortality risk by 1.8 to 2.5 times at 30 days [5]. Antimicrobial usage has enhanced animal and fish production globally, paralleling the demand. AMR is a major threat to food safety, food security, and socioeconomics of millions of farming communities.

Resistant bacteria are found in humans, animals, birds, aquatics, plants, and the environment (water, soil, and air), and they move between hosts and ecosystems [6]. In India, >70% of *Acinetobacter baumannii*, *E coli*, and *Klebsiella pneumoniae* and >50% of *Pseudomonas aeruginosa* were resistant to broad-spectrum antibiotics (fluoroquinolones and third-generation cephalosporins) [7]. Extended-spectrum beta-lactamase (ESBL)–producing *E coli* strains from chickens and multidrug-resistant *Salmonellae* species have been reported in India [8-12]. In New Delhi, metallo-β-lactamases (NDM-1, *superbug*), ESBL-producing Gram-negative bacteria, and vancomycin-resistant *S aureus* (VRSA) have been reported in milk from cows with mastitis [13,14]. ESBL-producing *Enterobacteriaceae* in tilapia fishes has been reported from urban water bodies and resistant Vibrios from shellfishes has been reported in the market [15,16]. Resistant bacteria and genes have also been isolated from hospital wastewater, sewage, rivers, surface water, and groundwater in India [17-20].

Although ABR and AMR emerges naturally, antibiotic consumption or usage in humans, animals, and agriculture, environmental waste contamination, sanitation, and infection control practices are the potential drivers for increase in ABR and AMR [1,7]. India's antibiotic consumption (absolute and percentage increase) is highest globally. Between 2000 and 2015, India's gross antibiotic consumption increased by 103% (3.2-6.5 billion defined daily doses [DDDs]) and antibiotic consumption rate increased by 63% (8.2-13.6 DDDs per 1000 inhabitants) [21]. The prescription behavior, fixed dose combinations, social pressures, and market influences are some of the factors [22]. In 2010, India was the fifth largest consumer of antibiotics in food animals (poultry, pigs, and cattle) and will become the fourth largest consumer of antibiotics in food animals by 2030 [23]. Approximately four-fifth of the antibiotics used in animals are growth promoters [24]. Approximately 40% of the chicken samples in India had high concentrations of antibiotics [25]. Antibiotic residues have been documented in animal milk [24,26]. India is a hot spot for antibiotic use in food animals, with a use of 30 kg per km^2, which will grow by 312% by 2030 [23]. The global consumption of antibiotics in animals is estimated to be twice that of humans [27].

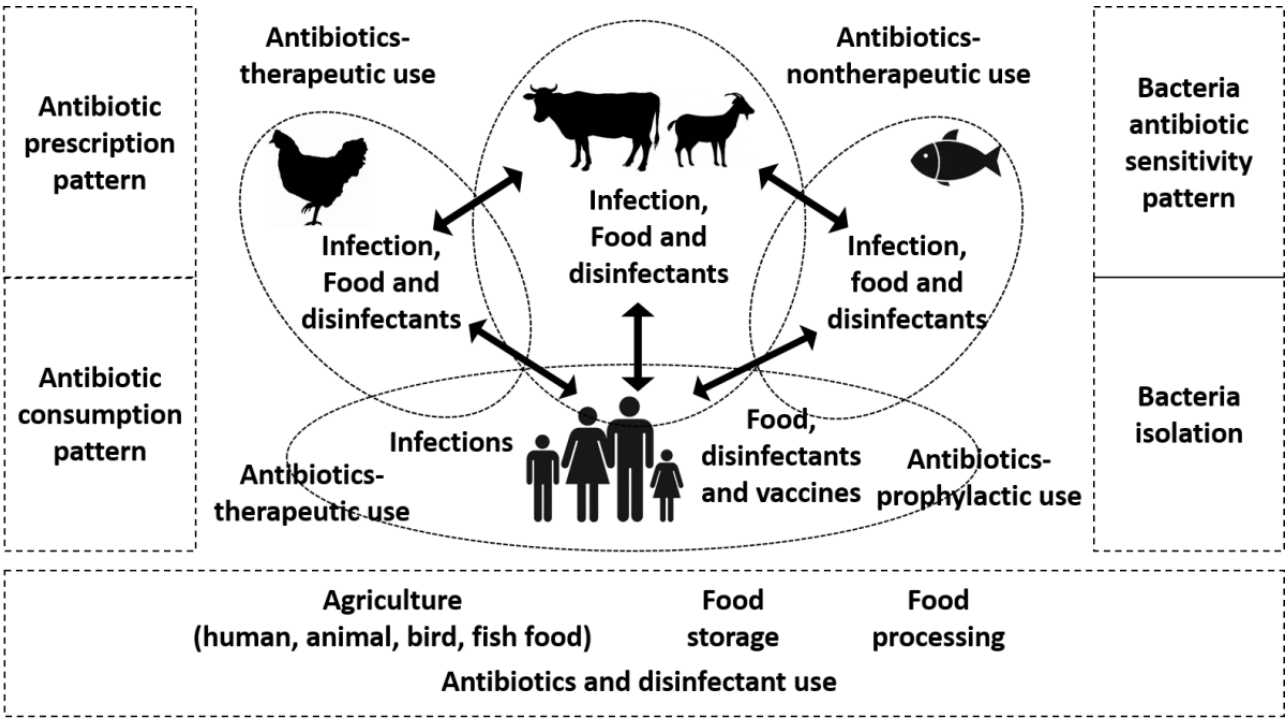
Surveillance is an essential tool to document and monitor the ABR and risk factors and appropriately inform policies, infection control, and prevention responses at local, national, and global levels. The Global AMR Surveillance System by the World Health Organization targets 8 bacterial species (*Acinetobacter spp., E coli, K pneumoniae, Salmonella, S aureus, Streptococcus pneumoniae, Shigella spp.*, and *Neisseria gonorrhoeae)* [6]. The Antimicrobial Resistance Surveillance Network coordinated by the Indian Council of Medical Research includes 9 types of bacteria (*E coli, K pneumoniae, Enterobacter spp., A baumannii, P aeruginosa, Salmonella spp., S pneumoniae, S aureus, and Enterococcus spp.*) [28]. These surveillance efforts are primarily targeted at human infections. Studies involving animals and environments have targeted isolation of resistant bacteria, resistance genes, and molecular characterization without crosslinking the hosts and their ecosystems [7].

The *One Health* approach attempts to address complex multidisciplinary problems through designing and implementing programs, framing policies and legislation, and conducting research where multiple sectors converge and collaborate for achieving better outcomes in public health, animal or bird or aquatics health, and environmental settings. The *One Health* approach has been advocated in infectious diseases including zoonoses, food safety, and AMR or ABR, considering the interdependence of human, animal, and environmental factors and determinants for emergence of resistance [29]. There is paucity of data from India on *One Health* surveillance. An integrated surveillance system considering data from humans, animals, food, and the environment and antibiotic usage or consumption for humans and animals appears to be critical.

As part of the *Grand Challenge India on Antimicrobial Resistance* program, this district-based ecological surveillance in India attempts to document the resistance pattern of 7 index bacteria isolated from multiple hosts, including humans, animals (livestock, food chain, and pets), birds (food chain birds such as chicken), and freshwater fishes, correlate with their exposure to antibiotics, disinfectants, and other risk factors at individual, household or farm, and community levels, and analyze the data applying geospatial epidemiology.

An intricate interplay of infections, exposure to antibiotics, and disinfectants at individual and community levels among humans, animals, birds, and fishes triggers the evolution and spread of ABR. The directions of ABR transmission across these species are unclear and probably multidirectional. We hypothesize that concurrent surveillance for index bacterial infections and ABR patterns, exposure to antibiotics and disinfectants, and relevant risk factors for different hosts and environments will improve the knowledge base. The application of multidimensional geospatial epidemiology analysis will inform about the interlinkages between exposures and ecosystems. This multisectoral, trans-species surveillance follows the *One Health* approach and includes 7 priority antibiotic-resistant bacteria: *A baumannii*, *P aeruginosa*, Enterobacteriaceae, *E coli*, *K pneumoniae*, *S aureus*, *Enterococcus faecium*, and *Salmonellae spp* [30]. Figure 1 shows the conceptual model for the current surveillance.

Figure 1. The proposed conceptual model of multihost surveillance for bacterial infections and antibacterial resistance.



Methods

Objectives

This surveillance aims to (1) document the pattern of infections because of the 7 index bacteria in humans, animals (including livestock, food chain, and pets), birds (food chain birds such as chicken), and freshwater fishes sharing the same environment and their resistance patterns, (2) document the risk factors for ABR at the individual and community level related to health, antibiotic consumption, and antibiotic usage in food animal breeding and agriculture, and (3) apply geospatial epidemiology analytical methodology to improve the understanding of bacterial infections and ABR.

This study aims to (1) conduct surveillance for infection with the index bacteria under study and ABR patterns in humans, animals (including livestock, food chain, and pets), birds (food chain birds such as chicken), and freshwater fishes over 1 year; (2) document the potential factors at the individual, household, or habitation or farm level related to illnesses, care seeking, antibiotic usage, and disinfection that influence resistance among the index bacteria under study, (3) document antibiotic prescription and antibiotic sales patterns for humans (therapeutic and nontherapeutic antibiotic usage in animals including livestock, food chain, and pets), birds (food chain birds such as chicken), and freshwater fishes and agriculture and food processing, and (4) apply multidimensional geospatial epidemiology analysis to generate epidemiological patterns of

bacterial infections and ABR and the linkages with the various potential risk factors under study.

Study Design

This study combines surveillance and cross-sectional design with mixed methodology (quantitative and qualitative) for data collection.

Study Setting

The study is being implemented at 4 medical college hospitals, 1 veterinary college hospital, and the fishery research institute located in Khurda district, including Bhubaneswar city. The fish samples are being collected from the farming sites in Khurda and the neighboring districts (fish supplying zone). The study is recruiting participants from Khurda district for data collection.

Study Participants

The study includes 3 categories of participants:

1. Hosts with infections: humans, animals (including livestock, food chain, and pets), birds (food chain birds such as chicken), freshwater fishes (excluding crustaceans) with any of the 7 index bacteria isolates.
2. Patients attending outpatient clinics: humans and animal or birds attended by doctors for prescription audits.
3. Stakeholders for in-depth interviews (IDIs).

The study also involves data collection from 3 types of facilities: (1) microbiology laboratories, (2) chemists and drug distributors for humans and veterinary medicines, and (3) fish farming sites. Table 1 details the categories and numbers of participants.

Table 1. The facilities and study participants for data collection under each category.

Serial no. and participant and facility category	Number
A: Study participants	
A1: Hosts with infections	N/A[a]
A1.1: Humans with positive isolates[b]; (newborns [n=25-30]; children >1 month to 5 years [n=25-30]; and >5 years including adults [n=50-60])	100-120
A1.2: Animals (including birds) with positive isolates[c]; (animals [n=30-35] and birds [n=20-25])	50-60
A1.3: Fishes with positive isolates[d]; (fish farms [n=20]; 5-6 fishes each weighing >100 grams per farm)	20
A2: Patients attending out-patient clinics	N/A
A2.1: Human patients for prescription audit (for antibiotics)	
Patients (400 per doctor; 100 every quarter)	6000
Doctors (for human patients) for prescription audit[e]; (disciplines: medicine [n=5], pediatrics [n=5], and surgery [n=5])	15
A2.2: Veterinary patients for prescription audit (for antibiotics)	
Animals or birds (100 per doctor; 25 every quarter)	800-1000
Veterinary doctors[e]	8-10
A3: Stakeholders for in-depth interview	50
Farmers (food and vegetable)	20
Agriculture stockists	5
Food animal breeders	5
Poultry breeders	5
Fish breeders or farmer	5
Animal food processors and distributors	10
B: Study facilities	
B1: Microbiology laboratories at the participating institutes	6
Medical microbiology laboratories	4
Veterinary microbiology laboratory	1
Fish microbiology laboratory	1
B2: Chemists and drug distributors for humans and animals	N/A
Medical chemists	12
Medical college pharmacy (n=4)	4
Other hospital pharmacy (n=4)	4
General chemist and distributor (n=4)	4
Veterinary chemists	4
Near the veterinary college	1
Other veterinary chemist	3
B3: Fish farming sites (for antibiotic usage)	4-5
Quarterly audit (4 per farm; once every quarter)	16-20

[a]N/A: not applicable.

[b]The patients with positive growth for any one of the 7 index bacteria from any of these samples: blood, urine, stool, pus, sputum, and other sterile body fluid such as cerebrospinal fluid, pleural fluid, and peritoneal fluid.

[c]The animal and bird with positive growth for any one of the 7 index bacteria from any of these samples: blood, urine, pus, stool, other body parts, and milk.

[d]Fish with positive growth for any one of the 7 index bacteria from gut and gill samples.

[e]The prescription audit includes consecutive new patients (not follow-up patients) seen by the respective doctor.

Selection of Participants

The various study participants and stakeholders shall be selected following strategy.

Humans With Positive Isolates

The eligibility criteria included (1) patients from Khurda district, (2) admitted to inpatient departments of the 4 medical college hospitals, and (3) positive culture growth for any index bacteria from samples collected within 48 hours of hospitalization shall be eligible. Of these eligible patients, we shall randomly select according to the age strata (newborns, >1 month to <5 years, and >5 years), type of bacteria, and departments to obtain representative distribution.

Animals With Positive Isolates

The eligibility criteria included (1) animal (including livestock, food chain, and pets) and birds (food chain birds such as chicken) with any infection from Khurda district attending the veterinary college hospital, (2) with positive culture growth for any index bacteria from samples, and (3) inpatient samples collected within 48 hours of hospitalization or outpatient samples collected from fresh patients or fresh samples collected from animals or birds in the farms. Of these eligible patients, we shall randomly select according to the animal or bird type; livestock, pet, or food chain animals and birds; and the specimen types to obtain a representative distribution.

Fish Farms With Positive Isolates

The eligibility criteria included (1) freshwater fish farms from Khurda or surrounding districts supplying to Khurda district and (2) with positive culture growth for any index bacteria from samples.

Doctors (for Human Patients) for Prescription Audits

The doctors shall be identified from the 4 hospitals (1 per discipline) and from other hospitals or clinics in the Bhubaneswar area. These doctors shall be informed about the activity and consent shall be obtained.

Veterinary Doctors for Prescription Audit

The doctors shall be identified from the veterinary hospital and other clinics in the Bhubaneswar area. These doctors will be informed about the activity and consent will be obtained.

Patients for Prescription Audit

The patients (humans and animals or birds) attending the selected doctors should be eligible. Patients attending for fresh illness (not follow-up visits) will be approached for consent and data collection.

Data Collection

Table 2 shows the data to be collected for different components and study participants. The data collection for different hosts is detailed below and in Table 2.

Table 2. The data components to be collected from various study participants.

Serial no. and category		Data components to be collected	Frequency
A: Study participants			
A1: Hosts with infections			
A1.1	Humans with positive isolates	• Sociodemography and occupation • Illnesses, care seeking, and antibiotic usage • Sanitation, waste handling, and disinfection practices and animals or birds exposure • Household location and environmental risk factors (GPS)	• Target: 100-120 • 10-12 per month • Once for each participant
A1.2	Animals with positive isolates	• Demography (types and number of animals or birds, location, and farming period) • Illnesses, care seeking, antibiotic usage, and outcome • Sanitation, waste handling, and disinfection practices • Feeding and nontherapeutic antibiotic usage • Caretaker's illness and antibiotic usage • Farm location and environmental risk factors (GPS)	• Target: 50-60 • 5 per month • Once for each animal or bird
A1.3	Fishes with positive isolates	• Demography (species, farm address, and farming period) • Any illness, antibiotics used, and outcome • Sanitation, waste handling, and disinfection practices • Feeding and nontherapeutic antibiotic usage, pesticides, and disinfectant usage • Caretaker's illness and antibiotic usage • Farm (habitation for domesticated or nonfarm animals or birds) location and environmental risk factors (GPS)	• Target: 20 farms • 5-6 farms per quarter • 5-6 fishes per farm • Once for each farm
A2: Patients attending outpatient clinics			
A2.1	Human patients for prescription audit	• Age, gender, diagnosis, and medicines prescribed • Doctor attended	• Once for each patient • 8-10 new prescriptions per week for specific doctor
A2.2	Veterinary patients for prescription audit	• Animal or bird type, diagnosis, and medicines prescribed • Doctor attended	• Once for each animal or bird • 8 new prescriptions per month for specific doctor
A3	Stakeholders for in-depth interview	• Perceptions, knowledge, attitude, practices, and barriers related to antibiotic usage in agriculture, animal breeding, food industry and potential influence on resistance	• Once for each participant • Interviews once during study period
B: Study facilities			
B1	Human and animal or bird microbiology laboratories	• Number of samples received, types of samples (body part or fluid), number of samples with positive bacteria growth, number of samples with positive index bacteria growth, and antibiotic sensitivity	• Daily screening
B2	Fish microbiology laboratory	• Number of samples collected and processed, types of samples (body part), number of samples with positive bacteria growth, number of samples with positive index bacteria growth, and antibiotic sensitivity	• Periodic, when sample collected or processed
B3	Chemists and drug distributors	For humans and animals: • Volume of antibiotics sold	• Monthly
B4	Fish farming sites	• Antibiotic usage, pesticides, and disinfectant usage on quarterly basis	• Quarterly

Infections in Humans

Surveillance of Bacterial Infections

At the 4 medical college hospitals, daily surveillance will be conducted to identify any positive index bacteria isolates from the samples of the hospitalized patients. For the positive index bacteria isolates, information about antibiotic sensitivity; dates of sample collection and admission; and patient information including diagnosis, antibiotics used, outcome, and basic demography (age and gender) will be documented. Among these patients with positive bacteria isolates, eligible patients (as per the eligibility criteria defined above) will be identified from the admission registers for detailed data collection at the household or farm level.

Detailed Individual Data Collection for the Humans With Positive Bacteria Isolates

Of the eligible patients, approximately 120 patients (10-12 patients every month) will be randomly selected. These selected patients (and family members) will be contacted after the discharge or death of the patient to schedule the home visit. During home visits, informed written consent will be obtained, followed by data collection using Case Record Forms (CRFs).

Infections in Animals and Birds

Surveillance of Bacterial Infections

For the veterinary college hospital, daily surveillance will be conducted to identify any positive index bacteria isolates from the samples of the animal or bird patients attending the hospital or those that were admitted. For the positive index bacteria isolates, information about antibiotic sensitivity, diagnosis, antibiotic use, outcome, and animal or bird type will be documented. Among these animal or bird patients with positive bacteria isolates, eligible animals or birds will be identified from the records for detailed data collection at the household or farm level.

Detailed Individual Data Collection for the Animals and Birds With Positive Bacteria Isolates

Of the eligible animal or bird patients, approximately 60 patients (5 patients every month) were randomly selected. For these selected animals or birds, their owners or caretakers will be contacted for scheduling household or farm visits. During household or farm visits, informed written consent from the owner or caretaker will be obtained, followed by data collection using the CRF.

Fish Farms With Positive Isolates

For the freshwater fish farms with positive isolates from fishes (not crustaceans), the owners or caretakers shall be contacted and farm visits shall be made for informed written consent followed by data collection using the CRF.

Antibiotic Sales

From the identified chemists and drug distributors for humans, animals, and birds at the hospitals and outside, the data on antibiotic procurement or indent and sales shall be collected on a monthly or quarterly basis. The list shall include oral (tablets, capsules, and syrups) and injectable forms for the different types of antibiotics.

Antibiotic Usage at Fish Farming Sites

For the fish farming sites, quarterly visits will be made to collect information on the use of different antibiotics or disinfectants or chemicals or growth promoters (therapeutic or nontherapeutic) and their quantity.

Doctors for Prescription Audits

For the doctors (human and veterinary), the hospital or clinic and specialty will be documented.

Patients for Prescription Audits

The consecutive patients (and their parents) attending the outpatient department of the identified doctors with a new illness will be approached at exit (consultation completed) for participation. For patients who consent, the age, sex, diagnosis, and medications prescribed will be captured. Similarly, for the animal or bird patients attending the veterinary doctors, the owners or caretakers will be approached for consent to participate. For the animals and birds, the species type, diagnosis, and medicines prescribed will be captured.

Geospatial Data Collection

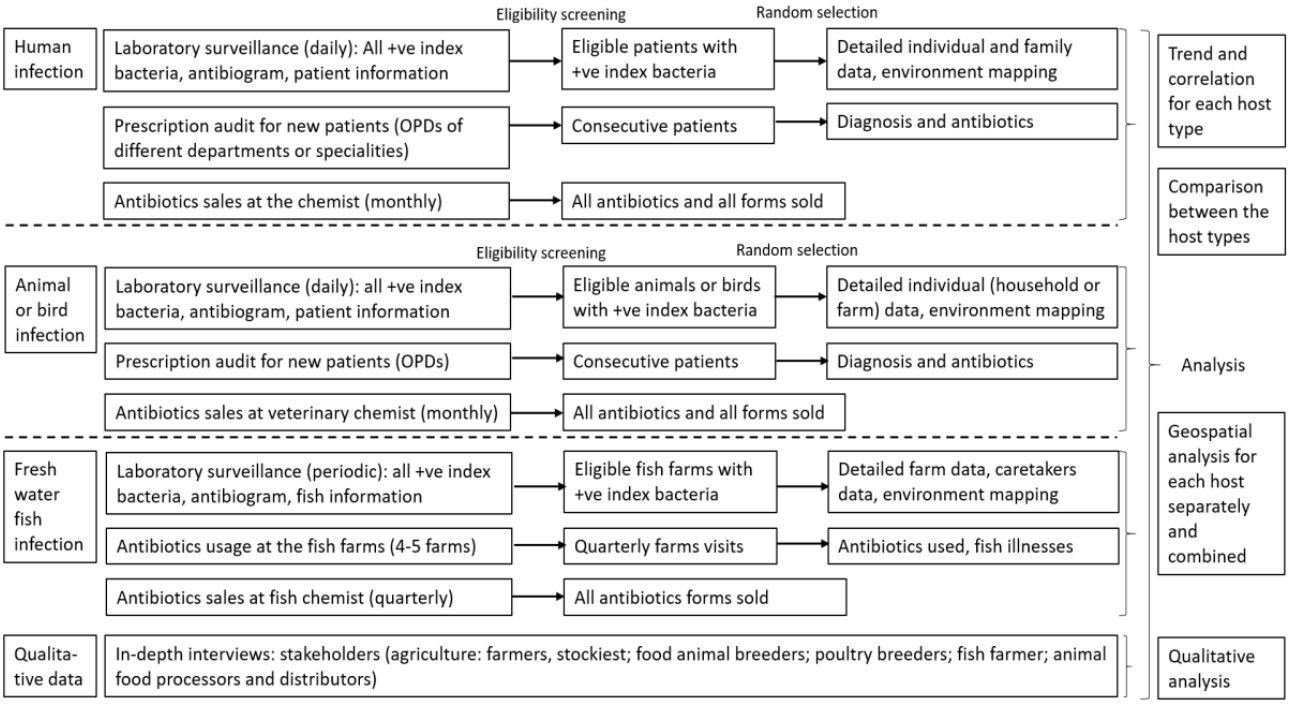
The precise location data (latitude and longitude) for the households or habitations or farms of the recruited human participants, animals and birds, and fish farming sites with positive bacteria isolates shall be collected using a GPS device (Garmin Montana 680, Garmin). For these participants, neighborhood mapping covering a 100-m radius around their locations will capture the potential risk factors for infection (garbage dump, wastewater, animal or poultry farm, egg or meat vending, hospital or clinic, chemist, hotel or food selling, industry, etc.) with their GPS positions. The technologies to be used for geospatial mapping include GPS, geotagging, and geographic information systems. The GPS data points collected shall be mapped on the state and district satellite map.

Stakeholders for IDIs

The stakeholders or key informants shall be identified purposively considering the profession (agriculturist, stockiest, breeder, food processing, and distribution) and geography to suit the objectives. All IDIs shall be conducted at a convenient place for the participant after obtaining informed consent and the conversation shall be digitally recorded with consent. The IDI will focus on exploring the perceptions, knowledge, attitude, practices, and barriers related to antibiotic use in agriculture, animal breeding and food industry and the potential influence on resistance. The IDIs conducted in local language shall be transcribed verbatim and translated to English. Quality checks of transcripts and translation will be performed for 25% of the audio recordings by another member.

The surveillance and data collection workflow are shown in Figure 2.

Figure 2. The workflow of surveillance data collection targeted at different hosts. OPDs: outpatient departments.



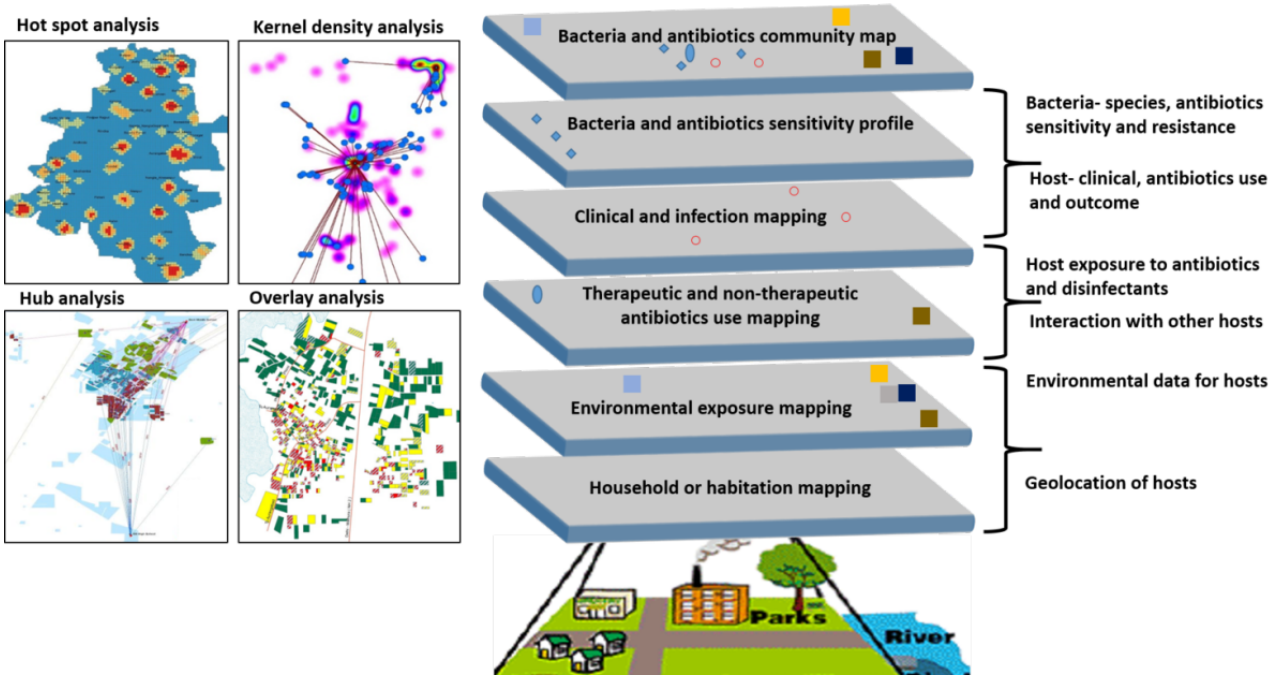
Data Management

The surveillance and quantitative data shall be collected using customized software installed on tablets (developed using open source platforms: Android; PHP, the PHP Group; and MySQL, Oracle Corporation) and uploaded to the server through a mobile network. The data collection and transmission process shall have encryption and security measures. The qualitative data shall be collected using IDI guides on paper, followed by transcription, translation, and data entry. All electronic data will be stored in a secured server with multilayered security and daily backup. The investigators and authorized research staff have data access.

Data Analysis

The quantitative data are expressed as means (with standard deviations), medians (with interquartile ranges), and proportions using descriptive statistics. The data for different groups will be compared using *t* tests, chi-square tests, Mann-Whitney test, and Kruskal-Wallis test, as appropriate. The Jonckheere-Terpstra test will be used to assess the monthly trend of bacteria isolates (proportions), the ABR pattern for antibiotics, antibiotic prescription, antibiotic sales, and statistical significance. The Pearson correlation coefficient will be used to examine the relationship between antibiotic prescription and sales and ABR rates. The qualitative data will be analyzed by content analysis as per the domains identified and follow processes: free listing, coding, axial coding, and cross tabulation. The spatial data will be analyzed using geospatial epidemiology principles, including point pattern analysis (clustering and density), kernel density map (hot spots and catchment), hub analysis (common exposures and catchment area), and overlay analysis (exposures or risk factors layering and spatial correlation; Figure 3). The GPS and geospatial data will be analyzed using ArcGIS, QGIS, and Global Mapper 2.0.

Figure 3. Proposed geospatial epidemiology analysis outputs.



Validity and Reliability

Uniform laboratory processing, antibiotic sensitivity testing, and interlaboratory comparison will be practiced. Monthly teleconference and quarterly site visits will focus on protocol adherence and data validation. The data collected will undergo consistency and range checks by the data management team.

Ethical Aspects

The study protocol was reviewed and approved by the INCLEN Ethics Committee, New Delhi (Ref: IIEC-056), Institute Ethics Committee, All India Institute of Medical Sciences, Bhubaneswar (Ref: T/EMF/Micro/18/6); Kalinga Institute of Medical Sciences Medical Research Committee (KIMS/R&D/255/2018), Institute Ethics Committee, Institute of Medical Sciences & SUM Hospital (Ref: DMR/IMS.SH/SOA/180167); Institutional Ethics Committee for Human Research, Hi-Tech Medical College & Hospital (Ref: HMCH/IEC/19-004). The participants are being recruited after obtaining written informed consent. Appropriate data confidentiality, storage, and access authorization procedures are being adopted.

Results

The study was funded in May 2019 and approved by Institute Ethics Committees in March 2019. The data collection started in September 2019 and shall continue till March 2021. As of June 2020, data for 56 humans, 30 animals and birds and fishes from 10 ponds have been collected. The other data collection is also in progress. Data analysis is yet to be done.

Discussion

Antibiotics Resistance Problem in India

A scoping report on ABR in India reported that resistance to broad-spectrum antibiotics fluoroquinolones and third-generation cephalosporin was >70% in *A baumannii*, *E coli*, and *K pneumoniae* and >50% in *P aeruginosa* [7]. The isolation of ESBL-producing *E coli* from chickens, multidrug-resistant *Salmonellae* from chicken meat samples, VRSA from cow milk samples, and ESBL-producing *Enterobacteriaceae* from fishes indicate the spread of ABR across all food animals and in the environment. Relatively unregulated and high antibiotic usage in humans and among animals and aquatics in India is worrisome. The heavy use of antibiotics is based on high infectious disease burden and past experiences of mortality and a limited understanding of the impact across sectors. The implementation of the One Health framework in policy and program has been challenging in view of simultaneous and connected evidence from the Indian context. There is a need to understand the drivers for the emergence of ABR and transmission across the host-environment systems for appropriate action.

Strengths and Limitations

The multihost simultaneous surveillance for the 7 resistant-priority bacteria among humans, animals, birds, and fishes following the One Health framework is a strength of this study. Therapeutic antibiotic usage for therapeutic purposes among these patients and nontherapeutic usage for animal breeding will allow drawing possible linkages with the resistance pattern. The geospatial epidemiology analysis is expected to provide information about the pattern and linkages between the variables. The shorter observation period may not permit inferring any causal association between the various risk factors and antibiotic resistance.

Conclusions

This study will generate evidence on (1) epidemiology of infections with 7 high-priority bacteria among the different hosts (human, animal, birds, and fishes) and their resistance patterns, (2) the potential risk factors for ABR in the infected hosts at individual and immediate environment levels, (3)

therapeutic and nontherapeutic antibiotic usage for humans, animals, fishes, agriculture, and food processing along with the potential triggers, and (4) potential linkages between data from various sources and identification of possible risk factors for ABR across various hosts and their ecosystems. India is critically important for ABR and transmission of multidrug-resistant bacterial species because of high antibiotic consumption, unrestricted therapeutic and nontherapeutic usage across all sectors, and other environmental and behavioral risk triggers. This multisectoral, trans-species surveillance for bacterial infection and ABR using *One Health's* perspective and geospatial epidemiology techniques will improve our understanding of the pattern and spread of resistance and potentially inform about the potential levers for actions in public health, animal, bird and aquatics health, and environmental settings.

Acknowledgments

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Authors' Contributions

This study was conceptualized by MD with inputs from SD, AM, S Mahapatro, BP, R Panigrahy, SP, S Mishra, PS, SS, and R Pillai. AM, S Mahapatro, BP, R Panigrahy, SP, S Mishra, PS, SS, JD, and MD supervised are supervising data collection. MD prepared the first draft of the manuscript. All authors have contributed to this manuscript and reviewed and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review reports from PMU-BIRAC.
[PDF File (Adobe PDF File), 8 KB - resprot_v9i10e23241_app1.pdf]

References

1. O'Neill J. Tackling Drug-resistant Infections Globally: Final Report and Recommendations. BioMérieux Connection. 2016. URL: https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf [accessed 2020-10-09]
2. Laxminarayan R, Duse A, Wattal C, Zaidi AK, Wertheim HF, Sumpradit N, et al. Antibiotic resistance-the need for global solutions. Lancet Infect Dis 2013 Dec;13(12):1057-1098. [doi: 10.1016/S1473-3099(13)70318-9] [Medline: 24252483]
3. Resistance Map: India. Center for Disease Dynamics Economics Policy. 2019. URL: https://resistancemap.cddep.org/resmap/c/in/India [accessed 2020-04-20]
4. Wolkewitz M, Frank U, Philips G, Schumacher M, Davey P, BURDEN Study Group. Mortality associated with in-hospital bacteraemia caused by Staphylococcus aureus: a multistate analysis with follow-up beyond hospital discharge. J Antimicrob Chemother 2011 Feb;66(2):381-386. [doi: 10.1093/jac/dkq424] [Medline: 21098543]
5. de Kraker ME, Davey PG, Grundmann H, BURDEN study group. Mortality and hospital stay associated with resistant Staphylococcus aureus and Escherichia coli bacteremia: estimating the burden of antibiotic resistance in Europe. PLoS Med 2011 Oct;8(10):e1001104 [FREE Full text] [doi: 10.1371/journal.pmed.1001104] [Medline: 22022233]
6. Global Antimicrobial Resistance Surveillance System (GLASS) Report Early Implementation 2017-18. World Health Organisation. 2018. URL: https://www.who.int/glass/resources/publications/early-implementation-report-2017-2018/en/ [accessed 2020-10-09]
7. Gandra S, Joshi J, Trett A, Lamkang AS, Laxminarayanan R. The Antimicrobial Resistance Situation in India. 2017. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6563737/ [accessed 2020-10-09]
8. Brower CH, Mandal S, Hayer S, Sran M, Zehra A, Patel SJ, et al. The prevalence of extended-spectrum beta-lactamase-producing multidrug-resistant in poultry chickens and variation according to farming practices in Punjab, India. Environ Health Perspect 2017 Jul 20;125(7):077015. [doi: 10.1289/EHP292] [Medline: 28749780]
9. Shrivastav A, Sharma RK, Sahni YP, Shrivastav N, Gautam V, Jain S. Study of antimicrobial resistance due to extended spectrum beta-lactamase-producing in healthy broilers of Jabalpur. Vet World 2016 Nov;9(11):1259-1263 [FREE Full text] [doi: 10.14202/vetworld.2016.1259-1263] [Medline: 27956778]

10. Kar D, Bandyopadhyay S, Bhattacharyya D, Samanta I, Mahanti A, Nanda PK, et al. Molecular and phylogenetic characterization of multidrug resistant extended spectrum beta-lactamase producing Escherichia coli isolated from poultry and cattle in Odisha, India. Infect Genet Evol 2015 Jan;29:82-90. [doi: 10.1016/j.meegid.2014.11.003] [Medline: 25445661]
11. Kaushik P, Anjay, Kumari S, Bharti SK, Dayal S. Isolation and prevalence of Salmonella from chicken meat and cattle milk collected from local markets of Patna, IndiaIndia. Vet World 2014 Feb;7(2):62-65 [FREE Full text]
12. Naik VK, Shakya S, Patyal A, Gade NE, Bhoomika. Isolation and molecular characterization of Salmonella spp from chevon and chicken meat collected from different districts of Chhattisgarh, India. Vet World 2015 Jun;8(6):702-706 [FREE Full text] [doi: 10.14202/vetworld.2015.702-706] [Medline: 27065633]
13. Ghatak S, Singha A, Sen A, Guha C, Ahuja A, Bhattacharjee U, et al. Detection of New Delhi metallo-beta-lactamase and extended-spectrum beta-lactamase genes in Escherichia coli isolated from mastitic milk samples. Transbound Emerg Dis 2013 Oct;60(5):385-389. [doi: 10.1111/tbed.12119] [Medline: 23870003]
14. Bhattacharyya D, Banerjee J, Bandyopadhyay S, Mondal B, Nanda PK, Samanta I, et al. First report on vancomycin-resistant staphylococcus aureus in bovine and caprine milk. Microb Drug Resist 2016 Dec;22(8):675-681. [doi: 10.1089/mdr.2015.0330] [Medline: 26990514]
15. Marathe NP, Gaikwad SS, Vaishampayan AA, Rasane MH, Shouche YS, Gade WN. Mossambicus tilapia (Oreochromis mossambicus) collected from water bodies impacted by urban waste carries extended-spectrum beta-lactamases and integron-bearing gut bacteria. J Biosci 2016 Sep;41(3):341-346 [FREE Full text] [doi: 10.1007/s12038-016-9620-2] [Medline: 27581926]
16. Sudha S, Mridula C, Silvester R, Hatha A. Prevalence and antibiotic resistance of pathogenic Vibrios in shellfishes from Cochin market. Indian J Geo-Mar Sci 2014 May;43(5):815-824 [FREE Full text]
17. Akiba M, Senba H, Otagiri H, Prabhasankar VP, Taniyasu S, Yamashita N, et al. Impact of wastewater from different sources on the prevalence of antimicrobial-resistant Escherichia coli in sewage treatment plants in South India. Ecotoxicol Environ Saf 2015 May;115:203-208. [doi: 10.1016/j.ecoenv.2015.02.018] [Medline: 25704279]
18. Akiba M, Sekizuka T, Yamashita A, Kuroda M, Fujii Y, Murata M, et al. Distribution and relationships of antimicrobial resistance determinants among extended-spectrum-cephalosporin-resistant or carbapenem-resistant Escherichia coli isolates from rivers and sewage treatment plants in India. Antimicrob Agents Chemother 2016 Mar 7;60(5):2972-2980. [doi: 10.1128/aac.01950-15]
19. Azam M, Jan A, Haq Q. bla CTX-M-152, a Novel Variant of CTX-M-group-25, Identified in a Study Performed on the Prevalence of Multidrug Resistance among Natural Inhabitants of River Yamuna, India. Front Microbiol 2016;7:176 [FREE Full text] [doi: 10.3389/fmicb.2016.00176] [Medline: 26941715]
20. Poonia S, Singh TS, Tsering DC. Antibiotic susceptibility profile of bacteria isolated from natural sources of water from rural areas of East sikkim. Indian J Community Med 2014 Jul;39(3):156-160 [FREE Full text] [doi: 10.4103/0970-0218.137152] [Medline: 25136156]
21. Klein EY, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proc Natl Acad Sci U S A 2018 Apr 10;115(15):E3463-E3470. [doi: 10.1073/pnas.1717295115] [Medline: 29581252]
22. Chandy SJ, Mathai E, Thomas K, Faruqui AA, Holloway K, Lundborg CS. Antibiotic use and resistance: perceptions and ethical challenges among doctors, pharmacists and the public in Vellore, South India. Indian J Med Ethics 2013;10(1):20-27 [FREE Full text] [doi: 10.20529/IJME.2013.005] [Medline: 23439193]
23. Van Boeckel TP, Brower C, Gilbert M, Grenfell BT, Levin SA, Robinson TP, et al. Global trends in antimicrobial use in food animals. Proc Natl Acad Sci U S A 2015 May 5;112(18):5649-5654. [doi: 10.1073/pnas.1503141112] [Medline: 25792457]
24. Vishnuraj M, Kandeepan G, Rao K, Chand S, Kumbhar V. Occurrence, public health hazards and detection methods of antibiotic residues in foods of animal origin: A comprehensive review. Cogent Food Agric 2016 Sep 21;2(1):- [FREE Full text] [doi: 10.1080/23311932.2016.1235458]
25. Sahu R, Saxena P. Antibiotics in Chicken Meat. Centre for Science and Environment. 2014. URL: https://www.cseindia.org/latest-study-by-cses-pollution-monitoring-lab-finds-antibiotic-residues-in-chicken-8498 [accessed 2020-10-09]
26. -. Chemical contaminants in milk and public health concerns: a review. Int J Dairy Sci 2007 Feb 1;2(2):104-115. [doi: 10.3923/ijds.2007.104.115]
27. Aarestrup F. Sustainable farming: get pigs off antibiotics. Nature 2012 Jun 27;486(7404):465-466. [doi: 10.1038/486465a] [Medline: 22739296]
28. Walia K, Madhumathi J, Veeraraghavan B, Chakrabarti A, Kapil A, Ray P, et al. Indian J Med Res 2019 Feb;149(2):164-179 [FREE Full text] [doi: 10.4103/ijmr.IJMR_226_18] [Medline: 31219080]
29. Harbarth S, Balkhy HH, Goossens H, Jarlier V, Kluytmans J, Laxminarayan R, et al. Antimicrobial resistance: one world, one fight!. Antimicrob Resist Infect Control 2015 Nov 18;4(1):49. [doi: 10.1186/s13756-015-0091-2]
30. Global Priority List of Antibiotic-resistant Bacteria to Guide Research, Discovery, and Development of New Antibiotics. World Health Organisation. 2017. URL: https://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en/ [accessed 2019-04-10]

Abbreviations

ABR: antibiotic resistance
AMR: antimicrobial resistance
CRF: Case Record Form
DDD: defined daily dose
ESBL: extended-spectrum beta-lactamase
IDI: in-depth interview
MRSA: methicillin-resistant Staphylococcus aureus
MSSA: methicillin-sensitive Staphylococcus aureus
NDM: New Delhi metallo-beta-lactamase
OPD: outpatient department
VRSA: vancomycin-resistant Staphylococcus aureus

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Protocol

Evaluating the Impact of a Risk Assessment System With Tailored Interventions in Germany: Protocol for a Prospective Study With Matched Controls

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Abstract

Background: With a worldwide increase in the elderly population, and an associated increase in health care utilization and costs, preventing avoidable emergency department visits and hospitalizations is becoming a global priority. A personal emergency response system (PERS), consisting of an alarm button and a means to establish a live connection to a response center, can help the elderly live at home longer independently. Individual risk assessment through predictive modeling can help indicate what PERS subscribers are at elevated risk of hospital transport so that early intervention becomes possible.

Objective: The aim is to evaluate whether the combination of risk scores determined through predictive modeling and targeted interventions offered by a case manager can result in a reduction of hospital admissions and health care costs for a population of German PERS subscribers. The primary outcome of the study is the difference between the number of hospitalizations in the intervention and matched control groups.

Methods: As part of the Sicher Zuhause program, an intervention group of 500 PERS subscribers will be tracked for 8 months. During this period, risk scores will be determined daily by a predictive model of hospital transport, and at-risk participants may receive phone calls from a case manager who assesses the health status of the participant and recommends interventions. The health care utilization of the intervention group will be compared to a group of matched controls, retrospectively drawn from a population of PERS subscribers who receive no interventions.

Results: Differences in health care utilization and costs between the intervention group and the matched controls will be determined based on reimbursement records. In addition, qualitative data will be collected on the participants' satisfaction with the Sicher Zuhause program and utilization of the interventions offered as part of the program.

Conclusions: The study evaluation will offer insight into whether a combination of predictive analytics and case manager-driven interventions can help in avoiding hospital admissions and health care costs for PERS subscribers in Germany living at home independently. In the future, this may lead to improved quality of life and reduced medical costs for the population of the study.

Trial Registration: Deutsches Register Klinischer Studien (DRKS), DRKS00017328; https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00017328

International Registered Report Identifier (IRRID): DERR1-10.2196/17584

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KEYWORDS

interventional study; personal emergency response system (PERS); population management; predictive modeling

Introduction

With the worldwide increase in the elderly population [1], chronic diseases and associated health care utilization, such as costly emergency department visits and subsequent hospitalizations, are also on the rise. Elderly patients >75 years of age account for up to a third of ambulance transports in Germany [2]. Following worldwide trends, German elderly aged 65-74 years, on average, show a 50% increase in health care expenditures compared to the 50-64 age bracket. For the elderly aged 75 and over, the increase is 100% [3]. Preventing avoidable emergency department visits and admissions in elderly patients is becoming a global priority [4,5] since emergency hospitalizations are particularly distressing for the elderly and have been associated with adverse events such as hospital-acquired infections, loss of functional independence, and falls [6].

A Personal Emergency Response System (PERS) service consists of a help call button worn by the subscriber on the wrist or as a pendant. When a PERS subscriber requires assistance, a press of the button will establish a live connection to a personal response agent in a response center. The agent is then able to triage the event, and when applicable, assist the subscriber, either over the live voice connection, or by contacting a relative, informal caregiver, care provider, or emergency services.

The main benefit of a PERS service is the reassurance that help will always be available in case of an emergency, such as a fall or respiratory issues. Previous studies in the United States (US) [7,8] have shown that PERS data can be used to develop prediction models of decline in patient status. Such models thus provide early warning signs of impending emergencies and can be used by case managers to provide timely intervention [9]. Currently, it is unknown whether the combination of predictive modeling and case manager interventions is also effective in Germany, with a different health care system and potentially a different PERS subscriber population compared to the US. Whereas the US health care system is characterized by vertically integrated care providers and a strong private pay mentality, the German system is fragmented with very limited ability of health insurances to create and enforce care pathways.

Risk prediction can play an important role in preventing future hospitalization by allowing an opportunity for timely interventions and can play an instrumental role in reducing health care costs and utilization [10-13]. In the Sicher Zuhause (Safe at Home) study, the risk scores are used by a case manager (along with other data such as demographics, medical alert history, or medical conditions) to determine participants potentially at risk of hospitalization in a German PERS subscriber population. The case manager may then proactively contact the at-risk participant, and if needed, intervene at an early stage, before hospitalization becomes inevitable.

Objectives

The aim of the Sicher Zuhause study—a collaborative effort by Philips, the Techniker Krankenkasse (TK), ServiceCall AG, and the German Red Cross (DRK)—is to evaluate whether the combination of risk scores determined through predictive modeling and targeted interventions offered by a case manager can result in a reduction of hospital admissions and health care costs in a German PERS subscriber population. The primary study aim is to determine whether there is a difference in the number of hospitalizations between the intervention group and the control group over the 8-month intervention period.

In addition, the study aims to assess several secondary outcomes; these are the impact on the number of hospitalizations leading to admissions, the number of days admitted to a hospital, the number of ambulatory visits, the hospital-related costs, and the overall health care costs. Further, qualitative data collected through questionnaires will be used to assess the participants' satisfaction with the PERS devices used in the study and with the Sicher Zuhause program as a whole.

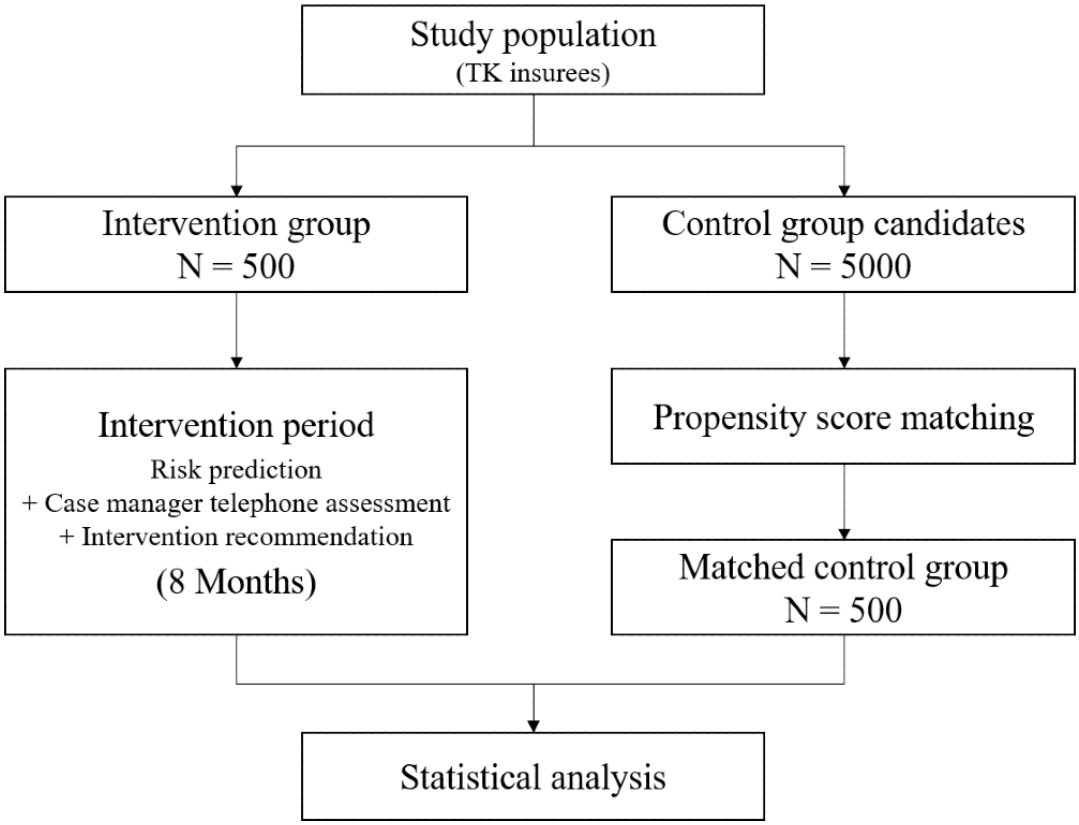
Methods

Study Design and Overview

The Sicher Zuhause study is a prospective interventional study with an intervention arm of 500 participants, which is compared to a matched population derived from historical PERS subscribers. The study tracks the health care utilization and expenditure of the participants over 8 months. During this period, the participants in the intervention arm may receive calls from one of the case managers in the study with the offer to discuss the participant's health status and care needs. Based on this discussion, the case manager may recommend one or more interventions.

The matched population serving as a control group does not actively take part in the study and is instead derived from the historical records of PERS subscribers. This population will be matched with the intervention arm to be as similar as possible compared to the intervention group using propensity score matching. An overview of the study design is shown in Figure 1.

Figure 1. Study design.



Participants and Selection Criteria

Study participants will be recruited from a pool of individuals who are insured by the TK—a statutory health insurance organization based in Hamburg. To be included in the study, participants must be eligible for PERS reimbursement, have a "care level" (Pflegegrad) as defined under the German health care system of at least 1 and at most 4, and be of at least 18 years of age.

Exclusion criteria for the study are severe cognitive impairments, severe hearing impairments, severe motor impairments, mental disorders, or other medical conditions that prohibit participation due to the inability to provide consent or to communicate with the case manager over the phone. Participants who are expected to be outside the home for a significant amount of time (due to planned hospital admission, for example) of the intervention period will be excluded. This applies to any single period of over 3 weeks or a cumulative period of over 2 months.

Enrollment

Potential study participants will be recruited through one of several ways:

1. New PERS customers or customers of the nursing service of ServiceCall or the DRK who are insured at the TK will be asked if they are interested in learning about the study.
2. Potential participants may be made aware of the study through articles published by the TK (for example, in their member magazine).
3. Potential participants may be identified from among existing TK customers. These potential participants may be contacted directly by the TK by phone or mail.

Identified individuals will be sent an information letter and informed consent. Individuals will be enrolled in the study after returning the signed informed consent letter.

Study Sites

The participants will use the PERS service in their own homes. During the study, the participants will make use of one of two response centers operated by ServiceCall (Kassel, Germany) and DRK (Düsseldorf, Germany).

Risk Score Calculation

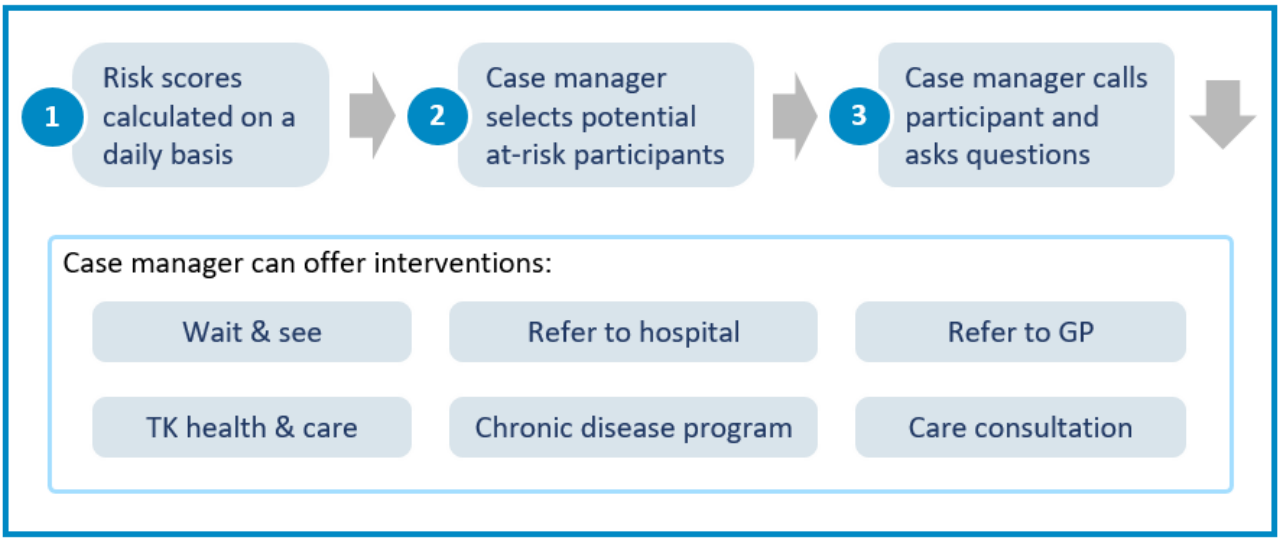
During the study, the participants' risk will be assessed by a predictive model of hospital transport in the next 30 days. This predictive risk model was developed on a retrospective data set of more than 8000 deceased German PERS subscribers using a methodology similar as described in [7], which is used by the Philips CareSage predictive analytics engine in the United States. The predictive model achieved an area under the receiver operator characteristic curve of 0.75.

The predictive model calculated the participants' risk based on a combination of medical alert pattern data collected by the call centers, as well as demographic information and self-reported medical conditions. The provided risk score is relative to the average risk of the population used to develop the model (eg, a risk of 2 indicated an estimated risk two times higher than the average). The distribution of the risk scores will be monitored during the study in case there are major differences between the study population and the population used to develop the model.

Intervention

Throughout the study, risk scores will be calculated daily and provided to a case manager. While risks are predicted for 30 days, daily calculations of the risk score allow for new information to be taken into account as soon as possible. Based on the height and trend of the risk scores, the history of response center interactions and demographic data, the case manager decides which participants to contact to further inquire about their health status and care needs (Figure 2).

Figure 2. Intervention protocol.



When a case manager contacts a participant, they will first evaluate the participant's health status through a triage protocol. Based on this conversation, the case manager may conclude to offer one or more interventions. As part of this study, the case manager may recommend:

1. No further action is needed at this time.
2. To plan a general practitioner visit.
3. To contact emergency medical services.
4. To enroll in one of the TK's existing health and care offers. These can, for example, include training programs on nutrition, a fall prevention course, or cardiovascular training.
5. To schedule a care consultation.

Interventions by the TK are offered free of charge. If one or more interventions are recommended, the case manager will schedule a follow-up call with the participant after 14 days. During the follow-up call, the case manager will inquire if the participant followed the suggested actions, and if so, what was the outcome (eg, referral to a specialist or dietary recommendations).

At the start of the study, participants will also receive a welcome call from the case manager to obtain a baseline measure of the participant's health status and already plan interventions if necessary. The participant may ask any questions that remain regarding the study.

Data Collection

The main source of data for the analysis of health-related outcomes will be the reimbursement records collected by the TK. These contain the type of care and the associated costs of care received by the participants during the intervention period. The expected time for these records to become available to the TK is approximately 1 month for hospital and PERS-related costs, and up to 9 months for ambulatory and specialist costs. At the end of the study period, participants will be asked to complete a questionnaire on health care utilization during the intervention period.

Response center data, including records of interactions with the personal response agents, demographics, and reported medical conditions, will also be collected during the intervention period for risk score calculation and the evaluation of the study. The case managers will also document the recommended interventions and actions taken by the participant during the follow-up call after an initial recommendation.

Data Analysis

The analysis of the primary outcome, the number of hospitalizations, will be based on a comparison of reimbursement records between the intervention arm and a matched population acting as a control group. Propensity score matching will be used to obtain a comparable control group [14,15] using a large pool of population characteristics (over 100 variables), which include the age at enrollment, gender, geographic location, care level, and presence or absence of common medical conditions. The intervention arm of 500 participants will be compared to an equal-sized matched control group of 500, determined by propensity score matching out of an initial pool of approximately 5000 candidates. Differences between groups will be analyzed through statistical testing, using the binomial rate test for the number of admissions and the t-test for differences in costs.

Analysis of the qualitative data provided by questionnaires will focus on evaluating the participants' satisfaction with the Sicher Zuhause program overall, and with the individual components such as the case manager interactions and the offered interventions. This will be done through descriptive statistics

such as the mean and standard deviations of the satisfaction and helpfulness measured on Likert scales.

The qualitative data will be used to provide insights into to outcomes of the primary objectives and may assist in the improvement of the CareSage predictive model.

Sample Size Calculation

A study with a comparable population by Coleman et al [16] reported a reduction for hospital visits over a 180-day period to 23% in the invention group versus 32% in matched controls. Based on these proportions, 80% power, and a type I error (alpha) of 0.05, at least 386 participants in each group are needed. Accounting for an estimated lost to follow-up of 15%, this increases to at least 454 participants. The sample size for the intervention arm was therefore set at 500.

Ethical Considerations

The Sicher Zuhause study will be conducted in accordance with the most recent version of the Declaration of Helsinki. The study has been assessed and approved by the internal board of ethics of Philips Research (Internal Committee of Biomedical Experiments), and has been reviewed and approved by the Western Institutional Review Board (WIRB, tracking number 20182221).

All data collected in the study will be maintained in compliance with the General Data Protection Regulation privacy directive and the German data protection law. Data will be pseudonymized where possible and kept encrypted both in transit and at rest.

Results

The enrollment of participants began mid-2019 and is expected to be complete by end of 2020. Enrollment is expected to take longer than usual based on the number of new PERS subscribers over time in the geographical area covered by the response centers in the study. Data collection is expected to be completed by summer of 2020. Initial results are expected to be available in fall of 2021.

Discussion

This protocol describes a study that aims to determine if the combination of risk scores determined through predictive modeling and interventions offered by a case manager can result in a reduction of hospital admissions and health care costs in a German PERS subscriber population. The rapidly aging population with multiple comorbidities presents numerous challenges to effective care management, and therefore, alternatives to hospital and institutional care are needed to optimize health care costs and improve patient outcomes [17]. In the future, the results of this study can lead to better health outcomes for the population described.

This study has a few limitations. First, it does not include a randomized design, and the use of a retrospective control group may lead to selection bias. In the study, this concern is partially addressed by the use of propensity score matching. Second, the effect of the risk prediction and the interventions cannot be easily separated. As such, the study aims to evaluate the combination of the two, where the predictive model helps to identify the right subset of participants to whom interventions should be offered. Further, analysis of the qualitative data can help to provide insights into the performance of the predictive model and the effectiveness of the interventions. Another option would be to include additional study arms; however, due to the expected recruitment rate, this is likely not feasible.

A third limitation is that it might be difficult to capture data on health care utilization that may be initiated outside of the PERS service. Capturing emergency department visits and hospitalizations is important because the study population is a high health care utilization group that is at risk for emergency transport, and patients are typically taken to the nearest medical center for emergency care services. However, self-reported data from patients may help mitigate some of these challenges.

Conflicts of Interest

MP, JodB, and AL are employed by Philips.

References

1. Suzman R, Beard JR, Boerma T, Chatterji S. Health in an ageing world—what do we know? The Lancet 2015 Feb;385(9967):484-486. [doi: 10.1016/S0140-6736(14)61597-X]
2. Messelken M, Kehrberger E, Dirks B, Fischer M. The quality of emergency medical care in Baden-Württemberg (Germany): four years in focus. Dtsch Arztebl Int 2010 Jul;107(30):523-530 [FREE Full text] [doi: 10.3238/arztebl.2010.0523] [Medline: 20737058]
3. Hagist C, Kotlikoff L. Health care spending: what the future will look like. Dallas: National Center for Policy Analysis; Jun 2006.
4. Iwata M, Kuzuya M, Kitagawa Y, Iguchi A. Emergency department use by nonagenarian patients. Geriatr Gerontol Int 2006 Mar;6(1):25-31. [doi: 10.1111/j.1447-0594.2006.00310.x]
5. Downing A, Wilson R. Older people's use of Accident and Emergency services. Age Ageing 2005 Jan;34(1):24-30. [doi: 10.1093/ageing/afh214] [Medline: 15496462]
6. De Vries EN, Ramrattan MA, Smorenburg SM, Gouma DJ, Boermeester MA. The incidence and nature of in-hospital adverse events: a systematic review. Qual Saf Health Care 2008 Jun;17(3):24-30 [FREE Full text] [doi: 10.1136/qshc.2007.023622] [Medline: 18519629]

7. Op den Buijs J, Simons M, Golas S, Fischer N, Felsted J, Schertzer L, et al. Predictive Modeling of 30-Day Emergency Hospital Transport of Patients Using a Personal Emergency Response System: Prognostic Retrospective Study. JMIR Med Inform 2018 Dec 27;6(4):e49 [FREE Full text] [doi: 10.2196/medinform.9907] [Medline: 30482741]
8. Op den Buijs J, Smits T, Pijl M, Simons M, Schertzer L. Predictive Modeling of Emergency Hospital Transport Using Medical Alert Pattern Data: Retrospective Cohort Study. iproc 2015 Oct 27;1(1):e19 [FREE Full text] [doi: 10.2196/iproc.4772]
9. Palacholla RS, Fischer NC, Agboola S, Nikolova-Simons M, Odametey S, Golas SB, et al. Evaluating the Impact of a Web-Based Risk Assessment System (CareSage) and Tailored Interventions on Health Care Utilization: Protocol for a Randomized Controlled Trial. JMIR Res Protoc 2018 May 09;7(5):e10045 [FREE Full text] [doi: 10.2196/10045] [Medline: 29743156]
10. Caplan GA, Williams AJ, Daly B, Abraham K. A randomized, controlled trial of comprehensive geriatric assessment and multidisciplinary intervention after discharge of elderly from the emergency department--the DEED II study. J Am Geriatr Soc 2004 Oct;52(9):1417-1423. [doi: 10.1111/j.1532-5415.2004.52401.x] [Medline: 15341540]
11. Coleman EA, Parry C, Chalmers S, Min S. The Care Transitions Intervention. Arch Intern Med 2006 Sep 25;166(17):1822-1828. [doi: 10.1001/archinte.166.17.1822]
12. Koehler BE, Richter KM, Youngblood L, Cohen BA, Prengler ID, Cheng D, et al. Reduction of 30-day postdischarge hospital readmission or emergency department (ED) visit rates in high-risk elderly medical patients through delivery of a targeted care bundle. J Hosp Med 2009 May;4(4):211-218. [doi: 10.1002/jhm.427] [Medline: 19388074]
13. Naylor MD, Brooten D, Campbell R, Jacobsen BS, Mezey MD, Pauly MV, et al. Comprehensive Discharge Planning and Home Follow-up of Hospitalized Elders. JAMA 1999 Feb 17;281(7):613-620. [doi: 10.1001/jama.281.7.613] [Medline: 25996397]
14. Linden A, Adams J. Using propensity score-based weighting in the evaluation of health management programme effectiveness. J Eval Clin Pract 2010 Mar;16(1):175-179. [doi: 10.1111/j.1365-2753.2009.01219.x] [Medline: 20367829]
15. D'Agostino RB. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Statist. Med 1998 Oct 15;17(19):2265-2281. [doi: 10.1002/(sici)1097-0258(19981015)17:19<2265::aid-sim918>3.0.co;2-b]
16. Coleman EA, Smith JD, Frank JC, Min S, Parry C, Kramer AM. Preparing patients and caregivers to participate in care delivered across settings: the Care Transitions Intervention. J Am Geriatr Soc 2004 Nov;52(11):1817-1825. [doi: 10.1111/j.1532-5415.2004.52504.x] [Medline: 15507057]
17. Matthew-Maich N, Harris L, Ploeg J, Markle-Reid M, Valaitis R, Ibrahim S, et al. Designing, Implementing, and Evaluating Mobile Health Technologies for Managing Chronic Conditions in Older Adults: A Scoping Review. JMIR mHealth uHealth 2016 Jun 09;4(2):e29. [doi: 10.2196/mhealth.5127] [Medline: 27282195]

Abbreviations

DRK: German Red Cross (Deutsches Rotes Kreuz)
DRKS: German clinical trials register (Deutsches Register Klinischer Studien)
PERS: personal emergency response system
TK: Techniker Krankenkasse
US: United States

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Protocol

Impact of Chronic Use of Antimalarials on SARS-CoV-2 Infection in Patients With Immune-Mediated Rheumatic Diseases: Protocol for a Multicentric Observational Cohort Study

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Abstract

Background: COVID-19, caused by the virus SARS-CoV-2, has brought extensive challenges to the scientific community in recent months. Several studies have been undertaken in an attempt to minimize the impact of the disease worldwide. Although new knowledge has been quickly disseminated, including viral mechanisms, pathophysiology, and clinical findings, there is a lack of information on the effective pharmacological management of this disease. In vitro studies have shown some benefits related to the use of antimalarials (chloroquine and hydroxychloroquine) for inhibiting SARS-CoV-2. However, the data from open clinical trials on COVID-19 patients are controversial.

Objective: We present the protocol for a research project that compares the potential protective effect of antimalarials in preventing moderate-to-severe forms of COVID-19 in two groups: (1) patients treated chronically with antimalarials for rheumatic diseases and (2) other members of the patients' household who have not been diagnosed with rheumatic diseases and are not taking antimalarials.

Methods: This is a 24-week, prospective, observational cohort study comprising patients from public and private health services across Brazil, who chronically use antimalarials for the treatment of immune-mediated rheumatic diseases, osteoarthritis, or chikungunya-related arthropathy. A total of six sequential phone interviews were scheduled during the COVID-19 outbreak in five different regions of Brazil. Information regarding social, epidemiological, and demographic data, as well as details about rheumatic diseases, antimalarials, comorbidities, and concomitant medication, is being recorded using a specific online form in the REDCap database. Symptoms suggestive of COVID-19, including fever, cough, dyspnea, anosmia, and dysgeusia, are being self-reported and collected via phone interviews. Our main outcomes are hospitalization, need of intensive care unit, and death.

Results: Recruitment began at the end of March 2020, and the inclusion was done during an 8-week period (from March 29 to May 17) with a total of 10,443 individuals enrolled at baseline, 5166 of whom have rheumatic diseases, from 23 tertiary rheumatology centers across 97 Brazilian cities. Data analysis is scheduled to begin after all inclusion data have been collected.

Conclusions: This study, which includes a large sample of chronic antimalarial users, will allow us to explore whether SARS-CoV-2 infection may be associated with immune-mediated rheumatic diseases and long-term antimalarial usage.

Trial Registration: Brazilian Registry of Clinical Trials RBR–9KTWX6; http://www.ensaiosclinicos.gov.br/rg/RBR-9ktwx6/

International Registered Report Identifier (IRRID): DERR1-10.2196/23532

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KEYWORDS

COVID-19; SARS-CoV-2; coronavirus; antimalarial; rheumatic diseases; mortality; immune system; immunology; protocol; observational; pharmacological; drug

Introduction

COVID-19, which originated from Wuhan, China, in December 2019, remains a major challenge for scientists and the medical community as it continues to spread rapidly across the world [1,2]. The rapid transmission of the disease, which is caused by the novel coronavirus SARS-CoV-2, and the need to minimize its impact have caused scientific research and information to emerge at a record speed, but there are still numerous knowledge gaps [3-6].

In recent months, a marked information revolution has been observed, relating to viral mechanisms, pathophysiology, and heterogeneous clinical findings with different severity grades. Those infected with COVID-19 range from asymptomatic individuals to critically ill patients with outcomes like severe acute respiratory syndrome, coagulopathy (a prothrombotic state triggered by inflammation and other factors), and death [7-13]. Age and concomitant diseases, especially hypertension, diabetes, and heart, kidney, and lung diseases, are associated with poor outcomes [14-18].

Considering there is no specific, effective pharmacological treatment for COVID-19, several drugs have been tested, such as antivirals (lopinavir-ritonavir, remdesivir, favipiravir); antimalarials alone or combined with azithromycine; interleukin 6 (IL-6) antagonists; Janus kinase inhibitors and interferon, as well as other procedures (extracorporeal membrane oxygenation and convalescent plasma). However, to date, there are no data on the potential preventive effect of any of these, regardless of timing (pre-exposure, symptomatic period, or inflammatory phase) [19-27].

The role of chloroquine and hydroxychloroquine in treating patients with malaria and immune-mediated rheumatic diseases (IMRD) is well-known, especially in cases of systemic lupus erythematous and rheumatoid arthritis. In vitro studies have shown antimalarials have an antiviral effect against some viruses, such as SARS-CoV (severe acute respiratory syndrome–associated coronavirus), MERS-CoV (Middle East respiratory syndrome coronavirus), SARS-CoV-2, HIV, Zika, and influenza A(H5N1), especially in relation to endosomal membrane pH changes and an inhibitory mechanism to hamper the viral entry inside the cells. However, clinical trials are controversial and present many methodological problems, including randomization, dosage, time of use, endpoint definitions, outcomes, and safety issues [28-35].

Among rheumatologists, antimalarials have been used safely and effectively for several decades in patients with rheumatic diseases [36]. For this reason, rheumatologists and rheumatic patients who are long-term users of antimalarials were involved in COVID-19–related discussions and research [37-39]. Our main hypothesis is that patients with rheumatic diseases who chronically use antimalarials could have a lower rate of moderate-to-severe forms of COVID-19 since these drugs work as immune modulators in mitigating cytokine storm and poor prognosis.

Objectives

Our primary aim is to assess the potential preventive effects of antimalarials in reducing the incidence of moderate-to-severe forms of COVID-19 in patients with rheumatic diseases. Secondarily, we aim to determine the frequency of SARS-CoV-2 infection in patients with rheumatic diseases who are chronic users of antimalarials. For both objectives, patients with rheumatic diseases will be compared with members of their household who are not taking antimalarials.

Methods

Design

The study design will be a prospective, multicentric, observational cohort study with a control group.

Sample Size

Considering a moderate-to-severe COVID-19 rate as the dependent variable, a rate which the current literature estimates to be 20% [4,6,10-18,40-42] as well as the proportion of 1 case for every 2 controls, the sample calculation was approximately 3000 antimalarial users and 6000 nonusers, with an error α=5% and β=20%.

Inclusion Criteria

The inclusion criteria are as follows:

- Men and women;
- >18 years of age;
- Use of antimalarials for at least 30 days before inclusion in the study;
- Diagnosis of IMRD (according to the criteria of the American College of Rheumatology or European League Against Rheumatism), rheumatoid arthritis [43], systemic lupus erythematosus [44], Sjögren's syndrome [45], systemic sclerosis [46], inflammatory myopathies [47], and mixed connective tissue disease [48];

- Diagnosis of osteoarthritis (subgroup) [49];
- Diagnosis of chikungunya-related arthropathy (subgroup).

Exclusion Criteria

The exclusion criteria, which apply to both patients and controls, are as follows:

- Previous use of chloroquine or equivalent that was not in the past 6 months;
- History of solid organ or bone marrow transplantation;
- Neoplasm of solid organs or lymphatic or myeloproliferative lineage in the past 12 months with or without adjuvant chemotherapy;
- Positive HIV status, regardless of highly active antiretroviral therapy;
- Use of intravenous human immunoglobulin in the past 30 days;
- End-stage renal disease on peritoneal dialysis and hemodialysis.

Control Group

The control group will consist of healthy individuals aged >18 years, who are household cohabitants or work colleagues of patients with rheumatic diseases in the intervention group.

Contact with a suspected or confirmed case of COVID-19 is defined as an individual sharing accommodations with a patient with a rheumatic disease (eg, residing in the same house or environment as roommates, occupational colleagues, etc). The exposure grade assessment is individualized, considering the type of environment and the exposure time.

For each case, two household and/or professional contact individuals will be selected as controls. The choice of the first control is prioritized by flu-like symptoms and defined as the "symptomatic group," including suspected or confirmed cases. Those without symptoms will comprise the "asymptomatic group;" both household and/or contact individuals can be selected, preferably paired for age and sex.

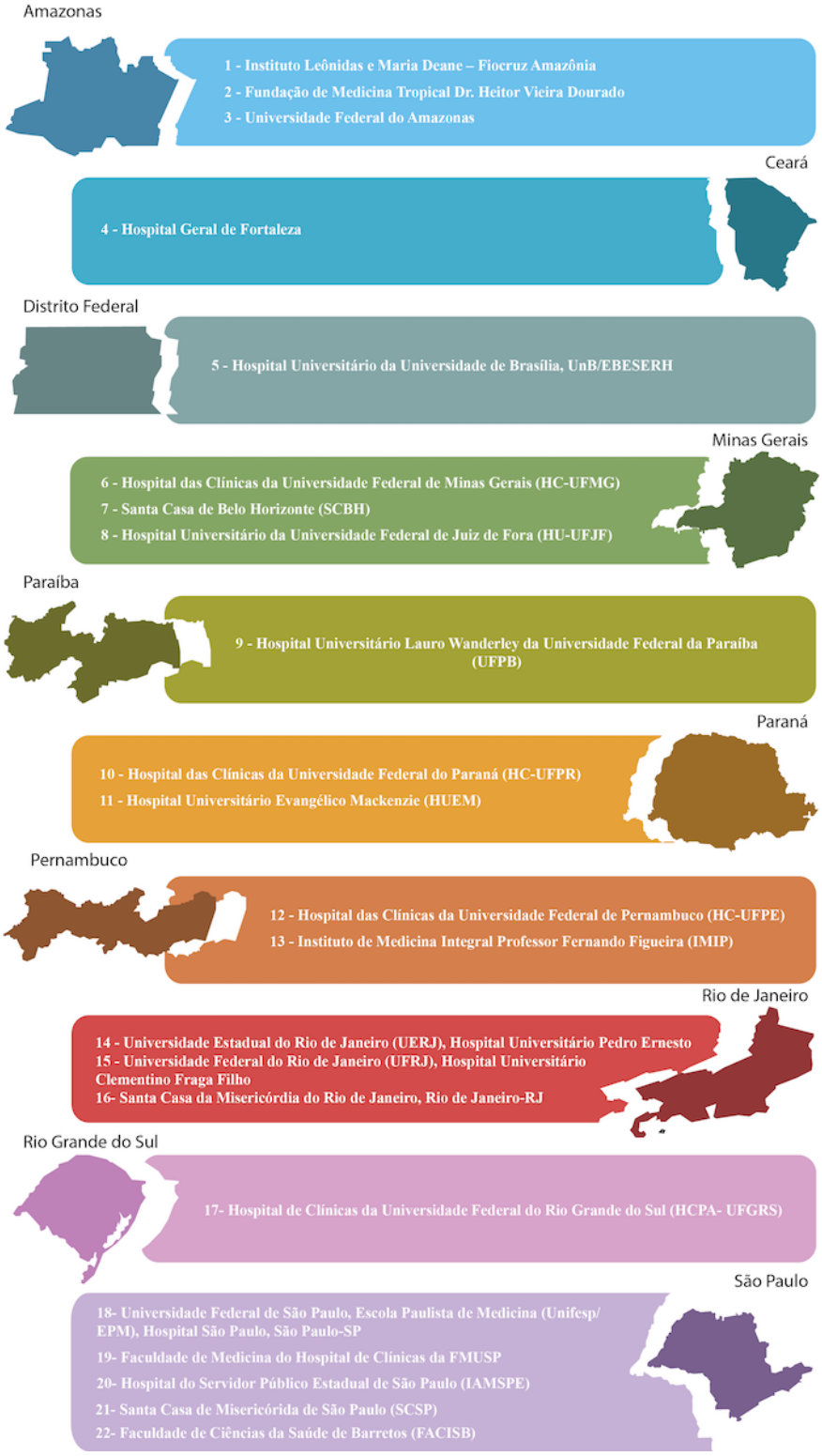
The household and/or workplace contacts were chosen to characterize the control group because of their high epidemiological value during community viral transmissions worldwide, instead of including nonusers of antimalarials with rheumatic diseases. Moreover, lupus patients without antimalarial treatment are quite uncommon, except in those with previous toxicity (maculopathy, allergy, long-term remission, etc).

Data Collection

Data are being collected regarding social, epidemiological, and demographic characteristics, as well as detailed information on antimalarials (type of salt, dosage, frequency, adherence during the pandemic) and rheumatic disease (diagnosis, disease activity). In addition, aspects related to comorbidities, smoking, alcohol intake, and concomitant medications are being recorded, as well as specific information about COVID-19 symptoms and main outcomes (hospitalization, need for intensive care unit, and death) in both groups (Multimedia Appendix 1).

All phone interviews are being conducted by health care professionals (eg, volunteer medical students), all previously trained by the principal investigator or subinvestigator from each rheumatology center (Figure 1). This training included a tutorial in PDF and video formats about each step of the study protocol. In addition, several WhatsApp-based groups were formed and supervised by the principal investigator, subinvestigator, or study coordinators to find the best solution for minimizing eventual problems.

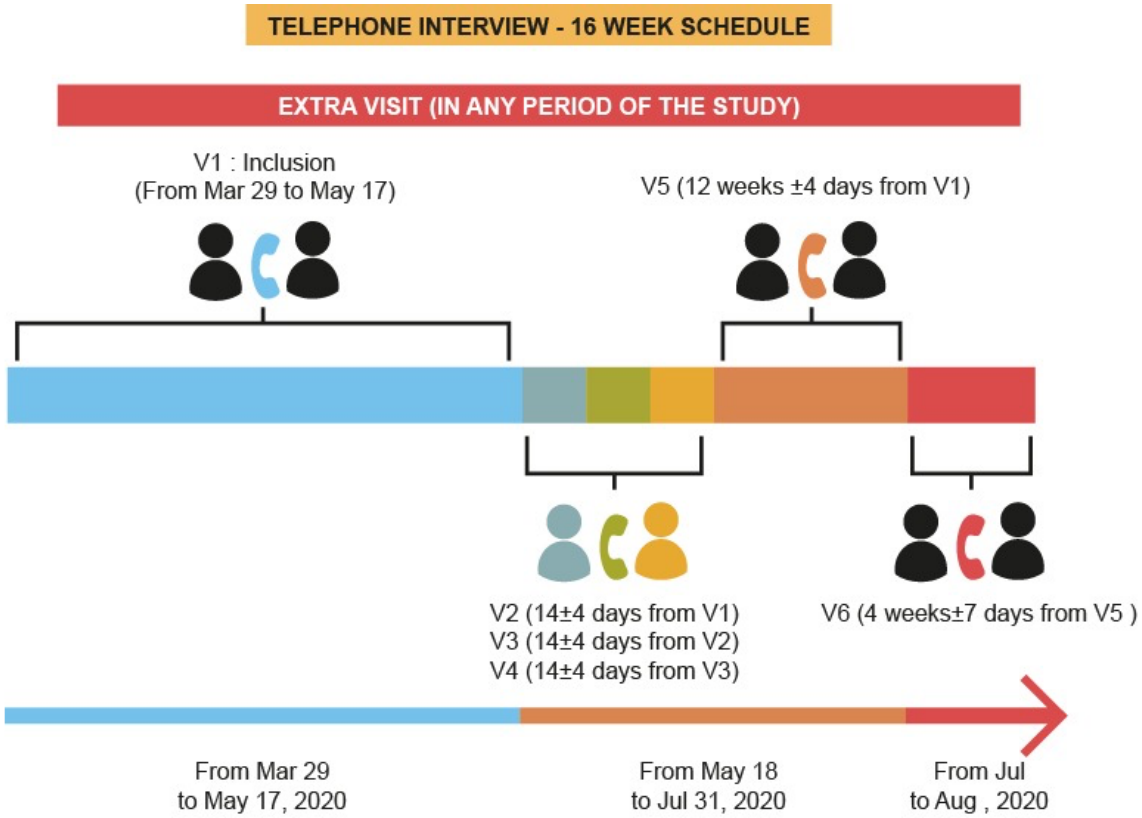
Figure 1. Centers participating in the study.



All patients and controls gave a verbal informed consent before participating in this cohort study. The need for signed informed consent was waived by the Brazilian National Ethics Committee (CONEP) due to the urgency of the pandemic. However, it is worth emphasizing that participation was voluntary for both groups. Research subjects will not be identified by their full name at any time and will not have their personal data disclosed.

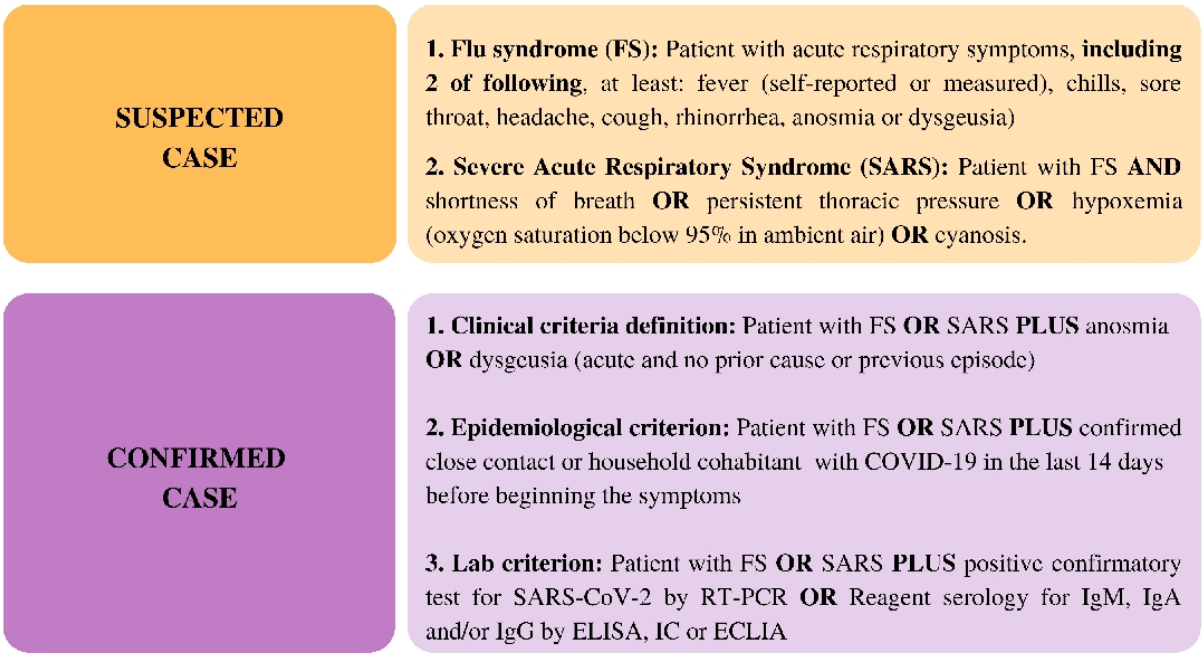
The data are being stored on the REDCap platform, with telephone interviews performed as shown in Figure 2. Interviews with patients with invalid contact information or who did not answer the telephone after three consecutive calls at intervals of 3 days were canceled, although patients were not removed from the study. All patients will be evaluated during the closing visit (V6), unless they decline to participate, regardless of whether intermediary visits were missed (V2 to V5).

Figure 2. Telephone interview schedule.



A clinically confirmed case of COVID-19 was defined according to the Brazilian Ministry of Health criteria [50] that included self-reported symptoms (fever, cough, nasal congestion, shortness of breath, malaise, myalgia, decline in general condition, and sudden anosmia and/or dysgeusia) and/or have been in contact with someone with a confirmed or suspected case of COVID-19. A positive PCR (polymerase chain reaction) test for SARS-CoV-2, via oropharyngeal and nasopharyngeal sampling or a specific confirmatory serology (immunoglobulin G and/or immunoglobulin M), is needed to test for infection, according to the Brazilian Ministry of Health [50] (Figure 3).

Figure 3. Suspected vs confirmed cases of COVID-19. RT-PCR: real-time polymerase chain reaction, IgM: immunoglobulin M, IgA: immunoglobulin A, IgG: immunoglobulin G, ELISA: enzyme-linked immunosorbent assay, IC: ion channel, ECLIA: electrochemiluminescence immunoassay.



Moderate-to-severe cases are defined as those that require hospitalization, mechanical ventilation, or result in death. Through direct contact with hospitals, hospitalized patients are being clinically evaluated in terms of longitudinal follow-up and treatment outcome, infection severity, length of stay, need for intensive care, mechanical ventilation, and cause of death.

Considering the heterogeneous community viral transmission in Brazil, some epidemiological approaches were developed to assure a similar path involving patients with rheumatic diseases and controls, such as the same pandemic COVID-19 curve in each city and region [41]. Therefore, after initial contact (V1), two strategies were adopted to maintain the follow-up of patients and to optimize the capture of main outcomes. Firstly, an active strategy is addressed in cases of flu-like syndrome and symptoms suggestive of COVID-19. For this strategy, the patient or household member is shown how to provide clinical data on the patient or his/her control through a toll-free telephone number (the 0800 system). Secondly, the patient is contacted every week by the REDCap team to gather relevant data on infection. An additional visit is conducted if the patient or control provides information about flu symptoms or disease activity via an unscheduled phone call or contact through the toll-free number. In both cases the individual will be advised to stay home and use painkillers or an antipyretic. In case of worsening/severe symptoms (eg, persistent cough or fever and shortness of breath), they will be advised to visit a hospital or to make an appointment with a physician involved in our study.

Outcomes

Primary outcomes (at baseline and during the 24-week study period) are as follows:

- SARS-CoV-2 infection (illness): suspected, suggestive, or confirmed
- Death
- Hospitalization
- Need for intensive care unit
- Need for mechanical ventilation
- Total hospitalization time
- Date of occurrence of an adverse event (eg, death, hospitalization)

Secondary outcomes are as follows:

- General clinical differences in COVID-19 course severity between rheumatic patients and nonrheumatic controls;
- Initial clinical differences and progression to moderate or severe course of disease between the two groups.

Confounding and adjustment variables are age, sex, comorbidities, concomitant medications, and flu vaccine.

Ethics

This project was registered with the Brazilian Registry of Clinical Trials (ID RBR-9KTWX6).

The project, which is currently in the data collection phase, was approved by the Brazilian Committee of Ethics in Human Research–CONEP (CAAE 30246120.3.1001.5505).

Statistical Analysis

The data will be analyzed using descriptive statistics—absolute and relative frequencies for categorical variables and quantitative measures (mean, quartiles, minimum, maximum, and standard deviation) for numerical variables. The normality of the data will be verified using the Kolmogorov-Smirnov test.

A chi-square test will be used to assess the association between categorical variables with standardized adjusted residual calculation; Fisher exact test will be used for small samples. The linear associations between two variables of a numerical nature will be evaluated using Pearson correlation.

To evaluate the behavior of clinical variables between two points in time by group, analysis of variance (ANOVA) will be used, with repeated measures. In the case of nonnormality of data, the means of the groups at each time point will be compared using the Kruskal-Wallis nonparametric test. To compare the means between phone visits in each group, the Wilcoxon nonparametric test will be used.

The comparison between the means of numerical variables with normal distribution will be verified through the Student *t* test. If the assumption of normality is violated, the Mann-Whitney nonparametric test will be used.

Adjusted multiple linear regression models will be used to assess the simultaneous effects of sex, age, duration of illness, comorbidities, concomitant medications, and other confounding variables, according to group and predefined outcomes. For dichotomous dependent variables, a logistic regression model will be preferred. Survival analysis models, including log rank and Kaplan-Meier tests, adjusted for confounding variables, will be developed to assess the main outcomes over time. The time defined as the end date will be the date of a major event, such as illness with confirmation or suspicion of infection, hospitalization, or death.

Correlation analysis will be performed using the Pearson test to assess the relationship between the incidence rate of confirmed COVID-19 cases per 100,000 inhabitants and the proportion of symptomatic patients and controls in municipalities. Data of confirmed cases per municipality are available through the Brasil.io project [51]. The QGIGS Desktop 3.6.0 (Open Source Geospatial Foundation) will be used for map plotting.

SPSS, version 20 (IMB Corp) will be used in all analyses, and a P value <.05 will be considered significant.

Results

This study is in the data collection phase. Study recruitment opened in March 2020. In an 8-week period (from March 29 to May 17), a total of 10,443 individuals enrolled at baseline (including 5166 patients with rheumatic diseases) from 23 tertiary rheumatology centers in 97 Brazilian cities. Data analysis is scheduled to start after all relevant data have been collected.

Discussion

This study's novel design, with its large sample of chronic antimalarial users, will enable us to perform a thorough prospective assessment (every 2 weeks) to explore whether vulnerability to SARS-CoV-2 infection may be associated with IMRD or to hydroxychloroquine after adjustments for cofounders, especially those related to other immunosuppressive drugs and comorbidities. On the other hand, it has some limitations, such as compliance and adherence; a potential shortage of HCQ (hydroxychloroquine) in some parts of our country; possible biases associated with recalling symptoms; inability to answer the phone (due to hospitalization or death), and lack of confirmatory tests (PCR tests for SARS-CoV-2 or antibody-based RNA [ribonucleic acid]) for all enrolled patients and controls, especially in those with nonsevere forms. Future randomized controlled trials may provide a better understanding of these differences.

Conflicts of Interest

LM has received personal or institutional support from Abbvie, Janssen, Pfizer and Roche, and has delivered speeches at events related to this work and sponsored by Abbvie, Boehringer Ingelheim, GSK, Janssen, Libbs, Lilly, Novartis, Pfizer, Roche, Sandoz, and UCB. AG has received personal or institutional support from Pfizer and Abbvie.

Multimedia Appendix 1
Data collection form.
[PDF File (Adobe PDF File), 44 KB - resprot_v9i10e23532_app1.pdf]

References

1. Salata C, Calistri A, Parolin C, Palù G. Coronaviruses: a paradigm of new emerging zoonotic diseases. Pathog Dis 2019 Dec 01;77(9):a [FREE Full text] [doi: 10.1093/femspd/ftaa006] [Medline: 32065221]
2. Li X, Wang W, Zhao X, Zai J, Zhao Q, Li Y, et al. Transmission dynamics and evolutionary history of 2019-nCoV. J Med Virol 2020 May 14;92(5):501-511 [FREE Full text] [doi: 10.1002/jmv.25701] [Medline: 32027035]
3. Bonini S, Maltese G. COVID-19 Clinical trials: Quality matters more than quantity. Allergy 2020 May 20 [FREE Full text] [doi: 10.1111/all.14409] [Medline: 32434272]
4. Teymoori-Rad M, Samadizadeh S, Tabarraei A, Moradi A, Shahbaz MB, Tahamtan A. Ten challenging questions about SARS-CoV-2 and COVID-19. Expert Rev Respir Med 2020 Jun 30:1-8. [doi: 10.1080/17476348.2020.1782197] [Medline: 32536226]
5. Khatami A. Filling in the gaps. J Paediatr Child Health 2020 Aug 29;56(8):1172-1172. [doi: 10.1111/jpc.15026] [Medline: 32596874]
6. Fidahic M, Nujic D, Runjic R, Civljak M, Markotic F, Lovric Makaric Z, et al. Research methodology and characteristics of journal articles with original data, preprint articles and registered clinical trial protocols about COVID-19. BMC Med Res Methodol 2020 Jun 22;20(1):161 [FREE Full text] [doi: 10.1186/s12874-020-01047-2] [Medline: 32571302]
7. Polak SB, Van Gool IC, Cohen D, von der Thüsen JH, van Paassen J. A systematic review of pathological findings in COVID-19: a pathophysiological timeline and possible mechanisms of disease progression. Mod Pathol 2020 Jun 22 [FREE Full text] [doi: 10.1038/s41379-020-0603-3] [Medline: 32572155]
8. Chang D, Zhao P, Zhang D, Dong J, Xu Z, Yang G, et al. Persistent Viral Presence Determines the Clinical Course of the Disease in COVID-19. J Allergy Clin Immunol Pract 2020 Sep;8(8):2585-2591.e1 [FREE Full text] [doi: 10.1016/j.jaip.2020.06.015] [Medline: 32574840]
9. Cleary S, Pitchford S, Amison R, Carrington R, Robaina CC, Magnen M. Animal models of mechanisms of SARS-CoV-2 infection and COVID-19 pathology. Br J Pharmacol 2020:e [FREE Full text] [doi: 10.22541/au.158861365.54417186]
10. Tu H, Tu S, Gao S, Shao A, Sheng J. Current epidemiological and clinical features of COVID-19; a global perspective from China. J Infect 2020 Jul;81(1):1-9 [FREE Full text] [doi: 10.1016/j.jinf.2020.04.011] [Medline: 32315723]
11. Hassan S, Sheikh F, Jamal S, Ezeh J, Akhtar A. Coronavirus (COVID-19): A Review of Clinical Features, Diagnosis, and Treatment. Cureus 2020 Mar 21;12(3):e7355 [FREE Full text] [doi: 10.7759/cureus.7355] [Medline: 32328367]
12. Park J, Jang W, Kim S, Lee J, Lim Y, Cho C, et al. The Clinical Manifestations and Chest Computed Tomography Findings of Coronavirus Disease 2019 (COVID-19) Patients in China: A Proportion Meta-Analysis. Clin Exp Otorhinolaryngol 2020 May;13(2):95-105 [FREE Full text] [doi: 10.21053/ceo.2020.00570] [Medline: 32434310]
13. Gulati A, Pomeranz C, Qamar Z, Thomas S, Frisch D, George G, et al. A Comprehensive Review of Manifestations of Novel Coronaviruses in the Context of Deadly COVID-19 Global Pandemic. Am J Med Sci 2020 Jul;360(1):5-34 [FREE Full text] [doi: 10.1016/j.amjms.2020.05.006] [Medline: 32620220]
14. Yang R, Gui X, Zhang Y, Xiong Y. The role of essential organ-based comorbidities in the prognosis of COVID-19 infection patients. Expert Rev Respir Med 2020 Aug 28;14(8):835-838 [FREE Full text] [doi: 10.1080/17476348.2020.1761791] [Medline: 32345072]

15. Asfahan S, Deokar K, Dutt N, Niwas R, Jain P, Agarwal M. Extrapolation of mortality in COVID-19: Exploring the role of age, sex, co-morbidities and health-care related occupation. Monaldi Arch Chest Dis 2020 May 21;90(2) [FREE Full text] [doi: 10.4081/monaldi.2020.1325] [Medline: 32447949]
16. Singh AK, Gillies CL, Singh R, Singh A, Chudasama Y, Coles B, et al. Prevalence of co-morbidities and their association with mortality in patients with COVID-19: A systematic review and meta-analysis. Diabetes Obes Metab 2020 Jun 23 [FREE Full text] [doi: 10.1111/dom.14124] [Medline: 32573903]
17. Ji W, Huh K, Kang M, Hong J, Bae GH, Lee R, et al. Effect of Underlying Comorbidities on the Infection and Severity of COVID-19 in Korea: a Nationwide Case-Control Study. J Korean Med Sci 2020 Jun 29;35(25):e237 [FREE Full text] [doi: 10.3346/jkms.2020.35.e237] [Medline: 32597048]
18. Ye C, Zhang S, Zhang X, Cai H, Gu J, Lian J, et al. Impact of comorbidities on patients with COVID-19: A large retrospective study in Zhejiang, China. J Med Virol 2020 Jun 16 [FREE Full text] [doi: 10.1002/jmv.26183] [Medline: 32543710]
19. Rabby MII. Current Drugs with Potential for Treatment of COVID-19: A Literature Review. J Pharm Pharm Sci 2020 Apr 04;23(1):58-64 [FREE Full text] [doi: 10.18433/jpps31002] [Medline: 32251618]
20. Xu X, Ong YK, Wang DY. Role of adjunctive treatment strategies in COVID-19 and a review of international and national clinical guidelines. Mil Med Res 2020 May 05;7(1):22 [FREE Full text] [doi: 10.1186/s40779-020-00251-x] [Medline: 32370766]
21. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: A single center experience. J Med Virol 2020 Jul 15;92(7):814-818 [FREE Full text] [doi: 10.1002/jmv.25801] [Medline: 32253759]
22. Zumla A, Hui DS, Azhar EI, Memish ZA, Maeurer M. Reducing mortality from 2019-nCoV: host-directed therapies should be an option. The Lancet 2020 Feb;395(10224):e35-e36. [doi: 10.1016/s0140-6736(20)30305-6]
23. Hung I, Lung K, Tso E, Liu R, Chung T, Chu M, et al. Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. The Lancet 2020 May;395(10238):1695-1704. [doi: 10.1016/S0140-6736(20)31042-4]
24. Venkatasubbaiah M, Dwarakanadha Reddy P, Satyanarayana SV. Literature-based review of the drugs used for the treatment of COVID-19. Curr Med Res Pract 2020 May;10(3):100-109 [FREE Full text] [doi: 10.1016/j.cmrp.2020.05.013] [Medline: 32572376]
25. Zhang L, Liu Y. Potential interventions for novel coronavirus in China: A systematic review. J Med Virol 2020 May 03;92(5):479-490 [FREE Full text] [doi: 10.1002/jmv.25707] [Medline: 32052466]
26. Juul S, Nielsen N, Bentzer P, Veroniki AA, Thabane L, Linder A, et al. Interventions for treatment of COVID-19: a protocol for a living systematic review with network meta-analysis including individual patient data (The LIVING Project). Syst Rev 2020 May 09;9(1):108 [FREE Full text] [doi: 10.1186/s13643-020-01371-0] [Medline: 32386514]
27. Jean S, Lee P, Hsueh P. Treatment options for COVID-19: The reality and challenges. J Microbiol Immunol Infect 2020 Jun;53(3):436-443 [FREE Full text] [doi: 10.1016/j.jmii.2020.03.034] [Medline: 32307245]
28. Pastick K, Okafor E, Wang F, Lofgren S, Skipper C, Nicol M, et al. Review: Hydroxychloroquine and Chloroquine for Treatment of SARS-CoV-2 (COVID-19). Open Forum Infect Dis 2020 Apr;7(4):ofaa130 [FREE Full text] [doi: 10.1093/ofid/ofaa130] [Medline: 32363212]
29. Saqrane S, El Mhammedi M. Review on the global epidemiological situation and the efficacy of chloroquine and hydroxychloroquine for the treatment of COVID-19. New Microbes New Infect 2020 May;35:100680 [FREE Full text] [doi: 10.1016/j.nmni.2020.100680] [Medline: 32322402]
30. Sun J, Chen Y, Fan X, Wang X, Han Q, Liu Z. Advances in the use of chloroquine and hydroxychloroquine for the treatment of COVID-19. Postgrad Med 2020 Jun 21:1-10 [FREE Full text] [doi: 10.1080/00325481.2020.1778982] [Medline: 32496926]
31. Meo S, Klonoff D, Akram J. Efficacy of chloroquine and hydroxychloroquine in the treatment of COVID-19. Eur Rev Med Pharmacol Sci 2020 Apr;24(8):4539-4547 [FREE Full text] [doi: 10.26355/eurrev_202004_21038] [Medline: 32373993]
32. Al-Bari MAA. Facts and myths: Efficacies of repurposing chloroquine and hydroxychloroquine for the treatment of COVID-19. Curr Drug Targets 2020 Jun 17;21. [doi: 10.2174/1389450121666200617133142] [Medline: 32552642]
33. Shukla AM, Archibald LK, Wagle Shukla A, Mehta HJ, Cherabuddi K. Chloroquine and hydroxychloroquine in the context of COVID-19. Drugs Context 2020 Apr 28;9:1-8 [FREE Full text] [doi: 10.7573/dic.2020-4-5] [Medline: 32373183]
34. Sarma P, Kaur H, Kumar H, Mahendru D, Avti P, Bhattacharyya A, et al. Virological and clinical cure in COVID-19 patients treated with hydroxychloroquine: A systematic review and meta-analysis. J Med Virol 2020 Jul 03;92(7):776-785 [FREE Full text] [doi: 10.1002/jmv.25898] [Medline: 32297988]
35. Liu W, Zhou P, Chen K, Ye Z, Liu F, Li X, et al. Efficacy and safety of antiviral treatment for COVID-19 from evidence in studies of SARS-CoV-2 and other acute viral infections: a systematic review and meta-analysis. CMAJ 2020 Jul 06;192(27):E734-E744. [doi: 10.1503/cmaj.200647] [Medline: 32493740]
36. Dos Reis Neto ET, Kakehasi AM, de Medeiros Pinheiro M, Ferreira GA, Marques CDL, da Mota LMH, et al. Revisiting hydroxychloroquine and chloroquine for patients with chronic immunity-mediated inflammatory rheumatic diseases. Adv Rheumatol 2020 Jun 09;60(1):32 [FREE Full text] [doi: 10.1186/s42358-020-00134-8] [Medline: 32517786]

37. Graef ER, Liew JW, Putman MS, Simard JF, Sirotich E, Berenbaum F, COVID-19 Global Rheumatology Alliance. : hydroxychloroquine, COVID-19 and the role of the rheumatologist. Ann Rheum Dis 2020 Jun 15;79(6):734-736 [FREE Full text] [doi: 10.1136/annrheumdis-2020-217480] [Medline: 32295786]
38. Misra DP, Agarwal V, Gasparyan AY, Zimba O. Rheumatologists' perspective on coronavirus disease 19 (COVID-19) and potential therapeutic targets. Clin Rheumatol 2020 Jul 10;39(7):2055-2062 [FREE Full text] [doi: 10.1007/s10067-020-05073-9] [Medline: 32277367]
39. Felten R, Chatelus E, Arnaud L. How and why are rheumatologists relevant to COVID-19? Joint Bone Spine 2020 Jul;87(4):279-280 [FREE Full text] [doi: 10.1016/j.jbspin.2020.04.006] [Medline: 32451147]
40. Coronavirus disease 2019 (COVID-19) — Situation Report – 51. World Health Organization. 2020. URL: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf?sfvrsn=1ba62e57_10 [accessed 2020-06-01]
41. Candido DS, Claro IM, de Jesus JG, Souza WM, Moreira FRR, Dellicour S, Brazil-UK Centre for Arbovirus Discovery, Diagnosis, GenomicsEpidemiology (CADDE) Genomic Network, et al. Evolution and epidemic spread of SARS-CoV-2 in Brazil. Science 2020 Sep 04;369(6508):1255-1260 [FREE Full text] [doi: 10.1126/science.abd2161] [Medline: 32703910]
42. Michaud K, Wipfler K, Shaw Y, Simon TA, Cornish A, England BR, et al. Experiences of Patients With Rheumatic Diseases in the United States During Early Days of the COVID-19 Pandemic. ACR Open Rheumatol 2020 Jun 09;2(6):335-343 [FREE Full text] [doi: 10.1002/acr2.11148] [Medline: 32311836]
43. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010 Sep 10;62(9):2569-2581 [FREE Full text] [doi: 10.1002/art.27584] [Medline: 20872595]
44. Aringer M, Costenbader KH, Daikh D, Brinks R, Mosca M, Ramsey-Goldman R, et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. Arthritis Rheumatol 2019 Sep 04;71(9):1400-1412 [FREE Full text] [doi: 10.1002/art.40930] [Medline: 31385462]
45. Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, International Sjögren's Syndrome Criteria Working Group. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: A consensus and data-driven methodology involving three international patient cohorts. Ann Rheum Dis 2017 Jan 26;76(1):9-16. [doi: 10.1136/annrheumdis-2016-210571] [Medline: 27789466]
46. van den Hoogen F, Khanna D, Fransen J, Johnson S, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum 2013 Nov;65(11):2737-2747 [FREE Full text] [doi: 10.1002/art.38098] [Medline: 24122180]
47. Lundberg IE, Tjärnlund A, Bottai M, Werth VP, Pilkington C, de Visser M, International Myositis Classification Criteria Project Consortium, the Euromyositis Register,the Juvenile Dermatomyositis Cohort Biomarker StudyRepository (UKIreland). 2017 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Adult and Juvenile Idiopathic Inflammatory Myopathies and Their Major Subgroups. Arthritis Rheumatol 2017 Dec 10;69(12):2271-2282 [FREE Full text] [doi: 10.1002/art.40320] [Medline: 29106061]
48. Kasukawa R. Mixed connective tissue disease. Intern Med 1999 May;38(5):386-393 [FREE Full text] [doi: 10.2169/internalmedicine.38.386] [Medline: 10397074]
49. Altman R, Alarcón G, Appelrouth D, Bloch D, Borenstein D, Brandt K, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. Arthritis Rheum 1990 Nov;33(11):1601-1610. [doi: 10.1002/art.1780331101] [Medline: 2242058]
50. Ministry of Health (BR), Health Surveillance Secretariat, Public Health Emergency Operations Center. Coronavirus disease 2019: expansion of surveillance, non-pharmacological measures and decentralization of laboratory diagnosis. 2020 Mar. URL: http://maismedicos.gov.br/images/PDF/2020_03_13_Boletim-Epidemiologico-05.pdf [accessed 2020-06-01]
51. Especial COVID-19: Dados Por Município. Brasil.io. 2020. URL: https://brasil.io/home/ [accessed 2020-06-01]

Abbreviations

ANOVA: analysis of variance
CONEP: Brazilian National Ethics Committee
IL-6: interleukin 6
IMRD: immune-mediated rheumatic diseases
MERS-CoV: Middle East respiratory syndrome coronavirus
PCR: polymerase chain reaction
RNA: ribonucleic acid
SARS-CoV: severe acute respiratory syndrome–associated coronavirus
V: visit

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Protocol

Evaluating a Longitudinal Cohort of Clinics Engaging in the Family Planning Elevated Contraceptive Access Program: Study Protocol for a Comparative Interrupted Time Series Analysis

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Abstract

Background: Access to high-quality, comprehensive contraceptive care is an inherent component of reproductive human rights. However, hindrances to specific aspects of contraceptive provision, including availability, accessibility, acceptability, and quality, continue to perpetuate unmet needs. The state of Utah has recently passed a series of contraceptive policies intended to improve contraceptive access. Despite these positive changes to theoretical access, fiscal appropriations to support the implementation of these policies have been minimal, and many individuals still struggle to access contraception.

Objective: The Family Planning Elevated Contraceptive Access Program (FPE CAP), part of a larger statewide contraceptive initiative, specifically aims to improve contraceptive access within health clinics. This paper describes the study protocol for evaluating the success of FPE CAP.

Methods: Health clinics apply for membership in the FPE CAP. On acceptance in the program, they receive a cash grant for clinical supplies, equipment, and personnel expenses; reimbursement for contraceptive services and methods for eligible clients; technical support, training, and proctoring on counseling and providing all methods of contraception; method stocking of intrauterine devices and implants; and demand generation activities, including local media campaigns, to inform community members about the FPE CAP and possible eligibility. FPE collects monthly service delivery reports from participating clinics for evaluation purposes. The primary outcomes of FPE CAP are level and trend changes in contraceptive service delivery among individuals earning ≤138% federal poverty level (FPL) following membership in FPE CAP and among FPE CAP clients earning between 139% and 250% FPL (including those ineligible for Medicaid) compared with historical data and control clinics. To assess this, we will conduct comparative interrupted time series analyses assessing the level and trend changes in intervention and control clinics 12 months before the intervention, for the 2-year duration of the intervention, and for the subsequent 12 months following the intervention.

Results: We found that the study is adequately powered (>80% power) with our planned number of clinics and the number of months of data available in the study. To date, we have successfully completed the recruitment and enrollment of 8 of the expected 9 health organizations and 4 of the control clinics. Completed health organization enrollment for both intervention and control organizations is expected to be completed in December 2020.

Conclusions: The study aims to provide insight into a new approach to contraceptive initiatives by addressing comprehensive aspects of contraceptive care at the health system level. Ongoing state policy changes and implementation components may affect the evaluation outcomes.

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KEYWORDS

contraception; family planning; contraceptive initiatives; study protocol; reproduction; contraceptive; reproductive health

Introduction

Background

Contraception has been a primary tool to achieve reproductive justice, allowing people to plan their families as they see fit [1]. Acceptability of family planning as a human right has increased and so have policies and approaches to expanding comprehensive access to a wide range of contraceptive methods. In the United States, there have been a number of proactive family planning–friendly policies, including mandated contraceptive coverage by insurers, telehealth contraceptive counseling, web-based provision of short-acting hormonal methods such as oral contraception, over-the-counter availability of emergency contraception, and pharmacy dispensing authorization of hormonal contraception without prescriptions [2-4].

Despite these advances, obstacles to comprehensive contraceptive access remain. An estimated 38 million women in the United States have unmet need for contraception, 20 million of whom are in need of publicly funded family planning services [5]. Furthermore, the majority of studies of unmet need focus on women rather than the more appropriate inclusion of any person who can become pregnant and any person that can contribute to a pregnancy. Inclusion of the contraceptive needs of men and nonbinary individuals likely increases the estimated number of people who need contraception. Meeting the needs of all people of reproductive age also highlights the importance of progress toward comprehensive contraceptive care that incorporates the needs of sexually expansive and gender-expansive individuals.

Contraceptive provision that supports reproductive autonomy, as outlined in the tenets of reproductive justice, involves several components that must work in tandem to reduce unmet need [1]. Several theoretical frameworks, including the Availability, Accessibility, Acceptability and Quality framework, the access framework, the 5As of access by Penchansky and Thomas [6], the Bruce-Jain Quality of Care framework, and the Human Rights–Based Family Planning Framework, are in agreement on many of the various attributes required for comprehensive, equitable contraceptive access, including availability, accessibility, acceptability, and quality (Textbox 1) [6-10]. Barriers to these components can be identified across policy and service delivery levels and within individual experiences [11-13].

Barriers to each of these aspects of contraceptive provision exist in the state of Utah and throughout the United States. Although some aspects of contraceptive provision in Utah do have similarities to other states, the state has a unique combination of geographic and political aspects that may add complexities to an individual's contraceptive access.

Textbox 1. Aspects of successful family planning provision included in multiple frameworks (Availability, Accessibility, Acceptability and Quality framework, Penchansky and Thomas J, Human Rights–Based Family Planning Framework, and Bruce-Jain Quality of Care).

Availability:

- Is the method offered to individuals through standard channels of care when they want it?

Accessibility:

- Can an individual get the method they desire?
- This can encompass financial, logistic, or geographic barriers

Acceptability:

- Is the method marketed or offered or distributed in a way that aligns with medical ethics, cultural, and individual values?

Quality:

- Is the method provided in a way that meets the highest medical and ethical standards?
- This includes ensuring dignity and respect for clients, informed consent through provision of accurate scientific information, ensuring client privacy and confidentiality, and meeting technical competence in provision of methods

Availability Barriers

Despite widespread method availability in the United States and Utah, barriers still exist. These availability barriers manifest primarily within the service delivery sector, through factors such as a lack of skilled providers, a limited selection of methods at clinics, and stockouts [14,15]. Subsidized or discounted purchasing, in the form of 340B federal drug pricing or group purchasing, has the potential to reduce the upfront cost of stocking methods (Multimedia Appendix 1 provides a glossary of health policy terminology). However, not all clinics providing contraception to low-income clients meet the 340B criteria, and discounted prices through group purchasing models may still be prohibitively high for smaller clinics. This leads clinics to make fiscal decisions about which methods to purchase and subsequently impacts the availability of methods. In addition, varying demand for the most expensive methods, such as intrauterine devices (IUDs) and contraceptive implants, increases the likelihood of stockouts, particularly among smaller clinics [16].

Furthermore, the availability of comprehensive contraceptive offerings including both long-acting reversible contraceptives (LARCs) and lesser used methods, such as fertility awareness–based methods, is limited in most publicly funded health clinics [17]. Expanded method choice is associated with increased utilization and method satisfaction among users [18], making a comprehensive contraceptive offering an important component of contraceptive availability.

Accessibility Barriers

The cost of health care, including contraceptive services, is a known barrier to use, particularly for individuals with low incomes. Several studies have demonstrated the removal of cost barriers, leading to increased utilization of methods, including LARC methods, which have the highest upfront costs [17,18]. Until recently, Utah was 1 of only 7 states that had not either expanded Medicaid through the Affordable Care Act or adopted a Medicaid Family Planning 1115 Waiver (Multimedia Appendix 1). As a result, an estimated 215,000 women in the contraceptive coverage gap needed publicly funded family planning services [19]. In addition, approximately 20% of existing insurance policies in Utah are considered noncompliant with the Affordable Care Act and do not necessarily require insurers to cover contraceptive services and methods [20].

Geographic access barriers also exist in the state. Utah is one of the largest states in the United States, but one of the least populous states. Approximately 25% of the state's population lives in rural or frontier areas, requiring traveling longer distances to receive care. Utah has a lower ratio of physicians per civilian population than the national average; this gap is particularly acute in rural health districts [21]. In 3 Utah counties, there are no primary care physicians [21]. This often translates into Utahns needing to factor transportation and time costs into their contraceptive utilization.

Recent changes in national Title X requirements resulted in Planned Parenthood withdrawing from Title X funding in 2019. Planned Parenthood clinics were Utah's only Title X provider, and their withdrawal from the program's federal funding has left Utahns without a single Title X provider. This has increased accessibility barriers to contraception for many primarily low-income and adolescent individuals.

Acceptability Barriers

A major aspect of contraceptive acceptability in Utah is tied to the high rates of residents' membership in the Church of Jesus Christ of Latter-Day Saints religion. Overall, 62% of people living in Utah report affiliation with this religion, although there are substantial regional differences across the state [22]. An even higher proportion (88%) of individuals serving in the Utah legislature identify as being affiliated with this religion [23]. Thus, much of the cultural acceptability of and policies related to contraception have roots in the dominant religion's beliefs about sex and sexuality. This includes topics such as extramarital sex (and by extension, adolescent sex), nonheterosexual sex, and abortion [24,25].

As of 2019, state code permits sex education curricula in Utah schools to describe contraceptive methods. Before 2019, sex education curricula were not allowed to describe contraceptive methods. A yet-unpublished survey of sexual health knowledge among students at the University of Utah found that although 82% of respondents reported being sexually active, 52% reported only having received abstinence-based sex education, and 63% reported that they wished they knew more about specific contraceptive methods [26]. Thus, contraceptive knowledge among Utahns is low, and methods are subject to common myths and misconceptions. In one such example of these misconceptions, a Utah-based medical practice received media attention in 2019 for the *premarital exams*, which are essentially provider-based sexual education visits, primarily directed at women [27].

Contraceptive acceptability also pertains to providers, particularly regarding the acceptability of certain methods in specific circumstances or for particular individuals. For example, a presurvey provided at a Utah contraceptive training conference found that 65% of respondents (n=29) perceived that intrauterine placements were less uncomfortable for recipients if provided during menstruation [28]. In addition, research on sexual minority women in Utah found that these individuals are less likely to report having had a provider offer contraception or discuss pregnancy intentions or reproductive life planning [29,30].

Quality Barriers

Attributes of quality contraceptive provision are evolving. For example, new evidence supports patient-centered decision making, which places the client as the primary decision maker in a contraceptive visit, with the provider in a supportive ancillary role [31]. Recommendations for high-quality contraceptive visits now include providing anticipatory guidance for managing side effects, advancing the provision of emergency contraception to individuals who would like it, and identifying alternative or backup methods for individuals who are unhappy or dissatisfied with their current method [31]. Yet, updated contraceptive education is limited for many established providers in Utah, particularly individuals in primary care settings in rural and frontier areas who may find it difficult to stay current on sexual and reproductive health topics, given competing priorities and training.

Current Policy Environment

In 2018, Utah legislators approved the request for a Medicaid 1115 waiver, expanding contraceptive coverage and family planning services for individuals with household incomes below 100% federal poverty level (FPL). In 2019, this waiver was absorbed into a larger targeted Medicaid expansion during the 2019 legislative session. The family planning waiver estimated increased contraceptive coverage to approximately 11,200 low-income individuals in the state [32]. The broader targeted expansion estimated that between 70,000 and 90,000 people would have increased coverage, which would include family planning services [33]. Finally, in January 2020, Medicaid was further expanded in the state to meet federal eligibility guidelines for individuals at or below 138% FPL.

However, theoretical access through coverage-related policy change does not always translate to actual access. Opportunities for successful policy implementation exist at both the individual

and health systems level and include educating Utahns about the new coverage options, enrolling eligible individuals, assisting newly enrolled individuals in using health care services, training providers on comprehensive method counseling and provision, purchasing necessary devices and equipment for care, and addressing increased demand within the clinic workflow. These essential aspects were not included in the fiscal appropriations of the expansion bill in 2019, nor in the expansion of 2020. In addition, the expansion of coverage to 138% FPL does not address contraceptive coverage for individuals who are documented immigrants (eg, have visas or green cards) or who are undocumented and ineligible for Medicaid. Furthermore, many individuals who are eligible for coverage through the Affordable Care Act marketplace struggle to pay for health care, have high deductible plans, or no prescription coverage. Research has demonstrated that the need for subsidized contraceptive care continues to be critical for individuals up to 250% FPL [33].

Family Planning Elevated (FPE) is a statewide contraceptive initiative that was developed in part to support the implementation of the evolving Medicaid policy and provide evidence about additional state-specific opportunities to further improve contraceptive availability, acceptability, accessibility, and quality in Utah. This paper provides an overview of the FPE Contraceptive Access Program (FPE CAP)—a subset of the initiative specifically aimed at (1) strengthening clinic capacity for expanded contraceptive service delivery to individuals covered by the new Medicaid expansion (>138% FPL) and (2) providing comprehensive no-cost contraceptive care to individuals between 139% and 250% FPL.

Methods

Study Design

The primary purpose of this quasiexperimental study is to determine whether the FPE CAP increased clinic provision of contraceptive services to Medicaid-insured individuals at 0% to 138% FPL and uninsured and underinsured individuals between 139% and 50% FPL, compared with clinics that did not receive the intervention program. A total of 9 health organizations will be selected in 3 cohorts, spaced 6 months apart, for a 2-year membership in the FPE CAP (February 2019 to February 2022) and will be matched in a 1:1 ratio to control clinics within the state to compare contraceptive service outcomes. The University of Utah Institutional Review Board (#00117213) approved this study.

Participants in this study are health organizations that are selected for membership within the FPE CAP. To be eligible for FPE CAP membership, a clinic must (1) serve a patient population that is at least 25% uninsured or underinsured; (2) accept Medicaid; (3) primarily serve clients below 250% FPL; and (4) be enrolled in, or eligible for, the federal 340B drug pricing program. Selection priorities are given to health centers in rural areas of Utah and those in counties with high unintended birth rates and low health care coverage rates.

The criteria for matching control clinics in Utah include clinic size (volume, estimated by the number of providers), a similar proportion of uninsured and underinsured population served, geographic denotation (urban, rural, and frontier), and acceptance of Medicaid. Eligible controls are those that both meet matching criteria and confirm that they do not intend to apply for the FPE CAP but are willing to provide service delivery data to the program as a control clinic. On selection of intervention clinics, control clinics were identified and recruited. Control clinics provide nominal compensation (US $100 per month) for the provision of their data over the study period.

Clinics interested in participating in the FPE CAP apply for membership in 1 of the 3 cohorts. In their applications, clinics provide FPE a self-assessment of the availability and accessibility of contraceptive methods in their individual organizations (eg, whether they had certain methods available, whether providers were trained on IUDs and implants, etc). On selection, receive a multifaceted intervention that includes several specific components (Table 1).

Table 1. Overview of Family Planning Elevated Contraceptive Access Program activities and their alignment with theoretical aspects of family planning care.

FPE CAP[a] intervention activities	Theoretical aspects of contraceptive provision addressed
FPE CAP membership specifically targeting geographic areas with high contraceptive need and low comprehensive contraceptive provision	• Increased geographic accessibility of comprehensive contraception in rural and frontier areas
Cash grant to support clinic capacity to provide contraception (ie, staffing, procurement of instruments and supplies)	• Improved availability of comprehensive contraception at clinics
No-cost contraception for all reversible methods of contraception for both eligible individuals between 139% and 250% FPL and individuals between 0% and 250% FPL who are Medicaid ineligible[b]	• Financial accessibility of comprehensive contraceptive methods
Provider and clinic training on contraceptive provision and contraceptive counseling (eg. Contraceptive Education and Training conference, in-clinic training, 1:1 proctoring)	• Increased availability of comprehensive methods, including provider-dependent methods (eg, long-acting reversible contraceptives, vasectomy) • Increased quality of family planning counseling and method provision in clinics
Tailored technical offerings to clinics, specific to requested areas of need (eg, adolescent friendly services, proctoring on intrauterine devices and implants)	• Increased quality of family planning counseling and provision in clinics
Tailored contraceptive social media campaigns specific to different communities, directing individuals to participating FPE CAP clinics	• Improved acceptability of comprehensive contraceptive methods within specific communities

[a]FPE CAP: Family Planning Elevated Contraceptive Access Program.

[b]FPL: federal poverty level.

First, each FPE CAP member receives a cash grant up to US $100,000 based on their budgeted need for equipment, supplies, or supplemental staffing to expand service capacity. Provision of provider-dependent methods such as IUDs and implants requires specific equipment for insertion and removal, and many clinics struggle with the initial cost of purchasing instruments, examination tables, and sterilization equipment. The expected increase in demand for health care services stemming from Medicaid expansion may place additional burdens on already busy clinics, and covering the initial costs of offering family planning services can increase immediate clinic capacity.

Member clinics must be able to provide all reversible methods of contraception to individuals between 139% and 250% FPL (and Medicaid-ineligible individuals between 0% and 250% FPL) at no cost to clients for the duration of the 2-year program, and clients are able to switch methods or discontinue at any time. To make this feasible, FPE CAP provides member clinics with a continuous supply of long-acting methods, including IUDs and implants, as these often have high upfront procurement costs, even with 340B pricing or other purchasing subsidization. In addition, FPE CAP reimburses clinics for all reversible methods and contraceptive services (including counseling, procedures, etc) at Medicaid rates. Clinics capable of providing vasectomy receive Medicaid reimbursement for that service as well. These reimbursements are meant to mimic the experience of a Medicaid family planning waiver expansion to 250% FPL or similar coverage expansion that could be implemented at a policy level and demonstrate the existing demand among this population. The FPE CAP tracks the supply and provision of all methods using both monthly service delivery data and monitoring data collected qualitatively in the quarterly report calls with individual clinics.

The full patient care team from administrators to providers at member clinics receives tailored education and training on a variety of topics, including person-centered contraceptive counseling, IUD and implant placement and removal, barriers, fertility awareness–based methods, clinic workflow, billing, coding, and other areas of need jointly identified by each clinic and the program team. Clinic staff at all levels, including front-desk staff and medical assistants, will be involved in education and training to support the systems' capacity for contraceptive provision throughout the entire clinic. FPE CAP members are asked to identify clinic champions at the provider, medical assistant, and administrative levels to support the project and to increase the likelihood of sustainability after the program ends. Clinic providers who receive IUD and implant training will also receive onsite proctoring and mentorship, clinical assistance with complex cases, and additional specific training, such as immediate postpartum insertions. Providers also have access to an on-call nurse practitioner who specializes in family planning care to support and troubleshoot any issues.

Finally, FPE CAP will develop demand generation activities and community outreach tailored for each member clinic to reduce unmet need for contraceptive services within the clinic communities. These activities will occur after the FPE CAP service intervention is successfully implemented within each clinic to ensure that the clinic has the capacity to increase service delivery while maintaining service quality.

Data Collection

To assess the primary outcomes, both intervention and control clinics agree to provide monthly service delivery data from their electronic health record systems to use for the program evaluation, following a standardized form developed by FPE (Multimedia Appendix 2). Clinics agree to provide data on (1)

total clinic volume (men, women, and children); (2) all clinical services (including noncontraceptive services) provided to women aged 18 to 50 years each month (including International Classification of Diseases, 10th Revision, codes, Evaluation and Management codes, Healthcare Common Procedure Coding System, and Current Procedural Terminology codes); and (3) sociodemographic variables of interest for each visit, including age, race, ethnicity, insurance status (private insurance, Medicaid, FPE CAP, self-pay, and other), and provider type. All clinics provide these data beginning from January 2018 to 12 months after their implementation period ends.

Other components of the FPE CAP intervention, including education, training, and demand generation, will be captured with subevaluations. These secondary analyses will assess changes in both knowledge and self-efficacy among providers, a media campaign evaluation, and a detailed process evaluation. Clinic service delivery quality will be assessed through yearly clinic visits by FPE staff and through periodic implementation of client exit surveys of individuals who received contraceptive services at member clinics. Additional subanalyses, including comparisons between FPE CAP clinics, are also planned.

FPE also includes monitoring and process evaluation components for the project, which assess aspects of adherence to the program and track components of dose and frequency as they relate to programmatic success. FPE's process evaluation uses the Consolidated Framework for Implementation Research as the formal tool for assessment. Further information about these components of the project has been reported elsewhere [34]. Our publication on the Open Science Framework provides an overview of all FPE monitoring and evaluation activities [35].

Statistical Analyses

Primary outcomes of the program will be assessed using comparative (intervention vs control), multiperiod (before, during, and after), interrupted time series analyses (ITSAs) [36,37]. ITSAs have increasingly been demonstrated to be reliable assessments of community interventions and implementation research, providing rigorous outcome assessments in circumstances where randomized controlled trials are infeasible [38,39]. For our purposes, our primary outcomes are increase in total contraceptive services among individuals between 139% and 250% FPL or who are undocumented and increase in total contraceptive services among individuals eligible for Medicaid. Total contraceptive services refer to any contraceptive service (ie, counseling, method provision, method removal, etc) that the clinic provides.

The 2 general approaches to ITSA are autoregressive integrated moving-average models [40] and ordinary least squares (OLS) models designed to adjust for autocorrelation [41]. We will use an OLS model because it is often more flexible and broadly applicable in an interrupted time series context than autoregressive integrated moving-average models [42,43]. To adjust for autocorrelation, we will fit an OLS model with Newey-West standard errors, which assume the error structure to be heteroskedastic and possibly autocorrelated up to some lag [44]. After fitting our model, we will check if the number of lags included in the model to account for autocorrelation was correctly specified and adjust accordingly using the Cumby-Huizinga general test for autocorrelation [45].

We conducted a Monte Carlo simulation to assess the power to detect significant differences between intervention and control clinics. Using initial, preintervention data from 9 identified potential clinics, the 6-month average number of monthly contraceptive service provision was 3, 28.4, 16.8, 16.9, 13.8, 23.2, 21.9, 16.4, and 5.4, with a mean of 16.2 (SD 8.1) contraceptive services provided per month. We used this SD to provide the correct amount of between-clinic variation in the simulation, with the assumption that this same SD will apply across all 3 periods (before, during, and postintervention) and would be equal between the 2 groups. We assumed that the 2 groups would be equal in the preintervention period and would have similar regression lines with a slope (background trend) of a 0.25% increase in contraceptive service provision per month. We assumed that this preintervention trend would continue in the control group across the intervention and postintervention periods, without interruption, and would be represented by one regression line across the entire study period. In the intervention group, we assumed an immediate jump (interruption) of 12 (which is about a relative 75% increase because the clinics now would have no-cost contraception to offer eligible clients), followed by a greater slope, now 1% per month in the intervention period (as providers and clinics would show improvements in contraception counseling and method availability). In the postintervention period, where no-cost contraception would no longer be available to provide to the clients, we assumed an immediate drop of 12 (losing the immediate gain at the beginning of the intervention period).

Using a normal random number generator, we generated a random data set based on our assumptions and performed the ITSA. We ran the simulation 1000 times and saved the significance determinations ($P<.05$). The mean of significance determinations, which is identical to the proportion of samples with statistical significance, is identical to the statistical power. The findings from our simulation are presented in Table 2. The Stata code for this power calculation, including notations around our assumptions, is available on the Open Science Foundation website [35]. All analyses were conducted using Stata version 15 or higher.

Table 2. Monte Carlo simulation for Family Planning Elevated Contraceptive Access Program study power calculation.

Comparison	Estimate (absolute % difference)	Power (%)
Preintervention period group difference in trend (slope)	0	11[a]
Intervention period group difference in trend	0.75	>99
Postintervention period group difference in trend	−1.25	86
Intervention period group difference in interruption (immediate effect of introducing intervention)	12	88
Postintervention period group difference in interruption (immediate effect of stopping intervention)	−12	93

[a]No difference assumed, so low power is expected.

Results

We found that the study was adequately powered (>80% power) with our planned number of clinics and the number of months of data available in the study. To date, we have successfully completed the recruitment and enrollment of 8 of the expected 9 health organizations and 4 of the expected 9 control clinics. Completion of health organization enrollment for both intervention and control organizations is expected finish in December 2020.

Discussion

Expanding family planning access through policy change is a critical component of reducing unmet need for contraceptives. However, changes to legislation require implementation support to translate policy change into literal, on-the-ground access at service delivery, community, and individual levels. Our statewide FPE program to align service delivery capacity with contraceptive policy is novel but is grounded in evidence-based theory on existing barriers to contraceptive access.

Implementing such a program is not without challenges. First, the program incorporates a diverse network of clinics, including federally qualified health centers, private clinics, and city and county clinics. Incorporating activities into multiple practices with varied protocols, policies, and norms involves significantly tailoring the intervention to meet individual clinic needs. For example, participating FPE CAP members invoice the FPE CAP for contraceptive services provided to eligible individuals, yet clinics vary widely on billing practices and capacities. Thus, reimbursement requires a tailored approach to education, training, and follow-up of clinic administrative staff as well as programmatic flexibility to accept and correctly interpret program billing inputs provided variably.

In addition, clinic capacity varies widely among FPE CAP members. In some participating clinics, all providers are already trained to provide LARC methods, whereas in others, no or very few providers have received training. Developing training materials that identify priority foci that apply to the full care team is important, as it meets the individual training needs of clinics that require more assistance. For example, all clinics receive training on evidence-based practices for contraceptive counseling, reproductive justice, and implicit bias; however, for practical skills, such as LARC insertion and removal, clinics may receive more or less training and supportive supervision, depending on experience levels. As such, education and training approaches are essentially tiered, with basic education for all clinics and then specialized education and training for those clinics that require additional assistance.

Furthermore, FPE CAP is operating in a busy clinical environment within member clinics that provide a wide range of services in addition to contraceptive care. The program is among a number of competing priorities for these clinics, which provide high-volume care to low-income and marginalized communities. The program is attempting to strike a balance between reasonable intervention requirements and reducing the burden of implementation in clinics. This has had a decisive impact on many programmatic aspects, such as the amount and type of data collection required, the number of educational training required, the reporting requirements, and other components of the intervention. Cognizance of *initiative fatigue* as a component of intervention design is important to ensure program participation, completion, and compliance.

In addition, there are data collection challenges inherent to working across clinical electronic medical records (EMRs) and systems as well as incorporating needed variables into clinical practice. FPE CAP clinics and controls use various EMRs, each of which has a different capacity to pull reports and variables required for data collection. To address challenges in developing a standardized report that meets study guidelines, our evaluation team conducts in-person data meetings at the outset of membership to help the intervention and control clinics develop the report according to the program needs. There are also vast differences in how organizations and providers document and code clinical encounters. This will likely be a limitation in future analyses, despite FPE CAP efforts to improve clinical coding capacity by providing standardized training, visual aids, and other materials to incentivize improved coding practices.

Finally, FPE CAP operates within a continuously changing health policy landscape. The subsumption of the Medicaid family planning waiver into the larger Medicaid expansion was both a positive development for health care in Utah as well as a challenge to the initiative. Rollout of the policy was delayed while the new legislation was being finalized, requiring member clinics to adopt variable patient eligibility parameters at the start of the intervention, after the targeted Medicaid expansion was approved, and once again after the full expansion took effect. Additional changes may yet occur to state Medicaid, which is currently being implemented with controversial components that have not been previously approved by the federal government, including work reporting requirements and per

capita caps. As decisions around these policy components are made and initially eligible individuals potentially lose coverage, there may be additional changes to FPE CAP operations, as the program strives to support individuals who fall in service gaps.

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Conflicts of Interest

The University of Utah Department of Obstetrics and Gynecology Program in Family Planning receives research funding from Bayer, Bioceptive, Sebela, Medicines 360, Merck, Cooper Surgical, Clinical Innovations, and Teva. The authors have no relevant conflicts of interest to report.

Multimedia Appendix 1
Health policy glossary.
[DOCX File , 12 KB - resprot_v9i10e18308_app1.docx]

Multimedia Appendix 2
Monthly service delivery report template.
[PNG File , 973 KB - resprot_v9i10e18308_app2.png]

References

1. Ross LJ. Understanding Reproductive Justice. SisterSong. 2006. URL: http://www.sistersong.net/publications_and_articles/Understanding_RJ.pdf [accessed 2006-05-01]
2. Birth Control Benefits. Health Care. 2020. URL: https://www.healthcare.gov/coverage/birth-control-benefits/ [accessed 2020-09-14]
3. Polis CB, Schaffer K, Blanchard K, Glasier A, Harper CC, Grimes DA. Advance provision of emergency contraception for pregnancy prevention (full review). Cochrane Database Syst Rev 2007 Apr 18(2):CD005497. [doi: 10.1002/14651858.CD005497.pub2] [Medline: 17443596]
4. Rafie S, Haycock M, Rafie S, Yen S, Harper CC. Direct pharmacy access to hormonal contraception: California physician and advanced practice clinician views. Contraception 2012 Dec;86(6):687-693. [doi: 10.1016/j.contraception.2012.05.010] [Medline: 22717185]
5. Contraceptive Use in the United States. Guttmacher Institute: Good Reproductive Health Policy Starts. 2018. URL: https://www.guttmacher.org/fact-sheet/contraceptive-use-united-states [accessed 2020-02-06]
6. Penchansky R, Thomas JW. The concept of access: definition and relationship to consumer satisfaction. Med Care 1981 Feb;19(2):127-140. [doi: 10.1097/00005650-198102000-00001] [Medline: 7206846]
7. Bruce J. Fundamental elements of the quality of care: a simple framework. Stud Fam Plann 1990;21(2):61-91. [Medline: 2191476]
8. Jain A, Bruce J, Mensch B. Setting standards of quality in family planning programs. Stud Fam Plann 1992;23(6 Pt 1):392-395. [Medline: 1293863]
9. Jain AK, Hardee K. Revising the FP quality of care framework in the context of rights-based family planning. Stud Fam Plann 2018 Jun;49(2):171-179. [doi: 10.1111/sifp.12052] [Medline: 29708277]
10. Hardee K, Kumar J, Newman K, Bakamjian L, Harris S, Rodríguez M, et al. Voluntary, human rights-based family planning: a conceptual framework. Stud Fam Plann 2014 Mar;45(1):1-18. [doi: 10.1111/j.1728-4465.2014.00373.x] [Medline: 24615572]
11. Choi Y, Fabic MS, Adetunji J. Measuring access to family planning: conceptual frameworks and DHS data. Stud Fam Plann 2016 Jun;47(2):145-161. [doi: 10.1111/j.1728-4465.2016.00059.x] [Medline: 27285425]
12. Puri MC, Moroni M, Pearson E, Pradhan E, Shah IH. Investigating the quality of family planning counselling as part of routine antenatal care and its effect on intended postpartum contraceptive method choice among women in Nepal. BMC Womens Health 2020 Feb 18;20(1):29 [FREE Full text] [doi: 10.1186/s12905-020-00904-y] [Medline: 32070339]
13. Cole MS, Boydell V, Hardee K, Bellows B. The extent to which performance-based financing programs' operations manuals reflect rights-based principles: implications for family planning services. Glob Health Sci Pract 2019 Jun;7(2):329-339. [doi: 10.9745/GHSP-D-19-00007] [Medline: 31249026]
14. Olson EM, Kramer RD, Gibson C, Wautlet CK, Schmuhl NB, Ehrenthal DB. Health care barriers to provision of long-acting reversible contraception in Wisconsin. WMJ 2018 Oct;117(4):149-155 [FREE Full text] [Medline: 30407764]

15. Politi MC, Estlund A, Milne A, Buckel CM, Peipert JF, Madden T. Barriers and facilitators to implementing a patient-centered model of contraceptive provision in community health centers. Contracept Reprod Med 2016;1:21 [FREE Full text] [doi: 10.1186/s40834-016-0032-3] [Medline: 29201410]
16. Heisel E, Kolenic GE, Moniz MM, Kobernik EK, Minadeo L, Kamdar NS, et al. Intrauterine device insertion before and after mandated health care coverage: the importance of baseline costs. Obstet Gynecol 2018 May;131(5):843-849. [doi: 10.1097/AOG.0000000000002567] [Medline: 29630013]
17. Sanders JN, Myers K, Gawron LM, Simmons RG, Turok DK. Contraceptive method use during the community-wide HER salt lake contraceptive initiative. Am J Public Health 2018 Apr;108(4):550-556. [doi: 10.2105/AJPH.2017.304299] [Medline: 29470119]
18. Secura GM, Allsworth JE, Madden T, Mullersman JL, Peipert JF. The contraceptive CHOICE project: reducing barriers to long-acting reversible contraception. Am J Obstet Gynecol 2010 Aug;203(2):115.e1-115.e7 [FREE Full text] [doi: 10.1016/j.ajog.2010.04.017] [Medline: 20541171]
19. Birth Control Access. Power to Decide, The Campaign to Prevent Unplanned. 2020. URL: https://powertodecide.org/what-we-do/access/birth-control-access [accessed 2020-02-06]
20. Hawley J. 2018 Health Insurance Market Report. The Producer Licensing Division. 2018. URL: https://insurance.utah.gov/wp-content/uploads/2018HealthMarketReport.pdf [accessed 2020-09-23]
21. Health Indicator Report of Personal Doctor or Health Care Provider. Utah's Indicator-Based Information System for Public Health Data Resource. URL: https://ibis.health.utah.gov/ibisph-view/indicator/view/PriProvUsuPl.LHD_AA.html [accessed 2020-09-14]
22. Canham M. Salt Lake County is Now Minority Mormon, and the Impacts Are Far Reaching. Salt Lake Tribune Internet. 2018. URL: https://www.sltrib.com/religion/2018/12/09/salt-lake-county-is-now/ [accessed 2020-02-05]
23. Mormons Account for Nearly 90 Percent of State Legislature. Associated Press News. 2019 Jan 27. URL: https://apnews.com/286983987f484cb182fba9334c52a617 [accessed 2020-02-05]
24. Gospel Topics: Abortion. Church of Jesus Christ of Latter-Day Saints Internet. URL: https://www.churchofjesuschrist.org/study/manual/gospel-topics/abortion?lang=eng [accessed 2020-02-05]
25. Gospel Topics: Same-Sex Attraction. Church of Jesus Christ of Latter-Day Saints Internet. URL: https://www.churchofjesuschrist.org/study/manual/gospel-topics/same-sex-attraction?lang=eng [accessed 2020-02-05]
26. Personal Conversation With Jessica Sanders, PhD, Author of Campus Contraceptive Initiative. -: -; 2020.
27. Jacobs B. Utah's Unusual 'Premarital Exams' for Women Are Being Rebranded as Sexual Health Visits for Everyone. The Salt Lake Tribune. 2019 Oct 22. URL: https://www.sltrib.com/news/2019/10/22/utahs-unusual-premarital/ [accessed 2020-02-06]
28. Email communication with R Simmons, PhD. -: -; 2019.
29. Everett BG, Higgins JA, Haider S, Carpenter E. Do sexual minorities receive appropriate sexual and reproductive health care and counseling? J Womens Health (Larchmt) 2019 Jan;28(1):53-62 [FREE Full text] [doi: 10.1089/jwh.2017.6866] [Medline: 30372369]
30. Higgins JA, Carpenter E, Everett BG, Greene MZ, Haider S, Hendrick CE. Sexual Minority Women and Contraceptive Use: Complex Pathways Between Sexual Orientation and Health Outcomes. Am J Public Health 2019 Dec;109(12):1680-1686. [doi: 10.2105/AJPH.2019.305211] [Medline: 31536410]
31. Dehlendorf C, Henderson JT, Vittinghoff E, Steinauer J, Hessler D. Development of a patient-reported measure of the interpersonal quality of family planning care. Contraception 2018 Jan;97(1):34-40. [doi: 10.1016/j.contraception.2017.09.005] [Medline: 28935217]
32. Ward R. Revised Fiscal Note: HB 12. Utah Legislature. 2018 Feb 19. URL: https://le.utah.gov/lfa/fnotes/2018/HB0012.fn.pdf [accessed 2020-09-14]
33. Musumeci M, Guth M, Rudowitz R, Hall C. From Ballot Initiative to Waivers: What is the Status of Medicaid Expansion in Utah? KFF - Health Policy Analysis, Polling and Journalism. 2019 Nov 15. URL: https://www.kff.org/medicaid/issue-brief/from-ballot-initiative-to-waivers-what-is-the-status-of-medicaid-expansion-in-utah/ [accessed 2020-02-06]
34. Baayd J, Simmons R. Protocol for a process evaluation of family planning elevated, a statewide initiative to improve contraceptive access in Utah (United States). BMJ Open 2020:- under review.
35. Open Science Framework. URL: https://osf.io/qjc9k/ [accessed 2020-09-17]
36. Linden A. Conducting interrupted time-series analysis for single- and multiple-group comparisons. Stata J 2018 Nov 19;15(2):480-500. [doi: 10.1177/1536867x1501500208]
37. Liu W, Ye S, Barton BA, Fischer MA, Lawrence C, Rahn EJ, et al. Simulation-based power and sample size calculation for designing interrupted time series analyses of count outcomes in evaluation of health policy interventions. Contemp Clin Trials Commun 2020 Mar;17:100474 [FREE Full text] [doi: 10.1016/j.conctc.2019.100474] [Medline: 31886433]
38. Biglan A, Ary D, Wagenaar AC. The value of interrupted time-series experiments for community intervention research. Prev Sci 2000 Mar;1(1):31-49 [FREE Full text] [doi: 10.1023/a:1010024016308] [Medline: 11507793]
39. Fretheim A, Tomic O. Statistical process control and interrupted time series: a golden opportunity for impact evaluation in quality improvement. BMJ Qual Saf 2015 Dec;24(12):748-752. [doi: 10.1136/bmjqs-2014-003756] [Medline: 26316541]

40. Box GE, Tiao GC. Intervention analysis with applications to economic and environmental problems. J Am Stat Assoc 1975 Mar;70(349):70-79. [doi: 10.1080/01621459.1975.10480264]
41. Crosbie J. Interrupted time-series analysis with brief single-subject data. J Consult Clin Psychol 1993 Dec;61(6):966-974. [doi: 10.1037//0022-006x.61.6.966] [Medline: 8113497]
42. Box G, Jenkins G. Time Series Analysis, Forecasting and Control. University of Michigan, USA: Holden-Day; 1976.
43. Velicer WF, Harrop J. The reliability and accuracy of time series model identification. Eval Rev 2016 Jul 26;7(4):551-560. [doi: 10.1177/0193841x8300700408]
44. Newey WK, West KD. A simple, positive semi-definite, heteroskedasticity and autocorrelation consistent covariance matrix. Econometrica 1987 May;55(3):703. [doi: 10.2307/1913610]
45. Cumby RE, Huizinga J. Testing the autocorrelation structure of disturbances in ordinary least squares and instrumental variables regressions. Econometrica 1992 Jan;60(1):185. [doi: 10.2307/2951684]

Abbreviations

EMR: electronic medical record
FPE: Family Planning Elevated
FPE CAP: Family Planning Elevated Contraceptive Access Program
FPL: federal poverty level
ITSA: interrupted time series analysis
IUD: intrauterine device
LARC: long-acting reversible contraceptives
OLS: ordinary least squares

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Protocol

The Diabetes Location, Environmental Attributes, and Disparities Network: Protocol for Nested Case Control and Cohort Studies, Rationale, and Baseline Characteristics

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Abstract

Background: Diabetes prevalence and incidence vary by neighborhood socioeconomic environment (NSEE) and geographic region in the United States. Identifying modifiable community factors driving type 2 diabetes disparities is essential to inform policy interventions that reduce the risk of type 2 diabetes.

Objective: This paper aims to describe the Diabetes Location, Environmental Attributes, and Disparities (LEAD) Network, a group funded by the Centers for Disease Control and Prevention to apply harmonized epidemiologic approaches across unique and geographically expansive data to identify community factors that contribute to type 2 diabetes risk.

Methods: The Diabetes LEAD Network is a collaboration of 3 study sites and a data coordinating center (Drexel University). The Geisinger and Johns Hopkins University study population includes 578,485 individuals receiving primary care at Geisinger, a health system serving a population representative of 37 counties in Pennsylvania. The New York University School of Medicine study population is a baseline cohort of 6,082,146 veterans who do not have diabetes and are receiving primary care through Veterans Affairs from every US county. The University of Alabama at Birmingham study population includes 11,199 participants who did not have diabetes at baseline from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, a cohort study with oversampling of participants from the Stroke Belt region.

Results: The Network has established a shared set of aims: evaluate mediation of the association of the NSEE with type 2 diabetes onset, evaluate effect modification of the association of NSEE with type 2 diabetes onset, assess the differential item functioning of community measures by geographic region and community type, and evaluate the impact of the spatial scale used to measure community factors. The Network has developed standardized approaches for measurement.

Conclusions: The Network will provide insight into the community factors driving geographical disparities in type 2 diabetes risk and disseminate findings to stakeholders, providing guidance on policies to ameliorate geographic disparities in type 2 diabetes in the United States.

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KEYWORDS

type 2 diabetes; built environment; social environment; disparities

Introduction

Background

An estimated 10.5% of the US population has diabetes, and these 34 million individuals are at an increased risk for coronary artery disease, cerebrovascular disease, and other complications [1,2]. Approximately 90% to 95% of people with diabetes have type 2 diabetes (T2D) [1]. Another 88 million individuals have prediabetes, defined as having elevated glucose levels above normal but below the threshold for diabetes, and are at elevated risk of developing T2D [3,4]. Diabetes prevalence and incidence vary substantially by geographic region [5-7]. In 2013, there was a six-fold difference between counties with the lowest and highest diabetes prevalence [6]. A large body of literature links community and environmental factors (hereafter referred to as community factors) to T2D and obesity, one of the risk factors for T2D [8-15]; however, the mechanisms for these links remain poorly understood. Moreover, there are inconsistencies in this body of literature. Identifying the community factors driving T2D disparities and the pathways through which these factors influence T2D is essential to informing geographically targeted policy interventions that reduce the risk of T2D and related outcomes.

Researchers have identified consistent associations of community-level socioeconomic factors (eg, community poverty rate) with T2D prevalence and incidence. However, findings related to aspects of the built (eg, food and physical activity establishment environment, land use environment) and natural environment (eg, greenness) and T2D risk have been less uniform [9-19]. This may be due, in part, to methodologic variations in measuring community factors, including differences in spatial scales, data sources, and measurement approaches [20].

Among the challenges to creating a cohesive body of research is a lack of consistent approaches to conceptualizing and operationalizing the geographic area in which community factors are thought to be relevant to health [19-22]. Furthermore, the size and boundaries of spatial scales most relevant to health may vary according to community type (eg, across the gradient from urban to rural). Community type is also an important consideration in measurement development, as measurement of the same community factors may require different approaches [23]. For example, car ownership may be a basic necessity for individuals living in rural areas but more of a luxury for individuals living in urban areas with good public transportation options. Thus, car ownership may work differently as an indicator of the neighborhood socioeconomic environment (NSEE) in urban versus rural areas [24]. This differential item functioning may contribute to inconsistencies observed in the literature as the same measure (eg, proportion who own a car) could hold different meanings in different community types.

Community and health research is also vulnerable to structural confounding, which occurs when individual and contextual factors strongly predict residence in a certain community [25,26]. In the presence of structural confounding, certain measures, owing to social sorting, are largely nonoverlapping, resulting in an inability to examine their independent influences on the outcome of interest. For example, in some settings, the distribution of persons across categories of the NSEE and racial residential segregation may reveal a lack of comparable groups across key strata, resulting in analytical challenges of nonpositivity that prohibit causal contrasts across levels of exposure [26]. Finally, capturing the complex interactions among multiple community factors on health can be challenging [27]. As a result, previous research has largely evaluated co-occurring community factors in isolation.

Objectives

The increasing availability of longitudinal, individual-level data from electronic health record (EHR) networks [28] and cohort studies, coupled with advances in geographic information systems (GISs), provides new opportunities to examine the effects of community factors on health. In 2017, the Diabetes LEAD (Location, Environmental Attributes, and Disparities) Network was established to identify the contributions of modifiable community factors on T2D risk. The Network includes researchers from 4 academic institutions who collaborate to address the methodological challenges previously described to investigate a range of community factors across the United States. The Network aims to guide policy decision making to reduce the burden of T2D across the United States. This paper aims to describe the Diabetes LEAD Network, its study populations, and the methodologies used to investigate the community factors that are associated with T2D onset and related outcomes.

Methods

Network Overview

The Diabetes LEAD Network is a research collaboration of 4 academic centers: Drexel University, Geisinger and Johns Hopkins University (G/JHU), New York University School of Medicine (NYU), and the University of Alabama at Birmingham (UAB). The Centers for Disease Control and Prevention (CDC) funded the Network to bring together institutions with diverse but complementary expertise and a rich array of data assets. Three study sites—G/JHU, NYU, and UAB—use longitudinal data, such as EHRs, administrative claims, and survey data on distinct populations and geographies in the United States (Tables 1-3; Figures 1-3). Drexel, the data coordinating center (DCC), is leading the development of a set of harmonized community factors, health outcomes, and analysis plans (Tables 4 and 5) that will be applied to each study site's cohort and geography.

Each site has its own set of study aims that examine community factors and T2D outcomes, including T2D onset, obesity, and other cardiometabolic conditions. Working collaboratively, the study sites and the CDC also developed a shared set of aims that complement site-specific aims (Textbox 1). We first describe the shared Network aims and then describe the site-specific aims.

Table 1. Diabetes Location, Environmental Attributes, and Disparities Network study site populations for Network-specific aims.

Study site, G/JHU[a] (n=578,485[b])	NYU[c] (n=6,082,246)	UAB[d] (n=11,199)
Study design		
Nested case control and cohort	Cohort[e]	Cohort
Source population		
All Geisinger patients (N=1,605,922)	All patients in the Veterans Affairs EHR[f] with at least one primary care visit since 1999 (N=8,346,280)	REGARDS[g] participants at baseline (2003-2007; N=30,239)
Exclusion criteria (sample size excluded)		
Patients with <2 primary care visits[h] (January 1, 2006 - December 31, 2016; n=970,785)	Patients with <2 primary care visits at least 30 days apart during the 5 years (before January 1, 2008; n=4,270,462)	Participants without a second visit (2013-2016; n=14,089)
Patients with a residential address outside of one of the 37 counties in the Geisinger primary service area (n=56,652)	Patients with diabetes[i] before or on January 1, 2008 (n=1,049,423)	Participants with diabetes[i] at baseline (n=2729) or missing diabetes status at baseline (n=521; combined, n=3250)
N/A[j]	N/A	Participants missing diabetes status at second visit (n=1580)
N/A	N/A	Unable to assign census tract using RECVD[k] data set (n=121)

[a]G/JHU: Geisinger and Johns Hopkins University.

[b]Study population will vary based on study design (ie, nested case control or cohort).

[c]NYU: New York University.

[d]UAB: University of Alabama at Birmingham.

[e]These numbers reflect only those entering the cohort on inception date (January 1, 2008). The dynamic cohort allowed patients to enter the cohort through December 31, 2016 (n=3,113,391). Total cohort population was 6,082,246.

[f]EHR: electronic health record.

[g]REGARDS: Reasons for Geographic and Racial Differences in Stroke study.

[h]Includes internal medicine, family medicine, pediatrics, and obstetrics or gynecology.

[i]See Table 5 for type 2 diabetes definitions.

[j]N/A: not applicable.

[k]RECVD: Retail Environment and Cardiovascular Disease.

Table 2. Location, Environmental Attributes, and Disparities Network study population characteristics by site.

Characteristics	G/JHU[a]	NYU[b]	UAB[c]
Study population, n	578,485	6,082,246	11,199
Sex, n (%)			
Male	254,218 (43.94)	5,578,056 (91.71)	4946 (44.16)
Female	324,267 (56.05)	504,020 (8.28)	6253 (55.83)
Age (years), n (%)[d]			
<18	132,341 (22.87)	0 (0)	0 (0)
18-29	92,458 (15.98)	450,504 (7.40)	0 (0)
30-39	67,185 (11.61)	550,910 (9.05)	0 (0)
40-49	67,996 (11.75)	753,811 (12.39)	649 (5.79)
50-59	74,641 (12.90)	1,168,452 (19.21)	3445 (30.76)
60-69	63,946 (11.05)	1,566,257 (25.75)	4547 (40.60)
≥70	79,918 (13.81)	1,592,179 (26.17)	2558 (22.84)
Race, n (%)			
Black	23,302 (4.02)	920,596 (15.13)	3672 (32.78)
American Indian or Alaska Native	655 (0.11)	56,928 (0.93)	0 (0)
Asian	4616 (0.79)	58,555 (0.96)	0 (0)
Native Hawaiian or other Pacific Islander	2746 (0.47)	60,441 (0.99)	0 (0)
White	542,128 (93.71)	4,411,233 (72.52)	7527 (67.21)
Ethnicity, n (%)			
Hispanic	25,274 (4.36)	331,376 (5.44)	0 (0)
Non-Hispanic	553,211 (95.63)	5,750,870 (94.55)	11,199 (100.00)
Setting of residential address, n (%)			
Higher density urbanized area	48,374 (8.36)	688,488 (11.31)	1809 (16.15)
Lower density urbanized area	76,301 (13.18)	2,139,912 (35.18)	4524 (40.39)
Suburban and small town (UC)[e]	178,548 (30.86)	1,328,278 (21.83)	2644 (23.60)
Rural	275, 272 (47.58)	1,781,743 (29.29)	2222 (19.84)
Diagnosed with type 2 diabetes by the end of the follow-up period, n (%)[f]	64,214 (11.10)	936,627 (15.39)	1408 (12.57)

[a]G/JHU: Geisinger and Johns Hopkins University.

[b]NYU: New York University.

[c]UAB: University of Alabama at Birmingham.

[d]G/JHU: age as of date of the data pull (2016); NYU: age calculated by subtracting year of birth from cohort entry year; UAB: age at baseline.

[e]UC: urban cluster

[f]See Table 5 for diabetes definitions. G/JHU: 2008 to 2016; NYU: 2008 to 2016; UAB: 2003 to 2016.

Table 3. Location, Environmental Attributes, and Disparities Network individual-level data elements available by study site for Network aims.

Data elements	G/JHU[a,b]	NYU[c]	UAB[d,e]
Individual-level data			
Demographic data (yes/no)	Yes	Yes	Yes
Residential address data	Most recent only	Longitudinal	Longitudinal
Socioeconomic data	Longitudinal	Longitudinal	Longitudinal
Health-related data			
BMI	Longitudinal	Longitudinal	Longitudinal
Vital signs (eg, blood pressure)	Longitudinal	Longitudinal	Longitudinal
Diagnoses	Longitudinal	Longitudinal	Longitudinal
Treatment	Longitudinal	Longitudinal	Longitudinal[f]
Biomarkers (type)	EHR[g] laboratory data	EHR laboratory data	HbA_{1c}[h] available on subset only[i]

[a]G/JHU: Geisinger and Johns Hopkins University.

[b]Includes only data in the EHR-based study. See Multimedia Appendix 1 for additional data collected in the primary data collection study.

[c]NYU: New York University School of Medicine.

[d]UAB: University of Alabama at Birmingham.

[e]Longitudinal data are available at 2 time points—baseline (2003-2007) and second in-home exam (2013-2016).

[f]Adjudicated (confirmed by review of medical records) coronary heart disease, stroke, end-stage renal disease, and death available throughout follow-up.

[g]EHR: electronic health record.

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

[i]n=2694 at baseline and n=2527 at follow-up examination.

Figure 1. Geographic coverage of Pennsylvania in the Geisinger and Johns Hopkins University study population: participants in each site by census tract. G/JHU: Geisinger and Johns Hopkins University.

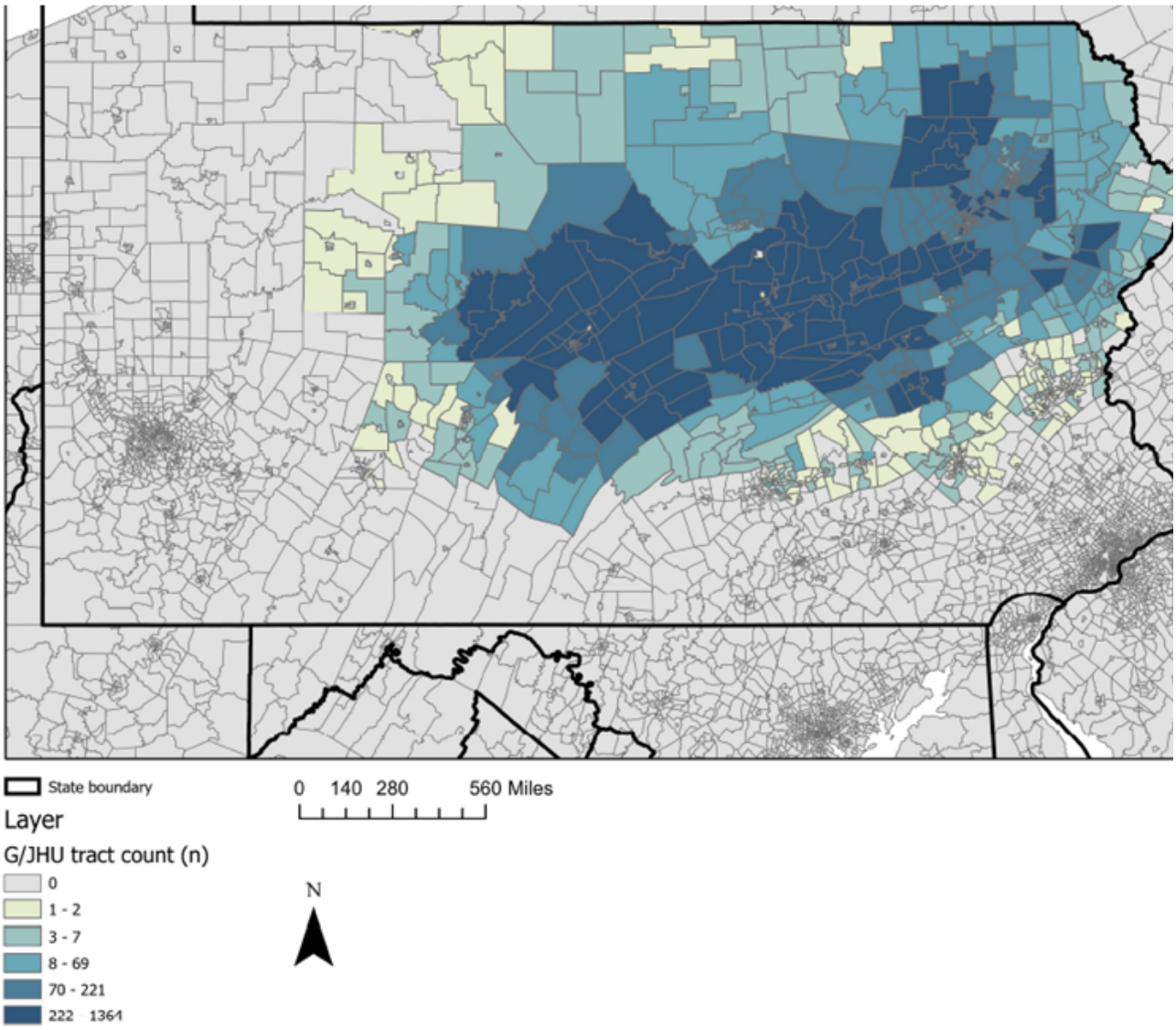


Figure 2. Geographic coverage of the New York University study population: participants in each site by census tract. NYU: New York University.

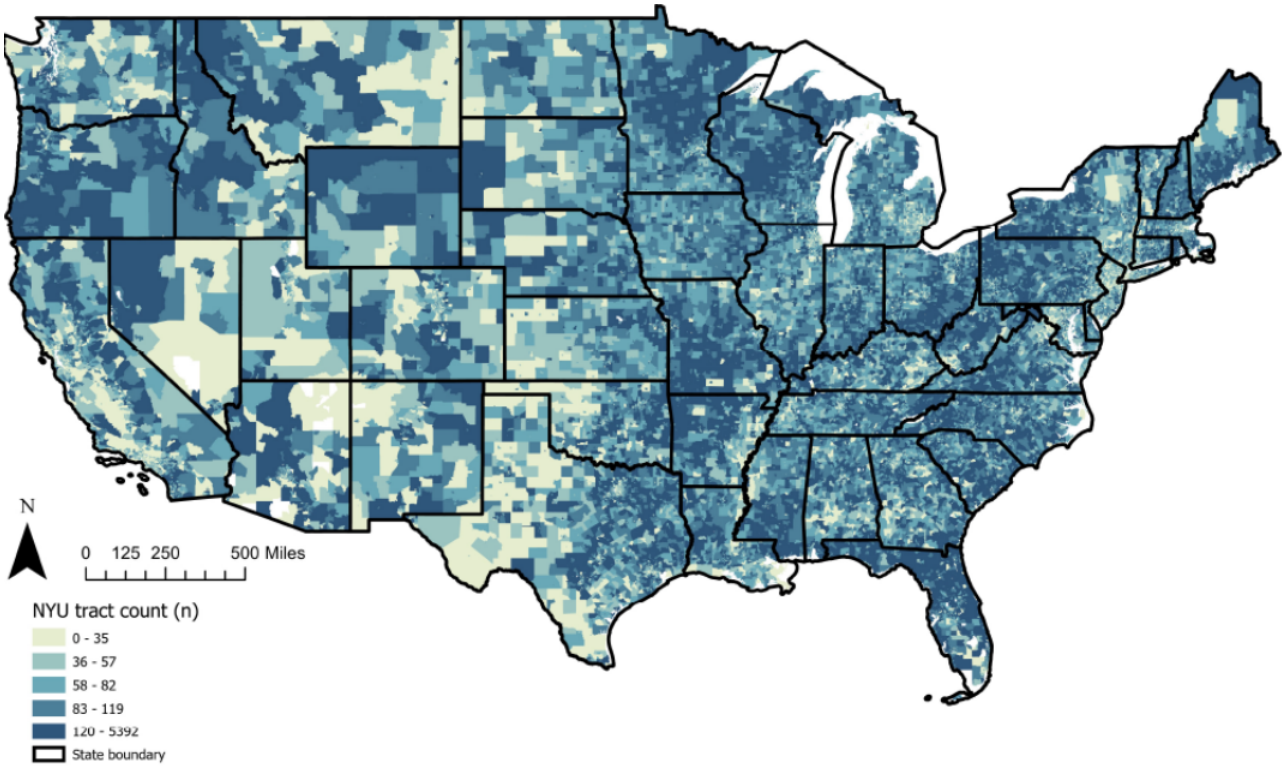


Figure 3. Geographic coverage of the University of Alabama at Birmingham study population in the Stroke Belt region and surrounding states: participants in each site by census tract. Participants are from all 48 contiguous states. The map reflects the Stroke Belt region and surrounding states. UAB: University of Alabama at Birmingham.

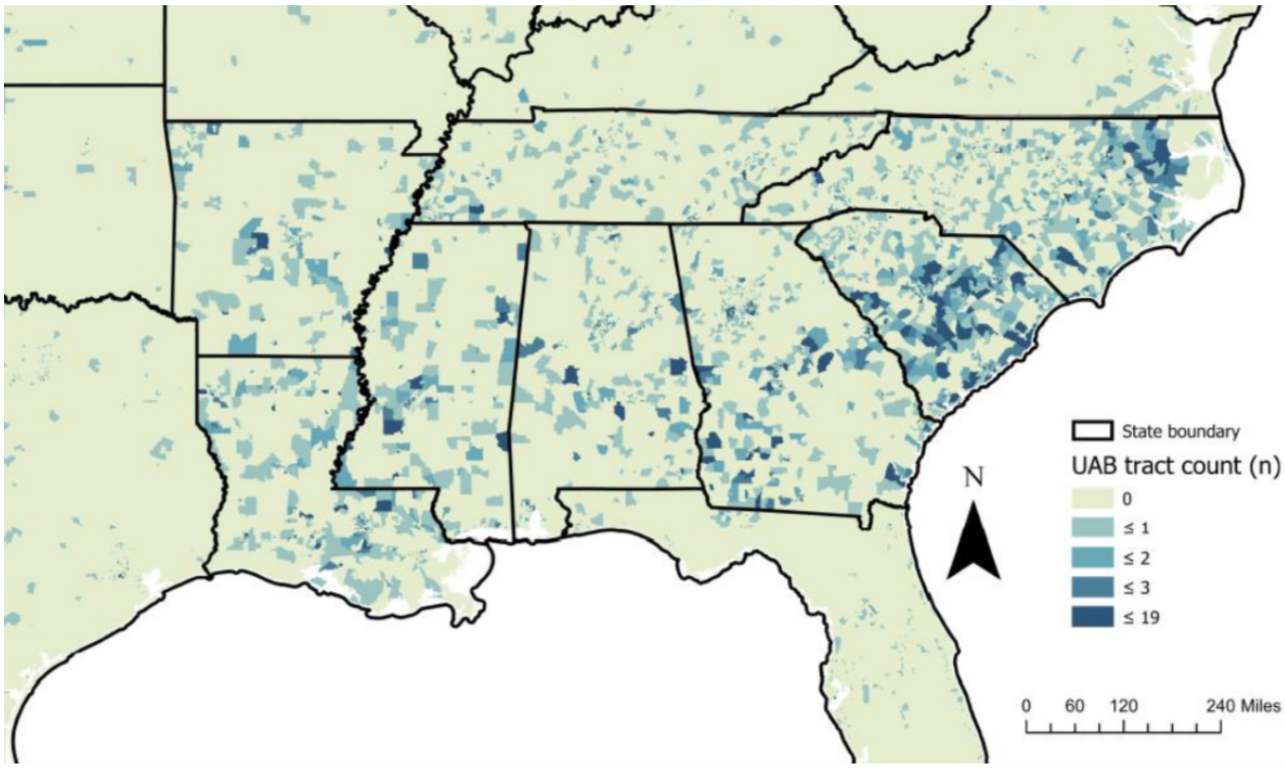


Table 4. Community and environmental domains for Network-wide aims.

Domain	Data source and years	Spatial scale	Description
Neighborhood socioeconomic environment	US Decennial Census and American Community Survey (5-year estimates; 2000, 2010, 2006-2010, and 2008-2012)	Census tract	Area-level index derived from a z-score sum of indicators of the community's social and economic characteristics [29]: percentage of males and females with less than a high school education, percentage of males and females unemployed, percentage of households earning less than US $30,000 per year, percentage of households in poverty, percentage of households on public assistance, and percentage of households with no cars
Food establishment environment	RECVD[a] Geocoded Business Level Data set, derived from NETS[b] (1997-2014)	Network buffer around the population-weighted centroid of census tracts	Area-level absolute and relative measures: density of supermarkets (including medium-sized grocers) and fast food restaurants (per square kilometer), ratio of supermarkets to all food stores, and ratio of fast food restaurants to all restaurants and eating places
Physical fitness establishment environment	RECVD Geocoded Business Level Data set, derived from NETS[b] (1997-2014)	Network buffer around the population-weighted centroid of census tracts	Area-level density of physical activity venues per square kilometer (eg, gyms, membership sports and recreation clubs, athletic organizations)
Land use environment	RECVD National Land Cover Database, ESRI StreetMap, RECVD NETS, US Decennial Census (2006, 2009, and 2010)	Census tract	Area-level index derived from a z-score sum of 7 indicators: average block length, average block size, intersection density, street connectivity, density of walkable establishments per square mile, percent developed land, and household density per square mile
Leisure-time physical activity environment	CDC's[c] Division of Population Health, National Center for Chronic Disease Prevention and Health Promotion. Derived from the Homeland Security Infrastructure Program Gold 2011 database[d], Environmental Systems Research Institute Arc Geographic Information System (ESRI ArcGIS) 10.1 Data DVD 2010	Census tract	Spatial access to parks measured by population-weighted distance to the 7 closest parks from the census tract's population-weighted centroid [30,31]

[a]Drexel University Urban Health Collaborative. The Retail Environment and Cardiovascular Disease (RECVD) Project.

[b]National Establishment Time-Series (NETS) database.

[c]CDC: Centers for Disease Control and Prevention.

[d]The Homeland Infrastructure Foundation-level Data Working Group NAVTEQ from Homeland Security Infrastructure Program Gold 2011 Database.

Table 5. Definition of type 2 diabetes.

Study site	Diagnoses codes	Laboratory measures[a]	Medication orders[b]	Exclusions
Geisinger and Johns Hopkins University	ICD[c]-9, ICD-10, or EDG[d] code for T2D on two separate dates	≥1 elevated HbA_{1c}[e] or glucose measure and ≥1 diagnosis code for T2D	≥1 T2D medication order	≥10 years of T1D[f] diagnoses and <5 years of T2D[g] diagnoses or first diabetes code before 10 years of age or only meet criteria during pregnancy
New York University School of Medicine	ICD-9 or ICD-10 code for T2D on two separate dates	≥2 elevated HbA_{1c} or glucose measure and ≥1 diagnosis code for T2D	≥1 T2D medication order	N/A[h]
University of Alabama at Birmingham[i]	N/A	Elevated glucose measure at study visit	Self-report of T2D medication	N/A

[a]HbA_{1c}≥6.5%, random glucose≥200 mg/dl, and fasting glucose≥126 mg/dl.

[b]Excluding Metformin and Acarbose: Reasons for Geographic and Racial Differences in Stroke project.

[c]ICD: International Classification of Diseases.

[d]EDG: Epic Diagnostic code Groupers.

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

[f]T1D: type 1 diabetes.

[g]T2D: type 2 diabetes.

[h]N/A: not applicable.

[i]From the Reasons for Geographic and Racial Differences in Stroke Study.

Textbox 1. Site-specific aims.

Geisinger and Johns Hopkins University:

- To evaluate associations of chronic environmental contamination [30] (eg, abandoned coal mine lands); the food environment; the physical activity environment; land use environment, the natural environment (eg, greenness); community type (eg, urban/rural); and community socioeconomic deprivation (CSD) with type 2 diabetes (T2D) onset and control and coronary heart disease (CHD) onset within communities.
- To evaluate mediating pathways (eg, food, physical activity environment) between the neighborhood socioeconomic environment and T2D onset (through LEAD Network Aim 1).
- To evaluate mediating pathways (eg, stress, health behaviors) between community factors and T2D control among 1000 individuals with T2D living in 40 communities.
- To evaluate potential effect modification by key individual (eg, age, Medical Assistance) and community factors (eg, CSD) of relations between community factors and T2D and CHD within communities.

New York University School of Medicine:

- Using public-use data sources, determine independent and joint association between novel community measures and county-level prevalence of outcomes (diabetes, obesity, and diabetes-obesity prevalence discordance profile), controlling for other county measures (eg, population density, socioeconomic status, and demographic distributions).
- Measure the impact of modifiable community characteristics such as food and housing environments on (a) risk of a new T2D diagnosis or (b) being obese (BMI≥30 kg/m^2) in a large cohort of Veterans Affairs patients, adjusting for community and individual-level covariates in multilevel regression models.
- Use mediation analysis to examine mediating pathways between modifiable community contexts and T2D.

University of Alabama at Birmingham:

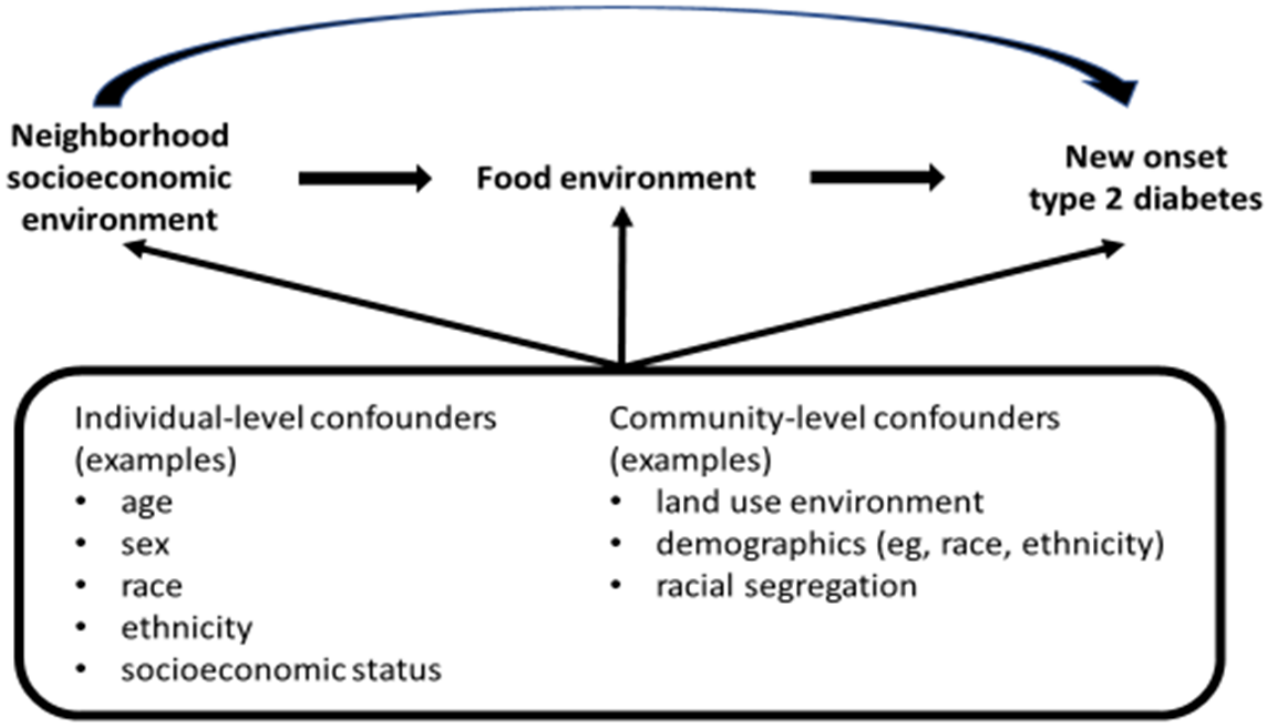
- To determine the association of community-level social determinants of health with the prevalence and incidence of T2D and hypertension, separately.
- To determine if pharmacologic treatment patterns and hospitalization rates vary by community-level social determinants of health for those with T2D and hypertension, separately.
- To determine if awareness and treatment of T2D and risk of cardiovascular complications varies by community-level and individual-level social determinants of health.

Network Aims

The Network aims to evaluate the association of community factors and T2D outcomes (aims 1 and 2) and to evaluate and address the previously described methodological challenges of community and health research (aims 3 and 4):

1. Evaluate the mediation of the association of NSEE with new-onset T2D. This aim reflects a conceptual framework (Figure 4) that proposes that NSEE influences T2D onset through other community pathways, including the food, physical activity (fitness and leisure) environments, and exposure to fine particulate matter (≤2.5 μ, particulate matter$_{2.5}$).
2. Define and test effect modifiers (eg, age, sex, race) of the association of NSEE with new-onset T2D.
3. Assess the differential item functioning of community measures by geographic region and community type.
4. Evaluate the impact of the spatial scale used to measure community factors (eg, buffer, census tract, county) on associations with new-onset T2D.

Figure 4. Conceptual framework for mediation of the association between neighborhood socioeconomic environment and type 2 diabetes: food environment as an example mediator.



Network Populations and Geographic Coverage

The Diabetes LEAD Network draws from individuals living in all 50 US states (Figures 1-3). The G/JHU participants were selected from among 1.6 million individuals in the Geisinger EHR, spanning 37 counties in central and northeastern Pennsylvania (Table 1). The G/JHU participants range in age from 10 to 97 years, are predominately White (542,128/578,458, 93.71%) and non-Hispanic (553,211/578,458, 95.66%), reflecting the region's population [32]. More than 40% of G/JHU participants reside in areas that the US Census Bureau categorizes as rural. The NYU population of veterans spans all US counties. NYU assembled a baseline cohort of veterans who do not have diabetes (n=6,082,246) and are receiving primary care through Veterans Affairs. Veterans are mostly male (5,578,056/6,082,246, 91.71%) and predominantly White (4,411,233/6,082,246, 72.53%) followed by Black (920,596/6,082,246, 15.14%).

These demographic groups are represented by large sample sizes. The UAB population includes participants from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study cohort [33]. At baseline (2003-2007), the REGARDS study enrolled 30,239 non-Hispanic Black and non-Hispanic White adults aged 45 years and older with oversampling of participants from the Stroke Belt region (Alabama, Arkansas, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, and Tennessee) [34]. To assess T2D onset, participants without T2D at baseline and who completed the follow-up in-home examination (n=11,199) will be evaluated. Patients were not invited to comment on the cohort development or study design.

Network Data Sources and Measurement

The DCC is leading the development of harmonized, Network-wide approaches to measuring community factors of interest and T2D outcomes. To develop measures of community factors (Table 4), the DCC is using archival data available at the national level, including publicly available data (eg, US Census) and data elements previously created for the Retail Environment and Cardiovascular Disease (RECVD) study. The RECVD study has longitudinal measures of food, fitness, and

social establishments based on the National Establishment Time Series (NETS), a data source that includes information on more than 58 million US business establishments from 1990 to 2014. For each community factor, the DCC has partnered with a study site with relevant expertise to make decisions regarding data sources, spatial scale, exposure assignment, and approach to measurement.

The DCC is applying a range of measurement techniques to define community factors, including data reduction and measurement models. Measurement development is stratified by community type at the census tract level using a modification of the Rural-Urban Commuting Area (RUCA) from the US Department of Agriculture developed by the Network [35]. After collapsing the original 10 RUCA categories into 3, the DCC further divided census tracts within urbanized areas into 2 categories based on land area, resulting in 4 community-type categories that reflect distinct typologies along the rural-urban continuum.

To the extent possible, the Network is harmonizing approaches to measure T2D onset (Table 5) and diabetes-related outcomes. G/JHU and NYU have worked together to develop EHR-based algorithms based on their previous work [36,37] and diagnosis criteria from the American Diabetes Association [38], using a combination of diagnosis codes, medications, and laboratory measures. With coordination from the DCC, the sites are also standardizing approaches to measure potential confounders, mediators, and effect modifiers.

Network Analyses

For each Network-wide aim, the study sites will conduct analyses among their study populations based on a common analytic plan. The DCC is coordinating the development of the analytic plan, harmonizing analytical approaches, including the selection of confounding, mediating, and modifying variables of interest, model building, and model diagnostics. Sites will conduct site-specific sensitivity analyses that include relevant data elements that may not be available Network-wide. This approach allows us to examine consistency in results while leveraging the unique data available at individual sites.

For aims 1 and 2, the Network will employ methods to account for group-level and individual-level data, including multilevel models, Bayesian approaches, and generalized estimating equation models. The Network will conduct causal mediation analysis for aim 1 [39]. For aim 2, we will evaluate effect modification through the inference of interaction terms, creating cross-products between our contextual domains of interest and a predetermined set of individual- and community-level variables, such as age, sex, and race. To guide model development for these aims, sites are developing causal diagrams to formulate and test theoretically based pathways, identify potential confounding influences, and account for potential interaction between measures (Figure 4) [40,41]. To assess spatial residual autocorrelation, the Network will calculate I statistics by Moran (local and global) [42] and use modeling approaches that account for spatial residual autocorrelation, if needed. The Network will conduct sensitivity analyses to evaluate how approaches to measurement of outcomes and community factors impact observed associations.

For aim 3, the Network is exploring strategies to evaluate and address nonpositivity, including propensity scores [43], stratification by community type for all analyses, and latent profile analysis to evaluate community typology [44]. For aim 4, we are evaluating community factors at multiple spatial scales (eg, census tract, network buffer around population-centroid). We will compare the associations of community factors measured at different scales with T2D to assess the influence of the modifiable areal unit problem [21]. The study sites also have site-specific aims, as described below.

Site Descriptions

Geisinger and Johns Hopkins University

The Environmental Health Institute, a joint collaboration between Geisinger, Johns Hopkins Bloomberg School of Public Health, and Johns Hopkins School of Medicine, is evaluating the influence of community factors on T2D onset and control and cardiometabolic outcomes in Pennsylvania (Textbox 1) using a combination of primary and secondary data collection. The team is conducting the study among patients from Geisinger, a health system serving 1.6 million patients in central and northeastern Pennsylvania. To be eligible for study, individuals had to reside in one of 37 counties in Geisinger's service area and have at least two Geisinger primary care visits from 2006 to 2016 (Table 1). The Geisinger primary care patient population represents the age, sex, and racial and ethnic distribution of the general population of the region [32]. The region's population is residentially stable, with an annual out-migration rate of approximately 1% in all but two counties according to US Census Bureau data.

G/JHU is evaluating the main effects of 8 community factors: NSEE, food environment, fitness environment, leisure-time physical activity environment, land use environment, greenness, blue space (aquatic environments such as coasts, lakes, and rivers), and chronic environmental contamination [45]. G/JHU has previously reported associations between these factors and obesity and glycated hemoglobin (HbA_{1c}) [46-51]. G/JHU is using data from publicly available sources (eg, US Census, American Community Survey [ACS], Moderate Resolution Imaging Spectroradiometer from the National Aeronautics and Space Administration's Terra satellite, Pennsylvania Department of Transportation, TeleAtlas) and commercial data to generate measures for these factors. For the Network aims, the team is working with the DCC to guide decisions on the land use and physical fitness environment measures.

For site-specific aims, G/JHU outcomes include T2D onset, T2D control, and cardiometabolic outcomes (Textbox 1). G/JHU is conducting 2 types of studies to evaluate the associations between community factors and T2D outcomes and mediation and moderation of these associations. EHR-based analyses will be used for both Network- and site-specific aims. A primary data collection study will be used for additional site-specific aims, as much of the data collected in this study will be uniquely available at the G/JHU site (Multimedia Appendix 1).

G/JHU is using a mix of nested case-control and retrospective cohort study designs to achieve site-specific aims, using logistic and linear regression as appropriate. To account for correlation

due to both place and space, G/JHU is using generalized estimating equations and multilevel modeling. To examine mediators of the association between NSEE and T2D onset (Network Aim 1), Geisinger will apply a nested case-control design and formal mediation models that include T2D onset cases (n=15,888) matched to controls (n=79,435) on age, sex, and year of encounter.

New York University School of Medicine

Investigators at NYU are examining the relationship between modifiable community factors and risk for T2D and obesity using a retrospective cohort assembled through EHR data from the Veterans Affairs Corporate Data Warehouse, a national repository of clinical and administrative data. The 2 primary exposures of interest are the food and housing environments. The assembled cohort includes more than 6 million veteran patients who were diabetes-free upon entry into the cohort from 2008 to 2016. Entry eligibility includes 2 primary care visits with no indication of diabetes within the 5 years before cohort entry, with at least two follow-up visits at least 30 days apart during the study period (2008-2018). The population has a well-documented high incidence of diabetes [36], providing adequate variation in contexts and outcomes to examine community factors in relation to T2D incidence.

For site-specific analyses, NYU's primary community factors of interest are the food and housing environments. Food environment metrics include 2 absolute measures and 2 relative measures created from the RECVD data (Table 4). The NYU team also has store-level Nielsen Retail Scanner data from 2006 to 2014, which will be used to examine potential mechanistic pathways, including whether risks associated with living in select food environments are partially mediated through per capita sales of sugar-sweetened beverages. The NYU team is guiding Network decisions on the food environment measure development and harmonization, in collaboration with the DCC. They are also engaging in site-specific analyses to examine the influence of housing affordability per ACS and Veterans Affairs data on T2D risk.

NYU study outcomes include diabetes incidence and control as well as obesity prevalence and incidence. Outcome data are extracted from EHRs, capturing demographic, clinical, and utilization data. To ensure participants in the cohort do not have diabetes at cohort entry, individuals with any diabetes (type 1 or type 2) International Classification of Disease version 9 or 10 (ICD-9/10) code or elevated HbA_{1c} at enrollment are excluded. Time-to-event analyses (Cox proportional hazards models with frailty to account for clustering within a community) will be used to examine the main effects of the food environment on T2D risk and its role in mediating the association between NSEE and T2D risk. Person-time is calculated as the date of a censoring event (diabetes diagnosis, death, loss to follow-up, or end of study period) minus the date of cohort entry. The date of death is obtained from the Veterans Affairs Vital Status and Beneficiary Identification Records Locator. Loss-to-follow-up is defined as no Veterans Affairs encounter for more than 2 years but patients can re-enter the cohort if they meet entry criteria again.

University of Alabama at Birmingham

The UAB site is investigating the association of NSEE with a greater burden of T2D and cardiovascular risk, particularly in southeastern United States. To address site-specific and Network-wide research questions, UAB is leveraging resources from the REGARDS study [33]. The REGARDS study is a longitudinal, population-based closed cohort study of 30,239 adults aged 45 years and older at baseline (2003-2007), designed to identify factors associated with higher stroke mortality. The study was designed to oversample non-Hispanic Black adults and residents of the Stroke Belt region, with 56% of the sample selected from the Stroke Belt and the remaining 44% selected from the other 40 contiguous states. Demographics, medical history, and lifestyle factors were assessed at baseline and an in-home physical exam was performed with blood and urine collection. Follow-up is ongoing every 6 months to assess vital status and hospitalizations and obtain medical records for adjudication of possible cardiovascular events. A second in-home physical exam was completed between 2013 and 2016.

For site-specific analyses, the primary exposure includes the NSEE as assessed using principal component analysis for measures of community-level income or wealth, education, housing, health systems or services, employment, social environment, and physical environment. The data to assess these characteristics include both publicly available databases (eg, US Census) and commercial databases (eg, Dun & Bradstreet). The primary outcomes are incident T2D and cardiovascular outcomes. Incident T2D will be assessed among 11,199 REGARDS study participants without prevalent T2D at baseline and who completed the follow-up in-home physical exam during which objective measurements (eg, glucose, use of medications) were collected (Table 2). Cardiovascular outcomes include hypertension (ie, mean blood pressure140/90 mm Hg or use of hypertension medications) and expert adjudicated clinical events (ie, coronary heart disease, stroke).

Separate from the analysis of the REGARDS study data, UAB will utilize Medicare administrative claims data to investigate the association of NSEE with T2D and hypertension incidence. These data consist of several federal health care insurance programs that cover adults aged 65 years and older and younger individuals who are disabled or have end-stage renal disease. Broadly, Medicare Part A covers hospital services, Medicare Part B covers outpatient and physician services, and Medicare Part D covers prescription drugs. UAB will use the 5% random sample of Medicare claims data available from 1999 to 2015 to investigate community-level determinants of T2D incidence, diabetes hospitalizations, and treatment patterns. An overview of the Medicare sample population and diabetes definitions used for site-specific analyses is provided in Multimedia Appendix 2. Statistical approaches include generalized linear models and spatial generalized linear mixed models.

Drexel Data Coordinating Center

The Drexel DCC provides the study sites with project coordination and statistical support, including advanced methodological and analytic approaches to data analyses driven by the Network aims and heterogeneous data from each study site. The expertise needed for this work is reflected in the

backgrounds of DCC team members, including biostatisticians and epidemiologists from the Dornsife School of Public Health and the Drexel Urban Health Collaborative (UHC), postdoctoral fellows, doctoral-level biostatistics students, data analysts and managers, and GIS experts. Through exploratory analytic work, including principal component analysis, exploratory factor analysis, GIS analysis and mapping, and correlation analysis of contextual indices against individual variables, the DCC supports the Network's collective decision making around defining exposure metrics for addressing Network aims. The relationship with the UHC also allows for access to data from RECVD and other sources; provides support for GIS methods, data distribution, and storage; and provides access to data engineering experts. Furthermore, the UHC has a Policy and Outreach Core, which helps provide guidance on disseminating LEAD Network findings.

Results

The Network has developed metrics for the community factors of interest: NSEE, food establishment, physical fitness establishment, leisure-time physical activity, and land use environments (Table 4). The Network has created these measures using data that are consistently available and contextually applicable to all geographies in the contiguous United States. This underscores the importance of the Network's development of a method for categorizing community types for stratified evaluation of community factors with T2D onset. With harmonized measures, the Network is poised to compare findings across the varying study sites.

The Network has reported findings based on work from the initial years of funding. Preliminary results have been presented at annual meetings of the Society for Epidemiologic Research, the American Diabetes Association, and the American Public Health Association [52,53]. The Network recently published a paper describing county-level determinants of diabetes status in the United States from 2003 to 2012 [54]. The NYU team published a paper describing the impact of changes in the built and social environment on BMI in US counties using data from the Behavioral Risk Factor Surveillance System [13]. Additional manuscripts are in press or in development.

Discussion

Strengths and Limitations

The Diabetes LEAD Network leverages a breadth of expertise and data to advance knowledge regarding modifiable community risk factors for T2D onset and related outcomes. The Network brings strengths to its collective mission to provide scientific evidence for targeted interventions and policies. First, the sites provide the Network with community data sources that collectively ensure widespread geographic coverage and variation of community types across a rural-to-urban spectrum. It was of particular importance to ensure representation by rural communities, since CDC reports that diabetes is 17% more prevalent in rural than urban areas [55]. Furthermore, understanding the association between community and health requires the assessment of a heterogeneous set of communities [12,56]. Each of the study sites contributes unique data sources to achieve this goal. The NYU cohort spans the nation, the UAB REGARDS study cohort offers a national study with in-depth data from a high-risk region (Stroke Belt), and the G/JHU population is a regionally representative sample with high rural representation and primary data collection.

A second contribution of the Network is the development of measures of 6 community factors (Table 4) to be examined across diverse geographies and community types. These measures are being developed with consideration of community types, examining community factors within strata of different community types defined along a rural-urban spectrum to avoid potential differential item functioning and nonpositivity [23]. In addition, Network investigators are examining individual and joint associations to better understand how these community factors work in concert to contribute to excess T2D risk. With access to individuals' residential and commercial addresses, the Network is evaluating spatial scales of various types and sizes to better understand the impact of scale on the findings.

Third, the range of expertise across institutions allows the Network to address methodological challenges common to community and health research [20]. In addition, the Network is advancing methods for conducting research on the role of community and health using data obtained from EHR systems, including extracting historical residential addresses to allow for time-varying exposure estimation. Finally, the Network is harmonizing community factor definitions and analytical approaches to facilitate comparable analyses and replicating analyses across 3 different study populations. This effort to harmonize approaches across multiple settings and populations will advance both the field of community and health research and generate data needed to guide evidence-based policies for T2D prevention in the United States.

There are some limitations to the Diabetes LEAD Network research portfolio. First, although access to longitudinal data will mitigate issues of temporality, the available data do not allow for investigation of early life exposures (eg, childhood) that may influence T2D risk [57]. Second, while the diversity of populations and geographies across the study sites is advantageous to expand the generalizability of findings and include previously underrepresented settings (ie, rural), it complicates comparison of results across sites. However, by harmonizing measurement and analytical approaches the Network will be well positioned to pinpoint reasons for any potential conflicting results that arise. Finally, despite employing advanced analytic approaches, the studies are all observational in design; thus, they are potentially constrained with respect to causal inference due to the risk of residual confounding and neighborhood self-selection [58,59]. The Network will consider methodological approaches such as propensity scores to address this limitation [43].

Conclusions

T2D is a leading cause of morbidity in the United States, with select populations, often defined by geography, affected by a disproportionate burden of disease. The Diabetes LEAD Network identifies modifiable community factors that influence geographic disparities in T2D risk across diverse communities and identifies policy levers to ameliorate these disparities.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Description of primary data collection study for Geisinger and Johns Hopkins University site-specific analyses.
[DOCX File , 16 KB - resprot_v9i10e21377_app1.docx]

Multimedia Appendix 2
Description of Medicare study population for University of Alabama at Birmingham site-specific analyses.
[DOCX File , 15 KB - resprot_v9i10e21377_app2.docx]

References

1. National Diabetes Statistics Report. Centers for Disease Control and Prevention. 2020. URL: https://www.cdc.gov/diabetes/data/statistics-report/index.html [accessed 2020-09-25]
2. Bhupathiraju SN, Hu FB. Epidemiology of obesity and diabetes and their cardiovascular complications. Circ Res 2016 May 27;118(11):1723-1735 [FREE Full text] [doi: 10.1161/CIRCRESAHA.115.306825] [Medline: 27230638]
3. American Diabetes Association. Prevention or delay of type 2 diabetes: standards of medical care in diabetes. Diabetes Care 2018 Dec 17;42(Supplement 1):S29-S33. [doi: 10.2337/dc19-s003] [Medline: 29222376]
4. Boyle JP, Thompson TJ, Gregg EW, Barker LE, Williamson DF. Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and prediabetes prevalence. Popul Health Metr 2010 Oct 22;8:29 [FREE Full text] [doi: 10.1186/1478-7954-8-29] [Medline: 20969750]
5. Dwyer-Lindgren L, Mackenbach JP, van Lenthe FJ, Flaxman AD, Mokdad AH. Diagnosed and undiagnosed diabetes prevalence by county in the US, 1999-2012. Diabetes Care 2016 Sep;39(9):1556-1562. [doi: 10.2337/dc16-0678] [Medline: 27555622]
6. Barker LE, Kirtland KA, Gregg EW, Geiss LS, Thompson TJ. Geographic distribution of diagnosed diabetes in the US: a diabetes belt. Am J Prev Med 2011 Apr;40(4):434-439. [doi: 10.1016/j.amepre.2010.12.019] [Medline: 21406277]
7. Cunningham SA, Patel SA, Beckles GL, Geiss LS, Mehta N, Xie H, et al. County-level contextual factors associated with diabetes incidence in the United States. Ann Epidemiol 2018 Jan;28(1):20-5.e2 [FREE Full text] [doi: 10.1016/j.annepidem.2017.11.002] [Medline: 29233722]
8. Fang M. Trends in the prevalence of diabetes among US Adults: 1999-2016. Am J Prev Med 2018 Oct;55(4):497-505. [doi: 10.1016/j.amepre.2018.05.018] [Medline: 30126668]
9. Creatore MI, Glazier RH, Moineddin R, Fazli GS, Johns A, Gozdyra P, et al. Association of neighborhood walkability with change in overweight, obesity, and diabetes. J Am Med Assoc 2016;315(20):2211-2220. [doi: 10.1001/jama.2016.5898] [Medline: 27218630]
10. Mezuk B, Li X, Cederin K, Rice K, Sundquist J, Sundquist K. Beyond access: characteristics of the food environment and risk of diabetes. Am J Epidemiol 2016 Jun 15;183(12):1129-1137 [FREE Full text] [doi: 10.1093/aje/kwv318] [Medline: 27240801]
11. Caspi CE, Sorensen G, Subramanian SV, Kawachi I. The local food environment and diet: a systematic review. Health Place 2012 Sep;18(5):1172-1187 [FREE Full text] [doi: 10.1016/j.healthplace.2012.05.006] [Medline: 22717379]
12. Feng J, Glass TA, Curriero FC, Stewart WF, Schwartz BS. The built environment and obesity: a systematic review of the epidemiologic evidence. Health Place 2010 Mar;16(2):175-190. [doi: 10.1016/j.healthplace.2009.09.008] [Medline: 19880341]
13. Rummo PE, Feldman JM, Lopez P, Lee D, Thorpe LE, Elbel B. Impact of changes in the food, built, and socioeconomic environment on BMI in us counties, BRFSS 2003-2012. Obesity (Silver Spring) 2020 Jan;28(1):31-39. [doi: 10.1002/oby.22603] [Medline: 31858733]
14. Walker BB, Shashank A, Gasevic D, Schuurman N, Poirier P, Teo K, et al. The local food environment and obesity: evidence from three cities. Obesity (Silver Spring) 2020 Jan;28(1):40-45 [FREE Full text] [doi: 10.1002/oby.22614] [Medline: 31774254]

15. Bilal U, Auchincloss AH, Diez-Roux AV. Neighborhood environments and diabetes risk and control. Curr Diab Rep 2018 Jul 11;18(9):62. [doi: 10.1007/s11892-018-1032-2] [Medline: 29995252]
16. Hipp JA, Chalise N. Spatial analysis and correlates of county-level diabetes prevalence, 2009-2010. Prev Chronic Dis 2015 Jan 22;12:E08 [FREE Full text] [doi: 10.5888/pcd12.140404] [Medline: 25611797]
17. Christine PJ, Auchincloss AH, Bertoni AG, Carnethon MR, Sánchez BN, Moore K, et al. Longitudinal associations between neighborhood physical and social environments and incident type 2 diabetes mellitus: the multi-ethnic study of atherosclerosis (MESA). JAMA Intern Med 2015 Aug;175(8):1311-1320 [FREE Full text] [doi: 10.1001/jamainternmed.2015.2691] [Medline: 26121402]
18. Auchincloss AH, Diez Roux AV, Mujahid MS, Shen M, Bertoni AG, Carnethon MR. Neighborhood resources for physical activity and healthy foods and incidence of type 2 diabetes mellitus: the multi-ethnic study of atherosclerosis. Arch Intern Med 2009 Oct 12;169(18):1698-1704 [FREE Full text] [doi: 10.1001/archinternmed.2009.302] [Medline: 19822827]
19. Booth GL, Creatore MI, Luo J, Fazli GS, Johns A, Rosella LC, et al. Neighbourhood walkability and the incidence of diabetes: an inverse probability of treatment weighting analysis. J Epidemiol Community Health 2019 Apr;73(4):287-294. [doi: 10.1136/jech-2018-210510] [Medline: 30696690]
20. Diez Roux AV. Estimating neighborhood health effects: the challenges of causal inference in a complex world. Soc Sci Med 2004 May;58(10):1953-1960. [doi: 10.1016/S0277-9536(03)00414-3] [Medline: 15020010]
21. Openshaw S. The Modifiable Areal Unit Problem. Norwich, CT: GeoBooks; 1984.
22. Boyle MH, Willms JD. Place effects for areas defined by administrative boundaries. Am J Epidemiol 1999 Mar 15;149(6):577-585. [doi: 10.1093/oxfordjournals.aje.a009855] [Medline: 10084248]
23. Messer LC, Jagai JS, Rappazzo KM, Lobdell DT. Construction of an environmental quality index for public health research. Environ Health 2014 May 22;13(1):39 [FREE Full text] [doi: 10.1186/1476-069X-13-39] [Medline: 24886426]
24. Reading R, Raybould S, Jarvis S. Deprivation, low birth weight, and children's height: a comparison between rural and urban areas. Br Med J 1993 Dec 4;307(6917):1458-1462 [FREE Full text] [doi: 10.1136/bmj.307.6917.1458] [Medline: 8281087]
25. Messer LC, Oakes JM, Mason S. Effects of socioeconomic and racial residential segregation on preterm birth: a cautionary tale of structural confounding. Am J Epidemiol 2010 Mar 15;171(6):664-673. [doi: 10.1093/aje/kwp435] [Medline: 20139129]
26. Oakes JM. Commentary: advancing neighbourhood-effects research--selection, inferential support, and structural confounding. Int J Epidemiol 2006 Jun;35(3):643-647. [doi: 10.1093/ije/dyl054] [Medline: 16556642]
27. Carroll-Scott A, Gilstad-Hayden K, Rosenthal L, Peters SM, McCaslin C, Joyce R, et al. Disentangling neighborhood contextual associations with child body mass index, diet, and physical activity: the role of built, socioeconomic, and social environments. Soc Sci Med 2013 Oct;95:106-114 [FREE Full text] [doi: 10.1016/j.socscimed.2013.04.003] [Medline: 23642646]
28. Casey JA, Schwartz BS, Stewart WF, Adler NE. Using electronic health records for population health research: a review of methods and applications. Annu Rev Public Health 2016;37:61-81 [FREE Full text] [doi: 10.1146/annurev-publhealth-032315-021353] [Medline: 26667605]
29. Xiao Q, Berrigan D, Powell-Wiley TM, Matthews CE. Ten-year change in neighborhood socioeconomic deprivation and rates of total, cardiovascular disease, and cancer mortality in older US adults. Am J Epidemiol 2018 Dec 01;187(12):2642-2650 [FREE Full text] [doi: 10.1093/aje/kwy181] [Medline: 30137194]
30. Wen M, Zhang X, Harris CD, Holt JB, Croft JB. Spatial disparities in the distribution of parks and green spaces in the USA. Ann Behav Med 2013 Feb;45(Suppl 1):S18-S27 [FREE Full text] [doi: 10.1007/s12160-012-9426-x] [Medline: 23334758]
31. Zhang X, Lu H, Holt JB. Modeling spatial accessibility to parks: a national study. Int J Health Geogr 2011 May 9;10:31 [FREE Full text] [doi: 10.1186/1476-072X-10-31] [Medline: 21554690]
32. Casey JA, Savitz DA, Rasmussen SG, Ogburn EL, Pollak J, Mercer DG, et al. Unconventional natural gas development and birth outcomes in Pennsylvania, USA. Epidemiology 2016 Mar;27(2):163-172 [FREE Full text] [doi: 10.1097/EDE.0000000000000387] [Medline: 26426945]
33. Howard VJ, Cushman M, Pulley L, Gomez CR, Go RC, Prineas RJ, et al. The reasons for geographic and racial differences in stroke study: objectives and design. Neuroepidemiology 2005;25(3):135-143. [doi: 10.1159/000086678] [Medline: 15990444]
34. Obisesan TO, Vargas CM, Gillum RF. Geographic variation in stroke risk in the United States. Region, urbanization, and hypertension in the third national health and nutrition examination survey. Stroke 2000 Jan;31(1):19-25. [doi: 10.1161/01.str.31.1.19] [Medline: 10625710]
35. Rural-Urban Continuum Codes. United States Department of Agriculture. URL: https://www.ers.usda.gov/data-products/rural-urban-continuum-codes/ [accessed 2020-04-30]
36. Miller DR, Safford MM, Pogach LM. Who has diabetes? Best estimates of diabetes prevalence in the department of veterans affairs based on computerized patient data. Diabetes Care 2004 May;27(Suppl 2):B10-B21. [doi: 10.2337/diacare.27.suppl_2.b10] [Medline: 15113777]

37. Hirsch AG, Scheck McAlearney A. Measuring diabetes care performance using electronic health record data: the impact of diabetes definitions on performance measure outcomes. Am J Med Qual 2014;29(4):292-299. [doi: 10.1177/1062860613500808] [Medline: 24006028]
38. American Diabetes Association. Classification and diagnosis of diabetes. Diabetes Care 2017 Dec 8;41(Supplement 1):S13-S27. [doi: 10.2337/dc18-s002] [Medline: 29222376]
39. VanderWeele TJ. Mediation analysis: a practitioner's guide. Annu Rev Public Health 2016;37:17-32. [doi: 10.1146/annurev-publhealth-032315-021402] [Medline: 26653405]
40. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. BMC Med Res Methodol 2008 Oct 30;8:70 [FREE Full text] [doi: 10.1186/1471-2288-8-70] [Medline: 18973665]
41. Suttorp MM, Siegerink B, Jager KJ, Zoccali C, Dekker FW. Graphical presentation of confounding in directed acyclic graphs. Nephrol Dial Transplant 2015 Sep;30(9):1418-1423. [doi: 10.1093/ndt/gfu325] [Medline: 25324358]
42. Moran PA. The interpretation of statistical maps. J R Stat Soc Series B Stat Methodol 1948 Dec 5;10(2):243-251. [doi: 10.1111/j.2517-6161.1948.tb00012.x]
43. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983;70(1):41-55. [doi: 10.1093/biomet/70.1.41]
44. Lekkas P, Stankov I, Daniel M, Paquet C. Finite mixture models in neighbourhoods-to-health research: a systematic review. Health Place 2019 Sep;59:102140. [doi: 10.1016/j.healthplace.2019.05.018] [Medline: 31374380]
45. Couch SR, Coles CJ. Community stress, psychosocial hazards, and EPA decision-making in communities impacted by chronic technological disasters. Am J Public Health 2011 Dec;101(Suppl 1):S140-S148. [doi: 10.2105/AJPH.2010.300039] [Medline: 21836109]
46. Hirsch AG, Durden ET, Nordberg C, Berger A, Schwartz BS. Associations of Four Community Factors With Longitudinal Change in Hemoglobin A Levels in Patients With Type 2 Diabetes. Diabetes Care 2018 Mar;41(3):461-468 [FREE Full text] [doi: 10.2337/dc17-1200] [Medline: 29258994]
47. Liu AY, Curriero FC, Glass TA, Stewart WF, Schwartz BS. The contextual influence of coal abandoned mine lands in communities and type 2 diabetes in Pennsylvania. Health Place 2013 Jul;22:115-122. [doi: 10.1016/j.healthplace.2013.03.012] [Medline: 23689181]
48. Schwartz BS, Stewart WF, Godby S, Pollak J, Dewalle J, Larson S, et al. Body mass index and the built and social environments in children and adolescents using electronic health records. Am J Prev Med 2011 Oct;41(4):e17-e28. [doi: 10.1016/j.amepre.2011.06.038] [Medline: 21961475]
49. Nau C, Ellis H, Huang H, Schwartz BS, Hirsch A, Bailey-Davis L, et al. Exploring the forest instead of the trees: an innovative method for defining obesogenic and obesoprotective environments. Health Place 2015 Sep;35:136-146 [FREE Full text] [doi: 10.1016/j.healthplace.2015.08.002] [Medline: 26398219]
50. Nau C, Schwartz BS, Bandeen-Roche K, Liu A, Pollak J, Hirsch A, et al. Community socioeconomic deprivation and obesity trajectories in children using electronic health records. Obesity (Silver Spring) 2015 Jan;23(1):207-212 [FREE Full text] [doi: 10.1002/oby.20903] [Medline: 25324223]
51. Poulsen MN, Glass TA, Pollak J, Bandeen-Roche K, Hirsch AG, Bailey-Davis L, et al. Associations of multidimensional socioeconomic and built environment factors with body mass index trajectories among youth in geographically heterogeneous communities. Prev Med Rep 2019 Sep;15:100939 [FREE Full text] [doi: 10.1016/j.pmedr.2019.100939] [Medline: 31360629]
52. Poulsen M, Hirsch A, Nordberg C. Community Determinants of High Blood Pressure Among Patients With Type 2 Diabetes. In: American Public Health Association. 2019 Presented at: APHA'19; November 2-6, 2019; New York, USA.
53. Lopez PM, feldman J, Rummo PE, Elbel B, Thorpe L. 1649-P: community predictors of diabetes prevalence and change in burden over time: US counties, 2003-2012. Diabetes 2019 Jun;68(Supplement 1):1649-P. [doi: 10.2337/db19-1649-p]
54. Feldman J, Lee D, Lopez P. Assessing county-level determinants of individual-level diabetes status in the United States. - 2020 May 20;2012:102324 (forthcoming). [doi: 10.1016/j.healthplace.2020.102324] [Medline: 32217279]
55. Division of Diabetes Translation At A Glance. Centers for Disease Control and Prevenrion. 2019. URL: https://www.cdc.gov/chronicdisease/resources/publications/aag/diabetes.htm [accessed 2020-01-20]
56. Richardson AS, Boone-Heinonen J, Popkin BM, Gordon-Larsen P. Are neighbourhood food resources distributed inequitably by income and race in the USA? Epidemiological findings across the urban spectrum. BMJ Open 2012;2(2):e000698. [doi: 10.1136/bmjopen-2011-000698] [Medline: 22505308]
57. Barker DJ. Maternal nutrition, fetal nutrition, and disease in later life. Nutrition 1997 Sep;13(9):807-813. [doi: 10.1016/s0899-9007(97)00193-7] [Medline: 9290095]
58. Oakes JM. The (mis)estimation of neighborhood effects: causal inference for a practicable social epidemiology. Soc Sci Med 2004 May;58(10):1929-1952. [doi: 10.1016/j.socscimed.2003.08.004] [Medline: 15020009]
59. Diez Roux AV, Mair C. Neighborhoods and health. Ann N Y Acad Sci 2010 Feb;1186:125-145. [doi: 10.1111/j.1749-6632.2009.05333.x] [Medline: 20201871]

Abbreviations

ACS: American Community Survey

CDC: Centers for Disease Control and Prevention
CHD: coronary heart disease
CSD: community socioeconomic deprivation
DCC: data coordinating center
EDG: Epic Diagnostic code Groupers
EHR: electronic health record
GIS: geographic information systems
ICD: International Classification of Diseases.
LEAD: Location, Environmental Attributes, and Disparities
NETS: National Establishment Time Series
NSEE: neighbourhood socioeconomic environment
RECVD: Retail Environment and Cardiovascular Disease
REGARDS: Reasons for Geographic and Racial Differences in Stroke
RUCA: Rural-Urban Commuting Area
T2D: type 2 diabetes
UHC: Urban Health Collaborative

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Protocol

Standardized Protocol Items Recommendations for Observational Studies (SPIROS) for Observational Study Protocol Reporting Guidelines: Protocol for a Delphi Study

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Abstract

Background: Approximately 90% of currently published clinical and public health research is in the form of observational studies. Having a detailed and registered study protocol prior to data collection is important in any empirical study. Without this, there is no reliable way to assess the occurrence of publication bias, outcome reporting bias, and other protocol deviations. However, there is currently no solid guidance available on the information that a protocol for an observational study should contain.

Objective: The aim of this study is to formulate the Standardized Protocol Items Recommendations for Observational Studies (SPIROS) reporting guidelines, which focus on 3 main study designs of analytical epidemiology: cohort, case-control, and cross-sectional studies.

Methods: A scoping review of published protocol papers of observational studies in epidemiology will identify candidate items for the SPIROS reporting guidelines. The list of items will be extended with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist items and recommendations from the SPIROS steering committee. This long list serves as the basis for a 2-round Delphi survey among experts to obtain consensus on which items to include. Each candidate item from the long list will be rated on a 5-point Likert scale to assess relevance for inclusion in the SPIROS reporting guidelines. Following the Delphi survey, an expert-driven consensus workshop will be convened to finalize the reporting guidelines.

Results: A scoping review of published observational study protocols has been completed, with 59 candidate items identified for inclusion into the Delphi survey, itself launched in early 2020.

Conclusions: This project aims to improve the timeliness, completeness, and clarity of study protocols of observational studies in analytical epidemiology by producing expert-based recommendations of items to be addressed. These reporting guidelines will facilitate and encourage researchers to prepare and register study protocols of sufficient quality prior to data collection in order to improve the transparency, reproducibility, and quality of observational studies.

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KEYWORDS

protocol; observational studies; SPIROS; guidelines; Delphi

Introduction

The protocol of any empirical study offers the researcher practical guidance in data collection, analysis, and reporting. It also forms the basis for subsequent replication of the study and detection of publication bias, outcome reporting bias, and other protocol deviations. A well-formulated study protocol uploaded prior to data collection through a time-stamped registry will allow a robust audit trail. This improves the chances that the study is appropriately planned, executed, and well documented, thus promoting optimal conduct, accountability, replicability, and overall research integrity. In summary, ensuring a high level of transparency in the research planning phase facilitates replicability of the study and fosters good research practices [1,2].

Although the value of registered study protocols and reporting guidelines on how to write them are widely recognized in the field of randomized control trials (RCTs) [3-5], reporting guidelines for study protocols of observational studies in analytical epidemiology (cohort, case-control studies, and cross-sectional studies) are currently absent. In many situations, observational studies may be the best or at least the only feasible way to answer important medical and public health questions in scenarios where RCTs are not possible for practical and ethical reasons. Therefore, the same rigorous standards that apply to RCTs must be maintained for observational studies.

An estimated 90% of currently published clinical or public health–related research is in the form of observational studies [6]. In particular, most research focusing on understanding causes and distribution of diseases relies on cohort, case-control, or cross-sectional studies. Additionally, a substantial body of evidence for diagnostic or prognostic research takes the form of observational studies. The absence of reporting guidelines on how to write these study protocols is problematic, as by design, observational studies have a nonnegligible risk of bias [7]. The risk of bias has been well recognized in experimental research, where guidelines for the development of RCT protocols are well established [1]. Additionally, large observational data sets without any statistical analysis plan readily allow data-driven post hoc analyses, leading to an exceedingly large number of potential associations that can be tested [8,9]. In such situations of multiple comparisons, there is increased likelihood of type I error and “p-hacking” by doing multiple statistical tests on the data and only reporting those that come back with significant results, causing false-positive results [10]. Therefore, it is important to ensure that study protocols are complete, well written, and registered prior to data collection in a suitable time-stamped repository (eg, ClinicalTrials.gov and Open Science Framework). This allows external bodies to consult the original study protocol and understand the specific hypotheses and the data analysis plan to which the researcher was committed, both for primary data analyses and for secondary analyses of existing data sets.

When protocols of observational studies do not provide sufficient details concerning the conduct of their preplanned study and are not preregistered or made openly available prior to data collection initiation, the scientific community is left with an incomplete picture of what the researchers intended to do and whether undisclosed protocol deviations and reporting biases occurred. Consequently, in the absence of registered protocols for observational studies, we are insufficiently able to judge the validity and reliability of the results. As such, interpretation of the results within the context of the study limitations becomes a potential major issue [2].

Methods

Overview of Objectives

The objective of this study is to develop reporting guidelines to be used in the design of observational study protocols. Our initiative has been given the acronym SPIROS (Standardized Protocol Items: Recommendations for Observational Studies). The project aims to improve the completeness and utility of study protocols for observational studies by producing expert-based recommendations for a minimum set of items these study protocols need to address. An item is defined as an important section, heading, or subheading within the study protocol, with each item describing an important methodological feature of the study. Our study is designed to meet three objectives.

Objective 1 is to conduct a scoping review of items addressed in study protocols of observational studies in epidemiology. The purpose of objective 1 is to develop a long list of candidate items that could a priori be incorporated in the draft reporting guidelines. This would serve as the basis for the first round of the Delphi survey (Objective 2).

Objective 2 is to conduct a Delphi survey with participants who are selected based on a prespecified range of expertise, with the intention of obtaining consensus on which items to include in the SPIROS reporting guidelines.

Objective 3 is to conduct a face-to-face consensus workshop to finalize the SPIROS reporting guidelines and then disseminate the results with an associated manual.

Methods to Conduct Scoping Review of Protocols (Objective 1)

A scoping review of published study protocols of observational studies will be conducted, in which every item mentioned more than once will be listed [11,12]. The study will be based on a systematic selection of up to 100 protocols of observational studies identified via published study design papers indexed by Web of Science Core Collections until information threshold saturation is achieved (defined as the point where no further items are identified after 15 consecutive paper reviews). The list of items will then be extended with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)

checklist items, which are developed as reporting guidelines for the publication of observational studies [13], the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist items for the reporting of protocols of experimental studies [3], and recommendations from an expert steering committee (the authors of this manuscript). The findings of the scoping review will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for scoping reviews [14].

Eligibility Criteria

Up to 100 protocols of observational studies (cohort studies, case-control studies, and cross-sectional studies) published in indexed journals from the Web of Science will be included in the present review. To ensure the most current state of affairs is assessed, only papers published between January 1, 2016, and May 1, 2018, will be included because, based on a preliminary assessment, the target number of studies is expected to be reached within this time range.

Information Sources

Data for this scoping review will be identified by searching the Web of Science Core Collection and references from relevant papers using the search terms “protocol” PLUS “observational study” AND/OR “cohort study” AND/OR “case control study” AND/OR “cross sectional study” AND/OR “prevalence study” AND/OR “survey” in the advanced search mode. A senior clinical librarian will be engaged to ensure that the search strategy is valid.

All the protocol items present in the headings, subheadings, or text of protocol papers will then be presented in the form of a table, following the structure of the STROBE checklist. Initially, all items will be categorized into the following themes: general information, introduction, methods, ethical considerations, reporting, dissemination, and others. However, if different themes emerge, this structure will be accordingly iteratively adapted.

Methods to Conduct Delphi Study (Objective 2)

Participant Recruitment

The long list of candidate items for the protocols of observational studies identified in the scoping review will be evaluated by experts. For this purpose, we will conduct a 2-round Delphi study [15-19]. We will aim for participation of 50 to 100 experts who represent the key stakeholders in observational research, including principal investigators, methodologists, journal editors, users of observational data, and representatives from research ethics review boards. Experts will need to have relevant knowledge and experience and be spread across geographical regions. Experts will be identified by a mixed approach, including nomination by other experts, PubMed and web search, ResearchGate, and participation in the development of previous reporting guidelines.

Round 1 of Delphi Survey

Each panelist will be asked to rate every candidate item from the long list on a 5-point Likert scale for relevance for inclusion in the reporting guidelines for protocols of observational studies (Table 1).

A field for adding free text will be provided for comments on comprehensiveness and comprehensibility for each item and to suggest alterations or additional items. Round 1 will also collect core demographic information (panelists’ working field and place of employment) and panelists’ self-rated level of expertise on the particular topic.

A threshold of 67% agreement among participants on a score of 4 or 5 for each candidate item will be considered to indicate consensus among the expert panel for consideration of inclusion in the SPIROS checklist. If agreement among participants is less than 67% scoring 4 or 5, the item will be considered discordant. The survey will be structured to last no more than 30 minutes and will be pretested and approved by the expert steering committee. The study protocol with any amendments will be uploaded in the Open Science Framework (OSF), as will the Delphi survey format, which will be updated, if needed, before the second round.

Table 1. Implication of Likert score on candidate items.

Likert score	Implication on candidate item
1	Unimportant—should be dropped as an item to consider
2	Of little importance
3	Moderately important
4	Important
5	Very important—should definitely be included

Round 2 of Delphi Survey

Round 2 will contain all original candidate items plus additional items nominated or identified during the first round. For each item, panelists will be provided with percentage agreement from the first round, while the themes of each item´s free text comments will be merged into an anonymized executive summary.

The participants will be asked to rerate the items and consider the comment themes. Once collated, all items reaching a 67% consensus agreement ranking of 4 or 5 on the Likert score will be included in the short list for the reporting guidelines and advance to the next stage of the process.

Data Collection and Statistical Analysis

A preset online survey questionnaire will be developed on the Google Forms online survey platform and uploaded to OSF

before being sent out to expert panelists via email. Medians, interquartile range, and percentage of agreement will be calculated for each item.

Consensus Workshop (Objective 3)

Following completion of the Delphi survey, the steering committee will convene a consensus workshop consisting of the steering committee plus 10 others previously involved in developing guidelines. Experts will review and adapt the draft reporting guidelines into a format appropriate for wider dissemination. A further workshop around dissemination strategy planning will also be convened, comprising experts involved with previous guideline dissemination, to ensure that a robust uptake mechanism is defined for widespread adoption of SPIROS, including choice of journal for publication of the final manuscript and content of a website exclusively for the initiative.

Dissemination, Implementation, and Ongoing Development (Objective 4)

The ultimate objective of this initiative is to facilitate widespread adoption of the SPIROS reporting guidelines. Therefore, all outputs of this initiative will be published as preprints and in open access journals or open choice access. This will include a detailed manual that explains and justifies the recommendations and includes examples of good reporting. We aim to have the SPIROS reporting guidelines adopted by journals and funders. The SPIROS protocol and final reporting guidelines will be published on a dedicated website (spiros-statement.org) and will be included in the Enhancing the Quality and Transparency of Health Research (EQUATOR) Network.

Data Management and Registration of Study Protocol

The study will comply with the EU General Data Protection Regulation. Prior to data collection, the study protocol and all appendices will be registered and made openly available on the OSF, and links will be provided to reviewers and readers of the paper. This will include the complete data management and data analysis plan, and on completion of the study, all anonymized data will additionally be made available on OSF with no restrictions.

Ethics Approval and Consent to Participate

Ethics approval has been obtained from the Ethics Review Committee of Maastricht University. The study will not collect any sensitive information, and the identity of each panel member will be fully protected and blinded to other panel members and the research group (except for the corresponding researcher). The burden for the panelists includes a maximum of 30 minutes for each of the Delphi survey rounds.

Online informed consent will be obtained from all panel members, which will comprise an introductory page and completion of the survey as consent. Participants of the Delphi consensus survey will be provided with a summary of the overall aim of the SPIROS project and a link to the complete protocol. The consent for the Delphi survey will explain the specific aim of the survey and an outline of the procedures involved, as well as the benefits, risks, and burdens involved in participating. If consent is given, panels member will be acknowledged in the publication of the SPIROS reporting guidelines. However, the option to not be mentioned in the acknowledgments will also be given.

Results

The scoping review of published protocols of observational studies has been completed, with 59 candidate items identified. This long list of candidate items has formed the basis of the 2-round Delphi survey launched in early 2020.

Discussion

Over the last decade, there has been an increasing call for prospective registration of observational study protocols [6,20-22]. Without a registered protocol, it is impossible to detect p-hacking and any intentional amendments in protocols to match with preferred results. To conduct research without a detailed protocol registered prior to data collection is increasingly considered questionable research practice, limiting reviewers' and readers' ability to assess the occurrence of intentional or nonintentional bias. A detailed study protocol is essential for replicability as well. That said, even with strict prospective registration of observational study protocols, including digital object identifier records of any amendments, there remains the chance of post hoc protocol amendments at a later stage to match with preferred results. Ultimately, there is no foolproof way to prevent scientific malpractice in this domain.

There are several recent projects, such as the Reproducible Evidence: Practices to Enhance and Achieve Transparency (REPEAT) initiative, that aim to improve transparency, reproducibility, and validity of database research [23]. At the same time, the need for one-size-fits-all guidance, or any guidance for protocol development of observational studies, remains a subject of debate [20,21,24,25]. For example, an industry-based epidemiological group have proposed a framework in which observational studies should be registered and can be exempted based on study design and study intent [25].

However, the absence of guidelines to develop protocols has historically resulted in a large proportion of observational research being conducted without quality-assured study protocols. Existing protocols are often not fit for purpose, and the proportion of researchers ensuring registration of protocols for observational studies prior to data collection remains negligible. Therefore, our study aims to develop reporting guidelines for protocols of observational studies by launching SPIROS. We expect this initiative to increase transparency of methods used in observational studies, and through standardizing protocols, we hope that study designs will be improved and more often be registered and published in a journal or in a repository.

The main limitation of our study is that SPIROS reporting guidelines will be developed primarily for cohort, case-control, and cross-sectional study designs but not for other observational research designs. Because of the wide scope of observational

study designs, it is difficult to prepare standard reporting guidelines that cover all observational study designs.

Nevertheless, as the first attempt to develop a guiding document for observational study protocols, our guidelines will fill an important gap. Once widely available, an impact assessment should be conducted after a 4- to 5-year period to determine whether more and higher-quality protocols have become available, similar to the approach adopted by other reporting guidelines [26].

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Authors' Contributions

RM, SB, and MPZ designed the final study protocol, had part in the technical design, and drafted the initial manuscript; MPZ conceived of the study. LMB, KS, AK, JK, PVD, SB, and MPZ had part in the technical design and are part of the expert steering committee of the SPIROS project. All authors reviewed and approved the final manuscript.

Conflicts of Interest

None declared.

References

1. Munafò MR, Nosek BA, Bishop DVM, Button KS, Chambers CD, Percie du Sert N, et al. A manifesto for reproducible science. Nat Hum Behav 2017 Jan 10;1(1). [doi: 10.1038/s41562-016-0021]
2. Nosek BA, Ebersole CR, DeHaven AC, Mellor DT. The preregistration revolution. Proc Natl Acad Sci U S A 2018 Mar 13;115(11):2600-2606. [doi: 10.1073/pnas.1708274114] [Medline: 29531091]
3. Chan A, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013 Feb 5;158(3):200-207. [doi: 10.7326/0003-4819-158-3-201302050-00583] [Medline: 23295957]
4. Tetzlaff JM, Chan A, Kitchen J, Sampson M, Tricco AC, Moher D. Guidelines for randomized clinical trial protocol content: a systematic review. Syst Rev 2012 Sep 24;1:43 [FREE Full text] [doi: 10.1186/2046-4053-1-43] [Medline: 23006870]
5. Chan A, Tetzlaff JM, Altman DG, Dickersin K, Moher D. SPIRIT 2013: new guidance for content of clinical trial protocols. Lancet 2013 Jan 12;381(9861):91-92. [doi: 10.1016/S0140-6736(12)62160-6] [Medline: 23305999]
6. Boccia S. Credibility of observational studies: why public health researchers should care? Eur J Public Health 2015 Aug;25(4):554-555. [doi: 10.1093/eurpub/ckv119] [Medline: 26138821]
7. Grimes DA, Schulz KF. Bias and causal associations in observational research. Lancet 2002 Jan 19;359(9302):248-252. [doi: 10.1016/S0140-6736(02)07451-2] [Medline: 11812579]
8. Bell S, Kivimäki M, Batty GD. Subgroup analysis as a source of spurious findings: an illustration using new data on alcohol intake and coronary heart disease. Addiction 2015 Jan;110(1):183-184 [FREE Full text] [doi: 10.1111/add.12708] [Medline: 25515832]
9. Kivimäki M, Singh-Manoux A, Ferrie JE, Batty GD. Post hoc decision-making in observational epidemiology--is there need for better research standards? Int J Epidemiol 2013 Apr;42(2):367-370 [FREE Full text] [doi: 10.1093/ije/dyt036] [Medline: 23569177]
10. Teixeira PM. p-Hacking - A call for ethics. Pulmonology 2018;24(3):207-208 [FREE Full text] [doi: 10.1016/j.pulmoe.2018.03.001] [Medline: 29627399]
11. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. BMC Med Res Methodol 2018 Dec 19;18(1):143 [FREE Full text] [doi: 10.1186/s12874-018-0611-x] [Medline: 30453902]
12. Tricco AC, Lillie E, Zarin W, O'Brien K, Colquhoun H, Kastner M, et al. A scoping review on the conduct and reporting of scoping reviews. BMC Med Res Methodol 2016 Feb 09;16:15 [FREE Full text] [doi: 10.1186/s12874-016-0116-4] [Medline: 26857112]
13. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg 2014 Dec;12(12):1495-1499 [FREE Full text] [doi: 10.1016/j.ijsu.2014.07.013] [Medline: 25046131]
14. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med 2018 Oct 02;169(7):467-473. [doi: 10.7326/M18-0850] [Medline: 30178033]
15. Yousuf M. The Delphi technique. Essays Educ 2007;20:80-89. [doi: 10.4018/978-1-4666-0074-4.ch011]
16. Crisp J, Pelletier D, Duffield C, Adams A, Nagy S. The Delphi method? Nurs Res 1997;46(2):116-118. [doi: 10.1097/00006199-199703000-00010] [Medline: 9105336]

17. Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. J Adv Nurs 2000 Oct;32(4):1008-1015. [Medline: 11095242]
18. Hsu C, Sandford B. The Delphi technique: Making sense of consensus. Pract Assessment, Res Eval 2007;12(10):8. [doi: 10.4018/978-1-4666-0074-4.ch011]
19. Okoli C, Pawlowski SD. The Delphi method as a research tool: an example, design considerations and applications. Inf Manage 2004 Dec;42(1):15-29. [doi: 10.1016/j.im.2003.11.002]
20. Dal-Ré R, Ioannidis JP, Bracken MB, Buffler PA, Chan AW, Franco EL, et al. Making prospective registration of observational research a reality. Sci Transl Med 2014 Feb 19;6(224):224cm1. [doi: 10.1126/scitranslmed.3007513] [Medline: 24553383]
21. Williams RJ, Tse T, Harlan WR, Zarin DA. Registration of observational studies: is it time? CMAJ 2010 Oct 19;182(15):1638-1642. [doi: 10.1503/cmaj.092252] [Medline: 20643833]
22. PLOS Medicine Editors. Observational studies: getting clear about transparency. PLoS Med 2014 Aug;11(8):e1001711 [FREE Full text] [doi: 10.1371/journal.pmed.1001711] [Medline: 25158064]
23. Wang S, Rassen J, Pinheiro S, Berlin J, Schneeweiss S. What Does Replicable and Robust Non-Randomized Database Evidence Look Like? 2019 Presented at: Abstracts of the 35th International Conference on Pharmacoepidemiology & Therapeutic Risk Management; Aug 24-28, 2019; Philadelphia, PA. [doi: 10.1002/pds.4864]
24. Loder E, Groves T, Macauley D. Registration of observational studies. BMJ 2010 Feb 18;340:c950. [doi: 10.1136/bmj.c950] [Medline: 20167643]
25. Chavers S, Fife D, Wacholtz M, Stang P, Berlin J. Registration of Observational Studies: perspectives from an industry-based epidemiology group. Pharmacoepidemiol Drug Saf 2011 Oct;20(10):1009-1013. [doi: 10.1002/pds.2221] [Medline: 21953845]
26. Chan A, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krle A-Jerić K, et al. SPIRIT 2013 Statement: defining standard protocol items for clinical trials. Rev Panam Salud Publica 2015 Dec;38(6):506-514 [FREE Full text] [Medline: 27440100]

Abbreviations

EQUATOR: Enhancing the Quality and Transparency of Health Research
OSF: Open Science Framework
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT: randomized control trial
REPEAT: Reproducible Evidence: Practices to Enhance and Achieve Transparency
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SPIROS: Standardized Protocol Items: Recommendations for Observational Studies
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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Protocol

Respiratory Health of Pacific Youth: An Observational Study of Associated Risk and Protective Factors Throughout Childhood

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Abstract

Background: Respiratory disease is the third most common cause of death in New Zealand, with Pacific people living in New Zealand bearing the greatest burden of this type of disease. Although some epidemiological outcomes are known, we lack the specifics required to formulate targeted and effective public health interventions. The Pacific Islands Families (PIF) birth cohort study is a study that provides a unique source of data to assess lung function and current respiratory health among participants entering early adulthood and to examine associations with early life events during critical periods of growth.

Objective: This paper aims to provide an overview of the design, methods, and scope of the *Respiratory Health of Pacific Youth Study*, which uses the overall PIF study cohort aged 18-19 years.

Methods: From 2000-2019, the PIF study has followed, from birth, the growth, and the development of 1398 Pacific children born in Auckland, New Zealand. Participants were nested within the overall PIF study (at ages 18-19 years) from June 2018, and assessments were undertaken until mid-November 2019. The assessments included respiratory and general medical histories, a general physical examination, assessment of lung function (forced expiratory volume and forced vital capacity), self-completed questionnaires (St George's Respiratory Questionnaire, European Quality of Life 5 Dimensions-3 Level, Epworth Sleepiness Scale for Children and Adolescents, and Leicester Cough Questionnaire), blood tests (eosinophils, Immunoglobulin E, Immunoglobulin G, Immunoglobulin A, Immunoglobulin M, and C-reactive protein), and chest x-rays. Noninferential analyses will be carried out on dimensionally reduced risk and protective factors and confounders.

Results: Data collection began in June 2018 and ended in November 2019, with a total of 466 participants recruited for submission of the paper. Collection and collation of chest x-ray data is still underway, and data analysis and expected results will be published by November 2020.

Conclusions: This is the first longitudinal observational study to address the burden of respiratory disease among Pacific youth by determining factors in early life that impose long-term detriments in lung function and are associated with the presence of respiratory illness. Identifying risk factors and the magnitude of their effects will help in adopting preventative measures, establishing whether any avoidable risks can be modified by later resilient behaviors, and provide baseline measurements for the development of respiratory disease in later adult life. The study results can be translated into practice guidelines and inform health strategies with immediate national and international impact.

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KEYWORDS

respiratory; Pacific Islands; public health; risk; growth and development; youth

Introduction

Background

Respiratory disease is the third most common cause of death in New Zealand [1,2], with 69,000 hospitalizations per year. Hospitalizations are 5.1 times higher and mortality is 2.7 times greater in the most deprived geographical areas compared with the least deprived areas [3]. Pediatric hospital admissions for bronchiolitis, asthma, wheezing, and viral pneumonia have increased since 2000 to over 21,000 per year [4]. In the same period since 2000, hospitalizations in all ages for bronchiectasis increased by 30%, with a doubling of deaths [3]. Over 28,000 people in New Zealand are estimated to have severe chronic obstructive pulmonary disorder (COPD), with up to 15% of the total population suspected to have the disease [3,5]. This may partly explain why this rise in respiratory disease is strongly demonstrated in South Auckland [4], a geographical area with very high levels of deprivation, particularly among its large Pacific and Māori populations.

Pacific people (Samoan, Tongan, Cook Islands Māori, Niuean, and Tokelauan) living in New Zealand are the fourth largest population group, and the third largest living in Auckland, New Zealand's biggest city [6]. Of the Pacific population resident here, 21% live in South Auckland (Manukau District) [7], and 76% of these people live in the most deprived areas [8]. Of all ethnic groups, Pacific people bear the greatest burden of respiratory diseases [2], and across all age groups, their hospitalization rates for these illnesses are 2.6 times higher than those for other ethnic groups [2,3,9]. Relative risks for the Pacific population range between 1.7 and 18.2 for asthma [10], bronchiectasis [10,11], bronchiolitis [12], pneumonia [13], COPD [14,15], and obstructive sleep apnea [16], compared with non-Pacific people. This represents a significant health disparity for Pacific people, who have the highest proportion of individuals in the 15- to 24-year age bracket [17], and is expected to constitute 10% of the population and 12% of the working-age population by 2026 [18].

Lung development starts in utero with substantial structural development and continues through early childhood, with the alveoli likely increasing in number, size, and complexity through adolescence [19,20]. Maximum lung volumes are reached around 20 to 22 years of age for males and slightly earlier (around 18-20 years) for females [21]. This represents a 30-fold increase in lung volume and a 20-fold increase in gas-exchanging surface area with at least a doubling of airway length and diameter. Nevertheless, after peaking in early adulthood, lung function gradually declines with age in healthy individuals because of factors including loss of lung elasticity, the decline in respiratory muscle strength, and reduced alveolar surface area [22].

Current scientific theory indicates that many adult respiratory diseases arise from early events during the period of rapid growth from infancy through childhood [19,23]. The impact of respiratory events early in life appears to be two-fold: (1) early insults may prevent attainment of peak lung function with a subsequent decline from a lower peak level and/or increase the rate of rapid decline and (2) early disease increases susceptibility to developing a later disease. These factors may predispose to the development of chronic lung diseases such as asthma, COPD, and bronchiectasis in adulthood [24].

Reduced Lung Function

Intrauterine growth restriction is a risk factor for reduced lung function during infancy [25], childhood [26], and adulthood (using self-reported birth weight) [27]. In-utero smoke exposure is associated with reduced lung function at birth [28], early childhood [29], and early adulthood [30,31], and is similarly associated with accelerated lung function decline [32]. Living with a smoker up to the age of 18 years increases the risk of cough and sputum production as adults [33]. In addition, asthma in childhood is associated with lower lung function in adulthood [34-36] and a more rapid decline in lung function [37].

Once airway restriction has occurred, the composite picture from other overlapping studies in healthy and asthmatic populations suggests that lung function centiles tend to track with time [38,39]. First, cohort studies in Tucson (n=826) [40], Perth (n=243) [41], Sydney (n=10,898) [42], Manchester (n=690) [43], and the Netherlands (n=838) [44] have shown that the majority of early infant wheezers have reduced lung function at school age. Second, these studies have also shown that from infancy to childhood (n=95) [41], infancy to early adulthood (n=169) [39], across childhood [41-43], and into early adulthood from 9 years (n=646) [45] and 11 years (n=600) [38], those with low lung function on the first assessment remained in the lower centile. A large community study on atherosclerosis risk (n=15,536) described an increased risk of COPD in those with accelerated lung function decline (excluding individuals who smoke) [46].

Early Disease Predisposing to Later Disease

In seminal research, Barker et al [47,48] reviewed death certificate data across several communities in England, showing that an area with a high infant pneumonia mortality rate had a high COPD mortality rate 15 years later, suggesting an individual-level association. Further studies indicate that the number of lower respiratory tract infections in childhood seemed to predict the presence of obstructive airway disease and ventilatory impairment in adults [49,50]. Childhood pneumonia is described as a sentinel event in 28% to 42% of adult populations with bronchiectasis [51-53], with 60% to 80% reporting wet cough since childhood [52,54].

In the Dunedin Study birth cohort, 26.9% of the participants had continuing symptoms of asthma, with half persistent and half recurring in early adulthood [38]. Admission for bronchiolitis or pneumonia when <5 years of age was associated

with an increased risk of doctor-diagnosed asthma and increased medication use [36,55], which in the European Community Respiratory Health Survey was shown to be further exacerbated by smoke exposure [36]. A history of asthma in childhood was also associated with a 5.2 to 12.5 increased risk of COPD [5,56]. However, most of these studies have sampled adult populations and relied on individual recall of childhood events. Asking a participant with a current respiratory diagnosis whether they had an infection in childhood may well introduce bias and, given the prevalence of respiratory infections in childhood, may not be discerning.

Fewer studies have examined the impact of risk or protective factors such as vitamin deficiencies, physical activity levels, and breastfeeding on respiratory function and later respiratory disease. Despite early pathological studies that indicated that the alveolar structure was complete by 2 years of age, recent magnetic resonance imaging suggests that the alveoli continue to develop into young adulthood [57-59]. This may widen the possibility of ongoing damage with new insults but theoretically also implies that resilient behaviors may improve later lung growth. In one study, breastfeeding was found to aid lung growth and was associated with improved forced vital capacity (FVC) at the age of 10 years but not 18 years [60,61].

Vitamin deficiencies (vitamins A, D, and E) seem to have a greater effect on alveolar development than on airway development [62,63]. Maternal vitamin A supplementation was shown to increase FVC and forced expiratory volume in 1 second (FEV1) among 1894 children aged 9 to 13 years living in Nepal (a population with high vitamin A deficiency) compared with children whose mothers had received a placebo [62]. A study examining dietary antioxidants among 243 healthy, nonsmoking students in the United States (mean age of 18.3 years, SD 1.95) showed that vitamin C and magnesium intake was associated with higher lung function in these college students [64]. Breastfeeding [65-68], immunizations [69,70], and adequate vitamin D levels [71-74] are all associated with fewer early childhood infections, which may protect lung development.

There are some known gender differences in respiratory disease patterns. Hospitalization rates for total respiratory admissions are higher in boys than girls when less than 15 years of age but become more common in women than in men as adults [75]. Hospitalization rates for asthma have a rate ratio of 2.75 for children (<15 years of age) when compared with adults (30-64 years of age), but there are clear gender differences. Girls with a rate ratio of 0.78 were compared with boys, but women with a rate ratio of 1.86 were compared with men. Similarly, medicated asthma in 2016 to 2017 was seen in 11.3% of girls and 17.2% of boys, whereas it was present in 14% of women but only 9.9% of men. Hospitalization for bronchiolitis, bronchiectasis, and pneumonia occurs more frequently in boys (rate ratios for girls between 0.64 and 0.98) [75]. Although hospitalization rates for COPD were significantly higher in women than men by 45 to 64 years of age, mortality was similar between genders, but mortality for women with bronchiectasis was higher than men [76]. Smoking rates also differed, with 28% of Pacific men and 22% of Pacific women smoking. In addition, Pacific people have the most rapid transition from experimentation to regular smoking of 2.7 years when compared with other community groups [77].

The Pacific Islands Families (PIF) study birth cohort is an ongoing observational study of the health and development of a birth cohort of children of Pacific ethnicity and their parents. The selected findings from the study included a high immunization uptake (89%) among the cohort over the first 2 years of life [78]. At 4 years of age, many children in the cohort and their mothers had poor basic oral hygiene (34% of mothers were brushing ≤1/day and 50% had either never seen a dentist or had not visited one in the last 5 years, 47% of the children brushed ≤1 time per day, and 47% had no adult assistance with brushing) [79]. Moreover, 57% of these children were routinely snacking or drinking immediately before bed, which substantially increased their health risk [79]. Parental smoking prevalence and secondhand smoke exposure among the cohort aged 11 years indicated very high prevalence rates (33% of mothers and 40% of fathers) [80], resulting in about 50% of families with at least one parent who smoked, and 25% with both parents who smoked [81]. This suggests that environmental smoke exposure is a significant health risk for children from the cohort living in these households. To date, there has been no formal respiratory assessment undertaken among the cohort. This paper provides an overview of the design, methods, and scope of *Respiratory Health of Pacific Youth*, a retrospective study of early childhood events and their impact on current respiratory status nested within the overall PIF study (at ages 18-19 years).

Study Objectives

This study will address 3 objectives: (1) estimate the effect of early life (eg, birthweight, antenatal smoke exposure, postnatal smoke exposure) and childhood risk factors (eg, allergies, dwelling conditions from the first 2 years of life, child smoking at 14 years) on peak lung function attainment and respiratory outcomes in Pacific youth aged 18 to 19 years; (2) determine modifiable childhood risk and protective factors; including breastfeeding, immunization, and nutrition during the first 2 years of life; exercise at ages 4, 11, and 14 years; peak flow at ages 6 and 9 years; respiratory infections, respiratory condition–related hospital admissions, and reported breathing problems in the first 2 years of life; and asthma in childhood) on lung function attainment and respiratory outcomes in Pacific youth aged 18 to 19 years; and (3) estimate the population attributable fraction and population avoidable fraction of modifiable early life risk factors and childhood resilience factors on these outcomes. We hypothesize that at age 18 to 19 years, (1) early life risks result in poorer lung function and respiratory outcomes in early adulthood in Pacific youth and (2) protective or resilience factors throughout childhood moderate the impact of these early life risks on these poorer lung function and respiratory outcomes in early adulthood.

Methods

Study Design

The PIF birth cohort study is a multidisciplinary study [82] tracking the health and development of 1398 Pacific children born at Middlemore Hospital, South Auckland, New Zealand,

in 2000. A child was defined to be of Pacific Islands ethnicity if at least one parent self-identified as being of that ethnicity and only eligible if at least one parent was a permanent resident of New Zealand [82]. The PIF study provides a unique source of data for research on growth, development, and psychosocial functioning at critical developmental stages within the family environment. The size of the cohort was chosen to enable the generation of findings that were specific to the predominant Pacific groups residing in New Zealand (Samoan, Tongan, and Cook Islands Māori) [83]. Assessments and interviews were conducted at 6 weeks of age, then at 1, 2, 4, 6, 9, 11, 14, and 17 years of age. This study collected cross-sectional data on respiratory outcomes from the cohort over 2018 to 2019, when they were aged 18 to 19 years. All antecedent data collected at previous measurement waves will be available for inclusion in the analysis where appropriate. Biological sex and gender stratification will also be considered in the analysis of respiratory data.

Study Population

In recognition of attrition and residential mobility of the initial PIF cohort (n=1398, 681 females and 717 males, to n=954, 463 females and 468 males) by age 14 years, we anticipated achieving a sample size of 750 youths from the original cohort. Since June 2018, an assessment of Pacific youth aged 18 to 19 years was initiated. The only exclusion criteria were (1) exclusion of cohort members whose current sickness would prohibit them from producing maximal effort during lung function testing and (2) exclusion of cohort members resident outside of Auckland, as assessments could only be undertaken in Auckland.

Study Procedures

Ethical approval for this study was obtained from the Central Health and Disability Ethics Committee on May 24, 2018 (reference 18/CEN/24). Written informed consent was obtained from the youth to participate in an assessment involving a series of physical and clinical assessments and self-administered web-based questionnaires. Arrangements were made for 2 research assistants of Pacific ethnicity to transport participants to and from a clinic set up for the respiratory assessments at the University of Auckland (Tāmaki campus) and Ascot hospital where chest x-rays and blood tests were performed. The youth were thanked with a gift voucher for their participation. The data sets used during this study are available from the corresponding author upon reasonable request.

Outcomes: Clinical Assessments

The primary outcome of this study was the FEV1 Z-score standardized for height, gender, and age (American Thoracic Society/European Respiratory Society criteria using Global Lung Initiative reference values) as a continuous variable. The FEV1 Z-score will be dichotomized to an indicator of a Z-score <−1.64 for estimating the population attributable risk.

Other clinical assessments involve the documentation of participants' respiratory and general medical histories, medications, a clinical examination (respiratory rate, cardiovascular, and ear, nose, and throat examinations), and a Bacillus Calmette–Guérin vaccine scar presentation, clubbing severity (categorized into mild, moderate, or severe), tonsil score (according to the Brodsky and Friedman Scales [84]), and Mallampati score (a visual assessment of the space between the base of the tongue and the roof of the mouth that is an independent predictor of obstructive sleep apnea [85,86]). In addition, social behavior questions on work and sleep schedules, housing conditions, and exercise routines were asked. Participants were also asked about their caffeine, alcohol, tobacco, and drug intake.

The number of pulmonary exacerbations in the previous 12 months was documented. Symptom severity (cough, sputum color, and dyspnea) was recorded on validated 5-point scales [87,88], including (1) cough severity rated on a Likert-like symptom scale, (2) dyspnea severity rated according to the Modified Medical Research Council Dyspnea Scale [89], and (3) sputum color rated according to a Bronkotest color chart [90].

In addition, oxygen saturation (SPO_2; Medtronic, Nellcor PM10N) and spirometry pre- and postsalbutamol (EasyOne Air Spirometer, NDD Medical Technologies) were assessed. Spirometry was performed according to American Thoracic Society standards [91] with predicted values from Global Lung Initiative reference values [92]. Baseline forced expiratory measurements were performed until 3 good quality, repeatable measures were obtained (FVC and FEV1 both within 0.15 l). This was followed immediately by the administration of 400 µg of salbutamol using a meter dose inhaler through a volumetric spacer device, and reversibility was tested by using spirometry after 15 min.

Nonfasting blood tests were completed at Ascot Hospital by Labtests, a pathology laboratory service accredited by the International Accreditation New Zealand. Trained phlebotomists drew 10 mL of blood for testing the levels of Immunoglobulin E, Immunoglobulin G, Immunoglobulin A, and Immunoglobulin M, eosinophils, and C-reactive protein. A further 6 mL of serum was stored at Middlemore Hospital tissue bank for future analysis of biomarkers; a separate consent for this analysis was obtained.

Chest x-rays (posteroanterior and lateral) were performed by Ascot Radiology. The radiation dose is 0.02 millisieverts with background radiation in comparison being 3 to 4 millisieverts, which is equivalent to 3 days of usual background radiation exposure. No chest x-rays were taken if a participant was pregnant. Chest x-rays were scored by 2 scorers using the Brasfield scoring system. The Brasfield system [93] consists of scoring chest x-rays using graded responses for 5 specific aspects: air trapping (scored 0-4), linear markings (bronchial wall thickening; 0-4), nodular cystic lesions (bronchiectasis; 0-4), large lesions (atelectasis and pneumonia; 0-5), and general severity (0-5). A score of 25/25 represents normal lungs, with numbers detracted for changes seen with lower scores representing more severe disease.

Outcomes: Physical Measurements

Body size and composition measurements included height (Seca 213), weight (Tanita BC545), waist circumference with a nonstretchable tape, standing hand-to-foot bioimpedance

analysis (ImpediMed Single Frequency 50 kHz Bioimpedance Analyzer, Tanita BC545), and blood pressure using an automated sphygmomanometer (Omron Auto Blood Pressure monitor IA2, Omron Healthcare) with appropriate cuff sizes.

Anthropometric and blood pressure measurements were repeated until 2 measurements were recorded within a predetermined tolerance (weight ±0.5 kg, height and waist ±0.5 cm, and systolic and diastolic blood pressure ±10 mm Hg). BMI was calculated as weight in kg/height in meters squared, and prevalence of obesity, overweight, and thinness were derived, standardized for age and gender using the Cole cutoffs [94].

Outcomes: Questionnaires

Participants self-administered 4 questionnaires on a tablet computer with the research nurse present to assist as necessary: St. George's Respiratory Questionnaire (SGRQ), European Quality of Life 5 Dimensions-3 Level, Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD), and the Leicester Cough Questionnaire (LCQ).

The SGRQ [95,96] includes 56 items across 3 domains: symptoms, activity, and impact. Component scores from each domain and a total score between 1 and 100 will be examined. Higher scores indicate poorer health.

The European Quality of Life-5 Dimensions is a generic measure of self-reported health status [97]. Health status was measured in terms of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a Visual Analogue Scale.

ESS-CHAD [98], a validated measure of daytime sleepiness for use with children and adolescents [99], was used to indicate the possibility of obstructive sleep apnea. A score of 13 to 15 represents a moderate risk and a score of >15 represents a severe risk for obstructive sleep apnea. The LCQ evaluates the impact of cough on the quality of life [100].

Any abnormal results were discussed on a case-by-case basis between the research nurses conducting the assessments and the coinvestigators of the study with backgrounds in respiratory medicine. In cases of incidental findings or results of concern, a referral letter was addressed to their general practitioner, along with notifying general practitioners of their patients' involvement in the study and that the chest x-ray and blood tests of their patients will be available from the standard clinical information portal (Concerto).

Data Analysis: Statistical Considerations

A research electronic data capture (REDCap) database (hosted on the Auckland University of Technology server and fully compliant with International Organization for Standardization standards and international data management) was set up to capture all data. REDCap is a web-based system that can be used for direct data input or secondary input from paper-based clinical record forms and questionnaires.

The key objective of the analysis was to obtain causal effect estimates of risk factors and modifiable protective factors on respiratory outcomes, conditional on preexisting risk factors and confounders. The analyses will be carried out in 3 stages: (1) dimensional reduction of the covariates, (2) causal modeling of the risk and protective factors, and (3) estimation of the population attributable and avoidable risks associated with the risk and protective factors.

Dimensional Reduction

A technical challenge to overcome in this study is the large dimensionality of the covariates involved, potentially leading to overfitting. To alleviate this problem, we will apply dimensional reduction techniques to the covariates, taking care to maintain interpretability where necessary, especially with regard to population attributable and avoidable risks. The dimensional reduction will proceed using variations in sliced inverse regression (SIR) [101] from the primary outcome. The variations considered are specifically adapted to longitudinal covariate data [102,103] and categorical covariate data [104]. This approach to dimensional reduction will determine, in practice, a set of linear combinations of the covariates corresponding to confounders or to a specific risk/protective factor or specific respiratory conditions that best explain the primary outcome (such linear combinations can be interpreted in a manner similar to factors in a factor analysis). In this fashion, we will reduce the dimensionality of the set of all confounders, the main purpose of this step, and may be able to reduce the dimensionality of a specific risk or protective factors for which we have longitudinal data (eg, exercise) or several simultaneous measures (eg, nutrition), preventing overfitting. Secondary outcomes will be analyzed using the dimensionally reduced covariates obtained from the SIR on FEV1 and will not themselves be the object of an SIR to promote interpretability.

Causal Inference

With Y_i representing the outcome of interest (primary outcome FEV1 Z-score or any of the secondary outcomes) in participant i, the causal model we will consider is a simple extension from Robins et al [105].

$$E[Y_i|X_i, R_i, Z_i, C_i] = \alpha' R_i + \beta' X_i + \gamma'(X_i{:}R_i) + g(C_i) + h(Z_i) \quad \textbf{(1)}$$

where α, β, and γ are the causal parameter vectors of interest; X_i and R_i denote the modifiable protective and risk factors, respectively, and $X_i{:}R_i$, their interaction; C_i denotes the confounders and Z_i the early life respiratory conditions; and g and h are semiparametric functions (typically smoothes or simply affine functions). Parameters, α, β, and γ are estimated as fully adjusted causal relationships using a two-stage estimation technique from Robins et al [105], which relies on the first-stage estimated conditional expectations $\hat{E}[R_i|C_i, Z_i]$, $\hat{E}[X_i|C_i, Z_i]$, and $\hat{E}[X_i{:}R_i|C_i, Z_i]$. These latter quantities are estimated using appropriate linear, logistic, and multinomial models and consist of the multivariate equivalent (from a data analytical point of view) of propensity scores (the distinction is that propensity scores apply when a single risk factor or treatment is involved). Causal inference is thus based on a semiparametric regression model that adjusts for multivariate propensity scores; the preferred method of propensity score inverse weighting as used in a study by Austin [106] is not

applicable in this case, precisely, due to the multiplicity of risk and protective factors.

For categorical outcomes, a logit link function is applied to the right-hand side of the above equation (see also the Inferential Setting section). The rest of the data analytical approach follows without modification.

We note that the estimation of α addresses hypothesis 1, whereas the estimation of β and the interaction term parameter γ addresses hypothesis 2. The causal model considered above treats early life respiratory conditions on an equal footing with confounders. We will also attempt the analysis by simultaneously fitting the following components, creating a mediation analysis where early life risk factors may affect later respiratory outcomes:

Direct path: $E[Y\_i|X_i, R_i, C\_i] = \alpha_0'R_i + \beta_0'X_i + \gamma_0' (X_i{:}R_i) + g_0(C_i)$ **(2)**

Mediated path: $E[Y\_i|X_i, Z_i, C\_i] = \xi'Z_i + \beta_1'X_i + g_1(C_i)$

$E[Z\_i|X_i, R_i, C\_i] = \alpha_2'R_i + \beta_2'X_i + \gamma_2' (X_i{:}R_i) + g_2(C_i)$

In our experience, mediated analyses such as equation 2 can easily become intractable numerically. We are likely to resort to the mediation model when considering specific early childhood conditions with reasonably high prevalence, such as asthma, as opposed to a full set of early childhood conditions.

To allay the bias potentially associated with attrition in the cohort, we applied inverse probability weighting (IPW), a recognized technique to compensate for selection bias [107]. IPW will be carried out by identifying early predictors of later loss to follow-up in a logistic regression model, which will provide a fitted probability of remaining in the cohort at the time of assessment for every cohort entrant. IPW will be applied to participants in all analyses, increasing the influence of individuals unlikely to self-select and correcting, to the extent possible from the attrition model, for selection bias.

Population Attributable and Avoidable Risks

The population attribute and avoidable risks (PAR) associated with each risk and protective factor will be estimated using a Monte Carlo approach [108] that fully accounts for the risk/protective factor interaction, confounding and other adjustments, and mediation, if applicable, as is necessary to avoid bias and correctly estimate the standard error of the PAR estimates [109]. PAR will be computed for each respiratory condition observed during the clinical assessment and a dichotomized version of the FEV1 Z-score primary outcome, namely, the indicator that lies below the lower end of normal (ie, 5% centile at −1.64). Such an approach is made possible by the completeness of the data in the early cohort assessments and allows the indirect estimation of the prevalence of respiratory conditions in the full cohort under mild assumptions on the loss-to-follow-up mechanism (see below).

As missingness in early childhood data is minimal, we will use a singly imputed data set obtained from a full conditional specification of the covariate distribution using a discriminant function for categorical values, for our analyses. There will be no attempt to impute missing outcome values, if any, from the clinical assessments.

Inferential Setting

All tests will be carried out at the 5% significance level, against two-sided hypotheses. Estimates will be reported as point estimates and 95% CIs. Standard descriptive quantities and simple regression results will be presented for all outcomes and main risk and protective factors. The main analysis will be handled through generalized additive models under a normal family with an identity link. Assumptions of residual normality will be checked visually and using standard distributional tests; departures from normality will be dealt preferentially with the selection of an alternative family and link, and, in case of variance behavior inconsistent with a known family, with a generalized additive model for location, scale, and shape [110]. The main analyses will be fully adjusted and attempt to present causal estimates, as indicated above. Analyses will be carried out using standard procedures from SAS version 9.4 and R version 3.x, and the study statistician will produce or supervise the production of custom code to obtain the causal parameter estimates and to carry out the Monte Carlo estimation procedure.

Results

This study was funded in October 2017 and received ethical approval in May 2018. Data collection began in June 2018 and ended in November 2019, with a total of 466 participants recruited for submission of the paper. Collection and collation of chest x-ray data is still underway, and data analysis and expected results will be published by November 2020.

Discussion

Principal Findings

To the best of our knowledge, this is the first observational study to address the high burden of respiratory disease in Pacific youth aged between 18 and 19 years by estimating its causal relationship with factors in early life (risk and protective), which impose long-term detriments in lung function and are associated with the presence of respiratory illness as this population moves into young adulthood and nears the lifetime peak lung function. It is also at the time when the difference in hospitalization rates for any respiratory illnesses moves from being higher in males throughout childhood to being higher in females in adulthood.

Although utilizing the PIF cohort entails some loss in representativeness with regard to the Pacific population at large, it brings advantages by avoiding the costs and risks of establishing a new study de novo. Attrition must be acknowledged in utilizing this PIF cohort, largely because of (1) transient residential mobility by the age of 18 years and (2) in part because of logistical difficulties. However, as an analytical epidemiological study, the sample needs only be representative with regard to the effect of interest to be an internally valid study. Even if, in the proposed study, attrition interacts with the relationship between covariates and outcomes, selection bias will be allayed at the analysis stage by IPW and plausible causal relationships, revealed [111].

Conclusions

This study will measure current lung function and assess the presence or absence of respiratory disease in the PIF study birth cohort, a group at increased risk of respiratory disease, which mainly resides in a region with a high prevalence of respiratory disease. Findings may be relevant for Māori, with approximately 8% of the original PIF cohort having Māori heritage, and Māori experiencing a similarly unacceptable high rate of respiratory illnesses in New Zealand. Moreover, this information can be directly used to formulate public health strategies to reduce future disease in this high-risk group for life, which will be relevant to the population as a whole.

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Authors' Contributions

ET, CB, CW, AV, AT, and LI participated in the study design. ET, SJ, LI, and CB drafted the manuscript. All authors revised the paper and agreed with the final version. All authors agree both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even those in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Conflicts of Interest

None declared.

References

1. World Health Organisation. Noncommunicable Diseases Country Profiles. Geneva, Switzerland: World Health Organisation; 2014.
2. Asthma and Respiratory Foundation of New Zealand: (The Breath of Life): National Respiratory Strategy. Wellington: The Asthma Foundation; 2015.
3. Telfar B, Baker M, Pierse N, Zhang J. The Impact of Respiratory Disease in New Zealand: 2014 Update. Wellington, USA: The Asthma and Respiratory Foundation of New Zealand; 2015.
4. Simpson J, Oben G, Craig E, Adams J, Wicken A, Duncanson M. Reddington A: the Determinents of Health for Children and Young People in the Northern District Health Boards. New Zealand Child and Youth Epidemiology Service, Dunedin, University of Otago. 2014. URL: http://hdl.handle.net/10523/6411 [accessed 2020-09-23]
5. Shirtcliffe P, Marsh S, Travers J, Weatherall M, Beasley R. Childhood asthma and GOLD-defined chronic obstructive pulmonary disease. Intern Med J 2012 Jan;42(1):83-88. [doi: 10.1111/j.1445-5994.2010.02238.x] [Medline: 20403069]
6. 2013 Census Ethnic Group Profiles. Statistics New Zealand. 2015. URL: http://archive.stats.govt.nz/Census/2013-census/profile-and-summary-reports/ethnic-profiles.aspx?url=/Census/2013-census/profile-and-summary-reports/ethnic-profiles.aspx [accessed 2019-09-03]
7. Stowers T, Lyndon M, Henning M, Hill A, Webber M. Exploring factors that motivate and influence medical students to attend medical school. Counties Manukau District Health Board. 2019. URL: https://countiesmanukau.health.nz/assets/About-CMH/Reports-and-planning/Annual-reports-and-plans/32b559edbd/2015-16-CMDHB-Annual-Plan.pdf [accessed 2019-09-03]
8. Winnard D, :ee M. Demographic Profile and Census, Population of Counties Manukau. Counties Manukau Health. 2015. URL: https://www.countiesmanukau.health.nz/assets/About-CMH/Demographics-and-populations/f17cdca696/Census-2013-profile-for-residents-of-Counties-Manukau.pdf [accessed 2019-09-03]
9. Craig E, Anderson P, Taufa S, Jackson C. The Health Status of Pacific Children and Young People in New Zealand. New Zealand Child and Youth Epidemiology Service. 2009. URL: https://www.otago.ac.nz/nzcyes/otago086605.pdf [accessed 2019-09-03]
10. Pattemore PK, Ellison-Loschmann L, Asher MI, Barry DM, Clayton TO, Crane J, ISAAC Study. Asthma prevalence in European, Maori, and Pacific children in New Zealand: ISAAC study. Pediatr Pulmonol 2004 May;37(5):433-442. [doi: 10.1002/ppul.10449] [Medline: 15095327]
11. Twiss J, Metcalfe R, Edwards E, Byrnes C. New Zealand national incidence of bronchiectasis 'too high' for a developed country. Arch Dis Child 2005 Jul;90(7):737-740 [FREE Full text] [doi: 10.1136/adc.2004.066472] [Medline: 15871981]
12. Grimwood K, Cohet C, Rich FJ, Cheng S, Wood C, Redshaw N, et al. Risk factors for respiratory syncytial virus bronchiolitis hospital admission in New Zealand. Epidemiol Infect 2008 Oct;136(10):1333-1341. [doi: 10.1017/S0950268807000180] [Medline: 18177522]

13. Grant C, Pati A, Tan D, Vogel S, Aickin R, Scragg R. Ethnic comparisons of disease severity in children hospitalized with pneumonia in New Zealand. J Paediatr Child Health 2001 Feb;37(1):32-37. [doi: 10.1046/j.1440-1754.2001.00583.x] [Medline: 11168866]
14. A Portrait of Health: Key results of the 2006/07 New Zealand Health Survey. Ministry of Health. 2008. URL: https://www.moh.govt.nz/NoteBook/nbbooks.nsf/0/9FF50018D90C43D3CC2574640009AE76/$file/portrait-of-health-june08.pdf [accessed 2019-09-03]
15. Yang IA, Brown JL, George J, Jenkins S, McDonald CF, McDonald VM, et al. COPD-X Australian and New Zealand guidelines for the diagnosis and management of chronic obstructive pulmonary disease: 2017 update. Med J Aust 2017 Nov 20;207(10):436-442. [doi: 10.5694/mja17.00686] [Medline: 29129177]
16. Mihaere K, Harris R, Gander, Reid PM, Purdie G, Robson B, et al. Obstructive sleep apnea in New Zealand adults: prevalence and risk factors among Māori and non-Māori. Sleep 2009 Jul;32(7):949-956 [FREE Full text] [doi: 10.1093/sleep/32.7.949] [Medline: 19639758]
17. 2013 Census QuickStats About Culture and Identity. Statistics New Zealand. URL: http://www.stats.govt.nz/Census/2013-census/profile-and-summary-reports/quickstats-culture-identity.aspx [accessed 2019-09-03]
18. National Ethnic Population Projections: 2006(Base)–2026 update. Statistics New Zealand. 2006. URL: http://www.stats.govt.nz/browse_for_stats/population/estimates_and_projections/nationalethnicpopulationprojections_hotp2006-26.aspx [accessed 2019-09-03]
19. Stocks J, Hislop A, Sonnappa S. Early lung development: lifelong effect on respiratory health and disease. Lancet Respir Med 2013 Nov;1(9):728-742. [doi: 10.1016/S2213-2600(13)70118-8] [Medline: 24429276]
20. Quanjer PH, Stanojevic S, Stocks J, Hall GL, Prasad KV, Cole TJ, Global Lungs Initiative. Changes in the FEV_1 /FVC ratio during childhood and adolescence: an intercontinental study. Eur Respir J 2010 Dec;36(6):1391-1399 [FREE Full text] [doi: 10.1183/09031936.00164109] [Medline: 20351026]
21. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J 2012 Dec;40(6):1324-1343 [FREE Full text] [doi: 10.1183/09031936.00080312] [Medline: 22743675]
22. Thomas ET, Guppy M, Straus SE, Bell KJ, Glasziou P. Rate of normal lung function decline in ageing adults: a systematic review of prospective cohort studies. BMJ Open 2019 Jun 27;9(6):e028150 [FREE Full text] [doi: 10.1136/bmjopen-2018-028150] [Medline: 31248928]
23. Bush A. COPD: a pediatric disease. COPD 2008 Feb;5(1):53-67. [doi: 10.1080/15412550701815965] [Medline: 18259975]
24. Savran O, Ulrik CS. Early life insults as determinants of chronic obstructive pulmonary disease in adult life. Int J Chron Obstruct Pulmon Dis 2018;13:683-693 [FREE Full text] [doi: 10.2147/COPD.S153555] [Medline: 29520136]
25. Hoo A, Stocks J, Lum S, Wade AM, Castle RA, Costeloe KL, et al. Development of lung function in early life: influence of birth weight in infants of nonsmokers. Am J Respir Crit Care Med 2004 Sep 1;170(5):527-533. [doi: 10.1164/rccm.200311-1552OC] [Medline: 15172896]
26. Kotecha SJ, Watkins WJ, Heron J, Henderson J, Dunstan FD, Kotecha S. Spirometric lung function in school-age children: effect of intrauterine growth retardation and catch-up growth. Am J Respir Crit Care Med 2010 May 1;181(9):969-974 [FREE Full text] [doi: 10.1164/rccm.200906-0897OC] [Medline: 20093643]
27. Lawlor DA, Ebrahim S, Smith GD. Association of birth weight with adult lung function: findings from the British women's heart and health study and a meta-analysis. Thorax 2005 Oct;60(10):851-858 [FREE Full text] [doi: 10.1136/thx.2005.042408] [Medline: 16055617]
28. Stocks J, Dezateux C. The effect of parental smoking on lung function and development during infancy. Respirology 2003 Sep;8(3):266-285. [doi: 10.1046/j.1440-1843.2003.00478.x] [Medline: 14528876]
29. Moshammer H, Hoek G, Luttmann-Gibson H, Neuberger MA, Antova T, Gehring U, et al. Parental smoking and lung function in children: an international study. Am J Respir Crit Care Med 2006 Jun 1;173(11):1255-1263. [doi: 10.1164/rccm.200510-1552OC] [Medline: 16484675]
30. Hayatbakhsh MR, Sadasivam S, Mamun AA, Najman JM, Williams GM, O'Callaghan MJ. Maternal smoking during and after pregnancy and lung function in early adulthood: a prospective study. Thorax 2009 Sep;64(9):810-814. [doi: 10.1136/thx.2009.116301] [Medline: 19525264]
31. Svanes C, Omenaas E, Jarvis D, Chinn S, Gulsvik A, Burney P. Parental smoking in childhood and adult obstructive lung disease: results from the European community respiratory health survey. Thorax 2004 Apr;59(4):295-302 [FREE Full text] [doi: 10.1136/thx.2003.009746] [Medline: 15047948]
32. Allinson JP, Hardy R, Donaldson GC, Shaheen SO, Kuh D, Wedzicha JA. Combined impact of smoking and early-life exposures on adult lung function trajectories. Am J Respir Crit Care Med 2017 Oct 15;196(8):1021-1030 [FREE Full text] [doi: 10.1164/rccm.201703-0506OC] [Medline: 28530117]
33. David GL, Koh WP, Lee HP, Yu MC, London SJ. Childhood exposure to environmental tobacco smoke and chronic respiratory symptoms in non-smoking adults: the Singapore Chinese health study. Thorax 2005 Dec;60(12):1052-1058 [FREE Full text] [doi: 10.1136/thx.2005.042960] [Medline: 16131525]

34. Edwards CA, Osman LM, Godden DJ, Campbell DM, Douglas JG. Relationship between birth weight and adult lung function: controlling for maternal factors. Thorax 2003 Dec;58(12):1061-1065 [FREE Full text] [doi: 10.1136/thorax.58.12.1061] [Medline: 14645976]
35. Oswald H, Phelan PD, Lanigan A, Hibbert M, Carlin JB, Bowes G, et al. Childhood asthma and lung function in mid-adult life. Pediatr Pulmonol 1997 Jan;23(1):14-20. [doi: 10.1002/(sici)1099-0496(199701)23:1<14::aid-ppul2>3.0.co;2-p] [Medline: 9035194]
36. Dharmage SC, Erbas B, Jarvis D, Wjst M, Raherison C, Norbäck D, et al. Do childhood respiratory infections continue to influence adult respiratory morbidity? Eur Respir J 2009 Feb;33(2):237-244 [FREE Full text] [doi: 10.1183/09031936.00062907] [Medline: 19010990]
37. Marossy AE, Strachan DP, Rudnicka AR, Anderson HR. Childhood chest illness and the rate of decline of adult lung function between ages 35 and 45 years. Am J Respir Crit Care Med 2007 Feb 15;175(4):355-359. [doi: 10.1164/rccm.200607-1023OC] [Medline: 17023728]
38. Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. N Engl J Med 2003 Oct 9;349(15):1414-1422. [doi: 10.1056/NEJMoa022363] [Medline: 14534334]
39. Stern DA, Morgan WJ, Wright AL, Guerra S, Martinez FD. Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. Lancet 2007 Sep 1;370(9589):758-764 [FREE Full text] [doi: 10.1016/S0140-6736(07)61379-8] [Medline: 17765525]
40. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The group health medical associates. N Engl J Med 1995 Jan 19;332(3):133-138. [doi: 10.1056/NEJM199501193320301] [Medline: 7800004]
41. Turner SW, Palmer LJ, Rye PJ, Gibson NA, Judge PK, Cox M, et al. The relationship between infant airway function, childhood airway responsiveness, and asthma. Am J Respir Crit Care Med 2004 Apr 15;169(8):921-927. [doi: 10.1164/rccm.200307-891OC] [Medline: 14764431]
42. Woolcock A, Leeder S, Peat J, Blackburn CR. The influence of lower respiratory illness in infancy and childhood and subsequent cigarette smoking on lung function in Sydney schoolchildren. Am Rev Respir Dis 1979 Jul;120(1):5-14. [doi: 10.1164/arrd.1979.120.1.5] [Medline: 464384]
43. Lowe LA, Simpson A, Woodcock A, Morris J, Murray CS, Custovic A, NAC Manchester AsthmaAllergy Study Group. Wheeze phenotypes and lung function in preschool children. Am J Respir Crit Care Med 2005 Feb 1;171(3):231-237. [doi: 10.1164/rccm.200406-695OC] [Medline: 15502115]
44. Brussee JE, Smit HA, Koopman LP, Wijga AH, Kerkhof M, Corver K, et al. Interrupter resistance and wheezing phenotypes at 4 years of age. Am J Respir Crit Care Med 2004 Jan 15;169(2):209-213. [doi: 10.1164/rccm.200306-800OC] [Medline: 14597483]
45. Chan JY, Stern DA, Guerra S, Wright AL, Morgan WJ, Martinez FD. Pneumonia in childhood and impaired lung function in adults: a longitudinal study. Pediatrics 2015 Apr;135(4):607-616 [FREE Full text] [doi: 10.1542/peds.2014-3060] [Medline: 25733757]
46. Mannino DM, Reichert MM, Davis KJ. Lung function decline and outcomes in an adult population. Am J Respir Crit Care Med 2006 May 1;173(9):985-990. [doi: 10.1164/rccm.200508-1344OC] [Medline: 16439715]
47. Barker DJ. The fetal and infant origins of adult disease. Br Med J 1990 Nov 17;301(6761):1111 [FREE Full text] [doi: 10.1136/bmj.301.6761.1111] [Medline: 2252919]
48. Barker DJ, Godfrey KM, Fall C, Osmond C, Winter PD, Shaheen SO. Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. Br Med J 1991 Sep 21;303(6804):671-675 [FREE Full text] [doi: 10.1136/bmj.303.6804.671] [Medline: 1912913]
49. Burrows B, Knudson R, Lebowitz MD. The relationship of childhood respiratory illness to adult obstructive airway disease. Am Rev Respir Dis 1977 May;115(5):751-760. [doi: 10.1164/arrd.1977.115.5.751] [Medline: 857715]
50. Burrows B, Lebowitz M, Knudson RJ. Epidemiologic evidence that childhood problems predispose to airways disease in the adult (an association between adult and pediatric respiratory disorders). Pediatr Res 1977 Mar;11(3 Pt 2):218-220. [Medline: 846771]
51. Kelly MG, Murphy S, Elborn J. Bronchiectasis in secondary care: a comprehensive profile of a neglected disease. Eur J Intern Med 2003 Dec;14(8):488-492. [doi: 10.1016/j.ejim.2003.10.002] [Medline: 14962701]
52. Pasteur MC, Helliwell SM, Houghton SJ, Webb SC, Foweraker JE, Coulden RA, et al. An investigation into causative factors in patients with bronchiectasis. Am J Respir Crit Care Med 2000 Oct;162(4 Pt 1):1277-1284. [doi: 10.1164/ajrccm.162.4.9906120] [Medline: 11029331]
53. Nicotra MB, Rivera M, Dale AM, Shepherd R, Carter R. Clinical, pathophysiologic, and microbiologic characterization of bronchiectasis in an aging cohort. Chest 1995 Oct;108(4):955-961. [doi: 10.1378/chest.108.4.955] [Medline: 7555168]
54. King PT, Holdsworth SR, Freezer NJ, Villanueva E, Holmes PW. Characterisation of the onset and presenting clinical features of adult bronchiectasis. Respir Med 2006 Dec;100(12):2183-2189 [FREE Full text] [doi: 10.1016/j.rmed.2006.03.012] [Medline: 16650970]

55. Backman K, Piippo-Savolainen E, Ollikainen H, Koskela H, Korppi M. Increased asthma risk and impaired quality of life after bronchiolitis or pneumonia in infancy. Pediatr Pulmonol 2014 Apr;49(4):318-325. [doi: 10.1002/ppul.22842] [Medline: 23836681]
56. Silva GE, Sherrill DL, Guerra S, Barbee RA. Asthma as a risk factor for COPD in a longitudinal study. Chest 2004 Jul;126(1):59-65. [doi: 10.1378/chest.126.1.59] [Medline: 15249443]
57. Herring MJ, Putney LF, Wyatt G, Finkbeiner WE, Hyde DM. Growth of alveoli during postnatal development in humans based on stereological estimation. Am J Physiol Lung Cell Mol Physiol 2014 Aug 15;307(4):L338-L344 [FREE Full text] [doi: 10.1152/ajplung.00094.2014] [Medline: 24907055]
58. Butler JP, Loring SH, Patz S, Tsuda A, Yablonskiy DA, Mentzer SJ. Evidence for adult lung growth in humans. N Engl J Med 2012 Jul 19;367(3):244-247 [FREE Full text] [doi: 10.1056/NEJMoa1203983] [Medline: 22808959]
59. Narayanan M, Owers-Bradley J, Beardsmore CS, Mada M, Ball I, Garipov R, et al. Alveolarization continues during childhood and adolescence: new evidence from helium-3 magnetic resonance. Am J Respir Crit Care Med 2012 Jan 15;185(2):186-191 [FREE Full text] [doi: 10.1164/rccm.201107-1348OC] [Medline: 22071328]
60. Ogbuanu IU, Karmaus W, Arshad SH, Kurukulaaratchy RJ, Ewart S. Effect of breastfeeding duration on lung function at age 10 years: a prospective birth cohort study. Thorax 2009 Jan;64(1):62-66 [FREE Full text] [doi: 10.1136/thx.2008.101543] [Medline: 19001004]
61. Soto-Ramírez N, Alexander M, Karmaus W, Yousefi M, Zhang H, Kurukulaaratchy R, et al. Breastfeeding is associated with increased lung function at 18 years of age: a cohort study. Eur Respir J 2012 Apr;39(4):985-991 [FREE Full text] [doi: 10.1183/09031936.00037011] [Medline: 21852333]
62. Checkley W, West KP, Wise RA, Baldwin MR, Wu L, LeClerq SC, et al. Maternal vitamin A supplementation and lung function in offspring. N Engl J Med 2010 May 13;362(19):1784-1794. [doi: 10.1056/NEJMoa0907441] [Medline: 20463338]
63. Zosky GR, Berry LJ, Elliot JG, James AL, Gorman S, Hart PH. Vitamin D deficiency causes deficits in lung function and alters lung structure. Am J Respir Crit Care Med 2011 May 15;183(10):1336-1343. [doi: 10.1164/rccm.201010-1596OC] [Medline: 21297070]
64. Lodge C, Tan D, Lau M, Dai X, Tham R, Lowe A, et al. Breastfeeding and asthma and allergies: a systematic review and meta-analysis. Acta Paediatr 2015 Dec;104(467):38-53. [doi: 10.1111/apa.13132] [Medline: 26192405]
65. Tujague J, Bastaki M, Holland N, Balmes JR, Tager IB. Antioxidant intake, GSTM1 polymorphism and pulmonary function in healthy young adults. Eur Respir J 2006 Feb;27(2):282-288 [FREE Full text] [doi: 10.1183/09031936.06.00033705] [Medline: 16452581]
66. Silvers KM, Frampton CM, Wickens K, Pattemore PK, Ingham T, Fishwick D, New Zealand Asthma and Allergy Cohort Study Group. Breastfeeding protects against current asthma up to 6 years of age. J Pediatr 2012 Jun;160(6):991-6.e1. [doi: 10.1016/j.jpeds.2011.11.055] [Medline: 22289356]
67. Duijts L, Jaddoe VW, Hofman A, Moll HA. Prolonged and exclusive breastfeeding reduces the risk of infectious diseases in infancy. Pediatrics 2010 Jul;126(1):e18-e25. [doi: 10.1542/peds.2008-3256] [Medline: 20566605]
68. Roth D, Caulfield LE, Ezzati M, Black RE. Acute lower respiratory infections in childhood: opportunities for reducing the global burden through nutritional interventions. Bull World Health Organ 2008 May;86(5):356-364 [FREE Full text] [doi: 10.2471/blt.07.049114] [Medline: 18545738]
69. Zar HJ, Ferkol TW. The global burden of respiratory disease-impact on child health. Pediatr Pulmonol 2014 May;49(5):430-434. [doi: 10.1002/ppul.23030] [Medline: 24610581]
70. Filoche S, Garrett S, Stanley J, Rose S, Robson B, Elley CR, et al. Wāhine hauora: linking local hospital and national health information datasets to explore maternal risk factors and obstetric outcomes of New Zealand Māori and non-Māori women in relation to infant respiratory admissions and timely immunisations. BMC Pregnancy Childbirth 2013 Jul 10;13:145 [FREE Full text] [doi: 10.1186/1471-2393-13-145] [Medline: 23837612]
71. Esposito S, Lelii M. Vitamin D and respiratory tract infections in childhood. BMC Infect Dis 2015 Oct 28;15:487 [FREE Full text] [doi: 10.1186/s12879-015-1196-1] [Medline: 26521023]
72. Monlezun D, Bittner E, Christopher K, Camargo C, Quraishi S. Vitamin D status and acute respiratory infection: cross sectional results from the United States National Health and Nutrition Examination Survey, 2001-2006. Nutrients 2015 Mar 13;7(3):1933-1944 [FREE Full text] [doi: 10.3390/nu7031933] [Medline: 25781219]
73. Grant C, Wall C, Gibbons M, Morton S, Santosham M, Black RE. Child nutrition and lower respiratory tract disease burden in New Zealand: a global context for a national perspective. J Paediatr Child Health 2011 Aug;47(8):497-504. [doi: 10.1111/j.1440-1754.2010.01868.x] [Medline: 21040074]
74. Grant CC, Kaur S, Waymouth E, Mitchell EA, Scragg R, Ekeroma A, et al. Reduced primary care respiratory infection visits following pregnancy and infancy vitamin D supplementation: a randomised controlled trial. Acta Paediatr 2015 Apr;104(4):396-404. [doi: 10.1111/apa.12819] [Medline: 25283480]
75. Telfar B, Zhang J. The impact of respiratory disease in New Zealand. University of Otago. 2019. URL: https://s3-ap-southeast-2.amazonaws.com/assets.asthmafoundation.org.nz/images/NZ-Impact-Report-2018_FINAL.pdf [accessed 2019-09-03]
76. Milne R, Beasley R. Hospital admissions for chronic obstructive pulmonary disease in New Zealand. N Z Med J 2015 Jan 30;128(1408):23-35. [Medline: 25662376]

77. Gurram N, Martin G. Disparities in Age of Smoking Initiation and Transition to Daily Smoking in New Zealand. Wellington, USA: Health Promotion Agency; 2019.
78. Paterson J, Schluter P, Percival T, Carter S. Immunisation of a cohort Pacific children living in New Zealand over the first 2 years of life. Vaccine 2006 May 29;24(22):4883-4889. [doi: 10.1016/j.vaccine.2006.02.050] [Medline: 16644070]
79. Schluter PJ, Durward C, Cartwright S, Paterson J. Maternal self-report of oral health in 4-year-old Pacific children from South Auckland, New Zealand: findings from the Pacific Islands Families Study. J Public Health Dent 2007;67(2):69-77. [doi: 10.1111/j.1752-7325.2007.00014.x] [Medline: 17557676]
80. Tautolo E, Iusitini L, Taylor S, Paterson J. Will New Zealand be smokefree by 2025? Smoking prevalence amongst a cohort of Pacific adults. N Z Med J 2014 May 02;127(1393):99-106. [Medline: 24816960]
81. Tautolo E, Schluter P, Taylor S. Prevalence and concordance of smoking among mothers and fathers within the Pacific Islands Families Study. Pac Health Dialog 2011 Sep;17(2):136-146. [Medline: 22675810]
82. Paterson J, Percival T, Schluter P, Sundborn G, Abbott M, Carter S, et al. Cohort profile: the pacific islands families (PIF) study. Int J Epidemiol 2008 Apr;37(2):273-279. [doi: 10.1093/ije/dym171] [Medline: 17846053]
83. Rush E, Oliver M, Plank LD, Taylor S, Iusitini L, Jalili-Moghaddam S, et al. Cohort profile: pacific islands families (PIF) growth study, Auckland, New Zealand. BMJ Open 2016 Nov 2;6(11):e013407 [FREE Full text] [doi: 10.1136/bmjopen-2016-013407] [Medline: 27807091]
84. Friedman M, Hwang MS. Brodsky and Friedman scales and clinical tonsil size grading in children. JAMA Otolaryngol Head Neck Surg 2015 Oct;141(10):947-948. [doi: 10.1001/jamaoto.2015.2056] [Medline: 26402214]
85. Mallampati SR, Gatt SP, Gugino LD, Desai SP, Waraksa B, Freiberger D, et al. A clinical sign to predict difficult tracheal intubation: a prospective study. Can Anaesth Soc J 1985 Jul;32(4):429-434. [doi: 10.1007/BF03011357] [Medline: 4027773]
86. Ramachandran SK, Kheterpal S, Consens F, Shanks A, Doherty TM, Morris M, et al. Derivation and validation of a simple perioperative sleep apnea prediction score. Anesth Analg 2010 Apr 1;110(4):1007-1015. [doi: 10.1213/ANE.0b013e3181d489b0] [Medline: 20357144]
87. Portenoy R, Thaler H, Kornblith A, Lepore JM, Friedlander-Klar H, Kiyasu E, et al. The memorial symptom assessment scale: an instrument for the evaluation of symptom prevalence, characteristics and distress. Eur J Cancer 1994;30A(9):1326-1336. [doi: 10.1016/0959-8049(94)90182-1] [Medline: 7999421]
88. Calverley P, Pauwels Dagger R, Löfdahl CG, Svensson K, Higenbottam T, Carlsson L, et al. Relationship between respiratory symptoms and medical treatment in exacerbations of COPD. Eur Respir J 2005 Sep;26(3):406-413 [FREE Full text] [doi: 10.1183/09031936.05.00143404] [Medline: 16135720]
89. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. Chest 1988 Mar;93(3):580-586. [doi: 10.1378/chest.93.3.580] [Medline: 3342669]
90. Pabreja K, Gibson P, Lochrin AJ, Wood L, Baines KJ, Simpson JL. Sputum colour can identify patients with neutrophilic inflammation in asthma. BMJ Open Respir Res 2017;4(1):e000236 [FREE Full text] [doi: 10.1136/bmjresp-2017-000236] [Medline: 29071085]
91. Hankinson JL, Gardner RM. Standardization of spirometry. Am Rev Respir Dis 1988 Feb;137(2):493-495. [doi: 10.1164/ajrccm/137.2.493c] [Medline: 3341641]
92. Brazzale D, Hall G, Swanney MP. Reference values for spirometry and their use in test interpretation: a position statement from the Australian and New Zealand society of respiratory science. Respirology 2016 Oct;21(7):1201-1209. [doi: 10.1111/resp.12855] [Medline: 27457870]
93. Cleveland RH, Stamoulis C, Sawicki G, Kelliher E, Zucker EJ, Wood C, et al. Brasfield and Wisconsin scoring systems have equal value as outcome assessment tools of cystic fibrosis lung disease. Pediatr Radiol 2014 May;44(5):529-534. [doi: 10.1007/s00247-013-2848-1] [Medline: 24370794]
94. Cole TJ, Flegal KM, Nicholls D, Jackson AA. Body mass index cut offs to define thinness in children and adolescents: international survey. Br Med J 2007 Jul 28;335(7612):194 [FREE Full text] [doi: 10.1136/bmj.39238.399444.55] [Medline: 17591624]
95. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St George's respiratory questionnaire. Am Rev Respir Dis 1992 Jun;145(6):1321-1327. [doi: 10.1164/ajrccm/145.6.1321] [Medline: 1595997]
96. Jones P, Quirk F, Baveystock C. The St George's Respiratory Questionnaire. Respir Med 1991 Sep;85 Suppl B:25-31; discussion 33. [doi: 10.1016/s0954-6111(06)80166-6] [Medline: 1759018]
97. EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy 1990 Dec;16(3):199-208. [doi: 10.1016/0168-8510(90)90421-9] [Medline: 10109801]
98. Johns M. The Assessment of Sleepiness in Children and Adolescents. Epworth Sleepiness Scale (ESS). 2015. URL: http://epworthsleepinessscale.com/wp-content/uploads/2016/06/ASA-sleepiness-2015.pdf [accessed 2019-09-03]
99. Janssen KC, Phillipson S, O'Connor J, Johns MW. Validation of the epworth sleepiness scale for children and adolescents using Rasch analysis. Sleep Med 2017 May;33:30-35. [doi: 10.1016/j.sleep.2017.01.014] [Medline: 28449902]
100. Birring S, Prudon B, Carr A, Singh S, Morgan M, Pavord ID. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). Thorax 2003 Apr;58(4):339-343 [FREE Full text] [doi: 10.1136/thorax.58.4.339] [Medline: 12668799]

101. Li K. Sliced inverse regression for dimension reduction. J Am Stat Assoc 1991 Jun;86(414):316-327 [FREE Full text] [doi: 10.1080/01621459.1991.10475035]
102. Jiang C, Yu W, Wang J. Inverse regression for longitudinal data. Ann Statist 2014 Apr;42(2):563-591 [FREE Full text] [doi: 10.1214/13-aos1193]
103. Pfeiffer RM, Forzani L, Bura E. Sufficient dimension reduction for longitudinally measured predictors. Stat Med 2012 Sep 28;31(22):2414-2427 [FREE Full text] [doi: 10.1002/sim.4437] [Medline: 22161635]
104. Wen X, Cook RD. Optimal sufficient dimension reduction in regressions with categorical predictors. J Stat Plan Infer 2007 Jun;137(6):1961-1978 [FREE Full text] [doi: 10.1016/j.jspi.2006.05.008]
105. Robins JM, Mark SD, Newey WK. Estimating exposure effects by modelling the expectation of exposure conditional on confounders. Biometrics 1992 Jun;48(2):479-495. [Medline: 1637973]
106. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 2011 May;46(3):399-424 [FREE Full text] [doi: 10.1080/00273171.2011.568786] [Medline: 21818162]
107. Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. Epidemiology 2004 Sep;15(5):615-625. [doi: 10.1097/01.ede.0000135174.63482.43] [Medline: 15308962]
108. Steenland K, Armstrong B. An overview of methods for calculating the burden of disease due to specific risk factors. Epidemiology 2006 Sep;17(5):512-519. [doi: 10.1097/01.ede.0000229155.05644.43] [Medline: 16804473]
109. Greenland S. Variance estimators for attributable fraction estimates consistent in both large strata and sparse data. Stat Med 1987 Sep;6(6):701-708. [doi: 10.1002/sim.4780060607] [Medline: 2825320]
110. Stasinopoulos DM, Rigby RA. Generalized additive models for location scale and shape (gamlss) in R. J Stat Soft 2007;23(7):- [FREE Full text] [doi: 10.18637/jss.v023.i07]
111. Rothman K, Greenland S. Lash TL: Modern Epidemiology. Third Edition. Sydney, Australia: Lippincott Williams & Wilkins; 2008.

Abbreviations

COPD: chronic obstructive pulmonary disorder
ESS-CHAD: Epworth Sleepiness Scale for Children and Adolescents
FEV1: forced expiratory volume in 1 second
FVC: forced vital capacity
IPW: inverse probability weighting
LCQ: Leicester Cough Questionnaire
PAR: population attribute and avoidable risks
PIF: Pacific Islands Families
REDCap: research electronic data capture
SGRQ: St. George's Respiratory Questionnaire
SIR: sliced inverse regression

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Protocol

Safety and Biovigilance in Organ Donation (SAFEBOD): Protocol for a Population-Based Cohort Study

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Abstract

Background: Tension lies between the need to increase access to organ transplantation and the equally urgent need to prevent inadvertent transmission of infectious diseases or cancer from organ donors. Biovigilance, or the evaluation of potential donors, is often time-pressured and may be based on incomplete information.

Objective: The Safety and Biovigilance in Organ Donation (SAFEBOD) study aims to improve estimates of infection and cancer transmission risk and explore how real-time data access could support decision-making.

Methods: We will link existing donor referral, actual donor, recipient, and health-outcome data sets from 2000-2015 in New South Wales. Organ donor data sets will include the Organ Donor Characterizing Risk-Profile of Donors Study, the National Organ Matching System, the Australian and New Zealand Organ Donor Register, and the Australian and New Zealand Living Donor Kidney Register. Recipient data sets will include the Australian and New Zealand Dialysis and Transplant Register, the Australian and New Zealand Cardiothoracic Register, the Australian and New Zealand Islet and Pancreas Register, and the Australian and New Zealand Liver Transplant Register. New South Wales health outcome data sets will include HIV and AIDS Notifications and Surveillance Data, the Notifiable Conditions Information Management System, Admitted Patient Data Collection, Emergency Department Data Collection, the Central Cancer Registry, and the Cause of Death Data Collection. We will link organ donors to transplant recipients and health outcomes data sets using probabilistic data-matching based on personal identifiers. Transmission and nontransmission events will be determined by comparing previous cases in donors and posttransplant cases in recipients. We will compare the perceived-risk at referral with the verified risk from linked health outcome data sets and the odds of cancer or contracting an infectious disease in organ recipients from donors based on their transmission-risk profile and estimate recipient survival by donor transmission risk group.

Results: Data were requested from each of the listed registries in September 2018, and data collection is ongoing. Linked data from all listed data sets are expected to be complete in September 2020.

Conclusions: The SAFEBOD study will overcome current limitations in organ donation by accessing comprehensive information on referred organ donors and recipients in existing data sets. The study will provide robust estimates of disease transmission and nontransmission events based on recent data. It will also describe the agreement between perceived risk estimated at the time of referral and verified risk when all health outcome data are accessible. The improved understanding of transmission and

nontransmission events will inform clinical decisions and highlight where current policies can be revised to broaden the acceptance of deceased donors.

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KEYWORDS

transplant recipients; organ donor; transplant; neoplasms; infectious; disease transmission; safety; biovigilance; organ; surgery; cohort study

Introduction

Biovigilance is intended to avoid inadvertent transmission of infectious disease or cancer from organ donors and is a central concern in transplant programs globally. In conflict with these safety concerns is the excess morbidity and mortality experienced by people with end-organ disease on transplant waiting lists. In Australia, increasing the organ donation rate is a national priority. The Australian Government formed the Organ and Tissue Authority (OTA) in 2009. The OTA's purpose is to increase the capability and capacity within the health system to maximize donation rates and to raise community awareness and stakeholder engagement across Australia to promote organ and tissue donation. Since 2009 the number of deceased organ donors has more than doubled, and the number of transplant recipients has increased by 75% [1]. However, the number of people in need of an organ transplant outweighs the number of organs available. At the end of 2017, 1388 patients with end-stage chronic disease remained active on the transplant waiting list (964 kidney, 171 liver, 80 heart, 108 lung, 65 pancreas, 3 intestine) [2]. The number of referrals of potential donors has increased exponentially over time, but the number of referrals who go on to become donors has increased modestly in comparison [3,4]. Thus, the proportion of total donor referrals who proceed to donation has decreased over time (Figure 1 [3]). A large proportion of donor referrals do not proceed to donation due to biovigilance concerns (Figure 2). Therefore, initiatives to increase the number of referred potential donors whose organs can be safely donated and transplanted are vital.

Figure 1. Number of organ donor referrals and actual donations in New South Wales, 2010-2018 [3].

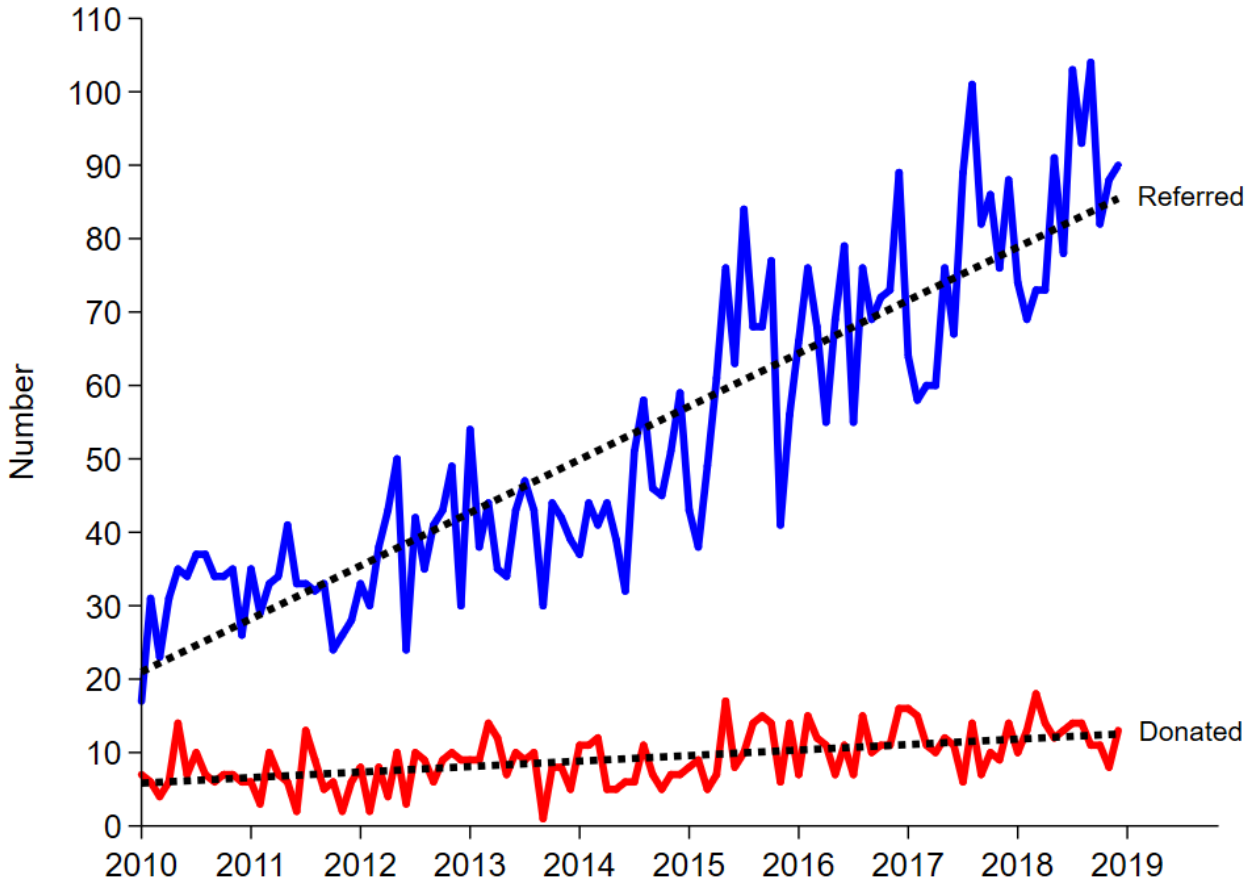
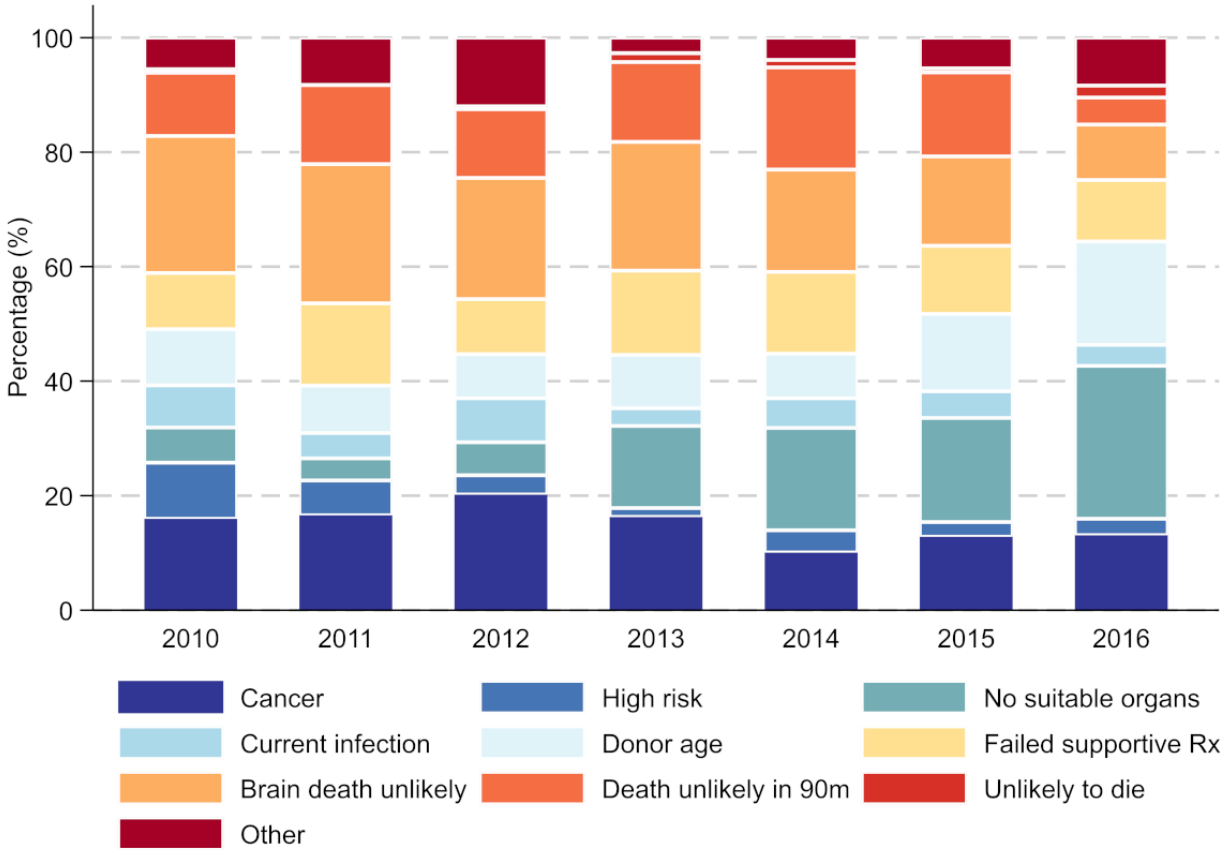


Figure 2. Primary reason donor referrals were found not medically suitable. Reasons of possible biovigilance concern highlighted in blue.



Decisions about donor medical suitability and biovigilance are informed by sparse data and tend to be risk averse. Using published medical literature to understand transmission risk is problematic due to publication bias (resulting in more events of disease transmission being reported than events where there was no disease transmission). Published transmission events are likely to be a biased subset of the global transplantation experience. Current estimates of transmission risk for bloodborne viruses or malignancies in organ donation include confirmed transmission events [5,6]. However, the proportion of organs transplanted from donors with a perceived increased risk of infection or malignancy, but there was no transmission, is unknown. The need for an evidence base to guide decision-making led to the formation of the NOTIFY project as a joint venture between the World Health Organization (WHO) and the Italian National Transplant Centre. NOTIFY collates a biovigilance database and recommends biovigilance systems in organ donation and transplant report all serious adverse events nationally [7].

Risk stratification recommendations for different infectious diseases and cancers are often complex, may not be derived for use in a transplantation setting, and may not be readily accessible in real-time to clinicians making decisions about donor safety. Inconsistencies in decisions about the medical suitability of referred donors suggest considerable clinical uncertainty [3]. For example, complex guidelines and uncertainty around the risk of transmission of primary brain malignancies from donor to recipient may have resulted in 23 missed donor opportunities where the transmission risk was subsequently ascertained to be low [4]. The inclusion of these donors would have increased the donor pool by 3.1%.

The Safety and Biovigilance in Organ Donation (SAFEBOD) study aims to estimate infection and cancer transmission risk and provide insight into how real-time access to linked existing data could support decision-making.

Methods

SAFEBOD is a cohort study using data linkage of existing state and national administrative health data sets. These data sets will establish estimates of the biovigilance risk of living and deceased organ donors, and potential deceased donor referrals that do not proceed, in New South Wales (NSW).

Aims

The study's primary objective is to develop clearer estimates of disease transmission in organ donation and transplant. Specifically, the study aims to (1) identify organ donors and recipients with recorded cancer or infectious disease, (2) determine the agreement between medical history ascertained at the time of donor referral (perceived risk) and that collated from existing mandated health data sets (verified risk), (3) identify suspected cases of donor-recipient disease transmission and nontransmission based on presence or absence of the corresponding disease in donor and recipient verified records. The study's findings will be used to develop decision support

recommendations and resources for clinicians making donation decisions in NSW and beyond.

Public Health Register

The database generated in this project will be established as the Biovigilance in Organ Donation and Transplantation Register (Biovigilance Register) under state law by the NSW Ministry of Health. The Public Health Act 2010 permits the linkage of existing health data sets to facilitate the identification and monitoring of risk factors for diseases or conditions that have a substantial adverse impact on the population and, to facilitate the care, treatment, and the follow up of persons who have diseases or have been exposed to diseases of public safety [8]. The sponsor of the Biovigilance Register is the NSW Chief Health Officer and Deputy Director-General, Population and Public Health. The data custodian of the Biovigilance Register is the Associate Director, Epidemiology and Biostatistics, Centre for Epidemiology and Evidence.

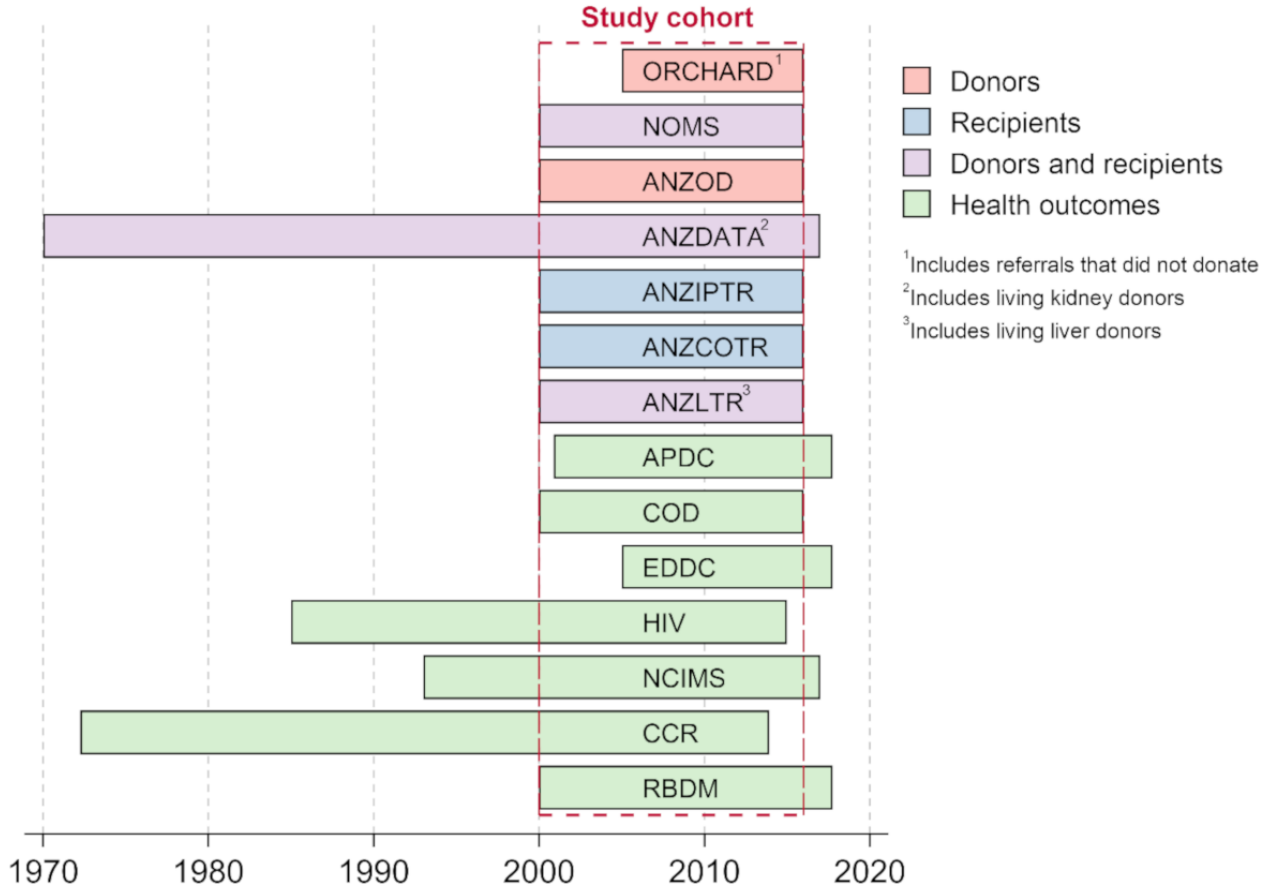
Population

The study will consist of four groups of participants: (1) Donor referrals that did not proceed to donation, (2) Deceased donors, (3) Living donors, and (4) Recipients of any organs from 2 and 3, for all solid organs used or procured for transplantation in NSW, 2000-2015.

Data Sources

The Biovigilance Register will source information from organ donor referral, living and deceased donor, recipient registries, and health outcome data sets (Figure 3). A description of each data set and the date range of available data follows.

Figure 3. Data sources included in the SAFEBOD study with date ranges of the data requested. Personal identifiers will be requested for individuals referred for donation, donated, or transplanted in New South Wales, 2000-2015 (dotted box) to define the study cohort.



Organ Donor Referral, Deceased Donor, and Living Donors

Organ Referral Characterisation Database (ORCHARD), 2005-Present

Developed by nephrologists Angela Webster and Kate Wyburn in association with the NSW Organ and Tissue Donation Service (OTDS) using the OTDS registry of referral logs for organ donation in NSW, ORCHARD records all donor referrals in NSW, regardless of referral outcome. The database includes information about perceived cases of cancer and infectious diseases in referrals who do and do not proceed to donation.

The National Organ Matching System (NOMS) Database, 2000-Present

The allocation of organs from a deceased donor to patients on the waiting list is determined by ranking generated by a computer program administered by the Australian Red Cross. NOMS holds additional identifiers for NSW donors and recipients useful for data linkage and immune profiles of donor and recipient pairs used to calculate their matching scores.

Australia and New Zealand Organ Donor (ANZOD) Registry, 1989-Present

This registry collects and records data on all organ donors within Australia and New Zealand. The database is essential to linking donor and recipient pairs identified in the donor and recipient registries.

Australia and New Zealand Living Kidney Donor Register, 2004-Present

This registry collects and records data on all living kidney donors within Australia and New Zealand.

Organ Transplant Recipients

Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry, 1977-Present

Records information for all people in Australia and New Zealand receiving treatment for end-stage renal failure, including those who have received a kidney transplant, updated annually.

Australian and New Zealand Islet and Pancreas Transplant Recipient Registry (ANZIPTR), 1984-present

Records all islet and pancreas transplants performed in Australia and New Zealand.

Australia and New Zealand Cardiothoracic Transplant Registry (ANZCOTR), 1984-Present

This registry contains every heart, heart/lung, and lung transplant performed in all six Australia and New Zealand Cardiothoracic Transplant centers.

Australia and New Zealand Liver Transplant Registry (ANZLTR), 1985-Present

This collaborative effort of the liver transplant units in Australia and New Zealand collects data on all patients listed for liver transplantation and their subsequent outcomes.

Health Outcomes

NSW Admitted Patient Data Collection (APDC) (Public Hospitals), and the NSW Inpatient Statistics Collection (Private Hospitals), 2001-2018

These comprise a census of all admitted patient services provided by NSW public hospitals, public psychiatric hospitals, public multi-purpose services, private hospitals, and private day procedure centers. It covers demographic information and information on diagnoses, procedures, and hospital care for every hospital separation in NSW. Admitted patient data are collected under administrative arrangements with public hospitals and the Private Health Facilities Act 2007 for private hospitals.

NSW Cause of Death Unit Record File (COD), 1985-2016

The Australian Coordinating Registry provides the COD on behalf of the data custodians, the Registry of Births, Deaths, and Marriages, and the State Coroner. The COD data set includes death registration information pertaining to all deaths occurring in NSW and includes demographic information, cause of death, and place of death as recorded either through the death registration process or by coroners. This information has been supplemented with codes derived by the Australian Bureau of Statistics, including the International Classification of Disease Codes.

NSW Emergency Department Data Collection (EDDC), 2005-2018

The EDDC registry records demographic and emergency treatment-related information for every person who presents to participating public emergency departments in NSW, including all emergency departments in metropolitan public hospitals and rural base hospitals. Information on emergency department attendances is collected under administrative arrangements with public hospitals.

HIV and AIDS Notifications and Surveillance Data Set (HIV), 1985-2014

HIV is notifiable to the Ministry of Health under the NSW Public Health Act 2010. Notifications of HIV are received from pathology laboratories and compiled in the HIV Notifications and Surveillance Dataset.

NSW Notifiable Conditions Information Management System (NCIMS), 1993-2017

The NCIMS manages the surveillance and reporting of diseases and conditions notifiable under the NSW Public Health Act 2010. The NSW Ministry of Health receives notifications of communicable diseases from general practitioners, hospitals, and pathology laboratories. All notifiable conditions included in NCIMS will be included in the Biovigilance Register except for adverse events following immunization and lead poisoning.

NSW Central Cancer Register (CCR), 1972-2015

The CCR records all new diagnoses of invasive cancer and in-situ breast cancer and melanoma in NSW residents but does not capture cancer recurrences.

NSW Registry of Births, Deaths, and Marriages (RBDM) Death Registrations, 1985-2018

This registry includes all deaths occurring in NSW. Demographic information and particulars of each death, including the cause of death, are recorded.

NSW Tuberculosis Contact Treatment Chest Clinics (TB), 2000-2015

Chest Clinic databases across NSW hold records of tuberculosis cases and people treated as contacts of cases.

South Eastern Area Laboratory Services (SEALS), 2008-Present

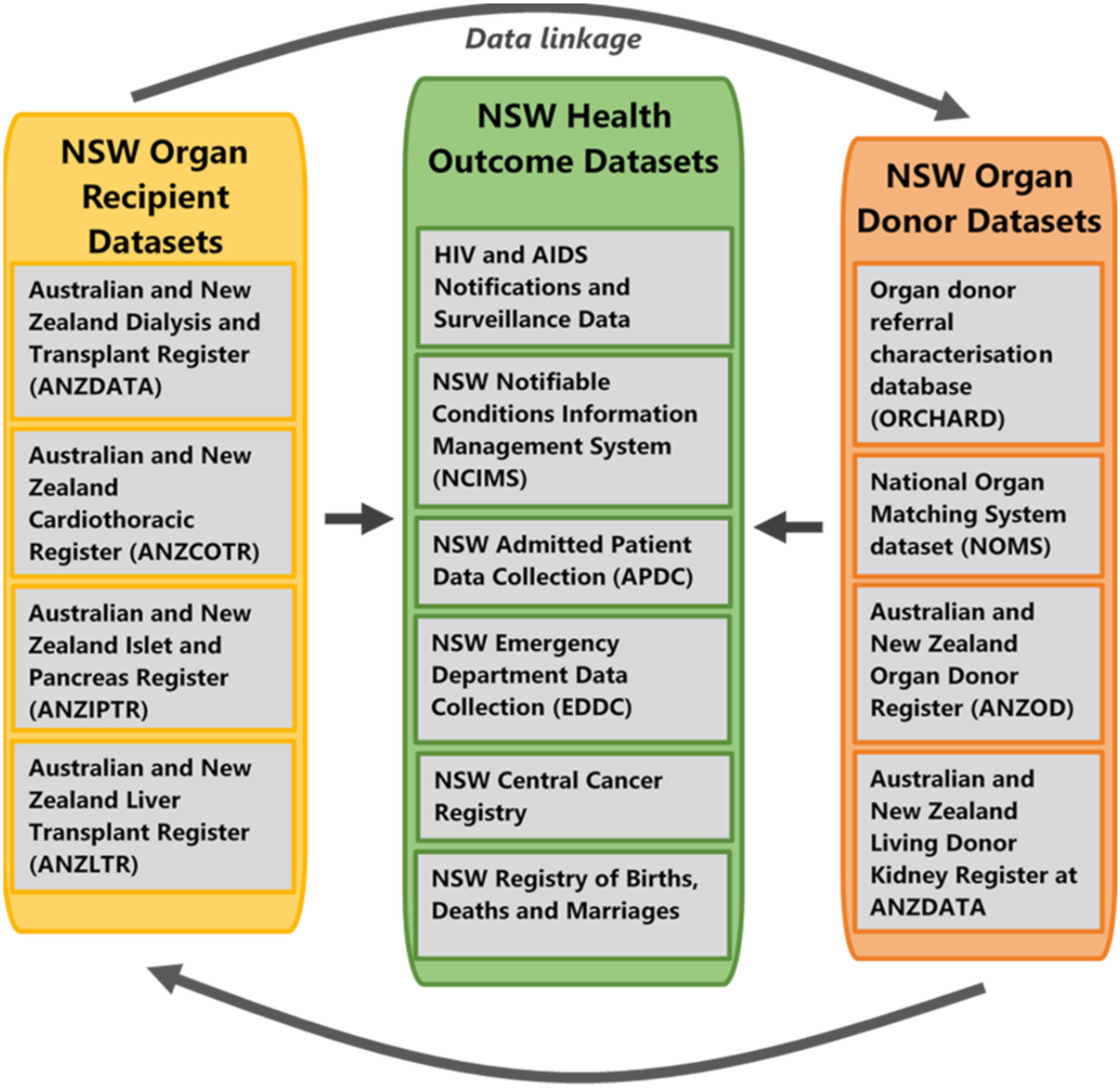
SEALS performs serological and nucleic acid testing for bloodborne viruses in organ donation in NSW. It holds records for HBV, HCV, and HIV results for intended and actual donors in NSW. These records are sought to complement and verify the HBV and HCV findings collated from other outcomes, donor, and recipient registries.

Data Linkage

Data linkage will be performed by the NSW Ministry of Health dedicated data linkage service, the Centre for Health Records Linkage (CHeReL). The CHeReL uses a separation model for data integration in order to maintain patient confidentiality [9]. Personal identifiers are split from health information for each

data set. Data custodians will send demographic data, including name, sex, date of birth, and address, if available to the CHeReL. These identifiers will be used to link individuals across data sets. The CHeReL will then randomly assign a unique identifier to individuals across data sets and match donor and recipient records. Linkage will be probabilistic for all data sets except ANZDATA, ANZOD, and the Living Kidney Donor registers, which are already deterministically linked [10]. The CHeReL will return unique individual identifiers to the data custodians, who then send the health-related data with the unique identifier back to the NSW Ministry of Health, who will create the Biovigilance Register (Figure 4). Data shared with the research team at The University of Sydney will be de-identified to maintain patient confidentiality. The risk of reidentification of patients is very low with the information held in the Biovigilance Register.

Figure 4. Data sources and data linkage process between organ recipient data sets, organ donor data sets, and health outcome data sets in New South Wales.



Outcomes

Agreement of Perceived and Verified Risk

The possible outcomes of decisions made according to perceived risk compared to verified risk are outlined in Table 1. When perceived risk and verified risk are concordant, donors are used effectively and efficiently. Donors perceived as high risk who truly pose a biovigilance risk are declined (Outcome 1), or their organs may be used with recipient consent, appropriate prophylaxis, and surveillance. In cases of known transmission (Outcome 2), the risk of transmission and recipient outcome is mitigated by early recognition and treatment, and the (infectious) disease may not manifest, a known nontransmission (Outcome 3). The most likely clinical scenario for donors is a perceived low risk, which can be verified as a known absence of biovigilance risk (Outcome 8).

When donors are incorrectly classified, they are not used effectively or efficiently. Incorrect classification occurs when verified low-risk donors are declined because of a high perceived risk (Outcome 6), or recipients are not perceived as at-risk of unknown or nontransmission (Outcomes 4 and 5) or exposed to unnecessary treatments and tests when donors are believed to be a risk for transmission when they are low risk (Outcome 7).

Table 1. Summary of possible donation outcomes and transmission events, according to perception and verification of donor biovigilance risk. Top left and bottom right: perceived risk and verified risk are concordant, and the donor is correctly classified. Top right and bottom left: perceived risk and verified risk are discordant, and the donor is incorrectly classified.

Perceived donor risk	Verified donor risk	
	High	Low
High	• Donor declined • Known transmission • Known nontransmission	• Donor declined • Misclassified known nontransmission
Low	• Unknown transmission • Unknown nontransmission	• Known absence of biovigilance risk

Suspected Cases of Donor-Derived Disease Transmission

Two statisticians will review donor and recipient records to identify suspected cases of donor-derived transmission events for infectious diseases and malignancies. Suspected cases will include recipients first diagnosed with the condition post transplant where (1) the donor was known to have the condition at the time of donation or (2) the donor was not known to have the condition at the time of donation, and more than one recipient from the same donor was diagnosed with the same condition. A standardized algorithm will be used to classify the likelihood of the transmission event being donor-derived from excluded to possible/probable/proven, as used by the Organ Procurement Transplant Network Disease Transmission Advisory Committee [11,12]. This algorithm considers several criteria for classification, including laboratory evidence in the donor, all recipients of the same donor, and pretransplant laboratory evidence of negative findings in the recipient before transplant and use of active prophylaxis or treatment. For infectious diseases, we will also consider the time from transplant to diagnosis to distinguish between donor-derived transmission events and de novo infections.

Statistical Analysis

Estimates of transmission through organ transplantation will be based on the recorded cases using linked health data in donors and recipients. Information from the linked health data will be used to identify known and unknown cases of donor infectious diseases and/or malignancies and linked to respective recipients to determine disease transmission and nontransmission events in patients transplanted in NSW.

Donor “perceived” risk for cancers and infectious diseases will be compared to “verified” risk using proportions (95%CI) and McNemar tests, and agreement will be assessed using the Kappa statistic. Cox or logistic regression models will be fitted to compare the hazard/odds of cancer or contracting an infectious disease in organ recipients from donors classified by the four transmission risk groups (classified according to Table 1). Other risk factors of recipient cancer or infection will be adjusted for in the analyses. Recipient survival by donor transmission risk groups will be summarised using Kaplan–Meier survival curves, and hazard ratios (95% CI) estimated using Cox regression models. Additional average life-years gained by using organs from donors stratified by risk of cancer transmission will be estimated from the area under the survival function curve up to 10 years after transplantation. All analyses will be conducted using STATA, R, or SAS statistical software programs.

Results

The SAFEBOD study was funded in 2016 by the Office of the Chair, NSW Ministry of Health. We received approval from the University of Sydney Human Research Ethics Committee (HREC 2016/758) on September 13, 2016. Data were requested from the listed registries in September 2018 and is ongoing. Linked data from all listed data sets is expected in September 2020.

Declarations

The SAFEBOD study was approved by the University of Sydney Human Research Ethics Committee (HREC 2016/758) on September 13, 2016. It includes the approval of data collection for three populations: deceased organ donors, organ transplant recipients, and living organ donors. HREC approved a waiver of consent to participate for deceased organ donors. HREC approved disclosure of health-related information for organ transplant recipients and living organ donors under the Public Health Act (1998) and the management of health services activity (HPP 10 (1) or 11(1)). The linked donor, recipient, and health-related data sets will form the Bioviglance in Organ Donation and Transplantation Register under state law by the NSW Ministry of Health, established by the authority of the Chief Health Officer for epidemiological data under the Public Health Act 2010. The Register will be housed by the NSW Ministry of Health and provided to the research group for investigation. The researchers will follow the NSW Health policy directive on Data Collections—Disclosure of Unit Record Data for Research or Management of Health Services (PD2015_037, September 15, 2015).

Availability of Data and Material

The data that support the findings of this study are available from the NSW Ministry of Health, Office of the Chair, but

restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Aggregate data are, however, available from the authors after publication of findings, upon reasonable request and with permission of the NSW Ministry of Health, Office of the Chair, and all other data custodians for the data sets named above.

Discussion

Organ donation remains a scarce resource despite a dramatic increase in organ donor referrals in the past ten years. Many donor referrals are declined due to the perceived risk of transmission of infectious disease or malignancy at the time of referral. Often, data collected at the time of referral is incomplete due to a lack of access to medical records to ascertain a donor's medical history within donation time-frame constraints and limits the opportunity for estimating biovigilance outcomes. Current estimates of disease transmission in organ donation and transplantation are biased towards transmission events and do not reliably capture nontransmission, leading to the over-estimation of biovigilance risk posed by referred donors.

Our proposed study will overcome these limitations using data linkage to develop clearer estimates of donor disease transmission and nontransmission in NSW. Our study cohort is uniquely placed for this work due to high-quality state data and linkage infrastructure and the use of the unique data set of contemporaneous potential donors, which are not recorded by deceased donor registries. Furthermore, it will describe the agreement between perceived risk of referred donors based on data collected at the time of referral and verified risk when mandatory health outcomes data are available. These results may reveal additional information available in health outcome data sets and support the use of real-time linkage at the time of donor referral to ascertain transmission risk.

Some practical and operational issues involved in performing the study arise from the use of state data in a nationally shared deceased donor organ allocation program. Cases will arise where deceased donor organs from interstate or NSW donor organs have been allocated to interstate recipients. In these cases, we will be unable to verify the perceived risk at the time of donation with outcomes collated from linked health records. However, these cases can contribute to the estimations of disease transmission based on donor histories collected at the time of referral and recipient outcomes recorded by transplant registries. Additionally, we will be unable to verify donor risk or censor those lost to follow-up (except kidney recipients in ANZDATA), living donors, and recipients who move interstate or overseas.

Findings from the SAFEBOD study will highlight where the current policy can be revised to accept more donors and increase transplant rates. Clear estimates of transmission risk will assist in clinical decision-making at the time of donor referral and may also be useful in conversations with potential recipients.

Acknowledgments

We want to acknowledge the NSW Ministry of Health, NSW OTDS, ANZDATA, ANZIPTR, ANZCOTR, ANZLTR, and NOMS for providing data for this work. The Australian Coordinating Registry provides the COD URF on behalf of the NSW Registry of Births, Deaths, and Marriages, the NSW Coroner, and the National Coronial Information System. We would also like to thank the Centre for Health Record Linkage for their assistance with data-linkage. This work has been published on behalf of the SAFEBOD Study Group; Dr Michael O'Leary, Prof William Rawlinson, Prof Geoff McGaughan, Prof Anne Keogh, Prof Stephen McDonald, Prof David Currow, Prof Jeremy Chapman, Dr Lee Taylor, and Ms Rebecca Hancock.

This work was supported by a research grant from the Office of the Chief Health Officer, NSW Minister of Health, as it closely aligns with NSW Health priorities concerning Organ Donation. The grant included funding over 3 years of the project and in-kind support for data-linkage and maintaining the Biovigilance Register.

Authors' Contributions

AW and KW, the chief investigators, were responsible for the conception and design of the SAFEBOD study and initiation of stakeholder collaborations. PK, CMV, BR, NDM, and JH provided expertise in the design of the SAFEBOD study, including for the development of the described statistical analysis plan, data requirements, and data linkage processes. AW, KW, and BR were responsible for the study's ongoing operations. LT reviewed the manuscript and provided expertise on the Public Health Act and register initiation. All authors drafted the manuscript and critically revised it for intellectual content.

Conflicts of Interest

The study investigators have no competing interests. All study members have declared all financial and nonfinancial affiliations to the HREC committee in the original ethics application. The data reported here have been supplied by the Australia and New Zealand Dialysis and Transplant Registry. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of ANDATA.

References

1. ANZOD Registry. 2018 Annual Report, Section 2: Deceased Organ. Australia and New Zealand Dialysis and Transplant Registry. Adelaide, Australia; 2018. URL: https://www.anzdata.org.au/report/anzod-annual-report-2018/ [accessed 2020-09-29]

2. ANZOD Registry. 2017 Annual Report, Section 11: Deceased Organ Transplant Waiting List. Australia and New Zealand Dialysis and Transplant Registry. Adelaide, Australia; 2018. URL: https://www.anzdata.org.au/report/anzod-annual-report-2018/ [accessed 2020-09-29]
3. Thomson IK, Rosales BM, Kelly PJ, Wyburn K, Waller KM, Hirsch D, et al. Epidemiology and Comorbidity Burden of Organ Donor Referrals in Australia. Transplantation Direct 2019;5(11):e504. [doi: 10.1097/txd.0000000000000938]
4. Thomson I, Hancock R, O'Leary M, Waller K, Wyburn K, Webster A. 552.9 Risky organs: trends in comorbidities among potential and actual Australian organ donors in New South Wales. In: Transplantation. 2016 Presented at: 26th International Congress of The Transplantation Society; July 2016, 2016; Hong Kong.
5. Avelino-Silva V, D'Albuquerque L, Bonazzi P, Song ATW, Miraglia JL, De Brito Neves A, et al. Liver transplant from Anti-HBc-positive, HBsAg-negative donor into HBsAg-negative recipient: is it safe? A systematic review of the literature. Clin Transplant 2010;24(6):735-746. [doi: 10.1111/j.1399-0012.2010.01254.x] [Medline: 20438579]
6. Xiao D, Craig J, Chapman J, Dominguez-Gil B, Tong A, Wong G. Donor cancer transmission in kidney transplantation: a systematic review. Am J Transplant 2013 Oct;13(10):2645-2652 [FREE Full text] [doi: 10.1111/ajt.12430] [Medline: 24034231]
7. Strong DM, Fehily D, Noel L, WHO Collaborating Centre on Vigilance and Surveillance for Human Cells Tissue and Organs. Vigilance and Surveillance of Medical Products of Human Origin. In: The NOTIFY booklet. Italy: Centro Nazionale Trapianti (Italian National Transplant Centre); 2014 Presented at: WHO Conference on Medical Products of Human Origin (MPHO); December 2014; Bologna, Italy URL: https://www.notifylibrary.org/
8. Public Health Act 2010 No. 127. Sydney, NSW: NSW Ministry of Health; 2010.
9. Centre For Health Record Linkage. How record linkage works. URL: https://www.cherel.org.au/how-record-linkage-works [accessed 2019-09-15]
10. Borthwick A, Buechi M, Goldberg A. Key concepts in the Choicemaker 2 record matching system. In: Journal of Information Sciences. 2003 Presented at: Proceedings of the KDD-2003 Workshop on Data Cleaning, Record Linkage, and Object Consolidation; 2003; Washington DC p. pp28160. [doi: 10.4324/9780203420928-1]
11. Ison M, Hager J, Blumberg E, Burdick J, Carney K, Cutler J, et al. Donor-derived disease transmission events in the United States: data reviewed by the OPTN/UNOS Disease Transmission Advisory Committee. Am J Transplant 2009 Aug;9(8):1929-1935 [FREE Full text] [doi: 10.1111/j.1600-6143.2009.02700.x] [Medline: 19538493]
12. Green M, Covington S, Taranto S, Gross T, Wolfe C, Kaul D. Donor Derived Transmission Events in 2013: A Report of The OPTN Ad Hoc Disease Transmission Advisory Committee (DTAC). Transplantation 2014;98:164. [doi: 10.1097/00007890-201407151-00499]

Abbreviations

ANZCOTR: Australia and New Zealand Cardiothoracic Transplant Registry
ANZDATA: Australia and New Zealand Dialysis and Transplant Registry
ANZIPTR: Australia and New Zealand Islet and Pancreas Transplant Recipient Registry
ANZLTR: Australia and New Zealand Liver Transplant Registry
ANZOD: Australia and New Zealand Organ Donor Registry
APDC: NSW Admitted Patient Data Collection
CCR: NSW Central Cancer Register
CHeReL: Centre for Health Record Linkage
CI: chief investigator
COD URF: NSW Cause of Death Unit Record File
EDDC: NSW Emergency Department Data Collection
HIV: HIV Notifications and Surveillance Dataset
NCIMS: NSW Notifiable Conditions Information Management System
NOMS: National Organ Matching System
NSW: New South Wales, Australia
ORCHARD: Organ Donor Referral Characterisation Database
OTDS: Organ and Tissue Donation Service
PDDT: potential donor-derived disease transmission
RBDM: NSW Registry of Births, Deaths, and Marriages
SAFEBOD: Safety and Biovigilance in Organ Donation Study
SEALS: South Eastern Area Laboratory Services
TB: NSW Tuberculosis Contact Treatment Chest Clinics
WHO: World Health Organization

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Protocol

The Technical Feasibility of Integrating Primary Eye Care Into Primary Health Care Systems in Nigeria: Protocol for a Mixed Methods Cross-Sectional Study

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Abstract

Background: Approximately 90% of the 253 million blind or visually impaired people worldwide live in low- and middle-income countries. Lack of access to eye care is why most people remain or become blind. The World Health Organization Regional Office for Africa (WHO-AFRO) recently launched a primary eye care (PEC) package for sub-Saharan Africa—the WHO-AFRO PEC package—for integration into the health system at the primary health care (PHC) level. This has the potential to increase access to eye care, but feasibility studies are needed to determine the extent to which the health system has the capacity to deliver the package in PHC facilities.

Objective: Our objective is to assess the technical feasibility of integrating the WHO-AFRO PEC package in PHC facilities in Nigeria.

Methods: This study has several components, which include (1) a literature review of PEC in sub-Saharan Africa, (2) a Delphi exercise to reach consensus among experts regarding the technical complexity of the WHO-AFRO PEC package and the capacities needed to deliver it in PHC facilities, (3) development of PEC technical capacity assessment tools, and (4) data collection, including facility surveys and semistructured interviews with PHC staff and their supervisors and village health workers to determine the capacities available to deliver PEC in PHC facilities. Analysis will identify opportunities and the capacity gaps that need to be addressed to deliver PEC.

Results: Consensus was reached among experts regarding the technical complexity of the WHO-AFRO PEC package and the capacities needed to deliver it as part of PHC. Quantitative tools (ie, structured questionnaires, in-depth interviews, and observation checklists) and topic guides based on agreed-upon technical capacities have been developed and relevant stakeholders have been identified. Surveys in 48 PHC facilities and interviews with health professionals and supervisors have been undertaken. Capacity gaps are being analyzed.

Conclusions: This study will determine the capacity of PHC centers to deliver the WHO-AFRO PEC package as an integral part of the health system in Nigeria, with identification of capacity gaps. Although capacity assessments have to be context specific, the tools and findings will assist policy makers and health planners in Nigeria and similar settings, who are considering implementing the package, in making informed choices.

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KEYWORDS

primary eye care; primary health care; implementation; visual impairment; technical feasibility; feasibility study; health policy; Nigeria; World Health Organization Regional Office for Africa; WHO-AFRO

Introduction

Approximately 253 million people are blind or visually impaired worldwide, 90% of whom live in low- and middle-income countries (LMICs) [1]. In Nigeria, about 4.25 million adults are blind or visually impaired and over 80% of the blindness is due to avoidable causes [2,3]. Lack of access to eye care services is one of the reasons why people remain or become blind [4]. Cataracts are the most common cause of blindness in Nigeria [2], and high-quality cataract surgery should be accessible and affordable for all. However, in the Nigeria National Blindness and Visual Impairment Survey, almost half of all eyes that had undergone a procedure for cataract treatment had undergone couching—a traditional procedure to treat cataracts—often with poor visual outcomes. Glaucoma, which causes irreversible visual loss, was the second-most common cause of blindness [2]. Although early treatment can prevent or slow progression of the disease, in Nigeria people with glaucoma present very late to eye care services, often already blind in one or both eyes.

Other blinding-eye conditions in Nigeria include uncorrected refractive error [5], trachoma, and diabetic retinopathy. Presbyopia, the age-related decline in near vision, affects an estimated 20 million adults in Nigeria [6] and can lead to considerable productivity losses if uncorrected. Although blindness in children is rarer than in adults, many of the blinding conditions in LMICs, such as measles infection and vitamin A deficiency, can be prevented at the primary level [7,8].

Other eye conditions that cause ocular morbidity for which access to eye care is needed include dry, irritable eyes and allergic and infective conjunctivitis [9]. There is, therefore, a need for LMICs to provide universal access to eye care, not just for blinding conditions but also for conditions causing troublesome symptoms. Approximately 25% of Nigerians have ocular conditions [9]; with a population of 200 million, this means that approximately 50 million Nigerians are in need of eye care.

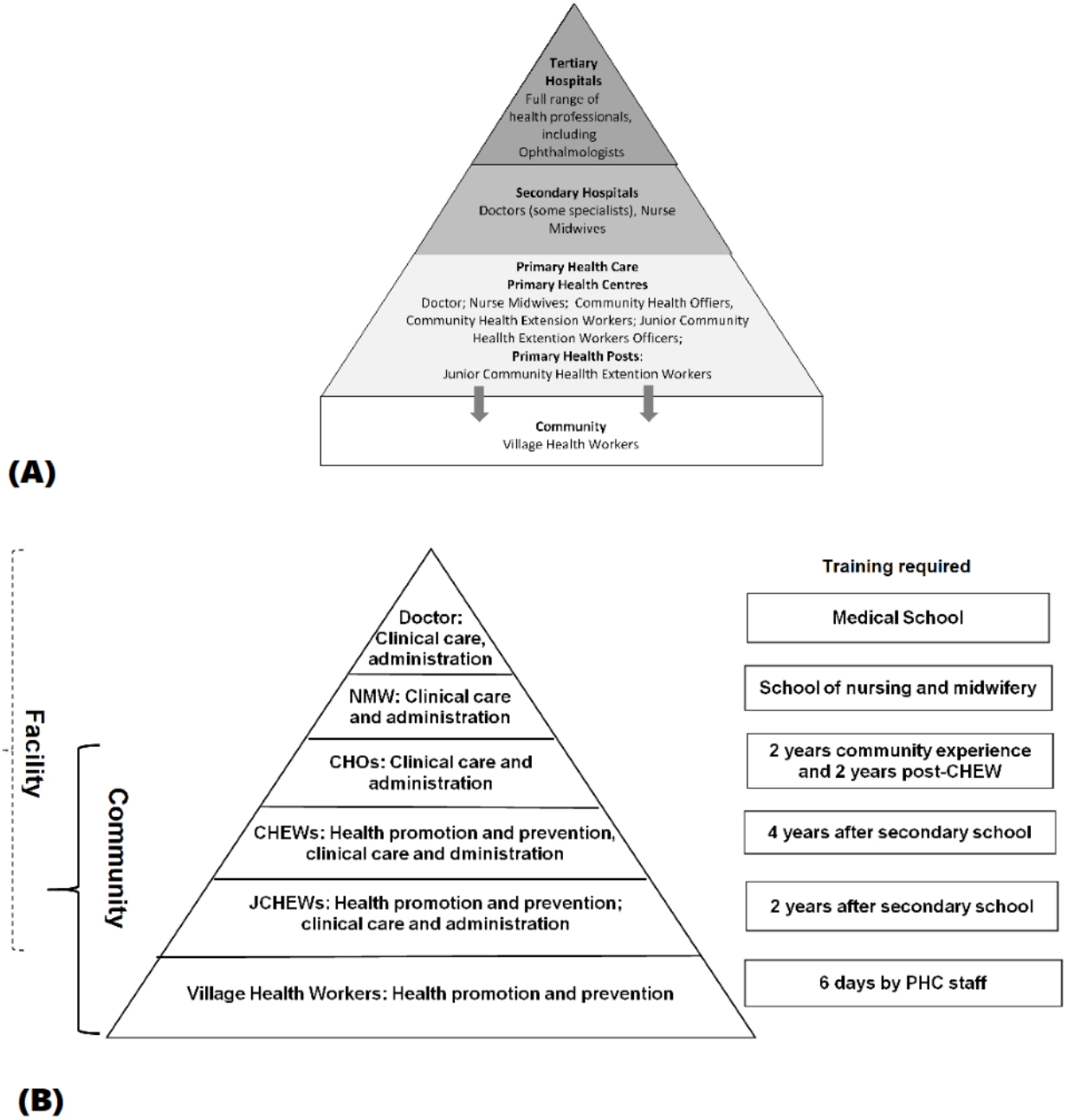
In LMICs, most eye care is delivered in secondary- and tertiary-level facilities, which are mainly located in urban areas. This leads to inequity in access, higher costs for patients and providers [10], and the patronage of other sources of care (eg, informal drugs sellers, traditional and spiritual healers, and couchers), which may exacerbate the visual loss through harmful practices or delayed access to appropriate treatment [9,11]. Over 35% of Nigerians with ocular problems consult an informal drug seller as a first option, primarily due to a lack of access to eye care services [9].

One way to improve access to eye care in LMICs is to integrate eye care into primary health care (PHC) [10], which is advocated by the World Health Organization (WHO) in their report Universal Eye Health: Global Action Plan 2014-2019 [12]. Primary eye care (PEC) entails the following elements: health protection, health promotion, specific preventive measures, detection and treatment of common eye conditions, detection and referral of more complex conditions, and record keeping. The health promotion elements can be delivered in the community as well as in facilities, while the other components principally take place in PHC facilities.

However, delivering PEC can have challenges; these include low PEC skill levels [13], inadequate supervision [14], and inadequate equipment and supplies [15]. A review of the literature on PEC in sub-Saharan Africa showed that there has been no consensus on the scope of PEC nor guidelines on the technical skills PHC workers require to implement eye care; this has resulted in deficient training and inadequate supervision [16]. To encourage uniformity of the scope of PEC in sub-Saharan Africa, the WHO Regional Office for Africa (WHO-AFRO) recently launched a package of evidence-based interventions for PEC: the WHO-AFRO PEC package [17]. The package can be subdivided into two broad elements: health promotion and facility-based eye care. The latter comprises five evidence-based algorithms and protocols on how to measure distance and near visual acuity, administer eye medication, remove foreign bodies, apply an eye patch, document findings, and refer and counsel patients. The purpose of the package is to strengthen the capacity of PHC workers in sub-Saharan Africa to manage patients with eye conditions [17] and widen access to eye care [18]. The package has been pilot-tested in Rwanda and Kenya [18].

In Nigeria, the health system has three tiers of service delivery—primary, secondary, and tertiary (see Figure 1, A)—staffed by appropriate cadres. The PHC system provides basic services and is often the first point of contact with the health system and the only source of health care for the majority of Nigerians in rural and remote communities [19]. PHC is delivered in health centers and smaller units called health posts. PHC staff comprise junior community health extension workers, community health extension workers (CHEWs), community health officers, and nurse midwives (see Figure 1, B).

Figure 1. Human resources for health in Nigeria (A) across the tiers of the health system and (B) at primary health care (PHC) facilities. CHEW: community health extension worker; CHO: community health officer; JCHEW: junior community health extension worker; NMW: nurse midwife.



Challenges of delivering PHC in Nigeria include, but are not limited to, shortage of health workers and absenteeism [20], infrastructural decay and poor funding [21], a dearth of basic equipment [22], and lack of trust in the system by the community [23]. Attempts have been made by nongovernmental organizations to implement PEC in some parts of Nigeria by training a limited number of staff using their own curricula and providing basic equipment. However, these initiatives were only scaled up with financial support in one state, so they were not scalable nor sustainable [24]. Nevertheless, to deliver an effective and sustainable intervention, it is important that feasibility studies are conducted in each implementation setting.

Feasibility research can help identify the opportunities and challenges in implementing a new health initiative, including PEC, which can only be as efficient as the PHC system into which it is built [16].

Feasibility is a complex construct [25], which has been defined in different ways. For example, Snowden et al define feasibility as encompassing the following domains: political, cultural, or community acceptability as well as technical, cost, and legal feasibility [26]. This study focuses on technical feasibility, which comprises the technical complexity of an intervention and the technical capacities needed to deliver it [27]. To our knowledge, no technical feasibility study in relation to PEC in

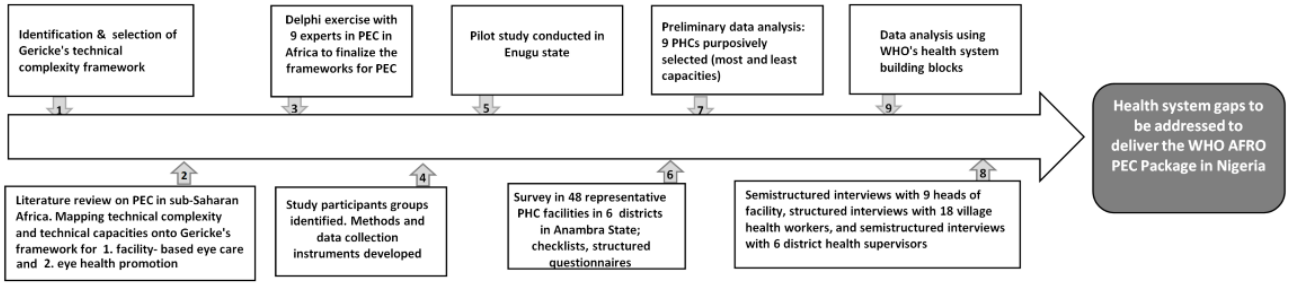
sub-Saharan Africa has been undertaken. Identifying the challenges, opportunities, and gaps in the technical capacities required will provide information for policy makers to make informed decisions about how the health system needs to be strengthened to deliver PEC as an integral component of PHC. The research is timely, as PHC reforms are currently underway in Nigeria, which include national policies to train primary-level staff and to provide essential drugs and consumables under the umbrella of Universal Health Coverage. These initiatives provide real opportunities to integrate PEC into PHC [24]. The overarching aim of this study is to determine the technical feasibility of implementing the WHO-AFRO PEC package into PHC facilities in Nigeria; in this paper, we describe, in detail, the methods to achieve this.

Methods

Overview

This study has several components, including a literature review on PEC in sub-Saharan Africa; a Delphi exercise to reach consensus among experts regarding the technical complexity of the WHO-AFRO PEC package and the capacities needed to deliver it in PHC facilities; development of PEC technical capacity assessment tools; and data collection, including facility surveys and semistructured interviews with PHC staff and their supervisors and village health workers (VHWs) to determine the capacities available to deliver PEC in PHC facilities (see Figure 2). Analysis will identify opportunities and the capacity gaps that need to be addressed to deliver PEC.

Figure 2. Flowchart of the study. PEC: primary eye care; PHC: primary health care; WHO-AFRO: World Health Organization Regional Office for Africa.



Components of the Study

Identification and Selection of Theoretical Framework

There are only a few analytical tools to assess the technical complexity of an intervention, one of which was proposed by Gericke et al [27]. This framework comprises four domains: (1) intervention characteristics, (2) delivery characteristics, (3) government capacity requirements, and (4) usage characteristics with criteria for each (see Table 1 [27]). A theoretical framework for assessing the technical feasibility of implementing the WHO-AFRO PEC package in PHC facilities in Nigeria has been designed by the investigators (see Figure 3 [27]), which builds on Gericke's framework of technical complexity [27]. This involves assessing the complexity of each component of the intervention and, from this, extrapolating to the technical capacities required to implement it. Analysis of the data collected will reveal the gaps that need to be addressed, which may be minimal or substantial. The size and nature of the gaps will determine the feasibility of implementing the intervention.

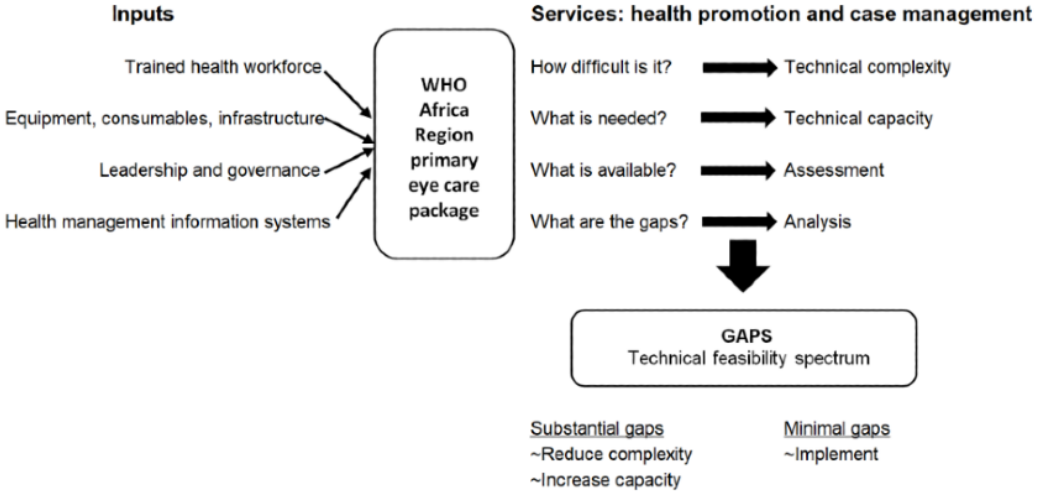
The Delphi method is a scientific, multistage approach to achieve consensus from combined expert opinion through a series of structured questionnaires completed anonymously. Advantages of the Delphi approach include anonymity and the achievement of consensus where definitive evidence is lacking [28,29].

A two-round Delphi exercise was used to build consensus on, first, the technical complexity of the WHO-AFRO PEC package and, second, the technical capacities required to implement it. The study was conducted over 5 months in 2018.

Table 1. Gericke et al's framework to assess the technical complexity of health interventions [27].

Category	Criteria
Intervention characteristics	
Basic product design	Stability
	Standardizability
	Safety profile
	Ease of storage
	Ease of transport
Supplies	Need for regular supplies
Equipment	High-technology equipment and infrastructure needed
	A number of different types of equipment needed
	Maintenance needed
Delivery characteristics	
Facilities	Retail sector
	Outreach services
	First-level care
	Hospital care
Human resources	Skill level required for service provision
	Skill level required for staff supervision
	Intensity of professional services in terms of frequency or duration
	Management and planning requirements
Communication and transport	Dependence of delivery on communication and transport infrastructure
Government capacity requirements	
Regulation and legislation	Need for regulation
	Need for monitoring regulatory measures and enforcement of regulation
Management systems	Need for sophisticated management systems
Collaborative action	Need for intersectoral action within government
	Need for partnership between government and external funding agencies
Usage characteristics	
Ease of use	Need for information and education
	Need for supervision
Pre-existing demand	Need for promotion
Black market risk	Need to prevent resale and counterfeiting

Figure 3. Theoretical framework for technical feasibility assessment derived from Gericke et al [27]. WHO: World Health Organization.



Literature Review of PEC in Sub-Saharan Africa and Mapping Onto the Appropriate Segment of Gericke's Framework to Form the Delphi Questionnaire

The WHO-AFRO PEC package was divided into two components: eye health prevention and promotion and facility-based case management. Gericke's framework was used to develop two questionnaires, one for health promotion and the other for facility-based care, which were entered into a Microsoft Excel 2016 spreadsheet.

In order to populate the two questionnaires, a literature search on PEC in sub-Saharan Africa was undertaken based on literature published in PubMed up to April 2018. Search terms included "primary eye care" and "sub-Saharan Africa." The bibliographies of the two most recent published reviews on PEC in sub-Saharan Africa were also reviewed [16,30]. A total of 173 articles were retrieved. Articles that were not related to PEC in sub-Saharan Africa were excluded, leaving 51 articles for inclusion, including 2 randomized trials.

Further implementation characteristics were identified by two of the authors (CG and AA) who have more than 40 years' combined experience in eye care in sub-Saharan Africa. These two sources yielded a list of key criteria for the technical complexity of PEC, which were used to populate the Delphi questionnaires. A 4-point Likert scale, ranging from 1 (strongly agree) to 4 (strongly disagree), was applied to each statement. The Delphi questionnaires were reviewed by an expert in international eye health (CG), a health interventions expert (HB), and a statistician (David MacCleod, London School of Hygiene & Tropical Medicine).

The Delphi Exercise

Selection of Experts for the Delphi Exercise

The main eligibility criteria for the Delphi panel included being an eye care professional with long-standing experience in community eye care in sub-Saharan Africa, preferably for a minimum of 10 years and who is still professionally active, and having experience in eye health policy. Panel members were selected by a modified, exponential, snowball-sampling method where an initial participant provides multiple referrals [31]. Each new referral was vetted and included in the study if the eligibility criteria were met.

Delphi Rounds

A total of 12 panel members were contacted by email and telephone, 9 of whom confirmed their willingness to take part. All 9 completed both rounds of the Delphi exercise.

For the first round, panel members were sent the following documents: the methods to be used during the Delphi exercise, an explanation of Gericke's framework of technical complexity, and the first pair of questionnaires on the technical complexities of PEC. Participants were invited to state their level of agreement with each statement by ticking the appropriate level in the Likert scale. A comments box was included beside each statement for comments or suggestions.

Once all the questionnaires had been received, they were analyzed for consensus, defined as at least 70% agreement on each statement in the upper-50th percentile (Likert scale scores of 1 and 2). Where consensus was reached, the statements were adopted. Statements where consensus was not reached were modified based on the suggestions and comments and were incorporated into the second round, as were newly identified statements.

For the second round, each of the agreed-upon statements on technical complexity were modified to reflect the technical capacities required for delivery, and Likert scales were added. Panel members were sent the questionnaires on technical capacities, which included the comments and suggestions of participants from the first round. Only statements that achieved consensus, as defined as above, were included in the final document. Any minority views (<70% consensus) were not adopted but were documented.

Development of PEC Technical Capacity Assessment Tools and Selection of Participant Groups

Overview

The technical capacities derived from the Delphi exercise were mapped onto the WHO's health systems framework, which comprises the health workforce, leadership and governance, financing, health management information systems, equipment, technology and infrastructure, and service delivery [32]. After reviewing the capacities needed, the optimal method of assessment was determined (ie, document review; structured questionnaires; observational checklists; in-depth interviews, using a structured topic guide; and the relevant participant groups: VHWs; PHC staff, including facility heads; CHEWs; and district supervisors) (see Table 2). Mixed methods were used to ensure a comprehensive understanding and to triangulate the data [33]. The instruments were developed in English and interviews were conducted in English, except for the VHW questionnaire, which was translated into Igbo and back-translated into English to ensure it retained its meaning.

Table 2. Methods of assessment for technical capacities and participants.

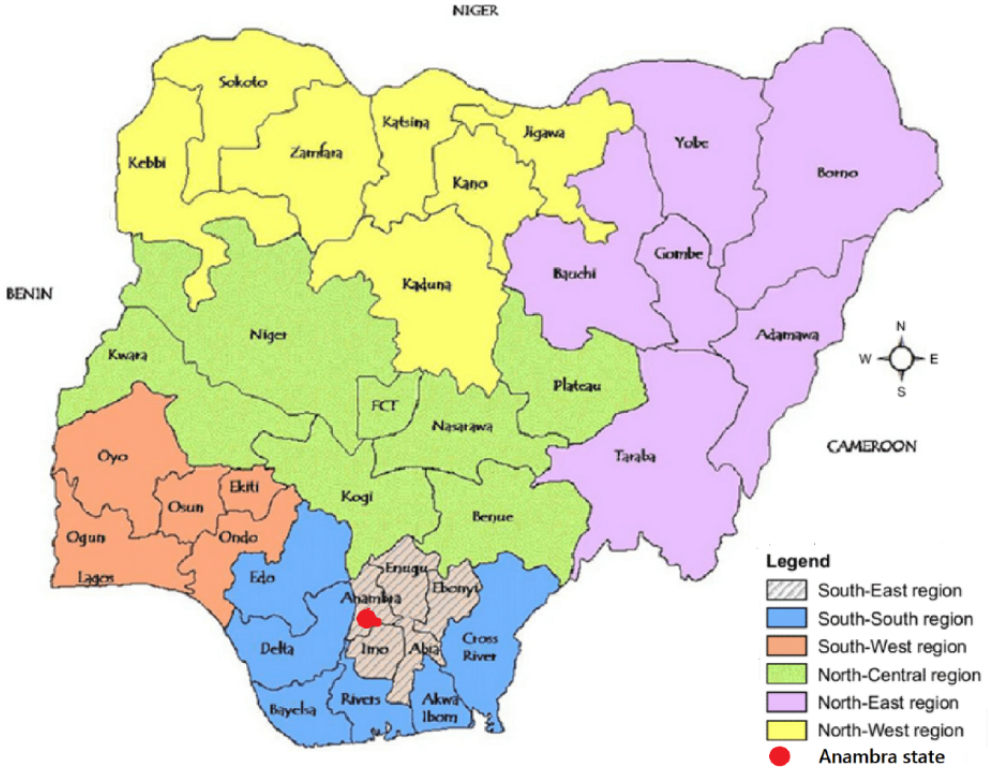
Assessment method	Participants	Data to be collected
Document review	N/A[a]	Policies that could support implementation of primary eye care (PEC)
In primary health care (PHC) facilities		
Structured questionnaire A	Heads of facilities, which can be any cadre	Facility practices that could support PEC implementation
Structured questionnaire B	Community health extension workers	Health promotion practices that could support PEC implementation
Observational checklist A	Heads of facilities	Equipment, consumables, infrastructure, and register data that could support PEC implementation in facilities
Observational checklist B	Community health extension workers	Equipment, consumables, infrastructure, and register data that could support health promotion of PEC
In purposively selected facilities		
In-depth interviews A	Heads of facilities	PHC experiences; extent to which PEC can be implemented in their facilities
Structured questionnaire C	Village health workers	Perspectives on PEC promotion and prevention
In each district		
In-depth interviews B	District PHC supervisors	PHC management experiences; extent to which PEC could be implemented in their districts

[a]N/A: not applicable; participants were not involved in the review of the document.

Study Area

Nigeria has 36 states in six geopolitical zones. Enugu State was selected for the pilot study and Anambra State for the main study, both of which are in the southeast zone (see Figure 4 [34]).

Figure 4. Map of Nigeria showing the six geopolitical zones and the 36 states [34].



Pilot Study in Enugu State

A pilot study was undertaken in three PHC facilities in one district in Enugu State to assess all the data collection instruments. Appropriate amendments were made to the study tools based on the responses of participants.

Main Study in Anambra State

Overview

Anambra state has 21 local government areas, or districts, which can be stratified into urban, semiurban, and rural. The main occupations are agriculture, manufacturing, and commerce. The literacy rate of individuals aged 6 years and older is 75.1% [35], and 11.3% are considered to be poor [36].

Participants

Participants included heads of facilities, CHEWs, district supervisors, and VHWs. If a facility had two or more CHEWs, one was randomly selected. Data to be collected from each participant group are summarized in Table 2. Facility surveys were undertaken in primary health centers and health posts.

Selection of Districts, Facilities, and Participants

As this was a descriptive study, a sample of 48 facilities was estimated for a baseline study to be sufficient to determine a prevalence of 50% of PHCs with the technical capacity to implement PEC, with a margin of error of 20% with a 95% confidence level, a cluster design effect of 1.8, and accounting for a 10% nonresponse rate [37].

Facilities for inclusion in the main study in Anambra State, which has 21 districts with 235 PHC centers and 112 health posts (ie, a ratio of 2:1), were selected using a two-stage process. First, a list of districts was drawn up, stratified by rural, semiurban, and urban location, to create a sampling frame. Six districts were selected by selecting the appropriate number within each stratum to represent their distribution (ie, three semiurban to two rural to one urban) using simple random sampling. Second, within each district a list of PHC facilities was obtained from the National Primary Health Care Development Agency. The number of facilities—PHC centers and health posts—within each stratum was selected by probability proportionate to size in each district and to represent the 2:1 distribution of health centers and health posts.

The principal researcher administered the head-of-facility questionnaires and facility observational checklists; trained research assistants administered the CHEW and VHW questionnaires and the health promotion observational checklists. Paper forms were used to collect the data.

Preliminary Data Analysis and Purposive Selection of Participants for Qualitative Interviews

Interim data analysis was undertaken using predetermined criteria (eg, the availability of regular supervision, availability and use of standard operating procedures [SOPs], health workforce strength, and number of patients attending the facilities). The highest- and lowest-scoring facilities were stratified by location (ie, urban, rural, or semiurban) and type of facility (ie, health center or health post).

Structured Interviews With VHWs and Semistructured Interviews With Facility Heads and District Supervisors

Based on the preliminary analysis, nine facilities (ie, six health centers and three health posts) were purposively selected. The principal researcher conducted in-depth interviews with the heads of these facilities using semistructured topic guides. A total of 2 VHWs from each of the nine facilities were also randomly selected, and the trained research assistants administered structured questionnaires. Finally, the principal investigator conducted in-depth interviews with the district supervisors of each of the six districts using semistructured topic guides. All the interviews were conducted in English apart from the questionnaires for VHWs, which were administered in the local language by bilingual research assistants.

Data Management

Overview

All the data from the two checklists and three questionnaires have been entered into specially prepared databases in Microsoft Access 2016 and transferred to Stata, version 15.1 (StataCorp LLC), using Stat/Transfer for analysis. Interviews with heads of facilities and district supervisors have been conducted and were recorded on an MP3 player. Verbatim transcription and reflection were ongoing during the interviews and evolving concepts were explored in subsequent interviews.

Quality assurance of data collection for the questionnaires was undertaken by training the research team with a daily debriefing. Each structured questionnaire was initialed by the research team member only when the form was correctly and completely filled out. For data entry, data validation rules were applied to the appropriate fields, which included range checks for numerical values. In addition, 10% of the questionnaires were randomly selected and data entry was cross-checked. During the semistructured interviews, the principal investigator was aware of her role as a benign interviewer and not a judgmental ophthalmologist. At the end of each interview, a summary of the participant's views was read to them for confirmation. The interview recordings were transcribed by the principal investigator and checked for errors or omissions by replaying the tapes.

All data have been stored in a backed-up hard drive in a password-encrypted laptop and in the institution's data repository (Filr) with controlled access limited to authorized users. Any data transferred through the internet have been encrypted. Data will be stored for 10 years to enable publications to be made from the data; they will then be deleted.

Data Analysis

Questionnaires and Checklists

Frequency tables will be generated from the data. Simple descriptive analyses will be performed (eg, the proportion of the facilities visited with tools for referrals). Existing capacities will be benchmarked against norms [38], when available (eg, staffing levels by cadre; SOPs; frequency of supervision; and some components of equipment, consumables, and medication, including systems to maintain the cold chain for vaccines). For indicators without norms, a descriptive analysis will be undertaken, benchmarking against the capacities required. The data will be analyzed based on the WHO health systems framework to highlight the elements that require strengthening.

In-Depth Interviews

Thematic analysis will be used to explore the data using OpenCode software, version 4.02. The data will be coded, categorized using the WHO health systems framework, and developed into themes. Data interpretation will be reviewed and discussed with the research team and qualitative experts. Final themes will be developed. The analysis will be supported by anonymized quotes from the data. Identification codes will be generated according to interview number, participant cadre, and type of facility. Reporting of the analysis of the interviews will follow COREQ (Consolidated Criteria for Reporting Qualitative Studies) guidelines [39].

Ethical Approval

Ethical approval was granted by the ethics review committees of the Federal Ministry of Health, Nigeria; the University of Nigeria Teaching Hospital; and the London School of Hygiene & Tropical Medicine. Written informed consent was obtained from each participant at the beginning of each interaction. For the interviews with heads of facilities and district supervisors, consent included permission to audio record the interviews and use anonymous quotes.

Results

Consensus was reached among experts during the Delphi exercise regarding the technical complexity of the WHO-AFRO PEC package and the capacities needed to deliver it in PHC facilities. Based on the agreed-upon technical capacities, quantitative tools have been developed and relevant stakeholders have been identified to assess the technical capacity of PHC facilities to deliver the WHO-AFRO PEC package (ie, structured questionnaires, observation checklists, and topic guides of in-depth interviews).

Results from the pilot study highlighted large gaps in human resources for health and supervision at the community level, and the study tools were amended to accommodate this. The pilot study involved staff in three health centers in one district in Enugu State. All the data collection tools were pilot-tested apart from the topic guide for supervisors and the structured questionnaire for VHWs, as they were not available. Only one change was made to data collection, which was that the main survey questionnaire be administered to the appropriate cadre, as health promotion was mainly undertaken by a different cadre than anticipated.

Key findings were that none of the facilities had the full complement of staff, and none had a doctor or nurse midwife. The only in-service training that staff had received in the previous 12 months was in child health, maternal health, and HIV. Regarding health promotion, in each facility senior members of staff were providing health promotion in the community, which focused almost exclusively on maternal and child health. The only health promotion topic of relevance to eye care was not to self-medicate. The only form of transport provided to visit communities was a motorbike in one facility. No facility used forms for referral, which was done verbally. For facility-based management, all three were observed to have standing orders, and all reported supervision to be irregular. The main focus of the services delivered was maternal and child health, and none provided any eye care. Two facilities were able to test blood sugar, and none provided services for the elderly. In relation to equipment for eye care, one facility had a visual acuity chart, none had flashlights, and only one had antibiotic eye ointment. The facility survey in 48 PHC facilities has been completed as planned, and interviews with district supervisors and facility heads of the nine purposively selected facilities have been undertaken.

Capacities to deliver PEC are being analyzed, and gaps are being identified. Findings from all sources will be reviewed, including from the desk review of guidelines and policy documents. The convergence of findings will highlight whether gaps in the capacity to deliver PEC are due to limitations in the national guidelines or policies and/or whether they are due to limitations in the current delivery of PHC at district and/or facility levels.

Discussion

This is the first study, to our knowledge, to assess the technical feasibility of integrating eye care into PHC in sub-Saharan Africa and the extent to which the health system needs to be strengthened to deliver it. An alternative approach to facilitate implementation in low-capacity settings would be to adapt the PEC package. There has been renewed interest in assessing the integration of services into health systems in LMICs [40], and the results from this study will be central to enabling policy makers to make an informed choice about what needs to be done to implement PEC in Nigeria.

The development of a conceptual framework for assessing health system interventions is important [41]. This study builds upon the technical complexity framework of Gericke to incorporate technical capacity assessments and will report a gap analysis in the system based on the WHO health systems framework. It is critical that countries implementing or scaling up new interventions have access to reliable, accurate, and comprehensive data on capacities and gaps in the system to deliver an equitable [42] and sustainable intervention. This study provides tools that could be adapted or modified for use in other countries in the region that plan to deliver the WHO-AFRO PEC package.

A limitation of the study is that it only addresses technical feasibility; other aspects of feasibility as delineated by Snowden, such as cultural, legal, financial, and political feasibility, may also need to be addressed. In addition, the assessment tools are cadre specific and designed for the Nigerian PHC context and may not be applicable to other settings. In this study, the sample size was 48 facilities. The study may not have been powered sufficiently to assess any capacity differences between health centers and health posts.

Results of the study will be disseminated to stakeholders in PHC and eye care in Nigeria by communique at stakeholders' meetings and at local, national, and international ophthalmology and public health conferences, as well as in peer-reviewed journals.

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Authors' Contributions

AA and CG conceived the study. AA, CG, HB, and JW made substantial contributions to the study design. AA, CG, HB, and SH designed the study tools. AA was responsible for data collection as part of the fulfilment for a research degree. CG and HB supervised the work. All authors made contributions and agreed to the final draft.

Conflicts of Interest

None declared.

References

1. Bourne R, Flaxman S, Braithwaite T, Cicinelli MV, Das A, Jonas JB, Vision Loss Expert Group. Magnitude, temporal trends, and projections of the global prevalence of blindness and distance and near vision impairment: A systematic review and meta-analysis. Lancet Glob Health 2017 Sep;5(9):e888-e897 [FREE Full text] [doi: 10.1016/S2214-109X(17)30293-0] [Medline: 28779882]
2. Abdull MM, Sivasubramaniam S, Murthy GVS, Gilbert C, Abubakar T, Ezelum C, Nigeria National Blindness and Visual Impairment Study Group. Causes of blindness and visual impairment in Nigeria: The Nigeria National Blindness and Visual Impairment Survey. Invest Ophthalmol Vis Sci 2009 Sep;50(9):4114-4120. [doi: 10.1167/iovs.09-3507] [Medline: 19387071]
3. Kyari F, Gudlavalleti MVS, Sivsubramaniam S, Gilbert CE, Abdull MM, Entekume G, Nigeria National Blindness and Visual Impairment Study Group. Prevalence of blindness and visual impairment in Nigeria: The National Blindness and Visual Impairment Study. Invest Ophthalmol Vis Sci 2009 May;50(5):2033-2039. [doi: 10.1167/iovs.08-3133] [Medline: 19117917]
4. Gilbert CE, Shah SP, Jadoon MZ, Bourne R, Dineen B, Khan MA, Pakistan National Eye Survey Study Group. Poverty and blindness in Pakistan: Results from the Pakistan National Blindness and Visual Impairment Survey. BMJ 2008 Jan 05;336(7634):29-32 [FREE Full text] [doi: 10.1136/bmj.39395.500046.AE] [Medline: 18087076]
5. Ezelum C, Razavi H, Sivasubramaniam S, Gilbert CE, Murthy GVS, Entekume G, Nigeria National Blindness and Visual Impairment Study Group. Refractive error in Nigerian adults: Prevalence, type, and spectacle coverage. Invest Ophthalmol Vis Sci 2011 Jul 23;52(8):5449-5456. [doi: 10.1167/iovs.10-6770] [Medline: 21330658]
6. Fricke TR, Tahhan N, Resnikoff S, Papas E, Burnett A, Ho SM, et al. Global prevalence of presbyopia and vision impairment from uncorrected presbyopia: Systematic review, meta-analysis, and modelling. Ophthalmology 2018 Oct;125(10):1492-1499 [FREE Full text] [doi: 10.1016/j.ophtha.2018.04.013] [Medline: 29753495]
7. Aghaji AE, Duke R, Aghaji UCW. Inequitable coverage of vitamin A supplementation in Nigeria and implications for childhood blindness. BMC Public Health 2019 Mar 08;19(1):282 [FREE Full text] [doi: 10.1186/s12889-019-6413-1] [Medline: 30849959]
8. Malik ANJ, Mafwiri M, Gilbert C. Integrating primary eye care into global child health policies. Arch Dis Child 2018 Feb;103(2):176-180. [doi: 10.1136/archdischild-2017-313536] [Medline: 28988214]
9. Senyonjo L, Lindfield R, Mahmoud A, Kimani K, Sanda S, Schmidt E. Ocular morbidity and health seeking behaviour in Kwara state, Nigeria: Implications for delivery of eye care services. PLoS One 2014;9(8):e104128 [FREE Full text] [doi: 10.1371/journal.pone.0104128] [Medline: 25165984]
10. Blanchet K, Gilbert C, de Savigny D. Rethinking eye health systems to achieve universal coverage: The role of research. Br J Ophthalmol 2014 Oct;98(10):1325-1328. [doi: 10.1136/bjophthalmol-2013-303905] [Medline: 24990874]
11. Onwubiko S, Eze B, Udeh N, Arinze OC, Okoloagu MN, Chuka-Okosa CM. Mapping the pathways to eye care in a rural south-east Nigerian population: Any implications for practice, eye care programs and policy? Rural Remote Health 2014;14(4):2729 [FREE Full text] [Medline: 25382094]
12. World Health Organization. Universal Eye Health: A Global Action Plan 2014-2019. Geneva, Switzerland: World Health Organization; 2013. URL: https://apps.who.int/iris/rest/bitstreams/489293/retrieve [accessed 2020-10-03]
13. Kalua K, Gichangi M, Barassa E, Eliah E, Lewallen S, Courtright P. Skills of general health workers in primary eye care in Kenya, Malawi and Tanzania. Hum Resour Health 2014;12 Suppl 1:S2 [FREE Full text] [doi: 10.1186/1478-4491-12-S1-S2] [Medline: 25860909]

14. Byamukama E, Courtright P. Knowledge, skills, and productivity in primary eye care among health workers in Tanzania: Need for reassessment of expectations? Int Health 2010 Dec;2(4):247-252. [doi: 10.1016/j.inhe.2010.07.008] [Medline: 24037865]
15. Mafwiri MM, Jolley E, Hunter J, Gilbert CE, Schmidt E. Mixed methods evaluation of a primary eye care training programme for primary health workers in Morogoro Tanzania. BMC Nurs 2016;15:41 [FREE Full text] [doi: 10.1186/s12912-016-0163-5] [Medline: 27390550]
16. Courtright P, Seneadza A, Mathenge W, Eliah E, Lewallen S. Primary eye care in sub-Saharan African: Do we have the evidence needed to scale up training and service delivery? Ann Trop Med Parasitol 2010 Jul;104(5):361-367. [doi: 10.1179/136485910X12743554760225] [Medline: 20819303]
17. World Health Organization. Regional Office for Africa. Primary Eye Care Training Manual: A Course to Strengthen the Capacity of Health Personnel to Manage Eye Patients at Primary-Level Health Facilities in the African Region. Brazzaville, Republic of Congo: World Health Organization. Regional Office for Africa; 2018. URL: https://www.afro.who.int/publications/primary-eye-care-training-manual
18. Graham R. Facing the crisis in human resources for eye health in sub-Saharan Africa. Community Eye Health 2017;30(100):85-87 [FREE Full text] [Medline: 29483753]
19. National Primary Health Care Development Agency, Federal Republic of Nigeria. National Guidelines for Development of Primary Health Care System in Nigeria. 4th edition. Abuja, Nigeria: National Primary Health Care Development Agency; 2012.
20. Abimbola S, Olanipekun T, Igbokwe U, Negin J, Jan S, Martiniuk A, et al. How decentralisation influences the retention of primary health care workers in rural Nigeria. Glob Health Action 2015;8:26616 [FREE Full text] [doi: 10.3402/gha.v8.26616] [Medline: 25739967]
21. Chukwuani CM, Olugboji A, Akuto EE, Odebunmi A, Ezeilo E, Ugbene E. A baseline survey of the primary healthcare system in South Eastern Nigeria. Health Policy 2006 Jul;77(2):182-201. [doi: 10.1016/j.healthpol.2005.07.006] [Medline: 16107291]
22. Bhatnagar A, Gupta S, Alonge O, George AS. Primary health care workers' views of motivating factors at individual, community and organizational levels: A qualitative study from Nasarawa and Ondo states, Nigeria. Int J Health Plann Manage 2017 Apr;32(2):217-233. [doi: 10.1002/hpm.2342] [Medline: 27062268]
23. Abdulraheem IS, Olapipo AR, Amodu MO. Primary health care services in Nigeria: Critical issues and strategies for enhancing the use by the rural communities. J Public Health Epidemiol 2012 Jan;4(1):5-13 [FREE Full text] [doi: 10.5897/JPHE11.133]
24. Aghaji AE, Gilbert C, Ihebuzor N, Faal H. Strengths, challenges and opportunities of implementing primary eye care in Nigeria. BMJ Glob Health 2018;3(6):e000846. [doi: 10.1136/bmjgh-2018-000846] [Medline: 30613423]
25. Bowen DJ, Kreuter M, Spring B, Cofta-Woerpel L, Linnan L, Weiner D, et al. How we design feasibility studies. Am J Prev Med 2009 May;36(5):452-457 [FREE Full text] [doi: 10.1016/j.amepre.2009.02.002] [Medline: 19362699]
26. Snowdon W, Lawrence M, Schultz J, Vivili P, Swinburn B. Evidence-informed process to identify policies that will promote a healthy food environment in the Pacific Islands. Public Health Nutr 2010 Jun;13(6):886-892. [doi: 10.1017/S136898001000011X] [Medline: 20196907]
27. Gericke C, Kurowski C, Ranson M, Mills A. Intervention complexity--A conceptual framework to inform priority-setting in health. Bull World Health Organ 2005 Apr;83(4):285-293 [FREE Full text] [Medline: 15868020]
28. Hohmann E, Brand J, Rossi M, Lubowitz J. Expert opinion is necessary: Delphi panel methodology facilitates a scientific approach to consensus. Arthroscopy 2018 Feb;34(2):349-351. [doi: 10.1016/j.arthro.2017.11.022] [Medline: 29413182]
29. Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. J Adv Nurs 2000 Oct;32(4):1008-1015. [Medline: 11095242]
30. du Toit R, Faal HB, Etya'ale D, Wiafe B, Mason I, Graham R, et al. Evidence for integrating eye health into primary health care in Africa: A health systems strengthening approach. BMC Health Serv Res 2013 Mar 18;13:102 [FREE Full text] [doi: 10.1186/1472-6963-13-102] [Medline: 23506686]
31. Dudovskiy J. Snowball sampling. Business Research Methodology. 2019. URL: https://research-methodology.net/sampling-in-primary-data-collection/snowball-sampling/ [accessed 2020-10-03]
32. Mounier-Jack S, Griffiths UK, Closser S, Burchett H, Marchal B. Measuring the health systems impact of disease control programmes: A critical reflection on the WHO building blocks framework. BMC Public Health 2014 Mar 25;14:278 [FREE Full text] [doi: 10.1186/1471-2458-14-278] [Medline: 24666579]
33. Ozawa S, Pongpirul K. 10 best resources on ... mixed methods research in health systems. Health Policy Plan 2014 May;29(3):323-327. [doi: 10.1093/heapol/czt019] [Medline: 23564372]
34. NIMC enrolment centres. National Identity Management Commission. 2019. URL: https://www.nimc.gov.ng/nimc-enrolment-centres [accessed 2019-07-18]
35. United Nations Educational Scientific Cultural Organization (UNESCO). Reaching the 2015 literacy target: Delivering on the promise. In: Proceedings of the High level International Round Table on Literacy. Paris, France: UNESCO; 2012 Presented at: High level International Round Table on Literacy; September 6-7, 2012; Paris, France p. 1-3 URL: https://unesdoc.unesco.org/ark:/48223/pf0000217802

36. University of Oxford. Global Multidimensional Poverty Index (MPI) Interactive Databank. University of Oxford. 2016. URL: http://www.dataforall.org/dashboard/ophi/index.php/ [accessed 2016-10-20]
37. Health Facility Assessment Sampling: Appropriate Methods for Small N. Geneva, Switzerland: The Global Fund; 2016 Feb 24. URL: https://www.scribd.com/document/478793819/Sample-Size-Phcs [accessed 2020-10-05]
38. National Primary Health Care Development Agency, Federal Ministry of Health. Minimum Standards for Primary Health Care in Nigeria. Abuja, Nigeria: National Primary Health Care Development Agency, Federal Government of Nigeria; 2015. URL: https://hfr.health.gov.ng/resources/download/Minimum%20Standards%20for%20Primary%20Health%20Care%20in%20Nigeria.pdf [accessed 2020-10-03]
39. Tong A, Sainsbury P, Craig J. Consolidated Criteria for Reporting Qualitative Research (COREQ): A 32-item checklist for interviews and focus groups. Int J Qual Health Care 2007 Dec;19(6):349-357. [doi: 10.1093/intqhc/mzm042] [Medline: 17872937]
40. Topp S, Abimbola S, Joshi R, Negin J. How to assess and prepare health systems in low- and middle-income countries for integration of services: A systematic review. Health Policy Plan 2018 Mar 01;33(2):298-312 [FREE Full text] [doi: 10.1093/heapol/czx169] [Medline: 29272396]
41. Adam T, Hsu J, de Savigny D, Lavis JN, Røttingen JA, Bennett S. Evaluating health systems strengthening interventions in low-income and middle-income countries: Are we asking the right questions? Health Policy Plan 2012 Oct;27 Suppl 4:iv9-iv19 [FREE Full text] [doi: 10.1093/heapol/czs086] [Medline: 23014156]
42. Nickerson JW, Adams O, Attaran A, Hatcher-Roberts J, Tugwell P. Monitoring the ability to deliver care in low- and middle-income countries: A systematic review of health facility assessment tools. Health Policy Plan 2015 Jun;30(5):675-686 [FREE Full text] [doi: 10.1093/heapol/czu043] [Medline: 24895350]

Abbreviations

CHEW: community health extension worker
COREQ: Consolidated Criteria for Reporting Qualitative Studies
LMICs: low- and middle-income countries
PEC: primary eye care
PHC: primary health care
SOP: standard operating procedure
VHW: village health worker
WHO: World Health Organization
WHO-AFRO: World Health Organization Regional Office for Africa

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Protocol

Rationale and Design of the Women's Health And Daily Experiences Project: Protocol for an Ecological Momentary Assessment Study to Identify Real-Time Predictors of Midlife Women's Physical Activity

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Abstract

Background: Midlife women are at an elevated risk for cardiovascular disease (CVD) and associated mortality. Those who have additional risk conditions such as obesity or hypertension report specific barriers to engaging in cardioprotective behaviors such as physical activity (PA). Considerable effort has been devoted to understanding PA determinants and designing interventions for midlife women, although with suboptimal success, as increasing PA could meaningfully attenuate CVD risk. An updated approach to understanding PA among midlife women could improve upon existing resources by focusing on novel psychosocial influences on PA in this population (ie, body satisfaction, social interactions, social comparisons, mood state) and within-person relations between these influences and PA in the natural environment.

Objective: The overarching goal of Project WHADE (Women's Health And Daily Experiences) is to use an ecological momentary assessment (EMA) approach to capture ecologically valid relations between midlife women's psychosocial experiences and PA as they engage in their normal daily activities. The primary aim of the study is to identify within-person psychosocial predictors of variability in PA (ie, experiences associated with higher vs lower PA for a given individual).

Methods: Midlife women (aged 40-60 years) with one or more additional risk markers for CVD (eg, hypertension) will be recruited from primary care clinics and the general community (target n=100). Eligible women will complete an initial survey and a face-to-face baseline session before engaging in a 10-day EMA protocol. Psychosocial experiences will be assessed using a brief self-report via a smartphone 5 times per day, and PA will be assessed throughout waking hours using a research-grade monitor. Participants will return for a brief exit interview at the end of 10 days. Multilevel models that address the nested structure of EMA data will be used to evaluate the study aims.

Results: Recruitment and enrollment are ongoing, and a total of 75 women have completed the protocol to date. Data collection is expected to be completed in Fall 2020.

Conclusions: Project WHADE is designed to identify naturally occurring psychosocial experiences that predict short-term variability in midlife women's PA. As such, the results of this study should advance the current understanding of PA among midlife women by providing further insight into within-person psychosocial influences on PA in this group. In the future, this information could help inform the design of interventions for this population.

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KEYWORDS

women's health; midlife; cardiovascular risk; physical activity; ecological momentary assessment; mobile phone

Introduction

This paper describes the rationale and design of Project WHADE (Women's Health And Daily Experiences), an intensive, observational study designed to improve upon the current understanding of midlife women's physical activity (PA) and inform PA interventions designed for this population. Midlife women (age 40-60 years [1]) currently account for the largest subset of US health care expenditures compared with other gender and age groups examined [2]. Much of their health care costs are associated with risk for cardiovascular disease (CVD), including conditions such as hypertension and type 2 diabetes [3]. During midlife, meaningful gender differences emerge with respect to CVD risk. For example, the onset of menopause confers a direct biological risk for women [4,5]. The risk of mortality from CVD events also increases more sharply for midlife women than men [6,7], in part because of gender differences in symptom presentation and concerns about seeking medical attention [8-11]. A focus on promoting cardioprotective behaviors among midlife women, particularly those who have additional risk factors for CVD (eg, hypertension), could help mitigate this gender disparity and reduce CVD mortality among women.

PA is a cardioprotective behavior known to attenuate CVD risk, as adequate levels of PA contribute to reducing CVD risk factors such as waist circumference and blood pressure [12] and improving metabolic functioning [13,14], particularly among women [15-17]. Despite these benefits, the gender difference in PA that is observed across the lifespan (with men engaging in more PA than women) widens during midlife [18,19]; many midlife women fall far short of the PA thresholds recommended for health [20,21] and are difficult to engage in PA programs [22]. Midlife women with additional CVD risk factors (eg, overweight or obesity, hypertension) tend to report low motivation for PA and a variety of barriers to PA engagement, such as difficulty with time amid professional responsibilities and family care (as primary caregivers) [23,24]. PA promotion work focused on addressing barriers such as lack of time and motivation (both among midlife women and in other populations) has generated meaningful insights but has not yet led to large PA increases that are sustained over time [25,26].

Increasing PA thus remains to be an important avenue for reducing midlife women's risk for CVD, and using new approaches to understanding facilitators of and barriers to PA could meaningfully improve intervention efforts for this group. Project WHADE addresses this need in 2 ways. First, by focusing on midlife women's psychosocial experiences that are indicated by both theory and evidence to serve as facilitators and barriers to their PA but are understudied in this group. These include *body satisfaction*, *perceptions of social interactions*, *social comparisons*, and *mood states*. Second, by assessing proposed predictors of PA at the *within-person* level (ie, fluctuations within the same person over short periods) rather than the between-person level (ie, global reports or averages across time). The typical approach to estimating PA engagement and its psychosocial correlates is for participants to wear a PA monitor for several days and then to average their PA across days of monitor wear to generate a between-person estimate. These averages are correlated with trait- or person-level psychosocial characteristics (eg, global level of motivation for PA or social support) to determine the type or types of individuals who do and do not achieve recommended levels of PA [27]. Interventions are then designed to address the person-level characteristics associated with low PA [28].

This approach assumes that the observed relations at the between-person level (which describes differences between people) correspond to the within-person level (which describes changes in the same person over a given time frame). In many cases, this assumption is incorrect. For example, although *individuals* who engage in PA more (vs less) often have lower resting heart rates, *when* a given individual engages in PA (vs sedentary behavior), their heart rate increases rather than decreases [29]. Similar discrepancies may exist concerning between- versus within-person relations between psychosocial experiences and PA; for instance, people who generally experience more (vs less) body satisfaction may also engage in more PA, although their PA may actually *decrease* at times when they experience more (vs less) body satisfaction. Failure to differentiate these processes and thus assuming the incorrect direction of a relation between a predictor and a health outcome such as PA could lead to inaccurate models of behavior change and ineffective interventions that are based on these models. In line with the body satisfaction example mentioned earlier, the between-person relation between body satisfaction and PA would suggest that improving an individual's body image should improve their PA, whereas within-person relations suggest the opposite effect. Thus, clarifying between- versus within-person relations between midlife women's psychosocial experiences and PA could improve both PA theory and interventions specific to this population [30] by more accurately specifying the levels and directions of these relations and the associated mechanisms for increasing PA. To this end, this study was designed to differentiate between- and within-person relations between midlife women's PA and their naturalistic experiences of body satisfaction, perceptions of social interactions, social comparisons, and mood state.

Facilitators and Barriers: Novel Psychosocial Influences on Midlife Women's PA

Accumulating evidence shows the importance of specific psychosocial facilitators of and barriers to PA for midlife women that differ from those of men [31-33]. We first describe the psychosocial processes hypothesized to influence midlife

women's PA (which have received less attention in this group than motivation or time management) and then detail the within-person approach in Project WHADE to assessment and the associated rationale.

In line with multiple theoretical models of health behavior and behavior change processes [34,35] and their evidence bases as mechanisms of behavior change [36-40], critical psychosocial influences on PA include *body satisfaction*, *social interactions*, *social comparisons*, and *mood state*. For example, social cognitive theory is an overarching framework that emphasizes self-perceptions, emotions, and behavior in the context of input from the social environment, including perceived norms and modeling [34]. Social comparison theory expands on a particular aspect of social influence to explain how self-evaluations relative to others can motivate (or demotivate) health behaviors such as PA [35]. At present, however, relations between these experiences and PA rarely are captured using within-person methods, particularly among midlife women. Differentiating within- versus between-person relations between midlife women's psychosocial experiences and PA would help to clarify whether and in what ways these experiences predict PA.

Body Satisfaction

Across the lifespan, women are more likely than men to use PA to manage weight or appearance [41,42]. Although physical changes (eg, weight gain) consequent to childbirth, aging, and menopause may make body satisfaction uniquely important for midlife women [43,44], most of the research on the relation between body satisfaction and PA has focused on younger women. This work has shown that PA may be most likely to occur in response to dissatisfaction with one's weight or shape [45], as women may be motivated to engage in PA with the expectation that it will reduce weight or otherwise improve their appearance. However, among overweight women, embarrassment, shame, and fear of judgment from others often lead to PA avoidance rather than engagement [46,47]. Feeling satisfied with one's body—a positive state that many interventions attempt to promote—also has been associated with future *decreases* in PA among young women [45]. Although body satisfaction traditionally has been conceptualized and measured as a stable difference between individuals, ample evidence indicates that body satisfaction fluctuates over short time frames and changes in response to context shifts [48] and deliberate intervention [49]. Ecological momentary assessment (EMA) methods have been used in several studies to assess within-person variability in body satisfaction among young women [50] but rarely have been employed among midlife women.

Thus, it appears that the relation between body satisfaction and PA is complex. Both high and low satisfaction could motivate PA, and the circumstances that determine the direction of the association are not yet clear, especially as they pertain to midlife women's experiences in their natural environments. Furthermore, engaging in PA for appearance-related reasons is associated with worse physiological health [51] and a lower likelihood of maintaining PA in the long-term compared with engaging in PA for enjoyment or health [52,53]. As such, a better understanding of how this relation manifests in midlife women's daily lives could eventually help to promote both healthy perceptions of one's body and healthy engagement in PA.

Social Interactions

For many individuals, interactions with other people occur on and off throughout the day; some interactions are more meaningful than others, in that they prompt consequential thoughts, emotions, or behaviors, whereas other interactions have little detectable effect on these outcomes [54]. Emerging evidence suggests that perceptions of social interactions influence PA in that self-reports of individuals' interpretations of the interaction or assessment of the positivity or negativity of the experience is associated with PA engagement [55]. Social influence may be exerted directly, via encouragement or discouragement of PA and other healthy behaviors, or may occur indirectly through creating norms (for or against PA) or limiting time or motivation for PA (eg, if negative interactions lead to stress or necessitate problem solving) [34,56]. For example, engaging in PA is a method for coping with negative experiences [41,42,57], including those that result from unpleasant social interactions, and women are more likely than men to use PA to cope with stress [58,59]. However, stronger (vs weaker) perceptions of positive social interactions are associated with adults' future PA engagement [60], and within-person, older adults have been shown to engage in PA at times when they report positive (but not negative) social interactions [61]. Thus, limited evidence shows that positive social interactions are associated with PA engagement; the role of negative interactions is less clear, and the conditions under which either type of interaction facilitates versus hinders PA have yet to be pinpointed.

In addition, the role of social interactions in PA appears to differ between women and men. Among adolescents and young adults, women cite the influence of social interactions on their PA decisions more often than men [62], although women perceive less support for PA from their family and peers compared with men [63,64]. Research focused on young women also indicates that positive interactions tend to motivate PA, whereas negative interactions tend to increase stress and interfere with PA [62,65] and show that greater objectively assessed PA occurs on days with more (vs less) positive social interactions and less (vs more) negative interactions [55]. To date, however, this work has spanned several distinct characteristics of social interaction, including the presence versus absence of interactions, number of interactions in a given time frame, and the perceived positivity or negativity of a single interaction or set of interactions.

Moreover, although the social benefits of PA are also rated as more important among older versus younger women [66] and are consistently associated with PA during midlife [31,33,52], critical aspects of the relations between social interactions and PA remain to be unclear. Specifically, whether a within-person relations between social interactions and PA among midlife women is driven by positive or negative interactions (or both, independently or under different circumstances) and whether it is the *quantity* of either type of interaction or the perceived intensity (*quality*) of the interactions that drives these effects. These characteristics have been differentially associated with

health and well-being outcomes in a range of populations [67-69]. As such, assessing their within-person relations with PA among midlife women would help to clarify the roles of distinct aspects of social interactions.

Social Comparisons

Social comparisons, or self-evaluations relative to others, represent an additional facet of social perception that may influence PA among midlife women. Comparisons with others are common in daily life and can be made across a range of domains (eg, appearance, wealth, work performance, health behaviors) and communication modes (eg, in person, via phone, via a social media platform) [70]. Social comparisons can have stronger effects on self-concept and behavior than comparisons with objective standards [71,72], and reported engagement in comparison shows both cross-sectional and prospective relations with health outcomes [35,73,74].

With respect to PA, social comparison may provide motivation via learning about discrepancies between one's own PA engagement and that of others [61]. For example, comparisons with others viewed as doing better than the self (ie, upward comparisons) could indicate that improvement is possible and provide guidance and inspiration for achieving a similar goal [75]. Conversely, comparisons with others viewed as doing worse than the self (ie, downward comparisons) could boost self-efficacy for achievement and motivate behavior maintenance to avoid becoming like the worse-off other [76].

Experimental exposure to PA-based social comparison opportunities (eg, PA leaderboards, step competitions) shows positive group-level effects on subsequent PA and outperforms behavior change techniques such as enhancing social support when individuals are experimentally exposed to only 1 technique [77-79]. Such comparisons may be more influential for women than men; women report greater attention to [80] and interest in role models [46,47] and show stronger positive responses to same-gender role models [81] than men. Exposure to others engaged in PA also increases the likelihood that women will engage in PA, but this association is not observed among men [80]. Among young women, one's tendency to make comparisons has been shown to change over 2 months, and this change mediates the effect of a brief intervention on unhealthy behaviors (eg, disordered eating and excessive exercise) [82]. Young women also show an ability to differentiate days and periods during which they recall making (vs not making) comparisons, and these distinctions are differentially associated with self-reported and objectively assessed PA [55,83]. Furthermore, shifts in the frequency of women's PA-based social comparison opportunities from week to week are associated with changes in their PA over the same time frame [84].

However, not all individuals respond positively to social comparison opportunities [85], and the same individual may vary in their responses to comparisons over time [86]. In addition to the potential positive outcomes of upward comparisons described earlier, these comparisons can highlight the comparer's worse-off status and generate demotivating frustration or hopelessness. Similarly, downward comparisons can signal that the comparer is already doing well (and thus, does not need to make much effort to maintain their status) or indicate that a negative future state is likely or inevitable (so efforts to prevent it seem futile) [87]. The contextual factors that determine positive versus negative responses to comparison are not yet clear, although some evidence suggests that the response may depend on the extent to which the comparer identifies with or contrasts themselves against the comparison target [75]. Specifically, focusing on similarities with an upward target (identification) and differences with a downward target (contrast) produces positive responses, whereas contrast with an upward target and identification with a downward target produce negative responses [88,89]. At present, evidence consistent with this model of comparison is restricted to self-reported affect and motivation for health behaviors, and its application to objectively assessed health behavior (such as PA) has not been evaluated.

Taken together, existing evidence indicates that social comparisons may have a meaningful influence on PA and that this influence may be stronger for women than men. However, relations between comparisons and PA have rarely been examined among midlife women, especially at the within-person level. Greater attention to social comparison in this context could help to clarify the extent of its influence on PA in an at-risk group and provide needed insight into contextual factors that may explain previous equivocal findings (eg, identification and contrast processes).

Mood State

Mood state describes an individual's immediate emotional experience or a combination of emotional experiences (eg, happiness, sadness, anger). These may remain stable over periods of weeks or months or fluctuate in response to daily or momentary changes in context [90,91]. Mood state is recognized as a primary and proximal determinant of behavior [92] that can be modified either directly (eg, relaxation exercises to reduce feelings of anxiety or stress) or indirectly (eg, by adjusting antecedent thoughts that give rise to a range of emotional experiences) [92].

Several different mood states have been shown to predict PA over a range of time frames [93]. For example, experiencing positive mood states, such as happiness or contentment, is generally associated with future PA engagement (vs sedentary behavior) [94-96], although greater variability (vs stability) in positive mood states has shown negative associations with future PA [97]. Evidence with respect to relations between other mood states and PA is more equivocal. The experience of stress often predicts lower PA, such that increases in perceived stress are associated with future decreases in PA [57]. However, a number of studies also document the opposite relation (ie, increases in stress associated with future increases in PA), suggesting that some PA engagement may be used as a stress management technique [57]. Among older women (aged 65 years and older), PA is cited as an antidote to anxiety about the aging process, reflecting a similar emotion regulation function of PA [98]. Although considerable research has shown that PA engagement is negatively associated with concurrent and future negative affect [99-101], there has been less empirical investigation of

whether negative affect (or positive affect) prospectively predicts PA [94].

Research specific to midlife women confirms that PA engagement is inversely associated with negative affect in this population [102-104]. However, as examinations of prospective relations between mood states and future PA engagement among midlife women are scarce, it is not yet clear which mood states (and contexts for these states) are associated with women's PA during midlife. For example, midlife women may be more likely to engage in PA when they experience positive (vs negative) emotions, or they may use PA to manage negative emotions (eg, stress) or physical symptoms (eg, menopause), or both, under different circumstances [105]. A better understanding of relations between mood state and subsequent PA for midlife women and contextual moderators of this relation (eg, certain types of social interactions) would help to clarify emotional predictors of PA in an at-risk group.

Assessing PA Influences Among Midlife Women Using Within-Person Methods

Recent evidence shows that when assessed repeatedly over hours and days, both PA and each of the psychosocial experiences described above (body satisfaction, social interactions, social comparisons, and mood state) can vary considerably within the same person [50,70,106,107], and relations at the between-person level may not translate to the within-person level. For example, a stronger (vs weaker) between-person tendency to make upward comparisons is associated with greater engagement in PA [108], although experiencing an upward comparison may be associated with less PA in the short term (if an individual engages in upward contrast) [75,109]. As such, additional work to clarify the nature and extent of relations between psychosocial experiences and PA will be most accurate and informative if it captures variability at both levels and differentiates within- from between-person relations. This requires repeated assessments of the same individual over multiple time points, gathering data as relevant experiences that occur in daily life. EMA is one such method that typically prompts self-reports multiple times per day. This limits the window for recall and the need for the respondent to aggregate across experiences, as required by global (person-level) self-report [54].

In an EMA design, self-reports can be prompted by signals to handheld devices such as mobile phones. The timing of responses can be verified by this technology, and item responses can be examined for temporal associations with one another or with other ambulatory assessments (eg, behavior in the real world). Examining within-person associations between EMA survey responses (eg, capturing psychosocial experiences) and objectively assessed PA in the natural environment is an underused approach to understanding PA variability and its influences in real time [110]. Although previous work has established the feasibility of using EMA with midlife women [111-113], to our knowledge, an EMA approach to understanding psychosocial predictors of PA variability has not yet been used among women in this life stage with elevated disease risk [114].

The primary aim of this study is to examine within-person relations between midlife women's psychosocial experiences (ie, body satisfaction, social comparison, social interactions, and mood state) and their PA to identify moment-level experiences associated with higher versus lower PA for this population. Secondary aims are to determine the timing and duration of these effects and to examine person-level moderators of within-person relations. Specific research questions to be addressed in this study include the following:

1. To what extent do body satisfaction, perceptions of social interactions, social comparisons, and mood state vary between- versus within-person among midlife women with elevated CVD risk?
2. To what extent does PA vary between- versus within-person among midlife women with elevated CVD risk?
3. Are moment-level differences in body satisfaction, perceptions of social interactions, social comparisons, and mood state related to differences in PA for these women (within-person)?
4. Do person-level characteristics such as age, BMI, or menopause status moderate within-person relations between psychosocial experiences and PA for these women?

Objective

The purpose of this paper is to present the protocol for an EMA study designed to capture within-person relations between psychosocial experiences (ie, body satisfaction, social interactions, social comparisons, mood state) and PA among midlife women with elevated cardiovascular risk.

Methods

Project Overview

Project WHADE is a study of relations between midlife women's psychosocial experiences and PA in everyday life. Midlife women (aged 40-60 years) with one or more CVD risk markers complete a 10-day EMA procedure, whereby they self-report on their recent body satisfaction, social interactions, social comparisons, and mood at 5 semirandom times per day. For the same 10 days, they also wear a waistband accelerometer to capture their PA during waking hours. All study activities were approved by the Rowan University and Rowan School of Osteopathic Medicine institutional review boards (approval Pro2018002377).

Target Population and Eligibility

Women are eligible if they are aged 40 to 60 years (inclusive) and have one or more additional cardiovascular risk factors. These include smoking (current or quit within the past 3 months) or diagnoses of prediabetes, type 2 diabetes, hypertension, prehypertension, hyperlipidemia, hypercholesterolemia, or metabolic syndrome. Additional inclusion criteria were English language proficiency, no medical contraindications to PA, not currently pregnant, not currently engaged in a formal weight loss program, no comorbid medical conditions or psychiatric symptoms that would impede participation (eg, injury, active psychosis), and the ability to complete momentary electronic surveys via a personal mobile device (eg, smartphone or tablet). Individuals are excluded from participation if they do not meet

the above criteria or if they state an intention to move away from the geographic area during the study period. Eligibility was not limited by current level of PA engagement, as existing evidence and pilot work suggested that engagement would range from low to moderate for the target population [115,116].

Sample Size and Recruitment

The recruitment goal for this study is 100 participants and still ongoing. The sample size was calculated for cross-level multilevel models (described below) following estimates from simulations by Hox [117,118]. Using conservative estimates of compliance from previous studies and our pilot data (ie, 80% of surveys completed in the correct time window [111,113]), a sample size of 100 participants (level 3) with 10 days of observation (level 2) 5 times per day (level 1) would generate a minimum of 4000 completed surveys (maximum 5000). This number of observations exceeds the thresholds identified for detecting between-person (level 3) moderators of time-sensitive relations (level 1).

This study uses 2 primary recruitment strategies: web or print advertisements and direct referrals from providers in family medicine clinics. Web advertisements include a study-specific webpage, email announcements for employees and students at the supporting institution, social media posts (eg, Craigslist, Twitter, Facebook), and advertisements on local news websites. Print advertisements (ie, flyers, postcards) are posted in public locations such as libraries and community centers and appear in local newspapers. All advertisements provide phone and email contact information for the research team and offer interested individuals the option to complete an initial survey as their first step (see below).

Direct referrals take place on-site in family medicine clinics run by Rowan School of Osteopathic Medicine. Study collaborators identify patients with upcoming appointments who meet the eligibility criteria (based on chart review) and provide them with study information following their medical visit. Study staff are available on certain days of the week to provide additional information to interested individuals and to schedule telephone screenings.

Telephone Screening

Potential participants are asked to complete a 10-min telephone screening with trained research staff, who verify eligibility, explain study procedures, and answer questions. Those who remain interested in participating are scheduled for a face-to-face setup appointment (baseline) and are directed to complete an initial electronic survey before their appointment. Women who take the initial survey as their first expression of interest receive a follow-up call and/or email from study staff to complete or schedule the screening call, respectively.

Initial Survey

Eligible women who engage in telephone screening and schedule an initial appointment are sent a Qualtrics survey link via email. This survey assesses demographics, contact information, recent psychosocial and physical experiences (eg, symptoms of depression and anxiety, health-related quality of life), global social perceptions (eg, social support, social comparison tendencies), and previous experience with PA promotion programs (self-guided and professionally supported). See Table 1 for additional description of the measures included. Study staff monitors for completion of this survey before the scheduled baseline appointment and prompts potential participants via phone or email if it is not completed by the morning of the appointment. As noted, the survey is also available as a first point of contact. For those who complete the survey first, study staff use the contact information entered into the survey to conduct or schedule the telephone screening.

Table 1. Baseline measures.

Construct	Description	Measure (reference)
Demographics	Age, self-reported height and weight, income, education, marital status, ethnicity, race, medical conditions, menopause status	Developed for this study
Social media behavior	Frequency of engagement with various social media platforms Example: How often to you use each of the following? (Facebook, Twitter, etc.) – Less than one day per week (1) to More than once per day (7)	Developed for this study
Health-related quality of life	Physical and mental quality of life over the past four weeks	SF-36[a] Health Survey [119]
Activity barriers	Factors that are perceived to get in the way of PA[b] engagement	Barriers to Being Active Scale [120]
Exercise motivation	Expected outcomes of PA	Outcome Expectancies for Exercise Scale [121]
Lapses in exercise	Successful and unsuccessful attempts to increase exercise in the past year Example: In the past year, how many times have you started a formal exercise program, such as joining an ongoing group at a gym? (Numeric entry)	Developed for this study
Anxiety	Symptoms of anxiety over the past month	Beck Anxiety Inventory [122]
Body image	Perceived influence of body image on quality of life	Body Image Quality of Life Inventory [48]
Depression	Symptoms of depression over the past four weeks	Center for Epidemiologic Studies Depression Scale [123]
Perceived stress	Perceived intensity of stress over the past month	Perceived Stress Scale [124]
Sleep quality	Subjective sleep quality and intensity of sleep disturbances over the past month	Pittsburgh Sleep Quality Index [125]
Problem orientation	Attitudes related to problem solving approach and abilities	Problem Orientation Questionnaire [126]
Social comparison orientation	Tendency to make social comparisons and value information from them	Iowa-Netherlands Social Comparison Orientation Measure [127]
Social support	Perceived support from family and friends	Social Support Appraisals Scale [128]

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

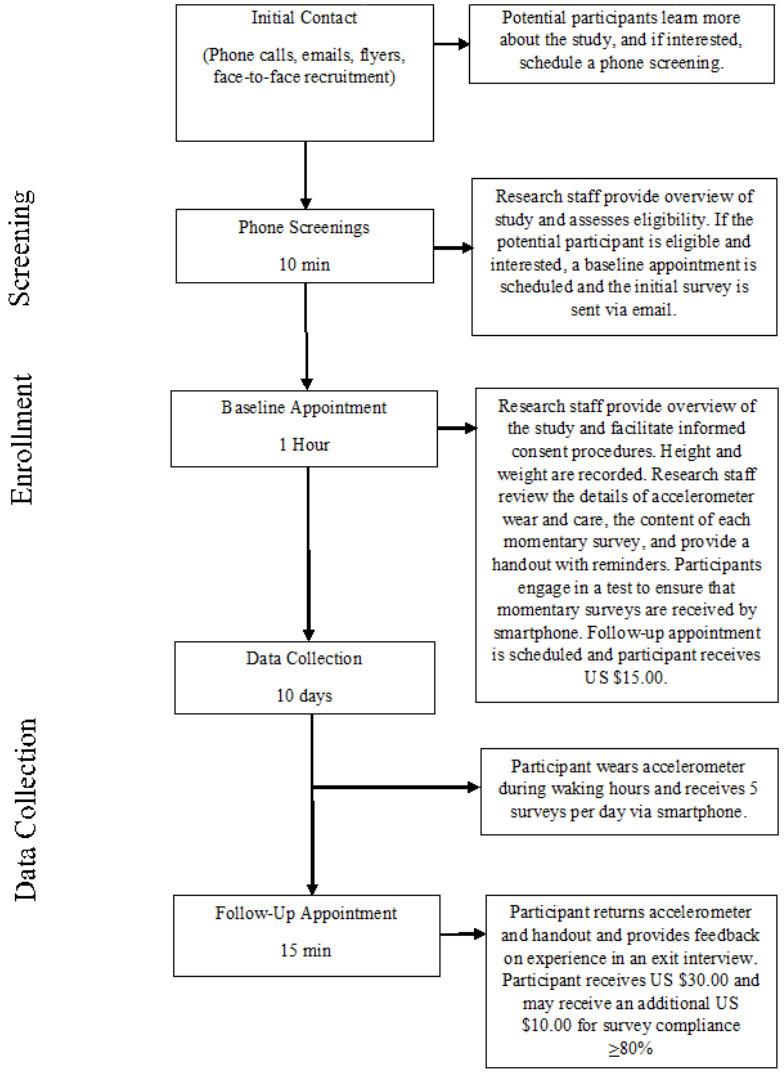
[b]PA: physical activity.

Baseline Appointment

Women who complete the initial survey attend an on-site, 1-hour individual session at a research center with a trained staff member. During the visit, the staff member obtains written informed consent, measures the participant's height and weight, and reviews study procedures. This includes wear and care of accelerometer and a detailed explanation of survey items. Instructions indicate that participants should complete EMA surveys within 1 hour of receiving them. This window for completing a survey was based on feasibility protocols from similar populations [111] and on pilot work with the population of interest to maximize survey completion within the context of participants' work and personal commitments.

Participants are also given a folder with study materials to take home (eg, reminders from the baseline discussion, frequently asked questions about the accelerometer, an accelerometer wear log). The 10 days of EMA data collection in the participant's natural environment are intended to begin the day after the participant's baseline appointment. At the end of the baseline visit, participants are scheduled for a 15-min follow-up appointment to take place after the last day of the EMA data collection. See Figure 1 for a timeline of enrollment and data collection procedures.

Figure 1. Screening, enrollment, and data collection procedures. EMA: ecological momentary assessment.



EMA Survey Schedule, Distribution, and Monitoring

The design of this study uses a signal-contingent approach, such that participants complete surveys in response to a signal (ie, text message). EMA surveys are scheduled and distributed via Qualtrics. Before study initiation, study staff generated survey schedules with semirandom timings anchored to 1 of 3 sets of specified times. These times were selected based on pilot work with the population of interest, which informed the expected frequency of events such as social comparisons, and were intended to maximize coverage of waking hours while minimizing reporting windows (and limiting retrospective recall) [129]. The sets of times were based on standard sleep or wake times for a 9:00 AM to 5:00 PM work schedule (8:30 AM, 12:15 PM, 3:45 PM, 6:30 PM, and 9:45 PM), an early-rising schedule (6:30 AM, 9:15 AM, noon, 3:30 PM, and 6:45 PM), and a late-rising schedule (11:00 AM, 2:35 PM, 5:45 PM, 8:45 PM, and 11:15 PM). The staff created 3 versions of each schedule and use a random number generator to assign 1 of the 3 survey schedules that match a participant's sleep or wake schedule. Survey schedules do not differ between weekdays and weekends.

Survey distribution via text message with embedded web links is programmed immediately after a participant's baseline appointment, and survey completion is monitored over the next 10 days. Research staff manually identify surveys outside of the 1-hour time window for reporting and surveys that repeat within the same 3-hour window (duplicates) for exclusion from statistical analyses.

Follow-Up Appointment

After completing the 10-day accelerometer and survey protocol, participants return to the research center for their scheduled follow-up visit. Participants are asked to bring their accelerometer and a record of wear. A staff member conducts a brief exit interview to assess any difficulties, answer questions, and gather information about the participant's preferences for future PA interventions. Participants who express interest in receiving mental and/or physical health resources are provided with materials sent via email. Those who indicate that they would like to view their PA engagement data are provided with a copy of their daily summaries. Summaries include daily totals for steps, sedentary time, and time spent in light, moderate, and vigorous activities.

Compensation

Participants receive up to US $55 as compensation. They receive US $15 for attending the baseline appointment and US $30

when they return for follow-up. Those who return their accelerometers and complete more than 80% of EMA surveys receive an additional US $10 bonus at follow-up.

EMA Survey: Self-Rated Measures

EMA items were initially based on those used in previous intensive longitudinal assessment studies and were pretested for revision with the target population in 2 ways. Initial items were generated using previous work as a guide and were distributed in a 7-day pilot EMA study with women who met the criteria for this study (June 2017-May 2018; n=13). These items were revised based on participant feedback, and modified items were discussed in individual face-to-face interviews with a different group of women who met the criteria for this study (October 2018-December 2018; n=10). Interview feedback informed further item refinement, and the items used in the EMA surveys are presented in Textbox 1. EMA surveys were designed to take no more than 5 min to complete. The second, third, and fourth surveys each day included 29 items each; additional items in the first and last surveys of the day brought the totals for these surveys to 30 and 32, respectively.

Textbox 1. Ecological momentary assessment survey construct and items.

Sleep quality (first survey of the day only):

- How would you describe your sleep last night?
  - Excellent
  - Good
  - Average
  - Poor
  - Terrible

Mood state:

- How much have you experienced the following emotions: angry or frustrated, sad, happy or excited, content, anxious or stressed?
  - Not at all
  - Somewhat
  - Very much

Pain:

- Have you had any physical pain in the last three hours?
  - Yes
  - No
- If yes, which areas of your body? List all that apply.
- If you have had pain, please rate the overall severity of your pain:
  - Mild
  - Moderate
  - Severe
  - Very severe

Positive social interactions:

- Did you have positive or pleasant social experiences with any of the following today?
  - Friends
  - Coworkers
  - Acquaintances
  - Family
  - Strangers
  - Other
- Total number of times you had positive or pleasant social experiences in the last three hours
- Overall, how positive or pleasant were your social experiences in the last three hours?
  - Not at all
  - Moderately
  - Very

Negative social interactions:

- Did you have negative or unpleasant social experiences with any of the following today?
  - Friends
  - Coworkers

- Acquaintances
- Family
- Strangers
- Other

- Total number of times you had negative or unpleasant social experiences in the last three hours
- Overall, how negative or unpleasant were your social experiences in the last three hours?
  - Not at all
  - Moderately
  - Very

Social comparisons:

- In the last three hours, did you think about or evaluate yourself or your behavior in comparison to someone else (or someone else in comparison to yourself)?
  - Yes
  - No
- How many times did you compare yourself to someone else in the last three hours?
- Did you communicate with the person you compared to?
  - Yes. I talked to them in person, or on the telephone, or online (eg, Facebook message)
  - No. I saw, heard about, read about, or thought about them but did not communicate
  - Both
- What aspects of yourself did you compare? Select all that apply.
  - Appearances
  - Health habits
  - Status
  - Emotions
  - Personality
  - Abilities
  - Other
- Below are some interpretations of the comparisons you may have made. Please indicate how many of each type you made since the last time you responded. Comparisons to people who
  - Seem to be doing better than I am
  - Seem to be doing about the same as I am
  - Seem to be doing worse than I am

Most recent comparison:

- Now consider only your most recent comparison. Did you communicate with the person you compared to?
  - Yes. I talked to them in person, or on the telephone, or online (eg, Facebook message)
  - No. I saw, heard about, read about, or thought about them but did not communicate
  - Both
- What aspects of yourself did you compare? Select all that apply.
  - Appearances
  - Health habits
  - Status

- Emotions
- Personality
- Abilities
- Other

- As you compared yourself, how much did you focus on each of the following: how similar I am to the person I compared to; how different I am to the person I compared to?
  - Not at all
  - Somewhat
  - Very much

- After the comparison, how much did you feel each of the following: inspired, encouraged, or hopeful about my own situation; anxious, frustrated, or discouraged about my own situation?
  - Not at all
  - Somewhat
  - Very much

Motivation for physical activity (PA):

- How motivated are you to be physically active in the next few hours?
  - Not at all
  - A little bit
  - Somewhat
  - Very

PA intentions:

- Do you have plans to do cardiovascular exercise in the next few hours (such as going for a brisk walk or doing a strength DVD routine)?
  - No, no plans to exercise
  - Yes

- If yes, how many planned minutes?
- If yes, what kind of exercise?

Overall rating of the day (last survey of the day only):

- Was today a typical day for you, with respect to physical activity or exercise?
  - Not at all. A lot less active than usual
  - Mostly. A little less active than usual
  - It was a typical day
  - Mostly. A little more active than usual
  - Not at all. A lot more active than usual

- Was today a typical day for you, with respect to eating?
  - Not at all. A lot worse than usual
  - Mostly. A little worse than usual
  - It was a typical day
  - Mostly. A little better than usual
  - Not at all. A lot better than usual
  - Number of meals eaten today
  - Number of snacks eaten today

Body Satisfaction

Current body satisfaction is assessed with 1 item ("How would you describe your body satisfaction right now?"). Responses are rated on a 4-point scale ranging from 1 (*very dissatisfied with my body*) to 4 (*very satisfied with my body*) [50,130].

Social Interactions

Perceptions of social interactions since waking up (first survey of the day) or in the last 3 hours (all subsequent surveys of the day) are assessed with 6 items; 3 items focus on *positive or pleasant* interactions, and 3 on *negative or unpleasant* interactions. For each type, participants are asked to report the category or categories of others they interacted with (eg, family, friends, coworkers, strangers), the number of individual interactions they recall in the respective time frame, and the overall intensity of the interactions in that time frame ("How positive/pleasant were these experiences?"). The latter is rated on a scale of 1 (*not at all*) to 3 (*very*). Instructions specify that the number of interactions refers to the number of events, rather than the number of people, such that an interaction with a group counts as a single instance [55,61,131].

Social Comparison

Occurrence, type, and response to social comparison are assessed with 10 items. Participants are asked to report how many times they made social comparisons since they woke up (first survey of the day) or in the last 3 hours (all subsequent surveys of the day). Instructions specify that comparison includes any instance of evaluating an aspect of the self or one's own behavior relative to that of others and that some comparisons might prompt emotional responses, whereas others might not. Both types should be counted in participants' responses. Those who report one or more comparisons are asked what aspect or aspects of the self they compared (eg, appearance, health habits, abilities, etc) and the direction or directions of their comparisons (if they perceived the target to be upward, lateral [same as the self], or downward). Participants are also asked to provide these details about their most recent comparison before completing the survey, with additional items related to identification or contrast processes and affective response to the comparison (Textbox 1) [70,132,133].

Mood State

Recent mood state is assessed with 5 items, referring to how much participants have experienced each emotion since they woke up (first survey of the day) or in the last three hours (all subsequent surveys of the day). Participants are asked to report on a three-point scale ranging from 1 (*not at all*) to 3 (*very much*) for the following mood states: angry, happy or excited, stressed or anxious, sad, and content [134,135].

PA Motivation and Intentions

These experiences are assessed using 4 items. First, participants are asked to report how motivated they are to be physically active within the next few hours (surveys 1-4 of the day) or on the following day (survey 5 of the day). Second, participants are asked whether they have intentions of doing cardiovascular exercise in the relevant time frame; if they answer "yes," they are asked to record the number of minutes they plan to exercise and the type of exercise they plan to do (eg, walking, taking an exercise class) [89,136-138].

Additional Experiences Assessed

EMA surveys also query for additional experiences that may affect engagement in PA and end-of-day reports on PA and other health behaviors. These include sleep quality (first survey of the day), pain (occurrence, location or locations, and intensity; all surveys), perception of whether the day was typical with respect to PA and eating behavior (last survey of the day), and the number of meals and snacks consumed that day (last survey of the day) [139-141].

Activity Monitor

PA is assessed using the ActiGraph GT3X triaxial accelerometer (ActiGraph Corporation). Participants are instructed to wear the device aligned with their dominant hip during waking hours for 10 days following their baseline visit. They are asked to keep the device near their beds to limit forgetting to put it on upon waking, and to remove it for activities such as showering and swimming. Participants are also asked to complete a paper log for any time they remove the device for longer than 15 min during their waking hours, which is provided in the folder of study materials to bring home with them. PA parameters, including minutes of sedentary, light, moderate, and vigorous activity, are calculated using the ActiPro package for R. Moderate and vigorous minutes will be combined to estimate moderate-to-vigorous intensity physical activity. Time frames of interest include the concurrent reporting window (ie, 3 hours before each survey) and 30, 60, and 120 min after each survey to clarify the timing and duration of any observed effects [142].

Data Analysis Plan

Multilevel models will be used to address the nested structure of self-report and accelerometer data: momentary assessments (level 1) within days (level 2) within individuals (level 3). Missing data patterns will be evaluated, and all models will employ maximum likelihood estimation techniques, which include all available cases and are robust to missing data (such as missed surveys or missed items within surveys). Initial empty models will evaluate the proportion of variance accounted for at each level for each PA parameter using the intraclass correlation coefficient. Within-person relations between psychosocial determinants and PA will be tested (in separate models for each PA parameter) by controlling for person-level covariates and the stable, person-level association between the predictor of interest and PA. These models allow for the identification of moment-level differences from an individual's average that are associated with higher- or lower-than-average PA. Age, BMI, menopausal status, and the number of CVD risk factors will be considered as covariates and may be examined as person-level moderators of within-person relations.

Results

To date, 172 women have expressed interest in participating via email, phone, family medicine clinics, or the initial survey. Of these women, 101 were contacted for screening and scheduled a baseline appointment; 76 women attended the appointment, and 75 of then completed the full EMA protocol

and returned for their follow-up appointment (99% retention). Most of the enrolled participants identified as white (56/75, 75%) and married (44/75, 59%); 23% (17/75) reported household incomes of less than US $50,000, and 23/75 (31%) did not finish a bachelor's degree program or received an associate's or technical degree. The largest subsets of participants qualify as obese (52/75, 69%), postmenopausal (29/75, 39%), and report a previous diagnosis of high cholesterol (39/75, 52%). Recruitment and enrollment will continue until the target sample size of 100 is reached (expected in Fall 2020).

Discussion

Project WHADE is designed to assess 4 psychosocial experiences that are hypothesized to predict midlife women's PA: body satisfaction, social interactions, social comparison, and mood state. This paper describes our approach to understanding within-person relations between these experiences and PA and highlights existing challenges to be considered in future work.

Methodological Challenges and Decisions

Given that EMA for capturing psychosocial influences on PA remains to be somewhat novel compared with other methods (eg, retrospective self-report, group-based experimental designs), there is limited evidence to inform key methodological decisions such as item wording for the constructs of interest, participant instructions, or optimal survey frequency and timing. As noted, we based the wording of our EMA items on those from existing, relevant studies and subjected them to 2 rounds of pilot testing with the population of interest. This also allowed us to gather feedback and estimates of survey and accelerometer compliance with the timing selected (ie, surveys 5 times per day and accelerometer wear for 10 days), which was intended to cover a representative subset of participants' typical experiences while maximizing power and minimizing recording burden [143]. In addition, we trained study staff to provide participants with scripted, detailed explanations of each item at baseline visits to limit individual differences in how participants understand each psychosocial construct and item; it is not clear how widespread such procedures are or how effective they might be for reducing reporting noise. As the use of EMA and other intensive assessment methods increases, it would be helpful to see more detailed reporting of processes for item construction, participant instructions, and pilot testing.

An advantage of EMA is its ability to assess experiences as they occur, using item wording that focuses on the present moment. In this study, we are intentionally using a different frame of reference (ie, "since you woke up/in the past three hours," to capture time since the previous prompt) to assess social interactions, social comparisons, and mood state. This decision was based on the low likelihood of capturing social interactions and social comparisons in the moments that they occurred, as participants were not expected to interrupt social activities to complete the surveys. This approach also allows survey responses to capture events in the very recent past, rather than missing them if they are not currently happening. Similarly, we expected mood state to fluctuate throughout the day, and for mood states that predominated over 3-hour spans to be more predictive of PA than immediate emotions (which might be fleeting). For this reason, mood state was assessed as a summary of the past three hours, rather than as a reflection of mood state at the immediate moment of survey completion. Although decisions about the time frames for these reports were based on existing research and our specific research questions, it is important to acknowledge the associated limitations. Primarily, recall bias and forgetting are inherent in any retrospective report, and it will be possible that reports be skewed toward salient experiences or underestimate their true frequency in the natural environment [129,144]. However, to remain consistent with existing EMA studies of body image [130,145,146], we focus our assessment of body satisfaction on participants' immediate experiences. Consequently, interpretation of findings will require attention to this difference between reporting time frames.

An early consideration involved the method of distribution of EMA surveys to participants' personal smartphones. Although professional services exist to manage survey distribution (and were considered for Project WHADE), payment regulations presented barriers to hiring outside assistance. Consequently, as in our pilot work, survey scheduling and distribution were managed by study staff, via Qualtrics. A strength of this method is that it offers researchers a great deal of control over and insight into the distribution process. However, this method is time-consuming for study staff and may be prone to error, and it requires additional time for rechecking to limit mistakes. The effectiveness of this method also depends on the cell phone carrier and network availability. For example, carriers periodically experience temporary outages during which text messages are not received. As individuals with certain coverage are not able to receive text messages from Qualtrics, a subset of participants are set up to receive EMA surveys via email and are asked to ensure that their smartphone email notifications mirror those of their text messages. To address this difference between participants, the method of survey delivery will be examined as a moderator of survey completion and responses and will be included as a covariate if it shows significant associations with either of these variables.

In addition, it is common for each survey to appear in a unique text message (rather than as a threaded conversation), and a small subset of participants has encountered confusion and completed the wrong survey when prompted. To ensure that the final dataset is accurate, survey numbers are coded manually by study staff based on their completion time stamps, and duplicates are deleted.

Significance of Project WHADE

Despite these challenges, this study should provide useful insights into midlife women's PA. Project WHADE is one of a limited number of studies that use EMA to identify within-person variability in and predictors of PA [114]. Unlike traditional (between-person) methods, this approach acknowledges that PA engagement varies within persons from day to day and throughout the day and that the pattern of PA variation may differ between people. As such, this study is powered to detect moderate effects of both within-person relations between proposed predictors and PA and between-person moderators of these relations. To our

knowledge, this is the first study to use an EMA approach to understanding influences on PA among midlife women with elevated risk for CVD. This is a population for whom increased PA would have particularly meaningful health benefits, and despite considerable effort to date, few effective PA interventions exist for this group.

An additional advantage of EMA (and similar designs) is that it can be useful for identifying both group- and individual-level patterns. For example, it is possible that some midlife women are more likely to engage in PA after making an upward comparison, whereas others are more likely to engage in a downward comparison. As such, if a social comparison was included as a behavior change technique to be harnessed in future interventions for this population, it is possible that providing only 1 type of comparison opportunity (eg, exposing all participants to upward targets) would work well for some participants and not others. The use of EMA to identify these differences, which represent individual differences in within-person relations, could inform the tailoring of the content provided by future interventions to particular subgroups and individuals [54]. Thus, an examination of PA at the within-person level could improve our basic understanding of the relations between day-to-day experiences and cardioprotective behavior in an at-risk group and potentially help to identify and clarify appropriate targets for tailored interventions for this population.

Together, these features of Project WHADE suggest that it is poised to address gaps in the current understanding of within-person processes associated with PA variability. We hope that a greater understanding of the within-person predictors of change in PA will provide information useful to the design of interventions, including novel just-in-time approaches that can respond to participants in real time [54]. Although Project WHADE will provide this information for a particular subset of adults (ie, midlife women with cardiovascular risk markers), the overall approach may serve as a model for future investigations of PA determinants and their potential for translation to intervention.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report.
[PDF File (Adobe PDF File), 629 KB - resprot_v9i10e19044_app1.pdf]

References

1. Brim O, Ryff C, Kessler R. How Healthy Are We? A National Study of Well-Being at Midlife. Chicago, IL: University of Chicago Press; 2004.
2. Age and Gender. URL: https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/Age-and-Gender [accessed 2020-03-30]
3. National Health Expenditure Data. URL: https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData [accessed 2020-03-24]
4. Matthews KA, Kuller LH, Sutton-Tyrrell K, Chang Y. Changes in cardiovascular risk factors during the perimenopause and postmenopause and carotid artery atherosclerosis in healthy women. Stroke 2001 May;32(5):1104-1111. [doi: 10.1161/01.str.32.5.1104] [Medline: 11340217]
5. Matthews KA, Crawford SL, Chae CU, Everson-Rose SA, Sowers MF, Sternfeld B, et al. Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition? J Am Coll Cardiol 2009 Dec 15;54(25):2366-2373 [FREE Full text] [doi: 10.1016/j.jacc.2009.10.009] [Medline: 20082925]
6. Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM. Sex-based differences in early mortality after myocardial infarction. National registry of myocardial infarction 2 participants. N Engl J Med 1999 Jul 22;341(4):217-225. [doi: 10.1056/NEJM199907223410401] [Medline: 10413733]
7. Mikkola TS, Gissler M, Merikukka M, Tuomikoski P, Ylikorkala O. Sex differences in age-related cardiovascular mortality. PLoS One 2013;8(5):e63347 [FREE Full text] [doi: 10.1371/journal.pone.0063347] [Medline: 23700418]
8. Meischke H, Larsen MP, Eisenberg MS. Gender differences in reported symptoms for acute myocardial infarction: impact on prehospital delay time interval. Am J Emerg Med 1998 Jul;16(4):363-366 [FREE Full text] [doi: 10.1016/s0735-6757(98)90128-0]
9. Milner KA, Vaccarino V, Arnold AL, Funk M, Goldberg RJ. Gender and age differences in chief complaints of acute myocardial infarction (Worcester heart attack study). Am J Cardiol 2004 Mar 1;93(5):606-608. [doi: 10.1016/j.amjcard.2003.11.028] [Medline: 14996588]

10. Moser DK, McKinley S, Dracup K, Chung ML. Gender differences in reasons patients delay in seeking treatment for acute myocardial infarction symptoms. Patient Educ Couns 2005 Jan;56(1):45-54. [doi: 10.1016/j.pec.2003.11.011] [Medline: 15590222]
11. Vaccarino V, Badimon L, Corti R, de Wit C, Dorobantu M, Manfrini O, et al. Presentation, management, and outcomes of ischaemic heart disease in women. Nat Rev Cardiol 2013 Sep;10(9):508-518. [doi: 10.1038/nrcardio.2013.93] [Medline: 23817188]
12. Barnett F. Do physical activity levels influence the cardiovascular-related physiological characteristics of postmenopausal women? Australas J Ageing 2009 Dec;28(4):216-218. [doi: 10.1111/j.1741-6612.2009.00389.x] [Medline: 19951345]
13. Kelley GA, Kelley KS, Roberts S, Haskell W. Efficacy of aerobic exercise and a prudent diet for improving selected lipids and lipoproteins in adults: a meta-analysis of randomized controlled trials. BMC Med 2011 Jun 15;9:74 [FREE Full text] [doi: 10.1186/1741-7015-9-74] [Medline: 21676220]
14. Hutchison SK, Stepto NK, Harrison CL, Moran LJ, Strauss BJ, Teede HJ. Effects of exercise on insulin resistance and body composition in overweight and obese women with and without polycystic ovary syndrome. J Clin Endocrinol Metab 2011 Jan;96(1):E48-E56. [doi: 10.1210/jc.2010-0828] [Medline: 20926534]
15. Sattelmair J, Pertman J, Ding EL, Kohl HW, Haskell W, Lee I. Dose response between physical activity and risk of coronary heart disease: a meta-analysis. Circulation 2011 Aug 16;124(7):789-795 [FREE Full text] [doi: 10.1161/CIRCULATIONAHA.110.010710] [Medline: 21810663]
16. Jeon CY, Lokken RP, Hu FB, van Dam RM. Physical activity of moderate intensity and risk of type 2 diabetes: a systematic review. Diabetes Care 2007 Mar;30(3):744-752. [doi: 10.2337/dc06-1842] [Medline: 17327354]
17. Church TS, Earnest CP, Skinner JS, Blair SN. Effects of different doses of physical activity on cardiorespiratory fitness among sedentary, overweight or obese postmenopausal women with elevated blood pressure: a randomized controlled trial. J Am Med Assoc 2007 May 16;297(19):2081-2091. [doi: 10.1001/jama.297.19.2081] [Medline: 17507344]
18. Caspersen CJ, Pereira MA, Curran KM. Changes in physical activity patterns in the United States, by sex and cross-sectional age. Med Sci Sports Exerc 2000 Sep;32(9):1601-1609. [doi: 10.1097/00005768-200009000-00013] [Medline: 10994912]
19. Finkel D, Andel R, Pedersen N. Gender differences in longitudinal trajectories of change in physical, social, and cognitive/sedentary leisure activities. J Gerontol B Psychol Sci Soc Sci 2018 Oct 10;73(8):1491-1500 [FREE Full text] [doi: 10.1093/geronb/gbw116] [Medline: 27624718]
20. Funderburk JS, Arigo D, Kenneson A. Initial engagement and attrition in a national weight management program: demographic and health predictors. Transl Behav Med 2016 Sep;6(3):358-368 [FREE Full text] [doi: 10.1007/s13142-015-0335-y] [Medline: 27528525]
21. ACSM's Guidelines for Exercise Testing and Prescription. Philadelphia, PA: Lippincott Williams & Wilkins; 2014.
22. Napolitano MA, Marcus BH. Breaking barriers to increased physical activity. Phys Sportsmed 2000 Oct;28(10):88-93. [doi: 10.3810/psm.2000.10.1260] [Medline: 20086605]
23. Mâsse LC, Ainsworth BE, Tortolero S, Levin S, Fulton JE, Henderson KA, et al. Measuring physical activity in midlife, older, and minority women: issues from an expert panel. J Womens Health 1998 Feb;7(1):57-67. [doi: 10.1089/jwh.1998.7.57] [Medline: 9511133]
24. Dearden JS, Sheahan SL. Counseling middle-aged women about physical activity using the stages of change. J Am Acad Nurse Pract 2002 Nov;14(11):492-497. [doi: 10.1111/j.1745-7599.2002.tb00081.x] [Medline: 12479151]
25. Sansano-Nadal O, Giné-Garriga M, Brach, Wert, Jerez-Roig, Guerra-Balic, Oviedo, Soto-Bagaria, Inzitari, et al. Exercise-based interventions to enhance long-term sustainability of physical activity in older adults: a systematic review and meta-analysis of randomized clinical trials. Int J Environ Res Public Health 2019 Jul 15;16(14):- [FREE Full text] [doi: 10.3390/ijerph16142527] [Medline: 31311165]
26. Lewis BA, Napolitano MA, Buman MP, Williams DM, Nigg CR. Future directions in physical activity intervention research: expanding our focus to sedentary behaviors, technology, and dissemination. J Behav Med 2017 Feb;40(1):112-126 [FREE Full text] [doi: 10.1007/s10865-016-9797-8] [Medline: 27722907]
27. Pinkasavage E, Arigo D, Schumacher LM. Social comparison, negative body image, and disordered eating behavior: the moderating role of coping style. Eat Behav 2015 Jan;16:72-77. [doi: 10.1016/j.eatbeh.2014.10.014] [Medline: 25464070]
28. Young MD, Plotnikoff RC, Collins CE, Callister R, Morgan PJ. Social cognitive theory and physical activity: a systematic review and meta-analysis. Obes Rev 2014 Dec;15(12):983-995. [doi: 10.1111/obr.12225] [Medline: 25428600]
29. Curran PJ, Bauer DJ. The disaggregation of within-person and between-person effects in longitudinal models of change. Annu Rev Psychol 2011;62:583-619 [FREE Full text] [doi: 10.1146/annurev.psych.093008.100356] [Medline: 19575624]
30. Im E, Stuifbergen AK, Walker L. A situation-specific theory of midlife women's attitudes toward physical activity (MAPA). Nurs Outlook 2010;58(1):52-58 [FREE Full text] [doi: 10.1016/j.outlook.2009.07.001] [Medline: 20113755]
31. Kelly S, Martin S, Kuhn I, Cowan A, Brayne C, Lafortune L. Barriers and facilitators to the uptake and maintenance of healthy behaviours by people at mid-life: a rapid systematic review. PLoS One 2016;11(1):e0145074 [FREE Full text] [doi: 10.1371/journal.pone.0145074] [Medline: 26815199]
32. Sallis JF, Hovell MF, Hofstetter CR. Predictors of adoption and maintenance of vigorous physical activity in men and women. Prev Med 1992 Mar;21(2):237-251. [doi: 10.1016/0091-7435(92)90022-a] [Medline: 1579558]

33. McArthur D, Dumas A, Woodend K, Beach S, Stacey D. Factors influencing adherence to regular exercise in middle-aged women: a qualitative study to inform clinical practice. BMC Womens Health 2014 Mar 26;14:49 [FREE Full text] [doi: 10.1186/1472-6874-14-49] [Medline: 24666887]
34. Bandura A. Health promotion by social cognitive means. Health Educ Behav 2004 Apr;31(2):143-164. [doi: 10.1177/1090198104263660] [Medline: 15090118]
35. Luszczynska A, Gibbons FX, Piko BF, Tekozel M. Self-regulatory cognitions, social comparison, and perceived peers' behaviors as predictors of nutrition and physical activity: a comparison among adolescents in Hungary, Poland, Turkey, and USA. Psychol Health 2004 Oct;19(5):577-593. [doi: 10.1080/0887044042000205844]
36. Rivera J, McPherson A, Hamilton J, Birken C, Coons M, Iyer S, et al. Mobile apps for weight management: a scoping review. JMIR Mhealth Uhealth 2016 Jul 26;4(3):e87 [FREE Full text] [doi: 10.2196/mhealth.5115] [Medline: 27460502]
37. Middelweerd A, Mollee JS, van der Wal CN, Brug J, te Velde SJ. Apps to promote physical activity among adults: a review and content analysis. Int J Behav Nutr Phys Act 2014 Jul 25;11:97 [FREE Full text] [doi: 10.1186/s12966-014-0097-9] [Medline: 25059981]
38. Direito A, Dale LP, Shields E, Dobson R, Whittaker R, Maddison R. Do physical activity and dietary smartphone applications incorporate evidence-based behaviour change techniques? BMC Public Health 2014 Jun 25;14:646 [FREE Full text] [doi: 10.1186/1471-2458-14-646] [Medline: 24965805]
39. Conroy DE, Yang C, Maher JP. Behavior change techniques in top-ranked mobile apps for physical activity. Am J Prev Med 2014 Jun;46(6):649-652. [doi: 10.1016/j.amepre.2014.01.010] [Medline: 24842742]
40. Noar SM, Zimmerman RS. Health Behavior Theory and cumulative knowledge regarding health behaviors: are we moving in the right direction? Health Educ Res 2005 Jun;20(3):275-290. [doi: 10.1093/her/cyg113] [Medline: 15632099]
41. Kilpatrick M, Hebert E, Bartholomew J. College students' motivation for physical activity: differentiating men's and women's motives for sport participation and exercise. J Am Coll Health 2005;54(2):87-94. [doi: 10.3200/JACH.54.2.87-94] [Medline: 16255320]
42. Egli T, Bland HW, Melton BF, Czech DR. Influence of age, sex, and race on college students' exercise motivation of physical activity. J Am Coll Health 2011;59(5):399-406. [doi: 10.1080/07448481.2010.513074] [Medline: 21500059]
43. Davis SR, Castelo-Branco C, Chedraui P, Lumsden MA, Nappi RE, Shah D, Writing Group of the International Menopause Society for World Menopause Day 2012. Understanding weight gain at menopause. Climacteric 2012 Oct;15(5):419-429. [doi: 10.3109/13697137.2012.707385] [Medline: 22978257]
44. Sammel M, Grisso J, Freeman E, Hollander L, Liu L, Liu S, et al. Weight gain among women in the late reproductive years. Fam Pract 2003 Aug;20(4):401-409. [doi: 10.1093/fampra/cmg411] [Medline: 12876110]
45. Arigo D, Butryn ML, Raggio GA, Stice E, Lowe MR. Predicting change in physical activity: a longitudinal investigation among weight-concerned college women. Ann Behav Med 2016 Oct;50(5):629-641 [FREE Full text] [doi: 10.1007/s12160-016-9788-6] [Medline: 26984236]
46. Cannioto R. Physical activity barriers, behaviors, and beliefs of overweight and obese working women: a preliminary analysis. Women Sport Phys Act J 2010;19(1):70-85. [doi: 10.1123/wspaj.19.1.70]
47. Reichert FF, Barros AJ, Domingues MR, Hallal PC. The role of perceived personal barriers to engagement in leisure-time physical activity. Am J Public Health 2007 Mar;97(3):515-519. [doi: 10.2105/AJPH.2005.070144] [Medline: 17267731]
48. Cash TF, Fleming EC. The impact of body image experiences: development of the body image quality of life inventory. Int J Eat Disord 2002 May;31(4):455-460. [doi: 10.1002/eat.10033] [Medline: 11948650]
49. Lewis-Smith H, Diedrichs PC, Rumsey N, Harcourt D. A systematic review of interventions on body image and disordered eating outcomes among women in midlife. Int J Eat Disord 2016 Jan;49(1):5-18. [doi: 10.1002/eat.22480] [Medline: 26607999]
50. Fuller-Tyszkiewicz M. Body image states in everyday life: evidence from ecological momentary assessment methodology. Body Image 2019 Dec;31:245-272. [doi: 10.1016/j.bodyim.2019.02.010] [Medline: 30852080]
51. di Bartolo P, Lin L, Montoya S, Neal H, Shaffer C. Are there 'healthy' and 'unhealthy' reasons for exercise? Examining individual differences in exercise motivations using the function of exercise scale. J Clin Sport Psychol 2007;1(2):120. [doi: 10.1123/jcsp.1.2.93]
52. Janssen I, Dugan SA, Karavolos K, Lynch EB, Powell LH. Correlates of 15-year maintenance of physical activity in middle-aged women. Int J Behav Med 2014 Jun;21(3):511-518 [FREE Full text] [doi: 10.1007/s12529-013-9324-z] [Medline: 23813123]
53. Segar M, Spruijt-Metz D, Nolen-Hoeksema S. Go figure? Body-shape motives are associated with decreased physical activity participation among midlife women. Sex Roles 2006 Feb;54(3-4):175-187. [doi: 10.1007/s11199-006-9336-5]
54. Smyth JM, Juth V, Ma J, Sliwinski M. A slice of life: ecologically valid methods for research on social relationships and health across the life span. Soc Personal Psychol Compass 2017 Sep 26;11(10):e12356. [doi: 10.1111/spc3.12356]
55. Arigo D, Pasko K, Mogle JA. Daily relations between social perceptions and physical activity among college women. Psychol Sport Exerc 2020 Mar;47:-. [doi: 10.1016/j.psychsport.2019.04.018] [Medline: 32831642]
56. McNeill LH, Kreuter MW, Subramanian SV. Social environment and physical activity: a review of concepts and evidence. Soc Sci Med 2006 Aug;63(4):1011-1022. [doi: 10.1016/j.socscimed.2006.03.012] [Medline: 16650513]

57. Stults-Kolehmainen MA, Sinha R. The effects of stress on physical activity and exercise. Sports Med 2014 Jan;44(1):81-121 [FREE Full text] [doi: 10.1007/s40279-013-0090-5] [Medline: 24030837]
58. Garett R, Liu S, Young SD. A longitudinal analysis of stress among incoming college freshmen. J Am Coll Health 2017 Jul;65(5):331-338 [FREE Full text] [doi: 10.1080/07448481.2017.1312413] [Medline: 28362146]
59. Cairney J, Kwan M, Veldhuizen S, Faulkner G. Who uses exercise as a coping strategy for stress? Results from a national survey of Canadians. J Phys Act Health 2014 Jul;11(5):908-916. [doi: 10.1123/jpah.2012-0107] [Medline: 23493043]
60. Rice E, Adair K, Tepper S, Fredrickson B. Perceived social integration predicts future physical activity through positive affect and spontaneous thoughts. Emotion 2020 Sep;20(6):1074-1083. [doi: 10.1037/emo0000616] [Medline: 31259591]
61. Dunton GF, Atienza AA, Castro CM, King AC. Using ecological momentary assessment to examine antecedents and correlates of physical activity bouts in adults age 50+ years: a pilot study. Ann Behav Med 2009 Dec;38(3):249-255 [FREE Full text] [doi: 10.1007/s12160-009-9141-4] [Medline: 20052568]
62. Gruber K. Social support for exercise and dietary habits among college students. Adolescence 2008;43(171):557-575. [Medline: 19086670]
63. Edwardson C, Gorely T, Pearson N, Atkin A. Sources of activity-related social support and adolescents' objectively measured after-school and weekend physical activity: gender and age differences. J Phys Act Health 2013 Nov;10(8):1153-1158. [doi: 10.1123/jpah.10.8.1153] [Medline: 23223792]
64. Hankonen N, Absetz P, Ghisletta P, Renner B, Uutela A. Gender differences in social cognitive determinants of exercise adoption. Psychol Health 2010 Jan;25(1):55-69. [doi: 10.1080/08870440902736972] [Medline: 20391207]
65. Cronon H, Biber D, Czech D. Understanding college females' intrinsic motives for physical activity: a qualitative comparison between athletes and non-athletes. J Sport 2015;4(2):- [FREE Full text]
66. Gill K, Overdorf V. Incentives for exercise in younger and older women. J Sport Behav 1994;17(2):87 [FREE Full text]
67. Shirado H, Fu F, Fowler JH, Christakis NA. Quality versus quantity of social ties in experimental cooperative networks. Nat Commun 2013;4:2814 [FREE Full text] [doi: 10.1038/ncomms3814] [Medline: 24226079]
68. Wu C, Stewart R, Huang H, Prince M, Liu S. The impact of quality and quantity of social support on help-seeking behavior prior to deliberate self-harm. Gen Hosp Psychiatry 2011;33(1):37-44. [doi: 10.1016/j.genhosppsych.2010.10.006] [Medline: 21353126]
69. Carmichael CL, Reis HT, Duberstein PR. In your 20s it's quantity, in your 30s it's quality: the prognostic value of social activity across 30 years of adulthood. Psychol Aging 2015 Mar;30(1):95-105 [FREE Full text] [doi: 10.1037/pag0000014] [Medline: 25774426]
70. Arigo D, Mogle JA, Brown MM, Pasko K, Travers L, Sweeder L, et al. Methods to assess social comparison processes within persons in daily life: a scoping review. Front Psychol 2019;10:2909 [FREE Full text] [doi: 10.3389/fpsyg.2019.02909] [Medline: 32038352]
71. Klein WM. Objective standards are not enough: affective, self-evaluative, and behavioral responses to social comparison information. J Pers Soc Psychol 1997 Apr;72(4):763-774. [doi: 10.1037//0022-3514.72.4.763] [Medline: 9108694]
72. Wood J, Wilson A. How important is social comparison? In: Handbook of Self and Identity. Second Edition. New York, USA: The Guilford Press; 2003.
73. Arigo D, Butryn ML. Prospective relations between social comparison orientation and weight loss outcomes. Behav Med 2019;45(3):249-254 [FREE Full text] [doi: 10.1080/08964289.2018.1481010] [Medline: 29944090]
74. Bennenbroek FT, Buunk BP, van der Zee KI, Grol B. Social comparison and patient information: what do cancer patients want? Patient Educ Couns 2002 May;47(1):5-12. [doi: 10.1016/s0738-3991(02)00018-6] [Medline: 12023095]
75. Buunk B, Ybema J. Social comparisons and occupational stress: the identification-contrast model. In: Health, coping, and well-being: perspectives from Social Comparison Theory. Mahwah, NJ: Lawrence Erlbaum Associates Inc; 1997.
76. Wills TA. Downward comparison principles in social psychology. Psychol Bull 1981;90(2):245-271. [doi: 10.1037/0033-2909.90.2.245]
77. Leahey TM, Crane MM, Pinto AM, Weinberg B, Kumar R, Wing RR. Effect of teammates on changes in physical activity in a statewide campaign. Prev Med 2010 Jul;51(1):45-49 [FREE Full text] [doi: 10.1016/j.ypmed.2010.04.004] [Medline: 20394768]
78. Uchino BN. Social support and health: a review of physiological processes potentially underlying links to disease outcomes. J Behav Med 2006 Aug;29(4):377-387. [doi: 10.1007/s10865-006-9056-5] [Medline: 16758315]
79. Irwin BC, Scorniaenchi J, Kerr NL, Eisenmann JC, Feltz DL. Aerobic exercise is promoted when individual performance affects the group: a test of the Kohler motivation gain effect. Ann Behav Med 2012 Oct;44(2):151-159. [doi: 10.1007/s12160-012-9367-4] [Medline: 22576339]
80. Bengoechea EG, Spence JC, McGannon KR. Gender differences in perceived environmental correlates of physical activity. Int J Behav Nutr Phys Act 2005 Sep 13;2:12. [doi: 10.1186/1479-5868-2-12] [Medline: 16159404]
81. Lockwood P. 'Someone like me can be successful': do college students need same-gender role models? Psychol Women Q 2016 Nov 25;30(1):36-46. [doi: 10.1111/j.1471-6402.2006.00260.x]
82. Arigo D, Smyth JM. The benefits of expressive writing on sleep difficulty and appearance concerns for college women. Psychol Health 2012;27(2):210-226. [doi: 10.1080/08870446.2011.558196] [Medline: 21678167]

83. Pila E, Barlow MA, Wrosch C, Sabiston CM. Comparing the body to superior others: associations with daily exercise and body evaluation in men and women. Psychol Sport Exerc 2016 Nov;27:120-127. [doi: 10.1016/j.psychsport.2016.08.001]
84. Arigo D. Promoting physical activity among women using wearable technology and online social connectivity: a feasibility study. Health Psychol Behav Med 2015 Dec 31;3(1):391-409. [doi: 10.1080/21642850.2015.1118350]
85. Brakel TM, Dijkstra A, Buunk AP, Siero FW. Impact of social comparison on cancer survivors' quality of life: an experimental field study. Health Psychol 2012 Sep;31(5):660-670. [doi: 10.1037/a0026572] [Medline: 22149129]
86. Haber M, Cohen J, Lucas T, Baltes B. The relationship between self-reported received and perceived social support: a meta-analytic review. Am J Community Psychol 2007 Mar;39(1-2):133-144. [doi: 10.1007/s10464-007-9100-9] [Medline: 17308966]
87. van der Zee K, Buunk B, Sanderman R, Botke G, van den Bergh F. The Big Five and identification-contrast processes in social comparison in adjustment to cancer treatment. Eur J Pers 1999;13(4):307-326. [doi: 10.1002/(sici)1099-0984(199907/08)13:4<307::aid-per342>3.0.co;2-r]
88. van der Zee K, Buunk B, Sanderman R, Botke G, van den Bergh F. Social comparison and coping with cancer treatment. Pers Ind Diff 2000 Jan;28(1):17-34. [doi: 10.1016/s0191-8869(99)00045-8]
89. Arigo D, Smyth JM, Suls JM. Perceptions of similarity and response to selected comparison targets in type 2 diabetes. Psychol Health 2015;30(10):1206-1220. [doi: 10.1080/08870446.2015.1040018] [Medline: 25871344]
90. Stone AA, Smyth JM, Pickering T, Schwartz J. Daily mood variability: form of diurnal patterns and determinants of diurnal patterns. J Appl Social Pyschol 1996 Jul;26(14):1286-1305. [doi: 10.1111/j.1559-1816.1996.tb01781.x]
91. Sperry S, Walsh M, Kwapil T. Emotion dynamics concurrently and prospectively predict mood psychopathology. J Affect Disord 2020 Jan 15;261:67-75. [doi: 10.1016/j.jad.2019.09.076] [Medline: 31600589]
92. Hollon S, Beck A. Cognitivecognitive-behavioral therapies. In: Lambert MJ, editor. Bergin and Garfield's Handbook of Psychotherapy and Behavior Change. Hoboken, NJ: Wiley & Sons Inc; 2013.
93. Liao Y, Chou C, Huh J, Leventhal A, Dunton G. Examining acute bi-directional relationships between affect, physical feeling states, and physical activity in free-living situations using electronic ecological momentary assessment. J Behav Med 2017 Jun;40(3):445-457 [FREE Full text] [doi: 10.1007/s10865-016-9808-9] [Medline: 27766481]
94. Liao Y, Shonkoff ET, Dunton GF. The acute relationships between affect, physical feeling states, and physical activity in daily life: a review of current evidence. Front Psychol 2015;6:1975 [FREE Full text] [doi: 10.3389/fpsyg.2015.01975] [Medline: 26779049]
95. Kelsey KS, DeVellis BM, Begum M, Belton L, Hooten EG, Campbell MK. Positive affect, exercise and self-reported health in blue-collar women. Am J Health Behav 2006;30(2):199-207. [doi: 10.5555/ajhb.2006.30.2.199] [Medline: 16533104]
96. Pasco JA, Jacka FN, Williams LJ, Brennan SL, Leslie E, Berk M. Don't worry, be active: positive affect and habitual physical activity. Aust N Z J Psychiatry 2011 Dec;45(12):1047-1052. [doi: 10.3109/00048674.2011.621063] [Medline: 22059484]
97. Maher JP, Dzubur E, Nordgren R, Huh J, Chou C, Hedeker D, et al. Do fluctuations in positive affective and physical feeling states predict physical activity and sedentary time? Psychol Sport Exerc 2019 Mar;41:153-161 [FREE Full text] [doi: 10.1016/j.psychsport.2018.01.011] [Medline: 30853854]
98. Bennett EV, Hurd Clarke L, Kowalski KC, Crocker PR. From pleasure and pride to the fear of decline: exploring the emotions in older women's physical activity narratives. Psychol Sport Exerc 2017 Nov;33:113-122. [doi: 10.1016/j.psychsport.2017.08.012]
99. Arent S, Landers D, Etnier J. The effects of exercise on mood in older adults: a meta-analytic review. J Aging Phys Act 2020;8(4):430. [doi: 10.1123/japa.8.4.407]
100. Dinas PC, Koutedakis Y, Flouris AD. Effects of exercise and physical activity on depression. Ir J Med Sci 2011 Jun;180(2):319-325. [doi: 10.1007/s11845-010-0633-9] [Medline: 21076975]
101. Kanning M, Schlicht W. Be active and become happy: an ecological momentary assessment of physical activity and mood. J Sport Exerc Psychol 2010 Apr;32(2):253-261. [doi: 10.1123/jsep.32.2.253] [Medline: 20479481]
102. Dugan SA, Bromberger JT, Segawa E, Avery E, Sternfeld B. Association between physical activity and depressive symptoms: midlife women in SWAN. Med Sci Sports Exerc 2015 Feb;47(2):335-342 [FREE Full text] [doi: 10.1249/MSS.0000000000000407] [Medline: 24914519]
103. Im E, Ham OK, Chee E, Chee W. Physical activity and depressive symptoms in four ethnic groups of midlife women. West J Nurs Res 2015 Jun;37(6):746-766 [FREE Full text] [doi: 10.1177/0193945914537123] [Medline: 24879749]
104. Pérez-López FR, Martínez-Domínguez SJ, Lajusticia H, Chedraui P, Health Outcomes Systematic Analyses Project. Effects of programmed exercise on depressive symptoms in midlife and older women: a meta-analysis of randomized controlled trials. Maturitas 2017 Dec;106:38-47. [doi: 10.1016/j.maturitas.2017.09.001] [Medline: 29150165]
105. Daley A, Stokes-Lampard H, Macarthur C. Exercise to reduce vasomotor and other menopausal symptoms: a review. Maturitas 2009 Jul 20;63(3):176-180. [doi: 10.1016/j.maturitas.2009.02.004] [Medline: 19285813]
106. Yang YS, Ryu GW, Choi M. Methodological strategies for ecological momentary assessment to evaluate mood and stress in adult patients using mobile phones: systematic review. JMIR Mhealth Uhealth 2019 Apr 1;7(4):e11215 [FREE Full text] [doi: 10.2196/11215] [Medline: 30932866]

107. Liu H, Xie QW, Lou VW. Everyday social interactions and intra-individual variability in affect: a systematic review and meta-analysis of ecological momentary assessment studies. Motiv Emot 2018 Oct 9;43(2):339-353. [doi: 10.1007/s11031-018-9735-x]
108. Caltabiano ML, Ghafari N. The effect of social comparison processes, athletic prototypes, perceived behavioural control and perceived threat on physical activity. Int J Health Promot Educ 2011 Jan;49(2):44-52. [doi: 10.1080/14635240.2011.10708208]
109. Li J, Liu X, Ma L, Zhang W. Users' intention to continue using social fitness-tracking apps: expectation confirmation theory and social comparison theory perspective. Inform Health Soc Care 2019 Sep;44(3):298-312. [doi: 10.1080/17538157.2018.1434179] [Medline: 29504821]
110. Dunton GF. Sustaining health-protective behaviors such as physical activity and healthy eating. J Am Med Assoc 2018 Aug 21;320(7):639-640. [doi: 10.1001/jama.2018.6621] [Medline: 29852046]
111. Ehlers DK, Huberty J, Buman M, Hooker S, Todd M, de Vreede GJ. A novel inexpensive use of smartphone technology for ecological momentary assessment in middle-aged women. J Phys Act Health 2016 Mar;13(3):262-268. [doi: 10.1123/jpah.2015-0059] [Medline: 26284689]
112. Elavsky S, Molenaar PC, Gold CH, Williams NI, Aronson KR. Daily physical activity and menopausal hot flashes: applying a novel within-person approach to demonstrate individual differences. Maturitas 2012 Mar;71(3):287-293 [FREE Full text] [doi: 10.1016/j.maturitas.2011.12.011] [Medline: 22226629]
113. Elavsky S, Kishida M, Mogle JA. Concurrent and lagged relations between momentary affect and sedentary behavior in middle-aged women. Menopause 2016 Aug;23(8):919-923 [FREE Full text] [doi: 10.1097/GME.0000000000000645] [Medline: 27326822]
114. Dunton GF. Ecological momentary assessment in physical activity research. Exerc Sport Sci Rev 2017 Jan;45(1):48-54 [FREE Full text] [doi: 10.1249/JES.0000000000000092] [Medline: 27741022]
115. Arigo D, Mogle JA, Brown MM, Roberts SR, Pasko K, Butryn ML, et al. Differences between accelerometer cut point methods among midlife women with cardiovascular risk markers. Menopause 2020 May;27(5):559-567. [doi: 10.1097/GME.0000000000001498] [Medline: 32049926]
116. Gabriel KP, Sidney S, Jacobs JD, Whitaker K, Carnethon M, Lewis C, et al. Ten-year changes in accelerometer-based physical activity and sedentary time during midlife: the Cardia study. Am J Epidemiol 2018 Oct 1;187(10):2145-2150. [doi: 10.1093/aje/kwy117] [Medline: 29893772]
117. Hox J. Multilevel Analysis: Techniques and Applications. 2nd Edition. New York, USA: Routledge; 2002.
118. Maas CJ, Hox JJ. Sufficient sample sizes for multilevel modeling. Methodology 2005 Jan;1(3):86-92. [doi: 10.1027/1614-2241.1.3.86]
119. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992 Jun;30(6):473-483. [Medline: 1593914]
120. Sechrist KR, Walker SN, Pender NJ. Development and psychometric evaluation of the exercise benefits/barriers scale. Res Nurs Health 1987 Dec;10(6):357-365. [doi: 10.1002/nur.4770100603] [Medline: 3423307]
121. Resnick B, Zimmerman SI, Orwig D, Furstenberg A, Magaziner J. Outcome expectations for exercise scale: utility and psychometrics. J Gerontol B Psychol Sci Soc Sci 2000 Nov;55(6):S352-S356. [doi: 10.1093/geronb/55.6.s352] [Medline: 11078112]
122. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol 1988 Dec;56(6):893-897. [doi: 10.1037//0022-006x.56.6.893] [Medline: 3204199]
123. Radloff LS. The CES-D scale. Appl Psychol Meas 2016 Jul 26;1(3):385-401. [doi: 10.1177/014662167700100306]
124. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983 Dec;24(4):385-396. [Medline: 6668417]
125. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res 1989 May;28(2):193-213. [doi: 10.1016/0165-1781(89)90047-4] [Medline: 2748771]
126. Robichaud M, Dugas MJ. Negative problem orientation (part II): construct validity and specificity to worry. Behav Res Ther 2005 Mar;43(3):403-412. [doi: 10.1016/j.brat.2004.02.008] [Medline: 15680934]
127. Gibbons FX, Buunk BP. Individual differences in social comparison: development of a scale of social comparison orientation. J Pers Soc Psychol 1999 Jan;76(1):129-142. [doi: 10.1037//0022-3514.76.1.129] [Medline: 9972558]
128. Vaux A, Phillips J, Holly L, Thomson B, Williams D, Stewart D. The social support appraisals (SS-A) scaletudies of reliability and validity. Am J Community Psychol 1986;14(2):195-218. [doi: 10.1007/bf00911821]
129. Smyth JM, Smyth JM. Ecological momentary assessment research in behavioral medicine. J Happiness Stud 2003;4(1):35-52. [doi: 10.1023/A:1023657221954]
130. Thøgersen-Ntoumani C, Dodos L, Chatzisarantis N, Ntoumanis N. A diary study of self-compassion, upward social comparisons, and body image-related outcomes. Appl Psychol Health Well Being 2017 Jul;9(2):242-258. [doi: 10.1111/aphw.12089] [Medline: 28598025]

131. Zhaoyang R, Sliwinski MJ, Martire LM, Smyth JM. Age differences in adults' daily social interactions: an ecological momentary assessment study. Psychol Aging 2018 Jun;33(4):607-618 [FREE Full text] [doi: 10.1037/pag0000242] [Medline: 29708385]
132. Leahey TM, Crowther JH, Ciesla JA. An ecological momentary assessment of the effects of weight and shape social comparisons on women with eating pathology, high body dissatisfaction, and low body dissatisfaction. Behav Ther 2011 Jun;42(2):197-210 [FREE Full text] [doi: 10.1016/j.beth.2010.07.003] [Medline: 21496506]
133. Wheeler L, Miyake K. Social comparison in everyday life. J Pers Soc Psychol 1992;62(5):760-773. [doi: 10.1037/0022-3514.62.5.760]
134. Dunton G, Liao Y, Intille S, Wolch J, Pentz M. Physical and social contextual influences on children's leisure-time physical activity: an ecological momentary assessment study. J Phys Act Health 2011 Jan;8(Suppl 1):S103-S108. [doi: 10.1123/jpah.8.s1.s103] [Medline: 21350250]
135. Dockray S, Grant N, Stone AA, Kahneman D, Wardle J, Steptoe A. A comparison of affect ratings obtained with ecological momentary assessment and the day reconstruction method. Soc Indic Res 2010 Nov;99(2):269-283 [FREE Full text] [doi: 10.1007/s11205-010-9578-7] [Medline: 21113328]
136. Schumacher L, Thomas C, Ainsworth M, Arigo D. Social predictors of physical activity intentions and behavior among college women. J Behav Med 2020:- in press(forthcoming).
137. Maher JP, Rhodes RE, Dzubur E, Huh J, Intille S, Dunton GF. Momentary assessment of physical activity intention-behavior coupling in adults. Transl Behav Med 2017 Dec;7(4):709-718 [FREE Full text] [doi: 10.1007/s13142-017-0472-6] [Medline: 28155108]
138. Homan KJ, Tylka TL. Appearance-based exercise motivation moderates the relationship between exercise frequency and positive body image. Body Image 2014 Mar;11(2):101-108. [doi: 10.1016/j.bodyim.2014.01.003] [Medline: 24529336]
139. Littlewood DL, Kyle SD, Carter L, Peters S, Pratt D, Gooding P. Short sleep duration and poor sleep quality predict next-day suicidal ideation: an ecological momentary assessment study. Psychol Med 2019 Feb;49(3):403-411 [FREE Full text] [doi: 10.1017/S0033291718001009] [Medline: 29697037]
140. O'Connor DB, Jones F, Conner M, McMillan B, Ferguson E. Effects of daily hassles and eating style on eating behavior. Health Psychol 2008 Jan;27(1S):S20-S31. [doi: 10.1037/0278-6133.27.1.S20] [Medline: 18248102]
141. May M, Junghaenel DU, Ono M, Stone AA, Schneider S. Ecological momentary assessment methodology in chronic pain research: a systematic review. J Pain 2018 Jul;19(7):699-716 [FREE Full text] [doi: 10.1016/j.jpain.2018.01.006] [Medline: 29371113]
142. Kim J, Conroy D, Smyth J. Bidirectional associations of momentary affect with physical activity and sedentary behaviors in working adults. Ann Behav Med 2020 Mar 24;54(4):268-279. [doi: 10.1093/abm/kaz045] [Medline: 31613961]
143. Conner T, Lehman B. Getting started: launching a study in daily life. In: Handbook of Research Methods for Studying Daily Life. New York, USA: The Guilford Press; 2012.
144. Schneider S, Stone AA, Schwartz JE, Broderick JE. Peak and end effects in patients' daily recall of pain and fatigue: a within-subjects analysis. J Pain 2011 Feb;12(2):228-235 [FREE Full text] [doi: 10.1016/j.jpain.2010.07.001] [Medline: 20817615]
145. Fardouly J, Pinkus RT, Vartanian LR. The impact of appearance comparisons made through social media, traditional media, and in person in women's everyday lives. Body Image 2017 Mar;20:31-39. [doi: 10.1016/j.bodyim.2016.11.002] [Medline: 27907812]
146. Fuller-Tyszkiewicz M, Chhouk J, McCann L, Urbina G, Vuo H, Krug I, et al. Appearance comparison and other appearance-related influences on body dissatisfaction in everyday life. Body Image 2019 Mar;28:101-109. [doi: 10.1016/j.bodyim.2019.01.002] [Medline: 30639976]

Abbreviations

CVD: cardiovascular disease
EMA: ecological momentary assessment
PA: physical activity
WHADE: Women’s Health And Daily Experiences

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Protocol

Digitalization and the Social Lives of Older Adults: Protocol for a Microlongitudinal Study

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Abstract

Background: Digital technologies are increasingly pervading our daily lives. Although older adults started using digital technologies later than other age groups, they are increasingly adopting these technologies, especially with the goal of communicating with others. However, less is known about how online social activities are embedded in older adults' daily lives, how they complement other (offline) social activities, and how they contribute to social connectedness and well-being.

Objective: Data generated by this project will allow us to understand how older adults use digital communication in their daily lives to communicate with others, how this relates to well-being and social connectedness, and how communication using digital technologies differs from other types of communication depending on situational and individual characteristics.

Methods: Microlongitudinal data were collected from 120 older adults from German-speaking regions of Switzerland to examine these questions. Data collection took place from April 2019 to October 2019. Data collection took place over different time scales, including event-based (reporting all social interactions for 21 days), daily (well-being, loneliness, and technology use every evening for 21 days), hourly (cortisol assessments 6 times per day for 3 days), and baseline (relevant interindividual characteristics, including sociodemographics, health, technology use, personality, and cognitive performance) assessments.

Results: Data collection for this study was completed in November 2019. Participants reported an average of 96.35 interactions across the 21 days. Among the total 11,453 interactions, 5494 (47.97%) were face-to-face, and around 16% each were interactions by phone (1858, 16.16%), email (1858, 16.22%), and text message (1853, 16.18%). Otherwise, 246 (2.15%) of the interactions took place on social media, 96 (0.84)% were letters, and 54 (0.47%) of the interactions took place on videochat.

Conclusions: Participants used a variety of modalities in their daily communication, including digital means such as text messages, email, and video calls. Further analysis will provide more detail as to the role that communication via digital media plays in older adults' daily lives.

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KEYWORDS

digitalization; older adults; microlongitudinal; social communication

Introduction

Background

Social interactions are a basic human need, serving a multitude of purposes by fulfilling the need for social integration and by providing feelings of closeness, relatedness, social support, and belonging with others [1-7]. The quantity and quality of social interactions have an impact on subjective well-being and quality of life [8,9], and are associated with better health [10-13].

The digital revolution has offered more and more possibilities for individuals to connect with others and share experiences. Younger people use the internet almost universally, while older adults increasingly use digital technology to communicate, albeit at lower proportions than younger adults [14]. Although the use of digital technology comes naturally to those who have been familiar with it their entire lives, or have used the technology during their professional lives, older generations might find it more difficult to become accustomed to using these new technologies. However, these technologies could be more and more useful for older people today. Growing distances between family members as well as declining marriage and birth rates [15,16] may lead to concerns that older adults are at increasing risk of loneliness. This stands in contrast to findings that show lower levels of loneliness in older adults currently compared to previous generations [17,18]. Therefore, it is vital to investigate possible mechanisms by which older adults might compensate for weaker family ties.

One compensatory mechanism is the move from mainly family-oriented to more friend-focused social circles [19,20]. In addition, a greater variety of living situations have become more accepted in recent years; for example, being divorced does not affect social loneliness to the same extent as in previous generations [21]. Finally, the digital revolution offers older adults the opportunity to stay in close contact with family and friends, regardless of geographical distance, as well as the opportunity to connect with new social contacts based on shared interests [22].

Older adults use the internet at increasing rates [14,23]. In Switzerland, 32% of older adults report having a smartphone and 26% own a tablet computer [24]. The internet is used most commonly to communicate with others [25], and the same is true for older adults' internet use: in Switzerland, 80% of older internet users report using the internet for social interactions [23]. In addition, older internet users agree that the internet has made it easier for them to reach people [26]. Despite the increase in older adults' internet use, some older people still do not have access to digital technologies. Sociodemographic characteristics play an important role [27], such as education [28] and age [14,23]. Furthermore, cognitive ability is a stronger predictor of older adults' internet use than age alone [29]. Need for cognition, a personality trait that reflects a preference for cognitively effortful activities, is also positively associated with the frequency of internet use in older adults [30].

Previous research has primarily focused on factors that predict internet use in older adults, as well as the activities older adults perform online. However, relatively little is known about how older adults integrate digital technologies into their day-to-day lives [31]. To begin to understand the role of digital technologies for social interaction and for reducing loneliness in old age, it is vital to investigate the (digital) social lives of older adults.

Information about social interactions is often gathered through retrospective self-reports; however, these responses may be biased by more salient recent events [32]. In contrast, in an event-contingent, microlongitudinal approach, participants answer a set of questions each time a prespecified event, in this case a social interaction, occurs [33]. This enables participants to report their experiences and reactions to this event immediately, or soon after it occurs, and minimizes retrospective bias. Several studies have investigated social interactions using such microlongitudinal designs [34,35]. One study reported an average of 7 interactions that lasted 5 minutes or longer [36,37], highlighting the large amount of data that can be collected using such a design. Thus, detailed information about the social lives of older adults will facilitate the investigation of a variety of research questions related to older adults' use of digital technology.

This Study

To study the day-to-day social experiences of older internet users, this study is based on an event-contingent microlongitudinal design. Specifically, participants were asked to complete a brief protocol on every social interaction lasting 5 minutes or longer, and on every text-based interaction (eg, letter, text message, email) over a period of 3 weeks. The brief protocol assessed information about the duration, conversation partner(s), and purpose, as well as the perceived quality of the conversation.

In addition to the interaction reports, participants were asked to fill in questionnaires every evening on their daily mood, health, and feelings of loneliness. At baseline, data on global measures of technology use, cognition, personality, loneliness, and quality of life were collected. Finally, participants were asked to provide 6 saliva samples per day for 3 days, which will be used to examine daily trajectories of diurnal cortisol. Salivary cortisol is a biomarker that is commonly used to assess stress and resilience [38] throughout the lifespan and is also related to loneliness [39]. Salivary cortisol has a detectable daily rhythm, showing high levels in the morning, around 30 minutes after awakening, and decreasing throughout the day [40,41]. This daily rhythm of cortisol secretion can reliably be detected in older adults, despite increased intraindividual variability [42].

Research Goals

The goal of this study is to understand daily social experiences and their associations with well-being in older internet users. Specifically, the analyses will focus on individual patterns of social communication and their relationship with facets of daily and global well-being, taking into consideration the modalities through which participants communicate.

Methods

Participants and Procedure

A total of 120 community-dwelling participants were recruited for this project. Inclusion criteria were being aged 65 years and above, using digital devices to communicate, sufficient vision and hearing, and being fluent in German. Inclusion criteria were aged 65 years and above, using digital devices to communicate, sufficient vision and hearing, and being fluent in German.

Participants were recruited via advertisements in local and national newspapers, and through a database of participants hosted at the University of Zurich. Initial contact took place via telephone or email, as preferred by the participant. Eligible participants were invited to a baseline session at the University

of Zurich, where they were given detailed information on the study, had the opportunity to ask questions before giving informed consent, received detailed instruction on the study protocol, and received study materials to complete the protocol, including the study smartphones, and Salivettes (Sarstedt AG & Co, Nürnbrecht, Germany) to prepare saliva samples. All information was also provided in written format for participants to take away with them. In addition, they received a phone number to call in case of any questions or problems. The study took place over 21 days starting the day after this initial session. After the first day of the study, participants received a phone call from a research assistant to clarify potential questions. During the study period, a research assistant was on call to answer questions and provide technical support. After 21 days, participants visited the lab to return study materials, give feedback and share their experiences, and to complete a battery of cognitive tests. Participants received CHF 150 (~US $164) to thank them for their participation.

This study protocol was reviewed by the Ethics Committee of the Faculty of Arts and Social Sciences at the University of Zurich (Nr. 19.2.17).

Design

This study is planned according to a microlongitudinal design with data collection occurring at different time intervals: event-based, time-based, daily, and single assessments at baseline, as summarized in Textbox 1. Participants were required to complete a brief protocol on every spoken social interaction lasting 5 minutes or longer and every text-based social interaction for a period of 21 days. The brief protocol assessed information about the duration, conversation partner(s), purpose, as well as the perceived quality of the conversation. In addition, data on participants' mood, loneliness, health, and technological issues were collected daily. For the first 3 days of the study period, participants were asked to prepare 6 saliva samples per day. Finally, questionnaires assessing sociodemographic information, health, quality of life, personality, and technology use and attitudes, as well as cognitive ability tests were completed at baseline.

Textbox 1. Data that will be collected throughout the project and timeline of data collection.

- Event-contingent measures

What: Interaction protocol

When: To be filled in after each interaction lasting more than 5 min

- Time-based/event-contingent combined (3 days)

What: Cortisol

When: After waking up, 30 minutes later, 12 pm, 4 pm, 8 pm, Just before going to bed

- Well-being

What: Mood, Loneliness, Health, Technical Issues

When: Daily

- Individual characteristics

What: Personality, Cognitive Performance, Loneliness, Quality of Life, Technology Use

When: Baseline

Apparatus

Interaction Data

Participants were given an iPhone 4S at the introductory session at the University of Zurich. The questionnaires were administered with the app "iDialogPad" (G Mutz, Cologne, Germany). This questionnaire was an adaptation of the Rochester Interaction Record [43] and included questions on the time, duration, and communication medium of the interaction; the purpose of the interaction and the interaction partner; as well as affective states and interpersonal behavior during and after the interaction (the full questionnaire can be accessed on the Open Science Framework platform [44]). Participants were asked to record interactions based on spoken conversations lasting longer than 5 minutes and any text-based conversation (eg, letters, emails, text messages). For conversations by text message, we asked participants to immediately record any text message they sent or received, unless they were aware from the beginning that there would be a longer exchange, in which case they could record this as one conversation, and indicate how many text messages each person sent or received.

Daily Well-Being

Participants filled in the Positive and Negative Affect Scale [45] each evening, with the addition of 4 items (2 positive and 2 negative) assessing loneliness. They also indicated the state of their health and physical well-being, as well as whether they had experienced any problems with technology (not necessarily related to social communication) that day. If they encountered such a problem, they were asked to describe it briefly using a few words. A daily reminder on the study smartphone reminded them to complete this questionnaire.

Cortisol

Participants were asked to provide a total of 18 saliva samples for 3 days (6 samples per day). The samples were prepared using Salivettes, which were labeled with the day and time they were intended to be used and the participant number. Participants were instructed to provide the first sample of each day before getting out of bed in the morning; the second sample 30 minutes later; the third, fourth, and fifth samples at 12 pm, 4 pm, and 8 pm, respectively; and the sixth sample just before going to bed. They were reminded by notifications on the study smartphone to collect each sample. Participants were asked not to eat, drink, smoke, or do any exercise for 30 minutes before providing each sample. Along with each sample, they were asked about their activities during the 30 minutes prior to providing the sample. During the initial session at the University of Zurich, research assistants explained exactly how to prepare the saliva samples using the Salivettes, and gave the participants the opportunity to try this out.

Participants were instructed to keep the samples in the freezer before bringing them to a final session at the University of Zurich. They were supplied with freezer elements to keep the samples cool during transport back to the university after the data collection period. Saliva samples were stored in a freezer until they were analyzed at the laboratory of the Clinical Psychology and Psychotherapy unit at the University of Zurich.

Interaction Partners

In the interaction questionnaire, participants were asked to report who they were interacting with by assigning a set of initials or another identifier to each interaction partner. To be able to remember the identifiers, participants were provided a form to note down the information. This form was not collected from participants to protect the identity of the interaction partners.

At the final session at the University of Zurich, participants were asked to fill in a short questionnaire asking about their relationship with each interaction partner. This also included questions about the age of the interaction partner as well as the participant's relationship to them, how long they had known each interaction partner, and their spatial distance. In addition, participants provided information about their social network using the hierarchical mapping technique [46]. Participants indicated how close they felt to each interaction partner and also included any other individuals whom they consider to be part of their social circle but who they were not in touch with during the study period. The full codebook can be accessed on Open Science Framework [44].

Baseline Measures

Participants filled in a set of questionnaires in their own time during the study period. They were given a choice between filling in an online version of the questionnaire that they could access through an emailed link or a pen-and-paper version that they could take home with them at the initial study session. The questionnaire included sociodemographic information, technology use [47-51], communication preferences, concerns related to internet use, social network [52,53], loneliness [54], well-being [45,55], health [56,57], and personality [1,58-64]. The full codebook can be accessed on Open Science Framework [44].

Cognitive Measures

Participants completed a battery of cognitive tests at the final session, including measures of reasoning (subtests of the Berlin Intelligence Structure test: numerical reasoning, delayed recall, numerical/logical reasoning, verbal reasoning/general knowledge, spatial reasoning, verbal reasoning, numerical reasoning/memory [65]) and the Leistungsprüfsystem für 50-90-jährige (LPS 50+; subtest 3, spatial reasoning [66], perceptual speed [67,68], vocabulary [69]).

Results

Sample Demographics and Descriptive Characteristics

Data collection started in April 2019 and was completed in November 2019. Participants were on average 73 years old (SD 5.08, range 66-95 years). Most of the participants were highly educated: 26.7% (32/120) completed their school education with the Swiss *Matura*, a secondary school degree qualifying for university education. The vast majority (98.3%, 118/120) completed further training after school with 22.5% (27/120) completing university, including 4.2% (5/120) participants with a PhD.

In general, participants were very technologically versed. On the computer proficiency questionnaire [47], they scored an average of 132 out of 160 possible points; 96.7% (116/120) of participants owned a computer, 86.7% (104/120) owned a smartphone, and 65.8% (79/120) owned a tablet. Generally, 40.0% (48/120) of participants reported that using the internet to communicate had made them feel closer to other people, 50.0% (60/120) reported that nothing had changed, and 10.0% (12/120) reported that they felt less close to other people.

Participants reported an average of 96.35 interactions across the 21 days (SD 67.57, range 9-517). These data are summarized Table 1. Women reported a higher average of interactions than men. The majority of interactions were face-to-face, followed by interactions by phone, email, and text message with relatively equal frequencies. Social media, letters, and videochat were the least frequent types of interactions reported.

Most conversations took place with people the participants knew, with less than 10% of the conversations taking place with people they did not know and service providers, respectively.

Table 1. Descriptive characteristics of the reported conversations (N=11,453).

Characteristic	Value
Number of conversations reported (mean)	
Total	96.35
Women	98
Men	71
Conversation modality, n (%)	
Face to Face	5494 (47.97)
Phone	1851 (16.16)
Email	1858 (16.22)
Text	1853 (16.18)
Social media	246 (2.15)
Letters	96 (0.84)
Videochat	54 (0.47)
Conversation partner, n (%)	
Known to the participant	9700 (84.69)
Unknown to the participant	936 (8.17)
Service providers	817 (7.13)

Examples of Planned Analyses

These data will enable more detailed investigation of how daily social interactions can shape older adults' daily lives, as well as how intraindividual interaction patterns are related to individual differences such as personality or cognition. Specifically, we will also be able to further examine the role of different patterns of communication through digital modalities in older adults' daily lives and well-being. To analyze the interplay between (digital) social communication, well-being, and individual differences, we will conduct multilevel analyses to capture the individual variety in communication patterns. This includes investigating the relationship between daily communication patterns and mood in relation to personality and closeness with interaction partners, the relationship between personality (especially openness) and use of digital technologies, and the relationships among daily communication patterns, loneliness, and diurnal cortisol.

Discussion

With the increasing digitalization of our society, communication using digital technologies is becoming more prevalent. Older adults have also adopted these technologies and are starting to use them widely. The data generated by this project will allow us to understand how older adults are using digital communication technologies in their day-to-day lives, and how the use of these technologies is related to social connectedness and well-being. Specifically, one of the major aims of our study is to understand the role of the quantity and quality of social interaction for social connectedness and well-being, and differences between communication media in this association. Furthermore, we will examine the role of situational and individual characteristics. Overall, the available data will allow us to examine these questions in rich detail.

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Conflicts of Interest

None declared.

References

1. Baumeister RF, Leary MR. The Need to Belong. Desire for Interpersonal Attachments as a Fundamental Human Motivation. In: Zukauskiene R, editor. Interpersonal Development. London: Routledge; 2017:57-89.
2. Cutrona CE, Russell D. The provisions of social relationships and adaptations to stress. In: Jones WH, Perlman D, editors. Advances in Personal Relationships. Greenwich, CT: JAI Press; 1987:37-67.
3. Deci EL, Ryan RM. The "What" and "Why" of Goal Pursuits: Human Needs and the Self-Determination of Behavior. Psychol Inq 2000 Oct;11(4):227-268. [doi: 10.1207/s15327965pli1104_01]

4. Fiori KL, Smith J, Antonucci TC. Social network types among older adults: a multidimensional approach. J Gerontol B Psychol Sci Soc Sci 2007 Nov 01;62(6):P322-P330. [doi: 10.1093/geronb/62.6.p322] [Medline: 18079416]
5. Gleason MEJ, Iida M. Social support. In: Mikulincer M, Shaver PR, Simpson JA, Dovidio JF, editors. APA Handbook of Personality and Social Psychology, Vol 3, Interpersonal Relationships. Washington, DC: American Psychological Association; 2015:351-370.
6. McAdams DP, Constantian CA. Intimacy and affiliation motives in daily living: An experience sampling analysis. J Pers Soc Psychol 1983;45(4):851-861. [doi: 10.1037/0022-3514.45.4.851]
7. Uchino BN. Understanding the Links Between Social Support and Physical Health: A Life-Span Perspective With Emphasis on the Separability of Perceived and Received Support. Perspect Psychol Sci 2009 May;4(3):236-255. [doi: 10.1111/j.1745-6924.2009.01122.x] [Medline: 26158961]
8. Diener E, Seligman MEP. Very happy people. Psychol Sci 2002 Jan;13(1):81-84. [doi: 10.1111/1467-9280.00415] [Medline: 11894851]
9. Myers D. Close relationships and quality of life. In: Kahnemann D, Diener E, Schwarz N, editors. Well-Being: The Foundations of Hedonic Psychology. New York, NY: Russell Sage Foundation; 1999:374-391.
10. Fiori KL, Jager J. The impact of social support networks on mental and physical health in the transition to older adulthood. Int J Behav Dev 2012 Mar 09;36(2):117-129. [doi: 10.1177/0165025411424089]
11. House JS, Landis K, Umberson D. Social relationships and health. Science 1988 Jul 29;241(4865):540-545. [doi: 10.1126/science.3399889] [Medline: 3399889]
12. Litwin H, Shiovitz-Ezra S. Network type and mortality risk in later life. Gerontologist 2006 Dec 01;46(6):735-743. [doi: 10.1093/geront/46.6.735] [Medline: 17169929]
13. Pietromonaco PR, Collins NL. Interpersonal mechanisms linking close relationships to health. Am Psychol 2017 Sep;72(6):531-542 [FREE Full text] [doi: 10.1037/amp0000129] [Medline: 28880100]
14. Zickuhr K, Madden M. Older adults and internet use. 2012. URL: https://www.pewresearch.org/internet/2012/06/06/older-adults-and-internet-use/ [accessed 2020-06-03]
15. Kalmijn M. Explaining cross-national differences in marriage, cohabitation, and divorce in Europe, 1990-2000. Popul Stud (Camb) 2007 Nov;61(3):243-263. [doi: 10.1080/00324720701571806] [Medline: 17979001]
16. World Health Statistics 2010. World Health Organization. 2010. URL: https://www.who.int/whosis/whostat/2010/en/ [accessed 2019-05-09]
17. Eloranta S, Arve S, Isoaho H, Lehtonen A, Viitanen M. Loneliness of older people aged 70: a comparison of two Finnish cohorts born 20 years apart. Arch Gerontol Geriatr 2015;61(2):254-260. [doi: 10.1016/j.archger.2015.06.004] [Medline: 26143336]
18. Hülür G, Drewelies J, Eibich P, Düzel S, Demuth I, Ghisletta P, et al. Cohort Differences in Psychosocial Function over 20 Years: Current Older Adults Feel Less Lonely and Less Dependent on External Circumstances. Gerontology 2016;62(3):354-361. [doi: 10.1159/000438991] [Medline: 26820135]
19. Böger A, Huxhold O, Wolff JK. Wahlverwandtschaften: Sind Freundschaften für die soziale Integration wichtiger geworden? In: Mahne K, Wolff JK, Simonson J, Tesch-Römer C, editors. Altern im Wandel. Wiesbaden, Germany: Springer Fachmedien; 2017:257-271.
20. Suanet B, van Tilburg TG, Broese van Groenou MI. Nonkin in older adults' personal networks: more important among later cohorts? J Gerontol B Psychol Sci Soc Sci 2013 Jul;68(4):633-643. [doi: 10.1093/geronb/gbt043] [Medline: 23696032]
21. van Tilburg TG, Aartsen MJ, van der Pas S. Loneliness after Divorce: A Cohort Comparison among Dutch Young-Old Adults. Eur Sociol Rev 2014 Dec 01;31(3):243-252. [doi: 10.1093/esr/jcu086]
22. Antonucci T, Ajrouch K, Manalel J. Social Relations and Technology: Continuity, Context, and Change. Innov Aging 2017 Nov;1(3):igx029 [FREE Full text] [doi: 10.1093/geroni/igx029] [Medline: 29795794]
23. Seifert A, Schelling HR. [Old and offline? : Findings on the use of the Internet by people aged 65 years and older in Switzerland]. Z Gerontol Geriatr 2016 Oct;49(7):619-625. [doi: 10.1007/s00391-015-0965-1] [Medline: 26496912]
24. Seifert A, Schelling H. Mobile use of the Internet using smartphones or tablets by Swiss people over 65 years. Gerontechnology 2015;14(1):57-62. [doi: 10.4017/gt.2015.14.1.006.00]
25. Nayak LUS, Priest L, White AP. An application of the technology acceptance model to the level of Internet usage by older adults. Univ Access Inf Soc 2010 Feb 16;9(4):367-374. [doi: 10.1007/s10209-009-0178-8]
26. Cotten SR, Anderson WA, McCullough BM. Impact of internet use on loneliness and contact with others among older adults: cross-sectional analysis. J Med Internet Res 2013 Feb 28;15(2):e39 [FREE Full text] [doi: 10.2196/jmir.2306] [Medline: 23448864]
27. Hargittai E, Dobransky K. Old Dogs, New Clicks: Digital Inequality in Skills and Uses among Older Adults. Can J Commun 2017 May 23;42(2). [doi: 10.22230/cjc.2017v42n2a3176]
28. Yu RP, Mccammon RJ, Ellison NB, Langa KM. The relationships that matter: social network site use and social wellbeing among older adults in the United States of America. Ageing Soc 2015 Jul 02;36(9):1826-1852. [doi: 10.1017/s0144686x15000677]
29. Hargittai E, Hsieh Y. Digital Inequality. In: Dutton WH, editor. The Oxford Handbook of Internet Studies. Oxford, UK: Oxford University Press; 2013:129-150.

30. Chopik WJ, Rikard R, Cotten SR. Individual difference predictors of ICT use in older adulthood: A study of 17 candidate characteristics. Comput Hum Behav 2017 Nov;76:526-533. [doi: 10.1016/j.chb.2017.08.014]
31. Hülür G, Macdonald B. Rethinking social relationships in old age: Digitalization and the social lives of older adults. Am Psychol 2020 May;75(4):554-566. [doi: 10.1037/amp0000604] [Medline: 32378949]
32. Moskowitz DS, Sadikaj G. Event-contingent recording. In: Mehl MR, Conner TS, editors. Handbook of Research Methods for Studying Daily Life. New York, NY: Guilford Press; 2012:160-175.
33. Bolger N, Laurenceau JP. Intensive Longitudinal Methods: An Introduction to Diary and Experience Sampling Research. US: Guilford Press; 2013.
34. Nezlek JB, Wesselmann ED, Wheeler L, Williams KD. Ostracism in Everyday Life: The Effects of Ostracism on Those Who Ostracize. J Soc Psychol 2015 Aug 12;155(5):432-451. [doi: 10.1080/00224545.2015.1062351] [Medline: 26267126]
35. Yao Q, Moskowitz DS. Trait agreeableness and social status moderate behavioral responsiveness to communal behavior. J Pers 2015 Apr 08;83(2):191-201. [doi: 10.1111/jopy.12094] [Medline: 24602021]
36. Ram N, Conroy DE, Pincus AL, Lorek A, Rebar A, Roche MJ, et al. Examining the Interplay of Processes Across Multiple Time-Scales: Illustration With the Intraindividual Study of Affect, Health, and Interpersonal Behavior (iSAHIB). Res Hum Dev 2014;11(2):142-160 [FREE Full text] [doi: 10.1080/15427609.2014.906739] [Medline: 26989350]
37. Wood J, Oravecz Z, Vogel N, Benson L, Chow S, Cole P, et al. Modeling Intraindividual Dynamics Using Stochastic Differential Equations: Age Differences in Affect Regulation. J Gerontol B Psychol Sci Soc Sci 2017 Dec 15;73(1):171-184 [FREE Full text] [doi: 10.1093/geronb/gbx013] [Medline: 28329860]
38. Adam EK, Quinn ME, Tavernier R, McQuillan MT, Dahlke KA, Gilbert KE. Diurnal cortisol slopes and mental and physical health outcomes: A systematic review and meta-analysis. Psychoneuroendocrinology 2017 Sep;83:25-41 [FREE Full text] [doi: 10.1016/j.psyneuen.2017.05.018] [Medline: 28578301]
39. Adam EK, Hawkley LC, Kudielka BM, Cacioppo JT. Day-to-day dynamics of experience--cortisol associations in a population-based sample of older adults. Proc Natl Acad Sci USA 2006 Nov 07;103(45):17058-17063. [doi: 10.1073/pnas.0605053103] [Medline: 17075058]
40. Pruessner JC, Wolf OT, Hellhammer DH, Buske-Kirschbaum A, von Auer K, Jobst S, et al. Free Cortisol Levels after Awakening: A Reliable Biological Marker for the Assessment of Adrenocortical Activity. Life Sciences 1997 Nov;61(26):2539-2549. [doi: 10.1016/s0024-3205(97)01008-4]
41. Adam EK, Kumari M. Assessing salivary cortisol in large-scale, epidemiological research. Psychoneuroendocrinology 2009 Nov;34(10):1423-1436. [doi: 10.1016/j.psyneuen.2009.06.011] [Medline: 19647372]
42. Ice GH, Katz-Stein A, Himes J, Kane RL. Diurnal cycles of salivary cortisol in older adults. Psychoneuroendocrinology 2004 Apr;29(3):355-370. [doi: 10.1016/s0306-4530(03)00034-9]
43. Reis HT, Wheeler L. Studying Social Interaction with the Rochester Interaction Record. Adv Exp Soc Psychol 1991;24:269-318. [doi: 10.1016/s0065-2601(08)60332-9]
44. Macdonald B, Hülür G. The Digital Lives of Older Adults. Open Science Framework. 2020. URL: https://osf.io/we65k/ [accessed 2020-09-04]
45. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol 1988 Jun;54(6):1063-1070. [doi: 10.1037//0022-3514.54.6.1063] [Medline: 3397865]
46. Antonucci TC. Hierarchical mapping technique. Generations 1986;10(4):10-12.
47. Boot WR, Charness N, Czaja SJ, Sharit J, Rogers WA, Fisk AD, et al. Computer proficiency questionnaire: assessing low and high computer proficient seniors. Gerontologist 2015 Jun;55(3):404-411 [FREE Full text] [doi: 10.1093/geront/gnt117] [Medline: 24107443]
48. Choi NG, Dinitto DM. The digital divide among low-income homebound older adults: Internet use patterns, eHealth literacy, and attitudes toward computer/Internet use. J Med Internet Res 2013 May 02;15(5):e93 [FREE Full text] [doi: 10.2196/jmir.2645] [Medline: 23639979]
49. van Boekel LC, Peek ST, Luijkx KG. Diversity in Older Adults' Use of the Internet: Identifying Subgroups Through Latent Class Analysis. J Med Internet Res 2017 May 24;19(5):e180 [FREE Full text] [doi: 10.2196/jmir.6853] [Medline: 28539302]
50. Kamin ST, Lang FR. The Subjective Technology Adaptivity Inventory (STAI): A motivational measure of technology usage in old age. Gerontechnology 2013;12(1):16-25. [doi: 10.4017/gt.2013.12.1.008.00]
51. Chen K, Chan AHS. Gerontechnology acceptance by elderly Hong Kong Chinese: a senior technology acceptance model (STAM). Ergonomics 2014 Mar 24;57(5):635-652. [doi: 10.1080/00140139.2014.895855] [Medline: 24655221]
52. Antonucci TC, Ajrouch KJ, Birditt KS. The convoy model: explaining social relations from a multidisciplinary perspective. Gerontologist 2014 Feb 19;54(1):82-92 [FREE Full text] [doi: 10.1093/geront/gnt118] [Medline: 24142914]
53. Schulz U, Schwarzer R. Soziale Unterstützung bei der Krankheitsbewältigung: Die Berliner Social Support Skalen (BSSS). Diagnostica 2003 Apr;49(2):73-82. [doi: 10.1026//0012-1924.49.2.73]
54. Russell D, Cutrona CE, Rose J, Yurko K. Social and emotional loneliness: An examination of Weiss's typology of loneliness. J Pers Soc Psychol 1984;46(6):1313-1321. [doi: 10.1037/0022-3514.46.6.1313]
55. Diener E, Emmons RA, Larsen RJ, Griffin S. The Satisfaction With Life Scale. J Pers Assess 1985 Feb;49(1):71-75. [doi: 10.1207/s15327752jpa4901_13] [Medline: 16367493]

56. Bullinger M, Kirchberger I. SF-36. Fragebogen zum Gesundheitszustand. Handanweisung SF-36 Health Questionnaire. Göttingen, Germany: Hogrefe; 1998.
57. Lawton MP, Brody EM. Assessment of Older People: Self-Maintaining and Instrumental Activities of Daily Living. Gerontologist 1969 Sep 01;9(3 Part 1):179-186. [doi: 10.1093/geront/9.3_part_1.179]
58. Dahme G, Jungnickel D, Rathje H. Güteeigenschaften der Achievement Motives Scale (AMS) von Gjesme und Nygard (1970) in der deutschen Übersetzung von Göttert und Kuhl - Vergleich der Kennwerte norwegischer und deutscher Stichproben. Diagnostica 1993;39(3):270.
59. Danner D, Rammstedt B, Bluemke M, Treiber L, Berres S, Soto C, et al. Die deutsche Version des Big Five Inventory 2 (BFI-2). Zusammenstellung Sozialwissenschaftlicher Items Skalen 2016. [doi: 10.1037/t73286-000]
60. John OP, Srivastava S. The Big Five Trait Taxonomy: History, Measurement,Theoretical Perspectives. In: Pervin LA, John OP, editors. Handbook of Personality Theory and Research, 2nd edition. New York: Guilford Press; 1999:102-138.
61. Lavigne GL, Vallerand RJ, Crevier-Braud L. The fundamental need to belong: on the distinction between growth and deficit-reduction orientations. Pers Soc Psychol Bull 2011 Sep 03;37(9):1185-1201. [doi: 10.1177/0146167211405995] [Medline: 21540365]
62. Leary MR, Kelly KM, Cottrell CA, Schreindorfer LS. Construct validity of the need to belong scale: mapping the nomological network. J Pers Assess 2013;95(6):610-624. [doi: 10.1080/00223891.2013.819511] [Medline: 23905716]
63. Mehrabian A. Measures of Achieving Tendency. Educ Psychol Meas 2016 Jul 02;29(2):445-451. [doi: 10.1177/001316446902900222]
64. Schönbrodt FD, Gerstenberg FX. An IRT analysis of motive questionnaires: The Unified Motive Scales. J Res Pers 2012 Dec;46(6):725-742. [doi: 10.1016/j.jrp.2012.08.010]
65. Jäger AO, Süss HM, Beauducel A. Berliner Intelligenzstruktur Test (BIS Test, Form 4): Handanweisung. Göttingen, Germany: Hogrefe; 1997.
66. Sturm W, Willmes K, Horn W. Leistungsprüfsystem für 50- bis 90-Jährige (LPS 50+). In: Dorsch Lexikon der Psychologie - Verlag Hans Huber. Göttingen, Germany: Hogrefe; 1993.
67. Wechsler D. Manual for the Wechsler adult intelligence scale. New York: Psychological Corporation; 1955.
68. Ekstrom RB, French JW, Harman HH. Kit of Factor-Referenced Cognitive Tests. Princeton, NJ: Educational Testing Services; 1976.
69. Lehrl S. Mehrfach-Wortschatz-Intelligenztest MWT-B. Balingen, Germany: Spitta Verlag; 2005.

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