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A Web-Based Intervention for Young Adults Whose Parents Have a Mental Illness or Substance Use Concern: Protocol for a Randomized Controlled Trial

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Abstract

Background: One in 5 young people grow up in a family where one parent has experienced a mental health problem or substance use concern. Compared with their same-aged peers, these youth are at a higher risk of academic failure and acquiring a substance abuse and/or mental health issue. There is a paucity of accessible, age-appropriate interventions that address their needs.

Objective: A 6-week, web-based intervention, "mental illness: supported, preventative, online, targeted" (mi.spot), was developed based on previous research and the competence enhancement model. This paper describes the protocol for a randomized controlled trial and details how the usage, safety, acceptability, and feasibility of the intervention will be determined.

Methods: Participants will be recruited through social media and clinician referral. A total of 70 Australians, aged 18 to 25 years, who grew up with parents with a mental illness or substance use concern will participate in a 2-arm parallel randomized controlled trial. The assessment will consist of a baseline measurement and 2 follow-up periods, posttest and 6-week follow-up, using the Mental Health Continuum short form; the Depression, Anxiety, and Stress Scale; the Coping Orientation to Problems Experienced inventory; the General Help Seeking Questionnaire; the Social Connectedness Scale; the Mental Health Literacy Scale; the General Self-Efficacy Scale; and the Attribution of Responsibility for Parental Mental Illness Measure. Impact will be examined at pre, post, and follow-up time periods using analyses of variance that will include a within-subjects factor (time) and a between-subjects factor (intervention/control). Facilitator interviews will ascertain intervention feasibility. Participant interviews will ascertain intervention acceptability. Interview data will be analyzed within a qualitative framework. Usage (data analytics) across site features and several indicators of clinical safety will also be reported.

Results: The impact of mi.spot will be examined at pre, post, and follow-up time periods using analyses of variance on each of the measures outlined above. There will be a within-subjects factor (time) and a between-subjects factor (intervention/control). Data analysis will employ the intention-to-treat principle by including all participants in the analyses. Qualitative interview data will be analyzed using interpretative phenomenological analysis along with respondent validation. The Monash University Human Research Ethics Committee (reference number: 2019-18660-30434) approved the trial on April 17, 2019. As of October 2, 2019, 30 participants were enrolled in the control group and 34 participants were enrolled in the intervention group. Result are expected to be submitted for publication in December 2020.

Conclusions: Study results will provide reliable evidence on a web-based intervention that has the potential to make a difference to the lives of many vulnerable young adults. Implementation guidelines are needed to embed the intervention in different service sectors.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12619000335190; https://anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12619000335190

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KEYWORDS

young adult; mental health; substance use; internet-based intervention

Introduction

Background

A systematic review recently substantiated that up to 45% of clients in adult mental health services are parents with children [1]. Maybery et al [2] estimated that more than 1 in 5 children have 1 parent with a mental health problem. Compared with their same-aged peers, these children are at high risk of school dropout and failure [3], being taken into care [4], and acquiring a substance misuse concern and/or mental illness [5]. Their problems often continue into adulthood; a 30-year follow-up found that the risk of major depression was approximately three times as high in the children whose parents had depression, with the period of highest risk for first onset between 15 and 25 years of age [6]. Given the prevalence and needs of this at-risk group of young people, it is imperative that there are evidence-based, easily accessible interventions targeted at their specific needs.

One of the traditional ways of supporting young people in these families has been through face-to-face peer support groups [7]. These aim to prevent the onset of mental health problems in young people by providing social support, psychoeducation, and training in adaptive coping [7]. In a randomized controlled trial based in the Netherlands, van Santvoort et al [8] showed that children in such an intervention experienced a greater decrease in negative cognitions and sought more social support compared with the control group. Notwithstanding these benefits, face to face programs have several recruitment issues related to stigma, referral pathways, transport, and time [9]. There are also relatively fewer programs for young people living in rural and remote areas compared with their urban counterparts [10]. In addition, face-to-face peer support programs target children aged 12 to 18 years and not older youth aged 18 to 25 years [7].

Web-Based Interventions

Web-based interventions have the potential to circumvent stigma, reach, and access issues. Furthermore, young adults are increasingly turning to the internet to search for health information and to share personal information [11,12] because it is highly engaging, accessible, anonymous, and often free of charge [13]. Young adults living in these families have indicated a preference for online support [14] with specific preferences for topics on psychoeducation, managing the parent-child relationship, and strategies to build resilience and improve coping and mental health [15]. There are some online interventions for youth aged 18 to 25 years whose parents have a mental illness/substance use concern, although none are in English and are still in the early stages of development [16-18]. For example, a randomized controlled trial in the Netherlands, of an online intervention called Kopstoring, found positive trends toward a reduction in internalizing symptoms but no significant differences in self-reported depressive symptoms and internalizing problems [18]. Further work is needed to consolidate and substantiate the evidence base in this area and ensure that interventions designed for this group are effective.

Objectives

This paper describes the protocol for a randomized controlled trial for the mental illness; supportive, preventative, online, targeted (mi.spot) intervention. It is hypothesized that following the mi.spot intervention, young adults will report the following:

- Significant improvements in mental health and well-being (primary outcomes)
- Significant improvements in coping, social connectedness, and attribution of responsibility for parental mental illness (secondary outcomes)
- Significant increases in help seeking and mental health literacy (secondary outcomes).

Furthermore, the study will determine what components of the site participants use and do not use, along with their views about intervention safety and acceptability. Facilitators' views of the feasibility of the intervention will also be sought.

Methods

Design

This 2-arm parallel randomized controlled trial will compare outcomes at posttest and 6-week follow-up for mi.spot and control participants. The protocol is in accordance with the Consolidated Standards of Reporting Trials of Electronic and Mobile HEalth Applications and onLine TeleHealth checklist. The study was undertaken in 2019. The protocol was registered by the Australian and New Zealand Clinical Trials Register on May 5, 2019. The registration number is ACTRN12619000335190.

Ethics

For inclusion, all participants must give implied consent online before completing the questionnaires. Written consent is required for the interviews. Ethics approval for this study was obtained from the Monash University Human Research Ethics

Committee (reference number: 2019-18660-30434) on April 17, 2019.

The Intervention

mi.spot is a 6-week professionally moderated online intervention for emerging adults (aged 18-25 years inclusive) who have a parent with a mental illness or substance use concern (Figure 1). It is based on the competence enhancement model, which incorporates cognitive behavioral principles and a strengths-based approach [19]. A reference group was formed to guide intervention development, consisting of expert clinicians, researchers, and young adults with lived experience. Drawing on the known risk and resilience factors for this particular group of young adults [20], the intervention aims to improve psychoeducation; increase adaptive coping, connectedness, and knowledge about healthy relationships; encourage help-seeking behaviors; decrease feelings of attribution about their parent's illness; and foster well-being and mental health (refer to the paper by Reupert et al [21] for further details regarding the theoretical background and empirical rationale for the intervention).

The site is anonymous, and participants give themselves a nickname they use in all online interactions. All features are optional, and participants may choose to *lurk* rather than actively contribute. The approach includes 6 professionally facilitated online weekly chats that run for 1 hour a week on set topics with accompanying video, audio, and print resources (Table 1). The accompanying resources are made available when the accompanying session is offered. There are also opportunities for private one-to-one online counseling sessions between the participant and the facilitator, which can be initiated by either the participant or by one of the facilitators if they believe the participant requires additional support.

The site includes mi.thoughts.spot, which functions as an asynchronous, online private diary for participants to use and which is visible only to the individual participant and facilitator. mi.thoughts.spot allows participants to record their feelings, practice reframing automatic negative thoughts and challenge unhelpful beliefs using a cognitive behavioral approach. There are also opportunities for participants to chat with each other on group threads. The facilitator's role is to monitor the site, encourage young adults to apply a strength-based cognitive behavioral model, facilitate weekly topics, and promote healthy peer sharing and support.

Figure 1. Screenshot of the mental illness; supportive, preventative, online, targeted intervention.

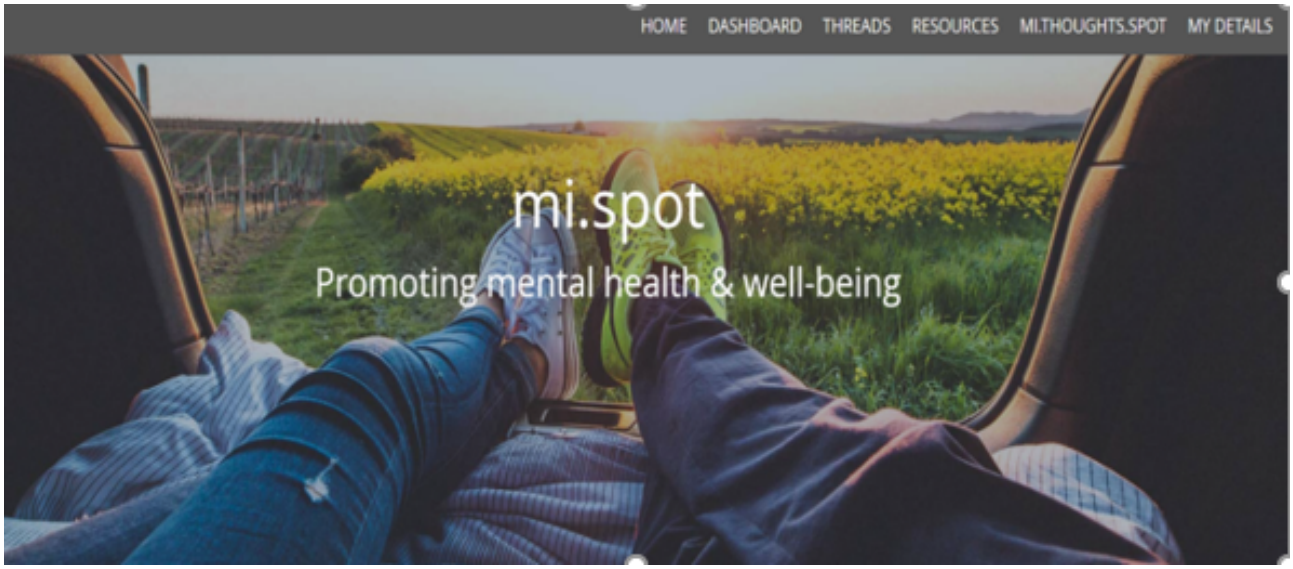

Table 1. The weekly mental illness; supportive, preventative, online, targeted topics.

Topic	Description
What is mi.spot all about?	This session introduces the site and provides participants with an opportunity to get to know each other and the facilitators. Guidelines (rules) for using the site are described, and the various components of the site are described. The cognitive behavioral approach is explained and practiced.
Learning more about mental health and illness	This session delivers basic psychoeducation about different types of mental illnesses. Participants are invited to reflect on what they know about their parent's illness or substance use issue, what they want to know, and how their parents' illness might impact their mental health and well-being. Specific genetic vulnerabilities are discussed. Ways to promote well-being are emphasized.
Me, my parent, and other relationships	In this session, participants reflect on their relationship with their parent(s) and consider how these relationships might inform other intimate relationships. Strategies for forming healthy relationships and boundary setting are also shared.
Managing stress	In this session, participants identify a current stressor and consider what they did or might do to manage this. They are prompted to share adaptive coping strategies and useful ways to regulate emotions.
Caring—who me?	Participants are invited to describe any caring responsibilities they may have and the potential positive and negative impacts that caring for others might have. The principles of self-care and self-compassion are also covered.
Taking control of my life	In the final week, participants consider what they have learnt over the 6 weeks. This session also covers help-seeking strategies, including an emphasis on asking for help early, who they might turn to, and how they might ask for help. A list of relevant services is shared.

Setting and Intervention Facilitators

The intervention will be delivered from the Krongold Clinic at Monash University, a university-based teaching and research clinic in Australia. Masters' level psychology students will deliver the intervention under the supervision of qualified and experienced psychologists. Conduct of the trial will be led by the principal investigator and supported by a research team, all of whom will receive training in the requirements of the study protocol. Before training, all students were required to have successfully completed a 2-day workshop on assessing and responding to suicide and self-harm.

Experienced practitioners will deliver training specific to mi.spot over 2 days. The first day will focus on generic online counseling skills (in both group and individual counseling mode) and the second day will specifically examine the mi.spot intervention and how it should be delivered using simulated online sessions. Face-to-face training will be undertaken 2 weeks before starting the intervention. Fidelity checks for the 6 weekly sessions are built into the program at the facilitator level to ensure that all topics are covered. All features of the intervention are manualized, with guidelines provided for each function of the website.

Safety

The safety protocol for the intervention consists of guidelines around privacy, online safety, and clinical safety. During the initial telephone call, during week 1, and as outlined under the online tab *things you need to know*, participants will be informed of and required to accept the terms of use for protecting their privacy and prohibited behaviors (ie, disrespectful, racist, or offensive comments or statements glorifying suicide or self-harm). The site will be checked, at a minimum twice a day, to ensure that there have been no rule violations (bullying, glorification of substance use, or self-harm). Participants will be informed that failure to comply may result in temporary or permanent withdrawal from the intervention.

In addition, every week, participants will be invited, via the site, to report any feelings of distress. If identified as being in distress, participants will be invited to an online one-to-one counseling session, with referrals provided if required. If a participant discloses statements indicating high distress (eg, suicidal ideation), the facilitator will conduct a telephone risk assessment and, where necessary, undertake 1 or more of the following procedures: (1) inform the supervisor, (2) inform the participant's nominated emergency contact, and/or (3) liaise with suitable emergency services. Safety procedures are clearly outlined in the manual for facilitators to follow for any adverse event. Moreover, the 24/7 emergency numbers are visible under the tab *crisis contacts*.

Safety will be recorded in terms of the number of inappropriate posts (eg, bullying, the glorification of substance use, and self-harm), the tracking of participants' mood over the 6 weeks, and participants' retrospective reports of feeling safe/unsafe during interviews post the intervention.

Study Population

The study includes 18- to 25-year-old (inclusive) Australians who identify as having a parent/caregiver with a mental illness and/or substance use concern (they do not have to be living with them). Potential participants will be contacted via telephone to ensure they are capable of providing informed consent and are currently not in distress or crisis (using self-report). They need to have access to a computer, mobile phone, or tablet and regular internet access. Those who reside outside Australia and cannot speak English are ineligible.

Recruitment and Screening

Participants will volunteer following a response to social media, referral from health professionals, or word of mouth. Those interested in participating will be referred to the study webpage, which provides further information about the intervention. On the webpage participants are invited to confirm their age, contact details, parent's mental health/substance use status, and

emergency contact details. A link is provided to a consent form. Participants then complete all baseline questionnaires and are allocated to the intervention or wait-list control group. Once completed, participants will be contacted via telephone within 2 to 3 weeks by an intervention facilitator.

The telephone call with potential participants serves several purposes. It aims to ascertain participants' expectations of the intervention and gives them an opportunity to ask any questions or voice any concerns they may have. The call helps to verify that the telephone number they provide is legitimate (important if the telephone number needs to be traced due to concerns regarding safety) and to confirm emergency contact details. During the call, the facilitator will gauge participants' mental health status, their ability to provide informed consent, and whether the intervention is appropriate for them. They will do this by asking participants to self-report their current distress level (on a scale from 0 being no distress to 10 being high distress). The reference committee decided against using a validated mental health screen to exclude participants on the basis of their mental illness, given the high proportion of young adults who come from these families who have a mental health condition [22]. Nonetheless, it will be made clear to participants that the intervention is not a crisis service. If the facilitator assesses a participant as being in distress or in crisis, he/she will provide a referral to another appropriate service. Participants will also be told, during the call, which group they are in and whether they have any questions about this. Those in the control group will be notified that they are required to complete questionnaires in 7 to 8 weeks and also in 13 to 14 weeks.

Allocation/Randomization

After completing baseline data collection, participants will be randomly allocated to 1 of the 2 study groups. Randomization will occur via a random number generator (using Statistical Package for Social Sciences), and participants will be allocated according to the timing (ie, order) of signing up for the study to intervention and control conditions. A permutation block of 70 will be used to ensure equivalence of intervention and control group allocations. The project manager will be responsible for the randomization, and the researchers will be blinded to the allocation of participants to the intervention and control conditions. The random number allocation procedure will occur before the commencement of the study. Participants will be informed about their allocation in the initial telephone call and follow-up email.

Those allocated to the intervention group will be provided with a link to the password-protected intervention. Participants in the control group will be given information about other local and national services they can access, including online and face-to-face services. They will be offered the intervention after those in the intervention group complete the postintervention questionnaires (approximately 12 weeks after randomization).

Assessments

The data collection methods were developed and refined for acceptability from a previous pilot [21]. All participants will complete measures before randomization and at equivalent time frames post intervention and follow-up. Posttest completion will be immediately after the 6-week intervention (approximately 6-8 weeks after the completion of the prequestionnaire), and the follow-up questionnaire will be completed 6 weeks after the posttest. Participants will be sent online survey links and reminders using the REDCap database.

Primary Outcome Measures

The primary outcome measures used in this study are as follows:

- The Mental Health Continuum short form is an internationally applied and thoroughly validated self-administered rating scale that contains items that measure 3 aspects of well-being: emotional, social, and psychological. Participants are asked the degree to which they have experienced emotional, social, and psychological well-being over the past month. The form includes a 6-point Likert scale from 0=never to 5 every day. Scores on this scale can range from 0 to 70, and higher scores indicate higher levels of well-being [23].
- The *Depression, Anxiety, and Stress Scale* is an internationally applied and thoroughly validated self-administered rating scale that measures levels of depression, anxiety, and stress. Participants are asked the degree to which they have experienced depression, anxiety, and stress over the past month. A 4-point Likert scale is used from 0 (did not apply to me at all) to 3 (applied to me very much or most of the time) within each of the 3 domains. Normal scores for depression, anxiety, and stress ranged from 0 to 4, 0 to 3, and 0 to 7, respectively, and scores above these ranges indicate mild to extremely severe levels in each domain [24,25].

Secondary Outcome Measures

The secondary outcomes measures used in this study are as follows:

- The *Coping Orientation to Problems Experienced* inventory is an internationally applied measure that evaluates an individual's levels of coping [26].
- The *General Help Seeking Questionnaire* is a measure that will be used to measure help-seeking behaviors [27].
- The *Social Connectedness Scale* will be used to measure an individual's perceptions of social connectedness [28].
- The *Mental Health Literacy Scale* will be utilized to measure an individual's level of psychoeducation [29].
- The *General Self-Efficacy Scale* will be employed to measure self-efficacy [30].
- The *Attribution of Responsibility for Parental Mental Illness Measure* was designed for the project to measure how responsible participants felt for their parents' issue. The measure builds on attributional theory [31] and other research that has found that young people often blame themselves for their parent's issue and consequently feel responsible for *fixing* it [32]. Examples of items were "I sometimes think my parent's illness is my fault." Items are scored on a 7-point Likert scale ranging from 1 (strongly disagree) to 7 (strongly agree).

Interviews: Determining Feasibility, Acceptability, and Safety

Individual interviews will be conducted with available (n=8) facilitators 1 to 2 weeks post the intervention to obtain their feedback on the training and the intervention in terms of feasibility, ease of use, practicality, and responsiveness. Individual interviews will also be conducted with 8 to 10 consenting mi.spot participants. Interview schedules for participants will be organized around safety as well as intervention acceptability, defined by the perceived benefit of the intervention and participants' self-reported confidence in change [33]. If applicable, participants will be asked for their reasons for poor engagement or dropout.

Usage

The total number and average length of log-ins will be recorded over 6 weeks. The number of attendees at each of the 6 weekly sessions, the number of participants who used the mi.thoughts.spot, and the number of participants who posted messages on the threads (including keeping track of repeat users) will be recorded. The number of facilitator-initiated and participant-initiated one-to-one sessions will also be recorded.

Reimbursement

At the end of the 3 assessment periods, participants who complete all questionnaires will receive a AUD $50 (US $32) electronic gift voucher to use in selected stores (not for alcohol or tobacco). Intervention participants who engage in an interview will be paid with AUD $20 (US $12.85) voucher. Payment is provided in recognition of their time and to encourage completion/engagement.

Participant Numbers

A total of 70 18- to 25-year-olds will be recruited. Participant numbers were initially determined by a power calculation indicating that a minimum of 44 participants, with Crit F=3.10 (using GPOWER 3.1, assuming 2 groups and 3 repetitions, a small effect size, an alpha of 5%, and power of 95%), will be required. However, based on previous dropout rates (the pilot study), it was considered that over the time frame of data collection (including the longer frame of the wait-list controls), there may be a dropout rate of up to 40%. As a consequence, recruitment numbers were increased to 70.

Results

Data Analysis

The impact of mi.spot on participants will be examined at pre, post, and follow-up time periods using analyses of variance on each of the measures outlined above. There will be a within-subjects factor (time) and a between-subjects factor (intervention/control). Data analysis will employ the intention-to-treat principle by including all participants in the analyses.

Interview data will be analyzed within a qualitative framework using interpretative phenomenological analysis (IPA). IPA is an approach that examines participants' experiences and meanings of a phenomenon [34], and in this case, the facilitator's and participants' experiences of mi.spot. IPA also provides a structure for coding and categorization of data [34] and will be used to develop responses to questions regarding feasibility and acceptability. Before analysis, respondent validation will occur, a process that entails providing participants with a copy of their transcript and an invitation to delete any information they believe may be identifiable and/or modify existing or add any information. A second researcher will independently analyze one third of all transcripts. Rather than a numerical index of agreement, consensus will be reached by discussion and referring back to participants' transcripts.

Dissemination Strategy

The outcomes of the trial will be disseminated at conferences and in peer-reviewed journals. The general public, including young adults and other interested family members, mental health practitioners, and policy makers, will be notified of the study through public forums, government reports, policy statements, newsletters, and traditional and social media.

Discussion

Principal Findings

This paper describes the evaluation protocol for mi.spot, an online intervention for young adults aged 18-25 years whose parents have a mental illness and/or substance use concern. The intervention has a strong theoretical basis, which is lacking in most interventions in this area [35]. Given that 21% to 23% of all young people have a parent with a mental illness [2], such an initiative has the potential to make a substantial difference to the lives of many young people. The results of this study will add to the high-quality evidence base of electronic health interventions for this group of young people [36].

Notwithstanding its potential, the typical low rates of engagement in other online interventions for young people [37] are concerning. The flexible nature of the intervention in which participants can do some, all, or none of site features (and just *lurk*) may mitigate problems with engagement. Whether greater involvement equates to greater gains and relatedly determining how much engagement is sufficient to promote change are research questions that warrant further investigation.

As age-specific interventions increase young adults' use of mental health services [38], interventions such as mi.spot may also promote the use of other, ongoing services for this group of young adults. Similarly, future investigations might investigate how online support could be integrated into face-to-face treatments and the types of referral pathways that are needed (both from and to mi.spot). Likewise, how an online intervention compares with similar face-to-face interventions [8] also remains to be investigated.

Limitations

Participants report their own diagnoses and that of their parents, and these are not independently verified. The aims of the intervention are made clear from the outset, and thus, all participants (including those in the control group) will have some understanding of the nature of mi.spot that may encourage them to seek support elsewhere during the wait period and hence

impact results [39]. Future considerations will need to investigate the cost effectiveness of the intervention and develop implementation guidelines to embed the intervention into routine care, which is important information for the long-term sustainable scale-up of effective public health interventions.

Conclusions

The transition to adulthood can be a vulnerable period for young adults who have a parent with a mental illness or substance use concern. Given the issues related to stigma, access, and reach, online interventions hold great promise in engaging and intervening with this at-risk group. Support for the mi.spot trial will enhance the evidence base of a highly accessible intervention, which aims to prevent or reduce the adverse impact of young adults' parents' mental illness and/or substance use, for a large (approximately 21-23% of the population) high-risk group of young adults.

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Conflicts of Interest

None declared.

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Abbreviations

IPA: interpretative phenomenological analysis
mi.spot: mental illness; supportive, preventative, online, targeted

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Protocol

Guided Internet-Based Cognitive Behavioral Therapy in Japanese Patients With Obsessive-Compulsive Disorder: Protocol for a Randomized Controlled Trial

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Abstract

Background: Cognitive behavioral therapy for obsessive-compulsive disorder has been established, but access to this therapy in Japan is limited. Internet-based cognitive behavioral therapy may improve treatment accessibility and sufficiently improve obsessive-compulsive symptoms. There are few randomized controlled trials examining the effectiveness of internet-based cognitive behavioral therapy in patients with obsessive-compulsive disorder. We designed a randomized controlled trial protocol to assess the effectiveness of guided internet-based cognitive behavioral therapy in Japanese patients with obsessive-compulsive disorder.

Objective: We aimed to develop a protocol for a randomized controlled trial of internet-based cognitive behavioral therapy in Japanese patients with obsessive-compulsive disorder.

Methods: The randomized controlled trial will compare internet-based cognitive behavioral therapy treatment and usual care groups, each consisting of 15 participants (n=30) diagnosed with obsessive-compulsive disorder. We will evaluate the effectiveness of a 12-week intervention. The primary outcome of symptom severity will be measured using the Yale-Brown Obsessive-Compulsive Scale. Secondary outcomes will be assessed with the Obsessive-Compulsive Inventory, Beck Anxiety Inventory, Patient Health Questionnaire-9, Generalized Anxiety Disorder-7, Working Alliance Inventory-Short Form, and the Euro Qol – 5 Dimension. All measures will be assessed at weeks 0 (baseline) and 12 (follow-up). In the statistical analysis comparing treatment effects, the least-squares means and their 95% CIs will be estimated by analysis of covariance with the change in total outcomes scores at week 12. All comparisons are planned, and all *P* values will be two-sided, with values <.05 considered statistically significant.

Results: The study will be performed from January 2020 to March 2021, and results are expected to be available in mid-2021.

Conclusions: The trial will demonstrate whether internet-based cognitive behavioral therapy improves access and is more effective than more usual care for patients with obsessive-compulsive disorder in Japan.

Trial Registration: University Hospital Medical Information Network (UMIN) 000039375; https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000044422

International Registered Report Identifier (IRRID): DERR1-10.2196/18216

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KEYWORDS

internet-based cognitive behavioral therapy; cognitive behavioral therapy; obsessive-compulsive disorder; randomized controlled trial; protocol

Introduction

Background

Obsessive-compulsive disorder (OCD) has been defined as a common, chronic, and long-lasting disorder in which a person has uncontrollable, reoccurring thoughts (obsessions) and/or behaviors (compulsions) that he or she feels the urge to repeat [1]. OCD is characterized by uncomfortable and painful obsessions and repeated obsessions. The 12-month prevalence of anxiety disorder including OCD in the Japanese adult general population is 5.3%, making it the most common psychiatric disorder [2]. Systemic reviews and meta-analysis show that cognitive behavioral therapy (CBT) is the most effective treatment for OCD [3] and is recommended as first-line therapy by the treatment guidelines of The National Institute for Health and Care Excellence in the United Kingdom (UK NICE) [4]. Telemedicine or remote treatment for patients living in rural areas via internet-based cognitive behavioral therapy (ICBT) has been established as a standard of care in Stockholm, Sweden [5]. In ICBT, patients and therapists interact primarily via email, with treatment including routine work such as explaining the symptoms of the patient's condition and introducing coping skills based on cognitive behavioral science. A systematic review with meta-analysis comparing 21 studies of face-to-face and guided self-help CBT (mostly ICBT) in 810 patients showed no clear differences in their treatment effect: The effect size was Cohen *d*=–0.02, and face-to-face CBT was smaller than ICBT [6]. Unlike ICBT for anxiety and depression, effectiveness of ICBT for OCD has been investigated in clinical trials. Japanese patients with OCD have significantly improved symptoms with ICBT via videoconference and the method achieved high acceptance [7,8]. Prior study results suggest guided ICBT with minimal therapist intervention may be as effective and accepted by Japanese patients with OCD as ICBT via videoconference [9].

Internet-Based Cognitive Behavioral Therapy for Obsessive-Compulsive Disorder

Previous randomized controlled trials for obsessive-compulsive disorder have been performed in Sweden, the United States, and Korea [10-12]. In a previous randomized study of 101 patients with OCD assigned to ICBT and online supportive psychotherapy followed by blinded assessments [10], ICBT showed significant improvements in the intervention group compared to the control group. Obsessive-compulsive symptoms as measured by the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) were improved, and the effect size was high (Cohen *d*=1.12). Another study of 56 patients with OCD included ICBT, reading therapy, and waiting groups [11]. The results of that study suggested that ICBT has a large effect size (Cohen *d*=1.57) among the waiting group at pre- and post- treatment. In Asia, a Korean research team conducted a randomized controlled trial and reported that the treatment group showed significantly improved symptoms over the waiting group, and 25.9% (17/42) responded to treatment, with a within-group effect size of 1.64 (Cohen *d*) [12]. Thus, ICBT, like face-to-face CBT [13], has been shown to be highly effective in the treatment of OCD.

More clinical trials are needed to draw general conclusions regarding the efficacy of ICBT because of substantial country-to-country variations in cultural background, the spread of information, availability of communication equipment, and literacy. Prior research has been performed in countries where the environment is conducive to ICBT, especially as developed countries have a well-established computerized social infrastructure [14]. The penetration rate of information and communication equipment in Japan is more than 90% of all households [15], and there is a favorable social infrastructure for verifying the effectiveness of ICBT. In Japan, our research team confirmed that all patients were in remission by conducting CBT on 3 patients with OCD in their 20s and 40s in the ICBT case series [9]. Based on this achievement, we developed an ICBT program that includes an electronic learning (e-learning) system and chat app. From January 2020 to March 2021, we are conducting a randomized controlled clinical trial in patients diagnosed with OCD.

Objective

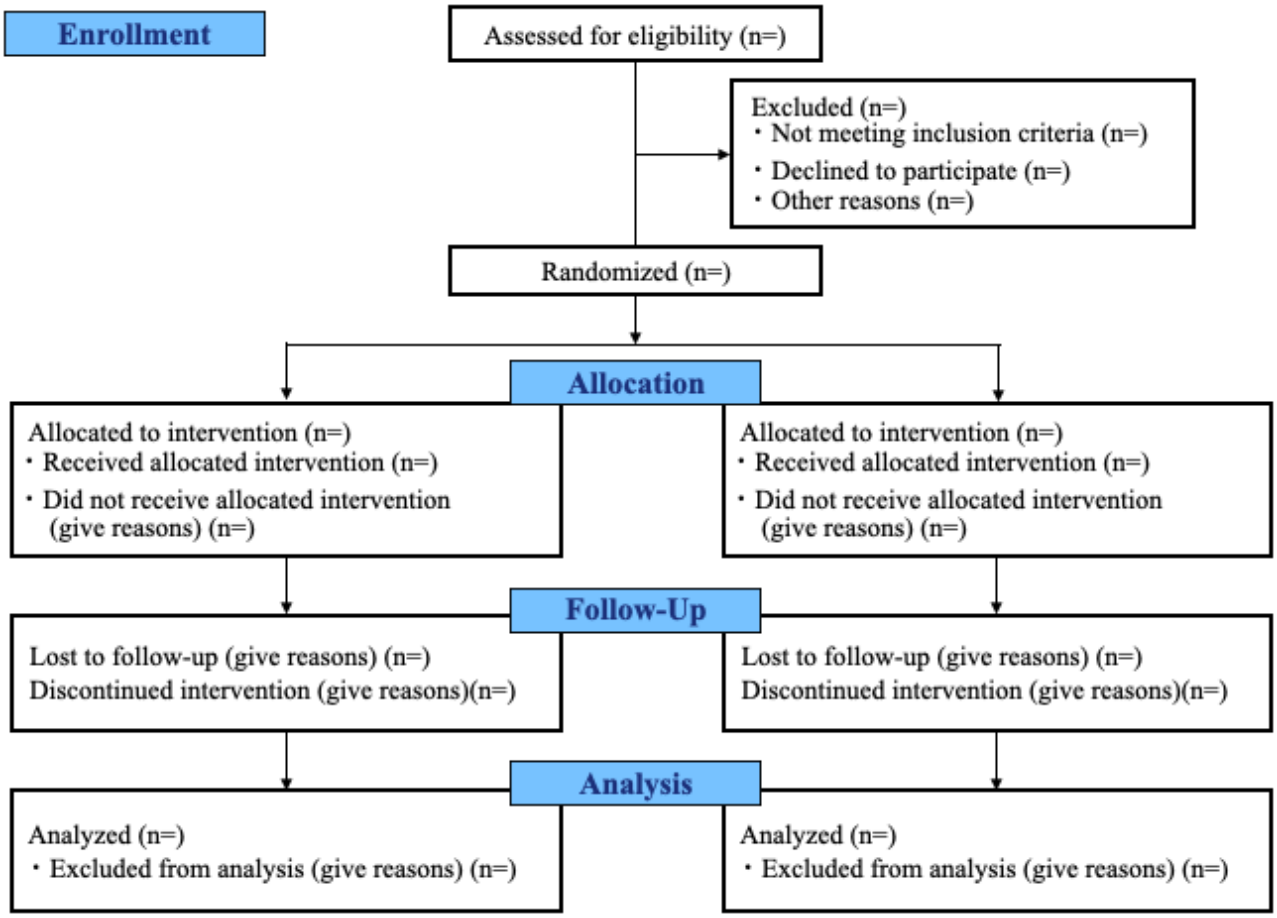
This paper describes the study protocol for a randomized controlled trial designed to evaluate the clinical effectiveness of ICBT versus usual care (UC) among patients diagnosed with OCD.

Methods

Study design

This study was designed as a prospective blinded randomized trial with two parallel intervention groups consisting of a 12-week treatment regime of UC alone or ICBT combined with UC (Figure 1) [15-18].

Figure 1. CONSORT flow diagram of a parallel randomized trial with two groups.



Participants and Eligibility Criteria

Inclusion criteria for this study include individuals aged 15-60 years having a primary diagnosis of OCD according to the Mini-International Neuropsychiatric Interview (MINI) and remaining symptomatic [19,20] with symptoms rated at least moderate in severity, based on a Y-BOCS score >14 [21,22], and with sufficient skills to send email and access the e-learning system. Participants with psychosis or organic mental disorder, or with a current high risk of suicide, substance abuse or dependence within the 12 months prior to enrollment, antisocial personality disorder, or unstable medical conditions will be excluded.

Recruitment

The planned recruitment rate is 3 participants per month from January 2020 to December 2020, or until a total of 30 participants are recruited. Participants will be recruited by placing informational posters and leaflets at medical institutions in Chiba and Fukui Prefecture and on the institutional homepage. All participants will continue to be treated by their general practitioners, whose permission must be granted prior to study enrollment. This study will be conducted at the outpatient clinic of Chiba University Hospital and Fukui University Hospital in Japan.

Interventions

Guided ICBT program

The ICBT program participants will engage in one program learning session per week. After working on the ICBT, the patient will email the therapist about their thoughts and questions about the study and behaviors suggested by the program for them to try in daily life. The therapist, as general rule, will contact the patient within 24 hours to encourage the patient's efforts, raise questions, and advise on CBT techniques to increase the effectiveness of treatment. The ICBT program consists of 12 weekly lessons, including the following elements: ICBT program guidance, psychological education and case conceptualization of obsessive-compulsive disorder, setting treatment goals and creating an anxiety hierarchy, explaining the behavioral experiment of catastrophic interpretation and the exposure-response disturbance method, and preventing recurrence.

Software

We will use LearningBox, a system developed by Tatsuno Information Systems [23] and MediLine, a medical chat service developed by Shar Medical to provide ICBT [24]. LearningBox (Multimedia Appendix 1) is an e-learning system that allows administrators to easily create and manage educational materials, manage members, and save and view grades. Video and PDF teaching materials can also be posted on the site and distributed to specific users. The e-learning system can store and manage

user results, but personal information is not stored during the present trial.

MediLine (Multimedia Appendix 2) is a medical chat service (medical social networking service) that replaces email and phone calls. It has strong encryption against military-level information leaks. MediLine communicates in a double-encrypted state according to the Japanese government guidelines [25-28]. Encryption is performed end-to-end in real time in the server, during communication, and in temporary memory at the terminal. In other words, it is designed so that information cannot be extracted during data transfer. Since identifiers are issued by in-house introduction, hijacking and spoofing are prevented. The staff registered by the organization can delete the account at the time of retirement and cannot view it thereafter, so there is no provision for information to be taken out of the hospital after retirement [24].

Usual Care (Control group)

Participants will be permitted to continue using antidepressant or other medicines during the study period. Participants' primary doctor will have right to change medication, to refer participants for counselling, and to secondary care if deemed clinically appropriate. All changes in conventional treatment, along with the reasons for those changes, will be recorded. Participants in the control group will be offered the ICBT treatment after the trial if they did not improve under the control conditions.

Outcomes

Baseline and Clinical Characteristics

Baseline characteristics will include gender, age, educational attainment, marital status, employment status, age at onset and duration of OCD, medications, and intelligence as measured by the Japanese Adult Rating Test (JART) [29,30].

Primary Outcome

The primary outcome will be measured by the Y-BOCS, which is a rated questionnaire consisting of 10 questions across two subscales, Obsession and Compulsion [21,22].

Secondary Outcomes

Secondary outcomes will include health-related quality of life, symptoms of depression and generalized anxiety, and therapeutic relationship. We will measure health-related quality of life with the EuroQol - 5 Dimension (EQ-5D) [31,32], the psychological bond between therapist and participant using the Working Alliance Inventory-Short Form (WAI-SF) [33], depressive symptoms using the Patient Health Questionnaire-9 (PHQ-9) [34], generalized anxiety symptoms using the Generalized Anxiety Disorder-7 (GAD-7) [35], and the Beck Anxiety Inventory (BAI) [36].

Sample Size

We used the statistical analysis software G*power 3.1 to estimate sample size of an unmatched t-test [37]. Sample size was estimated as 14 participants per group. The effect size predicted in this study is at least 1.00 from the two previous two clinical trials [8-10], the directionality of the test is a two-sided test, the significance level was set at 0.05%, the test was two-sided, and the test power (1-β) was set to 80%. The study will require a minimum 14 participants per group so we are setting a target enrollment of 30 participants to allow for a 5% dropout rate.

Randomization

Eligible participants will be randomly assigned to the ICBT or UC group at a ratio of 1:1, with assignments made using the minimization method, ensuring a balance in baseline Y-BOCS scores (Y-BOCS ≥20) and gender.

Statistical Analysis Plan

Statistical analysis and reporting will be conducted in accordance with CONSORT (Consolidated Standards of Reporting Trials) guidelines [38], with primary analyses based on the intention-to-treat principle. For baseline variables, summary statistics will be constructed, employing frequencies and proportions for categorical data and mean and SD for continuous variables. Baseline variables will be compared using the Fisher exact test for categorical outcomes and the unpaired *t*-test for continuous variables. For the primary analysis comparing treatment effects, the least-squares means and their 95% CIs will be estimated by analysis of covariance (ANCOVA) with the change in total Y-BOCS scores at week 12. This ANCOVA model will account for the variation caused by treatment effects, and gender and baseline Y-BOCS scores will be entered as covariates. Analyses of secondary outcomes will be performed in the same manner. All comparisons are planned, and all *P* values will be two-sided. *P* values <.05 will be considered statistically significant. All statistical analyses will be performed using the latest version of SAS (SAS Institute Inc).

Ethics and Dissemination

This study will be conducted at the Academic Outpatient Clinics of Chiba University and Fukui University in Japan. When potential participants contact the study trial office through the Chiba University, they will be informed of the study objectives and be asked if they are willing to participate by phone screening. Each participant will then be required to provide written informed consent for their participation in this study. Each participant will be informed that all participants will receive UC from their general practitioner and that half of the recruited participants will also receive ICBT in addition to their UC. All adverse events will be reported, and serious adverse events will be immediately reported to the Institutional Review Board of Chiba University Hospital in addition to being registered with the hospital risk management system. An adverse event will be defined as a symptom or disease occurring during the clinical trial, whether related to the ICBT program or not. The study will be conducted and reported according to CONSORT-ETHICS guideline recommendations [39].

This clinical trial protocol was approved by the clinical trial review committee of Chiba University Hospital on November 18, 2019 (G2019017) and approved by the ethics review committee of the Fukui University Graduate School (20190075). It is registered in the University Hospital Medical Information Network database of clinical trials in Japan (UMIN: 000044422).

Results

The study period is from January 6, 2020 to March 31, 2021. The case registration period is scheduled for 12 months from January 6, 2020 to December 31, 2020.

Discussion

This randomized controlled study will evaluate the effectiveness of ICBT for patients with OCD. The findings of this study will provide valuable evidence to facilitate development and establish treatment algorithms in ICBT for patients with OCD. The study will also introduce this method for providing ICBT in Japan, as patients will be given access to self-help materials using an e-learning system (LearningBox) and medical chat app (MediLine). The UC control group will be randomly assigned, and the multicenter study design will reduce bias and improve the likelihood of obtaining generalizable results. The study will also have limitations, including the inability to elucidate the specific effects of ICBT program because there is no placebo group to control for nonspecific factors. The study also will not control for medical therapies or treatment resistance. It is unclear whether pharmacotherapy plus CBT improves OCD symptoms more than pharmacotherapy alone [4,40]. Therefore, combination therapy with pharmaceuticals and ICBT should be tested in future trials to determine whether each is beneficial or if therapy is improved by combined therapies.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
LearningBox E-Learning System.
[PNG File , 219 KB - resprot_v9i6e18216_app1.png]

Multimedia Appendix 2
The MediLine Chat App.
[PNG File , 139 KB - resprot_v9i6e18216_app2.png]

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Abbreviations

BAI: Beak Anxiety Inventory
CBT: Cognitive Behavioral Therapy
EQ-5D: EuroQol-5-Divison
GAD-7: Generalized Anxiety Disorder-7
ICBT: Internet-Based Cognitive Behavioral Therapy
JART: Japanese Adult Rating Test
OCD: Obsessive-Compulsive Disorder
PHQ-9: Patient Health Questionnaire-9
RCT: Randomized Controlled Trial
UC: Usual care
WAI-SF: Working Alliance Inventory-Short From
Y-BOCS: Yale-Brown Obsessive-Compulsive Scale

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Protocol

Evaluation of the Clinical and Economic Effects of a Primary Care Anchored, Collaborative, Electronic Health Lifestyle Coaching Program in Denmark: Protocol for a Two-Year Randomized Controlled Trial

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Abstract

Background: Obesity is linked to a number of chronic health conditions, such as type 2 diabetes, heart disease, and cancer, and weight loss interventions are often expensive. Recent systematic reviews concluded that app and web-based interventions can improve lifestyle behaviors and weight loss at a reasonable cost, but long-term sustainability needs to be demonstrated.

Objective: This study protocol is for a 2-year randomized controlled trial that aims to evaluate the clinical and economic effects of a primary care, anchored, collaborative, electronic health (eHealth) lifestyle coaching program (long-term Lifestyle change InterVention and eHealth Application [LIVA] 2.0) in obese participants with and without type 2 diabetes. The program's primary outcome is weight loss. Its secondary outcome is the hemoglobin A_{1c} (HbA_{1c}) level, and its tertiary outcomes are retention rate, quality of life (QOL), and cost effectiveness. Analytically, the focus is on associations of participant characteristics with outcomes and sustainability.

Methods: We conduct a multicenter trial with a 1-year intervention and 1-year retention. LIVA 2.0 is implemented in municipalities within administrative regions in Denmark, specifically eight municipalities located within the Region of Southern Denmark and two municipalities located within the Capital Region of Denmark. The participants are assessed at baseline and at 6-, 12-, and 24-month follow-ups. Individual data from the LIVA 2.0 platform are combined with clinical measurements, questionnaires, and participants' usage of municipality and health care services. The participants have a BMI ≥30 but ≤45 kg/m2, and 50% of the participants have type 2 diabetes. The participants are randomized in an approximately 60:40 manner, and based on sample size calculations on weight loss and intention-to-treat statistics, 200 participants are randomized to an intervention group and 140 are randomized to a control group. The control group is offered the conventional preventive program of the municipality, and it is compared to the intervention group, which follows the LIVA 2.0 in addition to the conventional preventive program.

Results: The first baseline assessments have been carried out in March 2018, and the 2-year follow-up will be carried out between March 2020 and April 2021. The hypothesis is that the trial results will demonstrate decreased body weight and that the number of patients who show normalization of their HbA_{1c} levels in the intervention group will be much higher than that in the control group. The participants in the intervention group are also expected to show a greater decrease in their use of glucose-lowering medication and a greater improvement in their QOL when compared with the control group. Operational costs are expected to be lower than standard care, and the intervention is expected to be cost-effective.

Conclusions: This is the first time that an app and web-based eHealth lifestyle coaching program implemented in Danish municipalities will be clinically and economically evaluated. If the LIVA 2.0 eHealth lifestyle coaching program is proven to be effective, there is great potential for decreasing the rates of obesity, diabetes, and related chronic diseases.

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International Registered Report Identifier (IRRID): DERR1-10.2196/19172

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KEYWORDS

type 2 diabetes management; digital behavioral coaching; lifestyle change; health behavior change; obesity; weight loss; interactive advice; participant engagement; quality of life

Introduction

Background

With the incidence of chronic lifestyle-related diseases rapidly increasing, cost-effective management is needed [1]. Enabling individually tailored care at a low cost is the ambition when introducing lifestyle interventions as a cornerstone in the prevention and management of chronic diseases [2-6]. For example, type 2 diabetes is strongly related to weight gain in adult life, and pathophysiological studies have established how and why people with type 2 diabetes can be returned to normal glucose control and have shown that even marginal weight loss can have a large impact on disease progression, bringing between 46% and 54% of patients with type 2 diabetes in remission [5,7]. App and web-based interventions aiming to promote a healthy lifestyle have attracted much attention owing to their potential for scalability and accessibility, low cost, privacy and user control, usability in municipal settings, and opportunities for real-time modifications and interactive advice [3,8]. While systematic reviews have concluded that app and web-based interventions can improve lifestyle behaviors, the sustainability of these interventions has been shown to be variable, and long-term sustainability needs to be demonstrated [3,8-12]. The literature shows that the usage of personal feedback from a known health coach on users' own registrations, group support, and different behavioral change techniques (BCTs) is superior when compared with more automated services, especially on combining BCTs with face-to-face meetings [13].

A collaborative electronic health (eHealth) tool has shown promising results in weight loss among patients with diabetes when implemented in real-life settings [14]. In this study, our aim is three-fold as follows: (1) to measurably demonstrate the effect of a primary care, anchored, collaborative, eHealth lifestyle coaching program (long-term Lifestyle change InterVention and eHealth Application [LIVA] 2.0) on weight loss and diabetes regulation (hemoglobin A_{1c} [HbA_{1c}] level) in a strongly scientific and randomized controlled trial (RCT) setting; (2) to evidence the sustainability of a long-term intervention with follow-up measurements at 12 and 24 months; and (3) to assess the cost-effectiveness of a digital intervention in a municipal setting.

Product Development

The collaborative eHealth tool (version 1.0) was a web-based solution that users accessed using an internet browser on their personal computers. The present version of the collaborative eHealth tool (version 2.0) called LIVA has been developed based on experiences from approximately 140,000 individuals, who used the collaborative eHealth tool 1.0, over a period of 15 years. Besides general experience from using the eHealth tool 1.0, the research team conducted several qualitative research studies with the following three important stakeholder groups within weight loss interventions: patients, general practitioners, and health professionals practicing in eHealth coaching (health coaches) [8,15-19]. The key findings from the qualitative interviews regarding the use of version 1.0 of the collaborative eHealth tool can be summarized as follows: (1) establishment of an empathic relationship with a health coach; (2) an intuitive design that enables ease of use for both users and health coaches; (3) different modes of communication channels allowing for active communication at all weight loss steps among users; and (4) an intuitive backend design, including a text and video library, and communication templates enabling the optimization of tailored personal quality coaching.

A user-driven approach to the design of both the user and coach interfaces has enabled ease of use and has eased communication flow [20], allowing for tailored communication between the health coaches and the end users at all steps of the weight loss program [21]. An important feature of the intervention continues to be the initial establishment of an empathic relationship between the user and the health coach, who delivers effective remote digital coaching based on the user's own registration. Algorithms have not replaced health coaches, and instead, the features of the eHealth tool 1.0 enable individualized care at minimal effort from the health coach. Afshin et al concluded in 2016 that a direct interaction between a user and a health coach enhances the effectiveness of lifestyle interventions [3]. By establishing a personal relationship outside the digital environment, which is maintained through the platform with backend follow-ups, we believe that we are able to facilitate tailored care and sustained participant engagement over time with limited continued health coach input in the process of successfully changing and sustaining a lifestyle change [8,21].

Effectiveness of the Collaborative eHealth Tools 1.0 and 2.0

With version 1.0 of the collaborative eHealth tool, we found that personal eHealth lifestyle coaching combined with various BCTs, such as tailored information, self-monitoring, lifestyle coaching, personal feedback, reminders, and face-to-face support, led to relevant weight loss during a 20-month period

[21]. These results were confirmed in an English RCT in a municipality setting, showing weight loss of 5.4 kg among men with type 2 diabetes compared with weight loss of 2.8 kg in a control group receiving standard care [8]. A refinement of the collaborative eHealth tool 1.0 was implemented in 15 Danish municipalities between the summer of 2016 and the summer of 2017, with approximately 12,000 users on the eHealth platform. Besides smaller adjustments from the collaborative eHealth tool 1.0, version 2.0 is a smartphone solution, which is downloaded as an app called LIVA. A feasibility study among patients with type 2 diabetes using LIVA 2.0 in a cross-municipality setting demonstrated relevant weight loss of 4.7 kg among users who had been on the platform for over 90 days. Modeling the association between weight reduction and decreased health care costs indicated cost effectiveness in a municipal perspective 1 year after implementation [14].

Objectives and Hypotheses

Based on our previous research, we hypothesize that eHealth lifestyle coaching with the use of LIVA 2.0 will be effective in improving diet and increasing physical activity levels, thus reducing weight and improving HbA_{1c} levels after 1 year of intervention, with a sustained effect over time. This will result in increased health and quality of life (QOL) and decreased societal costs [22-27]. We expect that municipalities will find the intervention to be a cost-effective alternative for secondary prevention targeted at citizens who are at risk of developing chronic diseases, such as severe obesity, type 2 diabetes, cardiovascular disease, and cancer, and for tertiary prevention among patients with chronic type 2 diabetes, reducing the progression of diabetes and even resulting in its complete remission. To be able to investigate effects and cost-effectiveness among obese participants and obese patients with type 2 diabetes from a municipal perspective, the two target groups of the intervention are as follows: (1) obese citizens at risk of developing chronic diseases, such as severe obesity, type 2 diabetes, cardiovascular diseases, and cancer and (2) obese patients with type 2 diabetes. The intervention is compared with the conventional preventive program that the municipality offers to these two target groups. Furthermore, we investigate associations between participant characteristics and the success of LIVA 2.0 in providing novel insights regarding the associations between participant characteristics and success with a digital lifestyle intervention from both a 1-year and over 1-year perspective.

Research Questions Concerning Both Target Groups

With regard to the primary outcome, the research question is as follows: What is the effect of LIVA 2.0 on users' weight? With regard to the secondary outcome, the research question is as follows: What is the effect of LIVA 2.0 on users' HbA_{1c} levels? With regard to the tertiary outcomes, the research questions are as follows: (1) What is the effect of LIVA 2.0 on the need for medicine use? (2) What is the effect of LIVA 2.0 on users' QOL? (3) What is the cost-effectiveness from a municipal perspective? (4) Which participant characteristics are decisive for the effect and sustainability of LIVA 2.0?

Methods

Study Design

A multicenter RCT with a 1-year intervention and 1-year retention period with collection of clinical and questionnaire data is supplemented with long-term register-based follow-up.

Study Population, Inclusion Criteria, and Setting

Participants are recruited through advertising on social media platforms, general practices, and patient organizations. Potential participants need to meet the inclusion criteria of the study (Textbox 1). Participants who would like to participate and who think they meet the inclusion criteria can register at the app URL [28]. After registration, potential participants are contacted by phone and are sent an email with more written and detailed information about the study and with an invitation to a face-to-face baseline meeting with a LIVA health coach. The individual face-to-face baseline meeting is conducted over 1 hour with a trained health care professional, who is a clinical dietitian by profession and who has been working with eHealth lifestyle coaching for at least 2 years (referred to as the health coach). The face-to-face baseline meeting is scheduled to take place within 7 to 14 days after the information material is sent by email to the potential participant in order to ensure that the participant has sufficient time to reflect on the decision to participate in the study. At the face-to-face baseline meeting, the participant is invited to bring a friend or a family member. The meeting takes place at the research unit for general practice or in the municipality where the participant lives. At the meeting, the health coach confirms that the participant meets the inclusion criteria and explains the details of the study to the participant, and at the end of the meeting, the coach obtains signed informed consent if the potential participant still wishes to participate. Thereafter, the participant is measured according to defined clinical indicators and fills out questionnaires.

The recruitment process is continued until the necessary number of eligible participants are included in the intervention and control groups within the following two target populations: (1) obese citizens at risk of developing a chronic disease and (2) obese patients with type 2 diabetes.

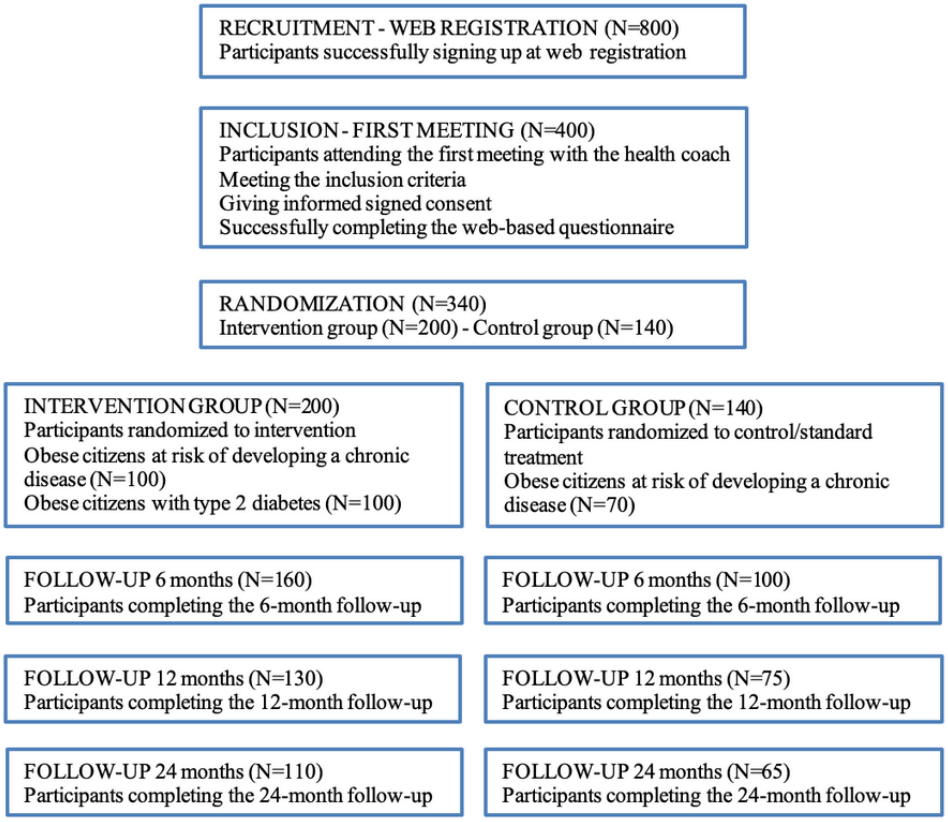
Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria
- BMI ≥30 but ≤45 kg/m^2
- Age 18-70 years
Exclusion criteria
- No informed consent
- No completion of the initial questionnaire
- No internet access in own home through a computer or smartphone
- Pregnancy or active attempts to get pregnant
- Serious or life-threatening disease

Randomization of Participants

After all participants successfully complete a web-based questionnaire and undergo baseline measurements, they are randomized via an automated computer algorithm. This procedure ensures that drop-out characteristics can be recorded. Participants are randomized in a 60:40 manner, where 60% of the recruited participants are randomized to the intervention group and the remaining 40% are included in the control group. Randomization is controlled to ensure that 50% of participants in the intervention group and control group will be obese citizens, who have not been previously diagnosed with type 2 diabetes, and the other 50% of participants in the intervention group and control group will be patients diagnosed with type 2 diabetes (BMI ≥30 but ≤45 kg/m^2) (Figure 1).

Figure 1. Illustration of participant flow.



Ethics

The intervention is not expected to cause any side effects or discomfort. The only recognized risk is in relation to eating disorders (pre-existing or developing during the study), and the dieticians and nurses involved in the study will specifically check for the indications. If an eating disorder is detected, the participant in question will be excluded from the study. The intervention is offered in addition to standard municipal care service, and participants can withdraw from the program at any time. The Regional Ethical Committee has approved the study according to Danish law (no. 18803). Participant data will be handled and stored in accordance with rules approved by the Danish Data Protection Agency. Permission to handle individual participant data from the national registries will be obtained from the Danish Data Protection Agency. All data will be analyzed in anonymized forms.

Intervention

Participants in the intervention group receive login information for LIVA 2.0 at the first personal face-to-face meeting (either physical or digital), after which the health coach introduces the LIVA 2.0 app. After the first personal meeting, the same health coach will be coaching the participant throughout the period. When a health coach is on vacation or is sick for a short period, coaching is postponed. If the health coach is sick for a long period, a personal meeting with a new health coach is arranged to secure a personal relationship, after which the new health coach will be coaching the participant for the rest of the period. Based on our experiences from earlier studies, a half-time health coach can manage between 200 and 250 individuals. The participant and health coach together agree on goals for diet, physical exercise, sleep, and all other life areas of relevance to the participant. All goals are participant driven on the basis of the initial motivational interview with the health coach. The health coach is required to identify what health initiatives will benefit the participant the most based on the participant's own wishes and to find out what is possible for the participant taking into account the participant's personal barriers and facilitators. Using the app, the participant provides a daily record and also enters comments, concerns, and questions for the health coach, who can see the entire profile of the participant. The health coach provides individual asynchronous online consultation according to the participant's needs and based on the participant's registrations. The health coach encourages and praises goal attainment and endeavors to keep the participant motivated. Additionally, the health coach provides advice related to setting goals based on the SMART model (specific, measurable, attainable, relevant, and timely) [29] according to a predefined guideline structure (Table 1) [27,29].

Table 1. Template of the Intervention Description and Replication checklist [30] for the eHealth lifestyle coaching tool (LIVA 2.0).

Item	Description
eHealth coaching sessions	Prior to the intervention, the health coaches receive training in setting SMART (specific, measurable, agreed upon, realistic, and time-based) goals [29] with the participants using the eHealth solution LIVA 2.0 and in setting up action and coping plans that address barrier identification and problem solving. Participants in the intervention group have one or two personal meetings (face-to-face or digital) with their health coach, followed by asynchronous web-based consultations based on dialog by means of text or video. The consultations address the participant's registrations, goal setting, and questions regarding diet, exercise, and lifestyle plans, taking into consideration chronic diseases. The LIVA 2.0 app is set up with short explanations about different functions, and notifications and reminders to the participants to register and give feedback about the health coaching. The sessions provide the participant with information in relation to their status, specific focus on goals, and recommendations on how to improve their behaviors.
	Include BCTs[a] from CALO-RE[b] taxonomy [31] (hereafter referred to as BCTs) as follows: provide information on the consequences of the behavior in *general* and *to theindividual*, goal setting, behavior and outcome, action planning, and barrier identification/problem solving; set graded tasks; prompt review of behavioral goals; prompt review of outcome goals; prompt rewards contingent on effort or progress toward behavior; prompt generalization of a target behavior; and provide feedback on performance (Multimedia Appendix 1).
Goals and inputs	Goals and inputs are always driven by the participant and are available to the participant, who can choose the focus area, set specific goals, and keep a record of specified behaviors by reporting them on a daily, weekly, or monthly basis. This allows the user and the health coach to follow progress or setbacks as the numbers and registrations are visualized using graphs and curves. All coaching by the health coach follows national guidelines from the Danish National Board of Health.
Dietary goals and plans	Dietary goals and plans can be set at many different levels (eg, from simple changes aiming at changing one meal a day to more complex changes aiming at a completely new diet for the remedying of digestion problems).
Physical activity goals and plans	Physical activity goals and plans involve goal setting and recording of the type of physical activity and time for executing the given physical activity. The participant receives advice and/or a video on activities in a variety of contexts to foster physical activity as a more integrated part of life (BCT: provide instruction on how to perform the behavior, prompt generalization of a target behavior, and provide relapse prevention/coping planning).
Life goals	Goals on a healthy joyful life as the participant sees it (eg, daily life with less stress, stronger social bonds with friends and family, coping skills for diseases, etc).
Weight	Set the current weight and goal for a lower or higher weight and register new measurements on a daily, weekly, or monthly basis.
Steps	When downloading the LIVA 2.0 app, the participant can accept direct import of the information on steps recorded on a smartphone, and tailored messages on progress toward a set goal appear simultaneously (BCT: teach-to-use prompts/cues). Step count monitoring is encouraged but not required to enter the LIVA study. Some participants will have other ways of registering their physical activity level.
Pain, sleep, and mood	Give daily feedback on pain, sleep, and mood, which can affect the ability to perform a given behavior (BCT: relapse prevention/coping planning).
Smoking	Set goals to bring down the number of cigarettes smoked on a daily basis, leading to cessation.
Blood glucose and blood pressure	Keep a record of specified measures expected to be influenced by the different behavior changes addressed. In LIVA, this includes blood glucose and blood pressure measurements (BCT: prompt self-monitoring of behavioral outcome and provide information on consequences of the behavior in *general* and *for theindividual*).
Forum	Online forum where the participant can exchange knowledge, gain social support, and build new relationships, and the health coach can provide advice to the participant (BCT: plan social support/change).
Coaching providers	Health coaches with basic training as nurses, physiotherapists, dieticians, or occupational therapists. In Denmark, all four education types consist of 420 European Credit Transfer System (ECTS) points (3.5 years of full-time education). In addition to their education as health care professionals, they all undergo special training in using digital health coaching and practice digital health coaching for at least 2 years.
Coaching approach	Individually delivered via the app or web-based delivery.
Coaching location	Initial personal meetings in municipality health centers, general practice medical centers, or the research unit for general practice at the University of Southern Denmark or over the internet, and then, solely web-based delivery.
Coaching time and quantity	The initial consultation with a health coach is estimated to last for approximately 45-60 minutes. The subsequent asynchronous eHealth coaching sessions are carried out once a week in the first 6 months and then every month for the last 6 months for maintenance. Thereafter, the participant could receive two eHealth coaching sessions and use LIVA 2.0 as a personal BCT tool (BCT: use of follow-up prompts).
Tailoring	Every participant receives personalized eHealth coaching sessions from their designated health coach. The provided feedback is based on the participant's inputs on LIVA 2.0.

[a]BCT: behavior change technique.

[b]CALO-RE: Coventry, Aberdeen and LOndon-REfined taxonomy [31].

Asynchronous online consultations are held weekly during the first 6 months. Thereafter, online consultations are held monthly over a period of 6 months. After 12 months, the participants enter a retention period for 12 months, where the health coach will follow the participants' registrations and may provide up to a maximum of four coaching sessions during that year. We expect that approximately 20% of participants will not be ready for retention after 1 year and these participants will be offered yet another year of intervention. This evaluation is performed by the health coach. The health coach endeavors to maintain participation through phone calls, text messages, and, if necessary, face-to-face meetings to prevent drop out. After 24 months of follow-up, participants are followed through national registers for long-term follow-up on a number of predefined endpoints. Participants in the intervention group receive the standard municipal preventive care service, such as diabetes education, to the extent that municipalities normally provide these care services throughout the observation period.

Conventional Care Service (Control Group)

Participants randomized to the control group are offered to receive the standard municipal secondary or tertiary preventive care service. A recent study aimed at examining Danish municipal weight loss care services and identifying and describing their content and structure found 234 different municipal weight loss care services. Although they were different, they most frequently contained information about diet and physical activity. They also sometimes included information about how to develop healthy habits, and a few of the care services even included the promotion of well-being and social participation [32]. The standard municipal care service within the control group is therefore not the same, but none of the care services resembled the LIVA 2.0 program. At follow-up measurements, the control group participants were asked to describe if they had participated in any interventions since baseline, and if so, describe the content of these interventions. This enabled a qualitative assessment and summary of the standard care services used in the control group.

Outcome Measures

Measurements are conducted by the health coach at baseline and at the 6-, 12-, and 24-month follow-ups. Data from national registers are collected before baseline and up to 3 years after the end of the intervention. Measurements are collected in a facility provided by the local municipality, the local general practitioner, or the clinical research center. Participants are scheduled for appointments by phone and with confirmation through e-mail. The facilities consist of a private consultation room with measurement equipment calibrated for use at relevant timelines and a waiting room area. Multimedia Appendix 2 describes all the included variables, definitions, categories, and sources for both assessments and explaining variables. No data from the participant records are obtained directly, and they are obtained only indirectly through registrations in national registers.

Clinical Assessments

Weight and HbA_{1c} are measured by the health coach using standard and validated measurement equipment (Tanita BC 420 S MA). Height, waist circumference, and hip circumference are measured, and BMI is calculated from the measured weight and height.

Lifestyle Assessment

QOL is measured through a validated questionnaire instrument (12-item Short Form Survey [SF-12]) [33].

Health Economic and Long-Term Assessments

Health care service usage, pharmaceutical consumption, and consumption of municipal care services, as well as morbidity status and mortality are measured through register data. Data from the Danish National Participant Register [34], the Danish National Prescription Registry [35], the Danish National Health Service Register [36], the Danish Civil Registration System [37], and relevant municipal statements and registers will be linked. Data linkage between registers is possible using the unique Danish Personal Identification Number, which is assigned to each Danish citizen and applied throughout the public and private sectors [37]. Productivity loss is evaluated through a questionnaire (Multimedia Appendix 2) [38].

Explaining Variables

Each participant's sociodemographic characteristics are obtained at the baseline face-to-face meeting and registered by the health coach. The explaining variables are used in the descriptive analyses of associations between the participants' characteristics and the success of using LIVA 2.0.

Health Economic Design

Within the scope of a cost-effectiveness analysis, expenditures related to the intervention, including acquisition, deployment, and operational costs, are compared with outcomes of the intervention in relation to the defined assessments. The cost effectiveness of the intervention is primarily assessed from the perspectives of the municipalities. The total cost of the intervention paid by a Danish municipality consists of investment costs as well as operating costs. Investment costs include expenditure for the training of health professionals as well as basic preparation cost. Operating costs cover the annual license fees for the individuals participating in the intervention as well as the individuals in the 1-year retention period. It is assumed that after 1 year in the intervention, participants will move to the retention period, where they will remain for 1 year; however, every year, 20% of the initial population will ultimately leave the intervention. Additionally, the operating costs include the salaries of the health professionals. The costs are compared to the effect of the intervention to evaluate cost effectiveness both in relation to the clinical effect and QOL [39].

Budget Impact Analysis

A municipal budget impact analysis is performed, subtracting possible savings for the municipality in relation to health care costs, nursing costs, and lost productivity from the investment costs [40]. As part of the budget impact analysis, the annual rate of return of municipality investments is estimated. Follow-up data covering 1 year before baseline until 3 years after are collected from national registers (Multimedia Appendix 2). To investigate the possible impact of the intervention on

health care service usage by participants, pharmaceutical consumption and municipal service usage as annual consumption are compared to a reference year 1 year before the intervention (baseline minus 1 year).

As part of the analysis, the following two scenarios are examined: (1) A_0, baseline scenario, where no intervention has been introduced. The health status of the examined population is expected to decrease, whereas the municipality costs are expected to increase; (2) A_1, alternative scenario, where the eHealth lifestyle coaching intervention has been introduced. The health status of the examined population is expected to increase owing to the intervention, whereas municipal costs are expected to decrease.

Long-Term Follow-Up

Since the target group involves participants with chronic diseases or having a risk of chronic diseases, the effect structure of a lifestyle change will first be visible over several years. These data will not be available within the current study design, and hence, the observed effects within the given time frame will be extrapolated over time. We will develop hypotheses for the effect structure according to the literature to be able to model the long-term (5 years) effect of the intervention [41,42].

Analysis Strategy

All data are analyzed according to the intention-to-treat principle [43]. Analyses are mainly carried out according to the two target groups. However, stratification according to participant characteristics and user experiences is applied to investigate associations between success and the different characteristics. Ordinary least square regression and difference between groups over time are used to explore significant associations. Statistical significance is inferred at a two-tailed *P* value <.05. Robust standard errors are calculated. Data are analyzed by experts in biostatistics. After the study, all data will be made accessible on request in anonymized form to allow full peer scrutiny and facilitate secondary research.

Sample Size Considerations

The primary objective of this study is the measurement of changes in body weight and waist circumference. Based on a recent study by Haste et al, which evaluated a web-based weight loss intervention among men with diabetes, we expect a weight loss of at least 4.5 kg at 12 months in the intervention group as compared with 2.5 kg in the control group [8] (Textbox 2).

Textbox 2. Sample size calculation.

A power calculation based on standard deviations observed in the study [8] shows that the detection of a difference in weight loss of 2.0 kg with a power of 0.95% requires 55 participants in the intervention group and 32 in the control group. To allow for drop out according to the experienced attrition rates in the same study [8] (39% of participants in the intervention group and 57% in the control group are expected to drop out at 12 months), we will recruit 100 participants in the intervention group and 70 in the control group (Figure 1). To be able to stratify analyses according to obese participants at risk of developing chronic diseases and obese participants with diabetes, we will recruit 100 obese participants at risk of developing chronic diseases and 100 obese participants with diabetes. Therefore, in total, we will consider 200 participants in the intervention group and 140 in the control group.

Prevention of Drop Out and Loss to Follow-Up

Based on prior experience, approximately 15% of participants will drop out during the first 2 weeks owing to technological challenges, etc. Likewise, after 3 months, approximately 20% of participants will lose motivation and be less active on the platform [8]. The coach will endeavor to maintain participation through phone calls, text messages, and, if necessary, face-to-face meetings. In the case of exclusion before the end of the trial (eg, due to pregnancy), the participant will be asked to complete a final questionnaire and have objective parameters measured in order to provide data for the intention-to-treat analysis.

Results

Progress

From March 2018 to March 2019, 799 potential participants were evaluated for participation. A total of 340 met the inclusion criteria, consented to participate, filled out the web-based questionnaire, and were randomized into study groups. Among participants with type 2 diabetes, 100 (49 female participants) were randomized to the intervention group and 70 (32 female participants) were randomized to the standard care group. Among overweight participants, 100 (81 female participants) were randomized to the intervention group and 70 (52 female participants) were randomized to the standard care group.

Findings

The hypothesis is that the intervention group will demonstrate decreased body weight and a much higher percentage of patients with normalization of their HbA_{1c} levels as compared with the control group. A relevant percentage of participants in the intervention group are expected to decrease their use of glucose-lowering medications and improve their QoL much more as compared with the control group. Operational costs are expected to be lower than standard care and the intervention is expected to be cost-effective for the intervention group.

Timeline

The first baseline assessments were carried out in March 2018. The trial has now reached the 12-month follow-up period for all included participants, and results are expected by the middle of 2020. The 2-year follow-up will be carried out between March 2020 and April 2021.

Discussion

This is the first time an app and web-based eHealth lifestyle coaching program implemented in Danish municipalities will be clinically and economically evaluated in a strong scientific

setup. The study is expected to show that human support through a digital lifestyle intervention program leads to relevant weight loss as compared with a control group receiving standard care, and more importantly, the study is expected to show that digital lifestyle support results in more than twice as many patients with type 2 diabetes reaching a relevant weight loss of 3% to 5% or more [8]. These results are expected to be clinically relevant for patients with type 2 diabetes when weight loss is sustained for more than 2 years [44]. Moreover, these findings will support that the remission rates of patients with type 2 diabetes can be improved by the use of digital lifestyle coaching at a level comparable to other more intensive resource-heavy strategies [5,7]. If the LIVA 2.0 eHealth lifestyle coaching program is proven to be effective, there is a great potential for decreasing obesity rates and rehabilitating patients with type 2 diabetes and other related chronic diseases cost-effectively though human digital lifestyle coaching.

Acknowledgments

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Authors' Contributions

CJB, JBN, and JS were involved in designing the trial. CJB, JTL, and CS developed the intervention. CJB, JBN, CS, and JS are responsible for implementing the trial. JTL, CJB, JBN, JRC, CS, and JS will oversee the data analysis. All authors will be involved in interpretation of the results. CJB and JRC wrote the first draft. All authors have contributed to, read, and approved the final manuscript.

Conflicts of Interest

CJB has co-founded LIVA Healthcare A/S and owns stock in LIVA Healthcare A/S, the company that developed parts of the technical platform and hosted some of it during the study. CJB works at the Research Unit for General Practice at University of Southern Denmark. CS is an employee of LIVA Healthcare A/S. JS, JBN, JRC, and JTL have no financial interests in LIVA Healthcare A/S or any other aspects of this study.

Multimedia Appendix 1
YouTube video showing an example of the LIVA app used in real life.
[DOCX File , 13 KB - resprot_v9i6e19172_app1.docx]

Multimedia Appendix 2
Included variables, definitions, categories, and source.
[DOCX File , 20 KB - resprot_v9i6e19172_app2.docx]

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Abbreviations

BCT: behavior change technique
DKK: Danish Krones
HbA_{1c}: hemoglobin A_{1c}
LIVA: long-term Lifestyle change InterVention and eHealth Application
QOL: quality of life
RCT: randomized controlled trial
SF-12: 12-item Short Form Survey
SMART model: specific, measurable, attainable, relevant, timely

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Protocol

Physical Activity With Tailored mHealth Support for Individuals With Intellectual Disabilities: Protocol for a Randomized Controlled Trial

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Abstract

Background: Individuals with intellectual disabilities (IDs) have lower levels of physical activity (PA) and greater barriers for participation in fitness activities compared with members of the general population. As increased PA has positive effects on cardiovascular and psychosocial health, it is exceedingly important to identify effective interventions for use in everyday settings. Mobile health (mHealth) methods such as motion sensor games (exergames) and smartphone reminders for PA have been explored and found to be promising in individuals with IDs.

Objective: The purpose of this study is to examine the effectiveness of an individually tailored PA program with motivational mHealth support on daily levels of PA in youth and adults with IDs.

Methods: The trial uses a randomized controlled design comprising 30 intervention participants and 30 control group participants, aged 16 to 60 years, with sedentary lifestyles or low PA levels. While the controls will receive standard care, the intervention aims to increase the level of PA, measured as steps per day, as the primary outcome. Secondary outcome variables are body mass index, blood pressure, physical performance, social support for PA, self-efficacy in a PA setting, behavior problems, and goal attainment. The intervention involves the delivery of tailored mHealth support, using smartphones or tablets to create structure with focus on the communicative abilities of individual participants. Rewards and feedback are provided in order to motivate individuals to increase participation in PA. Participants in the intervention group, their close relatives, and care staff will be invited to participate in a preintervention goal-setting meeting, where goal attainment scaling will be used to select the participants' PA goals for the intervention period. All participants will be assessed at baseline, at 3 months, and at 6 months.

Results: Enrollment was planned to start in April 2020 but will be delayed due to the pandemic situation. The main contribution of this paper is a detailed plan to run our study, which will produce new knowledge about tailored mHealth to support PA in individuals with intellectual disabilities.

Conclusions: We expect the new intervention to perform better than standard care in terms of improved PA, improved self-efficacy, and social support for activities. Technology offers new opportunities to promote healthy behaviors. The results of the study will determine the effectiveness and sustainability of a tailored mHealth support intervention to increase PA in youth and adults with IDs.

Trial Registration: ClinicalTrials.gov NCT04079439; https://clinicaltrials.gov/ct2/show/NCT04079439

International Registered Report Identifier (IRRID): PRR1-10.2196/19213

(JMIR Res Protoc 2020;9(6):e19213) doi:10.2196/19213

KEYWORDS

intellectual disability; physical activity; technology; mHealth; mobile phone; goal attainment; social support; self-efficacy

Introduction

The prevalence of intellectual disabilities (IDs) is estimated to be 1% of the world's population [1,2]. Compared with the general population, individuals with IDs have worse health and lower levels of activity [3-5], and they have greater barriers for participating in fitness activities [6] and accessing health care services [7,8].

Physical Activity Guidelines

The World Health Organization (WHO) guidelines for physical activity (PA) state that typical adults should spend a minimum of 150 minutes per week engaged in moderate-intensity PA or 75 minutes engaged in vigorous-intensity PA [9]. One systematic review found that only 9% of individuals with IDs met the WHO´s minimum PA guidelines [4]. Norwegian guidelines are in line with the international guidelines and recommend 150 minutes of moderate- to vigorous-intensity PA per week for adults [10] and 60 minutes per day for children and youths [11]. As high PA is a determinant of health and increased activity has positive effects on cardiovascular and psychosocial health, identifying effective interventions for use in everyday settings is exceedingly important.

Physical Activity Interventions

Some well-designed studies have not been able to demonstrate improved levels of PA in intervention groups of individuals with IDs after the intervention period has ended. One theory-based randomized controlled study of adults with all types of IDs did not find any significant increases in levels of PA (steps per day) using a walking program [12]. Furthermore, the results of a cluster-randomized study of older adults in the Netherlands showed marginal effects and substantial missing data, despite being well prepared with a published protocol and using day-activity centers for the intervention [13]. Past controlled studies on the effects of PA interventions on individuals with IDs have primarily included adults with mild to moderate IDs, and effect sizes have been small [5,14]. Some studies have reported improved effects on physical fitness indicators such as balance and muscle strength [15], psychological well-being [16], perception of social competence [17], and work routines [14] after increasing levels of PA. One recent study included individuals with severe or profound IDs in a technology-aided program for promotion of PA and found positive results in energy expenditure and independent engagement in light to moderate PA [18], but with a small number of participants. Findings from previous studies indicate that a more flexible approach [19], greater use of theory in intervention design, stronger research design (as there are few randomized controlled studies), and better translation of interventions to community-based settings [20] are needed. Future studies could also have an ecological approach, where the interplay between individual, interpersonal, and environmental factors are considered [1,21]. Motivational issues have been challenging, particularly for approaches that aim for sustainable effects [17], and should be considered when designing future PA interventions.

Mobile Health Interventions

Mobile health (mHealth) provides a wide range of possibilities for monitoring and motivating individuals in the self-management of chronic illnesses [22-24]. Motion sensor games (exergames) have been explored and have been found to be promising in individuals with IDs [25]. For these solutions to move out of the lab and into actual use, they need to first meet users' needs [26]. The mobile platform is ubiquitous, and the touch interface has proven to have a low level of cognitive demand and could be used to improve adherence to PA [27]. At present, few mobile apps have incorporated games strategies, such as goal setting or rewards, to increase PA in individuals with various disabilities [28]. To our knowledge, there has been only 1 preliminary report (letter) of a randomized controlled trial using smartphone support to increase motivation for PA in youth and adults with IDs [29].

Methods that could facilitate the development of individualized mHealth support solutions include tailoring, individual goal setting [30], and adjusting communication to meet the specific needs of individuals with IDs [31]. Studies on motivation for PA in the IDs population have shown that predictability with routine and familiarity, communication of purpose, and enjoyable and social activities promote motivation and participation [21,32]. Family and care staff involvement will be central, and we expect the study's implementation in a natural setting to enhance the effect [33]. We also expect the systematic use of mHealth with rewards and gamification to be beneficial. In Norway, many individuals with IDs have a smartphone or a tablet that they can use for tailored PA interventions. However, this use has not been tested previously. We expect a motivational app for smartphones and tablets to promote adherence to PA in individuals with IDs. According to the *World Report on Disability*, health promotion efforts targeting this population can improve lifestyle behaviors [34]. The report states that these individuals have the right to be included in all PA programs.

Thereby, the present study aims to examine the effectiveness of an individually tailored PA program with motivational mHealth support on everyday levels of PA in youth and adults with IDs, targeting individual, contextual, and interactional factors of PA participation [21]. In addition to higher levels of PA, we expect improvements in psychological health, self-efficacy in activities [32], and social support for physical activity participation [35].

Methods

Design

The current study has a randomized controlled clinical design with assessments at baseline, 3 months, and 6 months. Participants will receive either the tailored mHealth-supported PA program or standard care with access to the mHealth support system once the trial is completed. Family and care staff will be involved in the program for support and follow-up.

Participants

A total of 60 participants will be recruited into the trial through health care and other related organizations in the municipality of Tromsø in northern Norway. Information about the study will be delivered at meeting places, such as day and activity centers. If the number of included participants is insufficient, more municipalities in Northern Norway will be included, or a multicenter approach will be considered.

Inclusion and Exclusion Criteria

Individuals will be included if they have a sedentary lifestyle [1] or a low level of PA, determined with the question, "In how much of your leisure time have you been physically active in the last year?" [8]. The question has 4 response categories and has been used in population-based studies of the general population [36] and in European health indicator studies of individuals with IDs [8]. Individuals with a sedentary lifestyle (eg, primarily engaged in reading, watching television, or other mainly sedentary activities) and a low level of PA (eg, engaged in walking or other light PA for less than 4 hours a week) will be included in the study. Other inclusion criteria will be as follows: (1) diagnosis of ID (mild, moderate, severe, or profound), (2) aged between 16 and 60 years, (3) ability to participate in the intervention, (4) ability to walk with or without support, and (5) able to provide written informed consent or written informed consent can be obtained from a representative. Prior to enrollment, all participants will be screened for readiness, and, if necessary, medical clearance will be obtained. The Physical Activity Readiness Questionnaire [37] will be used for this purpose. Exclusion criteria will be as follows: (1) medical contraindications for participation in programs with increased exercise as advised by the primary care or ID specialist physician, (2) high level of physical activity, and (3) inability to provide written informed consent and written informed consent cannot be obtained from a representative.

Ethics

This study has been approved by the Regional Committee for Medical and Health Research Ethics in northern Norway (number 2016/1770). The protocol has been registered at ClinicalTrials.gov under the identifier NCT04079439. The project adheres to the Consolidated Standards of Reporting Trials guidelines. Written informed consent will be obtained from each participant, their legal representative, or both prior to inclusion in the study and baseline assessment. If the participant has impaired capability to consent, consent will be sought from the nearest relative or guardian as well as from the individual with IDs, or as representative consent. Ethical issues will be continuously considered. Any adverse events will be recorded.

Randomization

Participants will be randomized with a computer program to either the PA intervention with mHealth support group or the standard care control group.

Intervention Group

This randomized controlled trial is part of our project to develop a tailored mHealth support system that promotes PA in individuals with IDs [38]. In previous parts of the project, we conducted a qualitative study on motivation for participation in PA for individuals with IDs [21], held workshops and collaborated with mHealth developers, and performed usability tests. This process is illustrated in Figure 1.

Findings from the qualitative study, discussions in workshops, and creative meetings among developers and researchers showed that many individuals with IDs experience difficulties participating in PA because of individual, interactional, and contextual factors. Some of these factors include individual difficulties in initiating activities; preferences for fun and social activities; and lack of social support, availability of activities, resources and preparation, predictability, and collaboration in activities. After examination of these findings, a prototype of an app was created and presented in one of the workshops. The feedback was promising, and development of the mHealth support system continued. The main emphasis in the app is individually chosen activities, tailored communication, predictability, use of rewards, and involvement of support persons. Activities will be chosen during a goal attainment meeting (using goal attainment scaling) [39] with the individual with ID and a support person (usually a family member or health care provider). Goal attainment is widely used as an outcome measure within rehabilitation medicine [39] and has been used in studies with individuals with IDs [40]. The research group is familiar with the use of goalsetting processes in previous studies with individuals with IDs. The final intervention will consist of an advanced activity planner based on the platform for the app Active Leisure (Smart Cognition AS). Actiplan features and tracks daily physical activities. The app offers different interface options (symbols only, easy-to-read text, plain text, and read aloud). See Figure 2 for examples. The activity planner will mostly be used by the individual with ID and a support person (caregiver or health care provider). After completing an activity, a simple reward is available (eg, a smiling face or sharing a picture with other users of the app). The use of tailored communication [41] is available through personalization, including the use of the individual's first name in the activity planner, individually chosen activities, adjusted communication (eg, symbols, easy-to-read text, or plain text),

preparation and planning, and feedback. Rewards and positive feedback after activities have been performed are expected to increase motivation, and thereby lead to higher levels of PA.

In addition, 3 individual exercise apps have been developed as potential alternatives that can be added to Actiplan: (1) an exergame or game-inspired app that promotes outdoor PA; (2) an ergometer bike or outdoor bike placed inside the home, with a mounted screen showing a video or other visually interesting features; and (3) a game-inspired, avatar-based health platform for monitoring PA and motivating users to increase their PA levels [38].

To explore the participants' expectations and experiences of the intervention and the mHealth support, a qualitative pilot study recruiting 10 of the first participants in the intervention group will be performed.

Figure 1. Development process of the electronic health support component of the study.

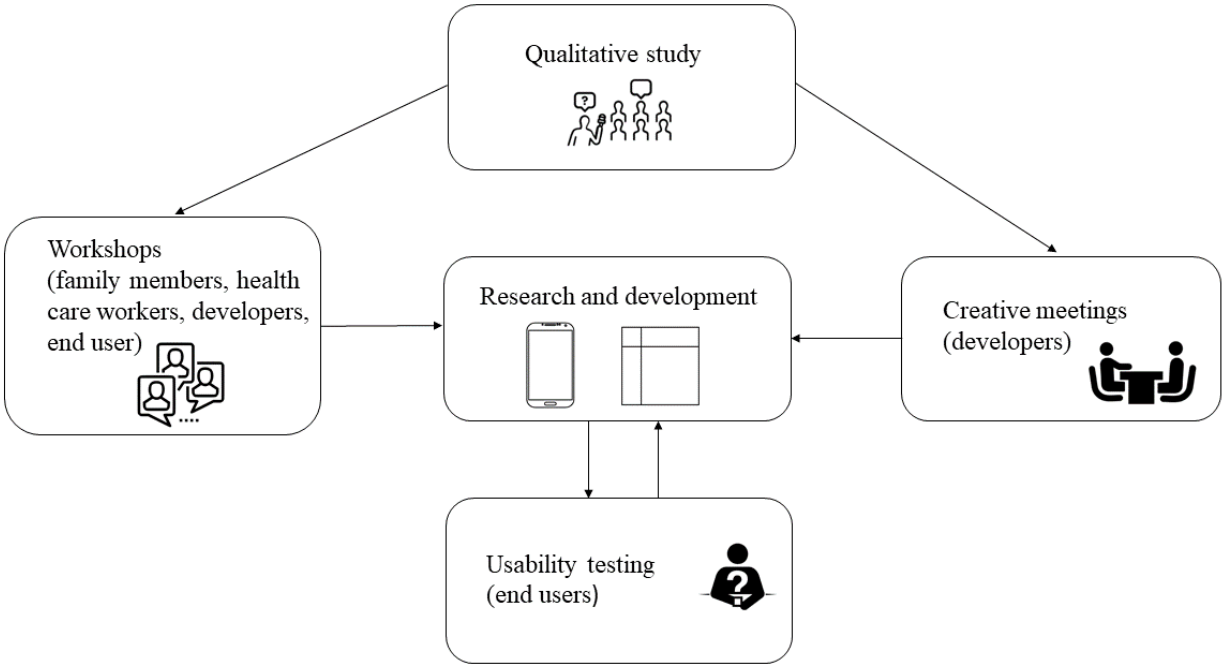
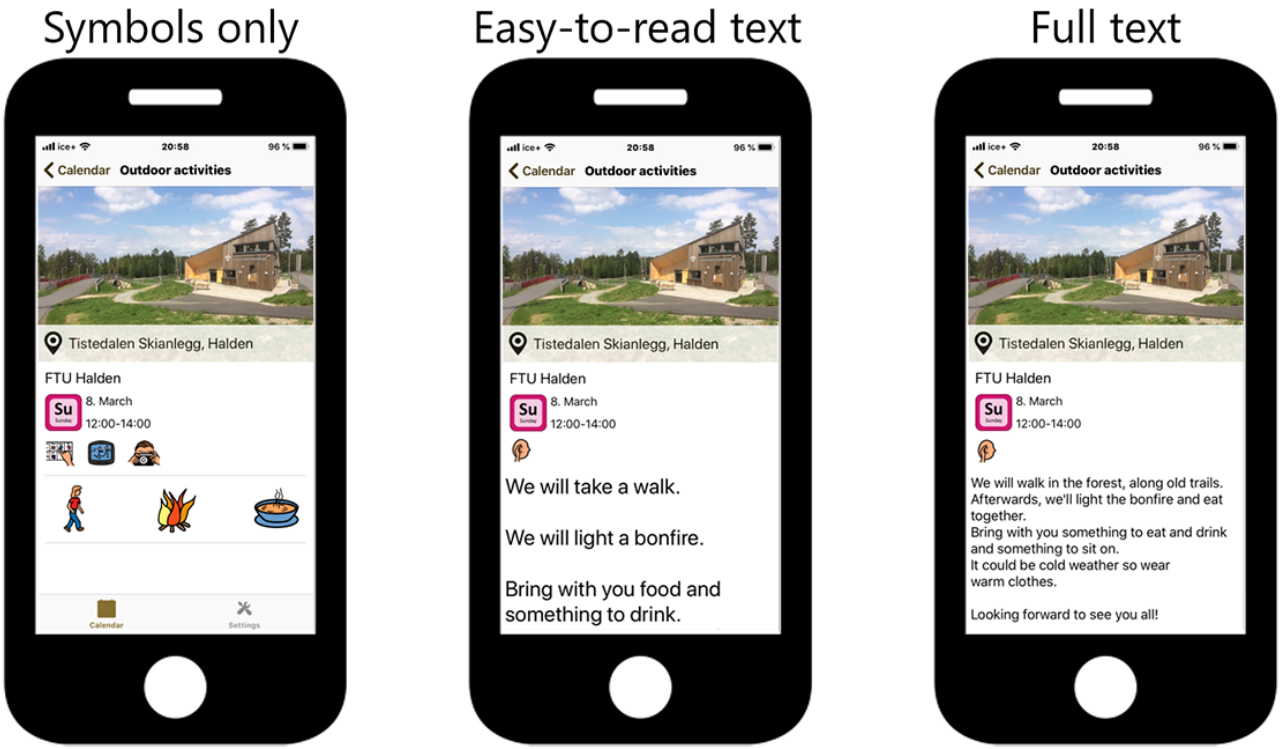


Figure 2. Interface options of the Actiplan app: symbols only, easy-to-read text, or plain text. The app also has read-aloud capabilities.



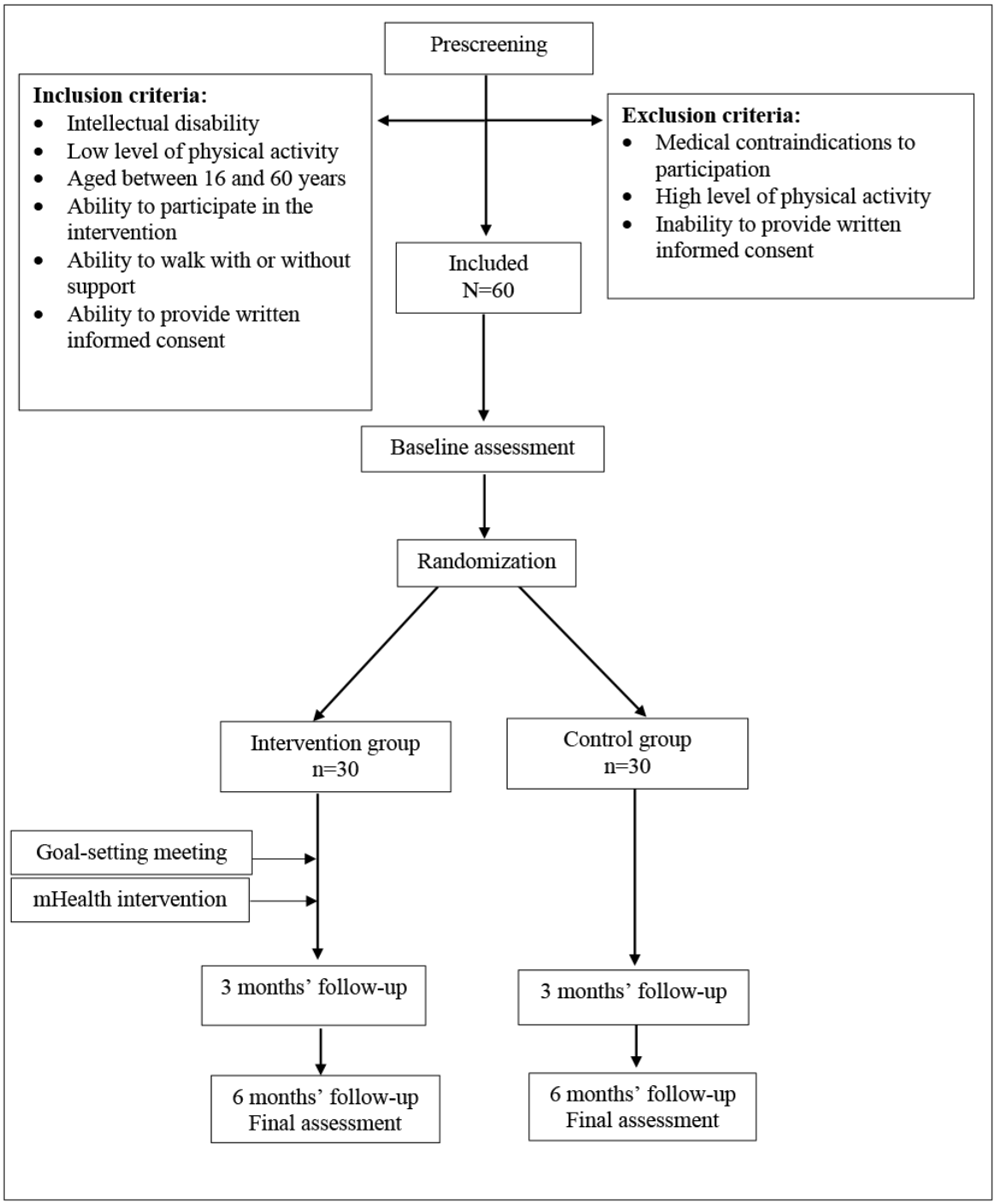
Control Group

Participants in the control group will be administered the assessments at baseline, 3 months, and 6 months, and otherwise continue with their standard everyday activities during the study period. They will be invited to use the mHealth support system at the end of the 6-month intervention period.

Data Collection

Data will be collected at baseline, 3 months, and 6 months, as seen in Figure 3. Baseline data will include baseline PA activity level and will be collected before randomization. Follow-up data will be collected regardless of the participant's compliance with the study protocol. Participants and assessors will not be blinded. Background data on the participants will be collected at baseline and will include age, gender, educational level, marital status, living condition, employment status, educational status, job-related or day center activities, leisure time activities, smoking habits, level of ID (ie, mild, moderate, severe, or profound), genetic diagnosis, gross motor function classification [42,43], communication level [44], medical history/readiness for the PA intervention, and use of medication. In addition, we will ask questions about barriers for participation in physical activities.

Figure 3. Consolidated Standards of Reporting Trials flow diagram of the study. mHealth: mobile health.



Outcome Measures

Primary Outcome

The primary outcome of this study will be objectively measured PA, as assessed by steps per day measured with a wrist-worn commercial accelerometer (Fitbit Versa; Fitbit Inc). The device will assess level of PA and sedentary time [45]. The watch will be covered (neutral screen) during baseline and follow-up assessments in both the intervention and control groups. Screen neutrality is achieved by running a custom app on the watch that disables all buttons and prevents screen feedback (except showing current time). This app cannot be disabled by the participant. Level of PA will be measured for 7 days at each assessment, with a minimum of 3 consecutive days of measurement because previous research has shown that 3 days of PA can predict the weekly level of PA [14,46]. Many of the commercial fitness trackers have been validated for use in research [47], including devices from Fitbit Inc [48,49].

Secondary Outcomes

Secondary outcome measures will include minutes of moderate PA per day, PA questionnaire, body mass index, blood pressure, physical performance, social support for physical activity, self-efficacy in a PA setting, behavior problems, and goal attainment. See Table 1 for a summary of all outcome measures.

Table 1. Summary of outcome measures.

Measurement	Type of outcome	Measure
Steps per day	Primary outcome	Fitness tracker
Minutes of moderate activity	Secondary outcome	Fitness tracker
Body mass index	Secondary outcome	kg/m^2
Blood pressure	Secondary outcome	Blood pressure monitor
Physical performance	Secondary outcome	Short Physical Performance Battery [50]
Behavior problems	Secondary outcome	Aberrant Behavior Checklist–Community [51]
Social support for PA and self-efficacy in PA setting	Secondary outcome	The Self-Efficacy/Social Support for Activity for Persons With Intellectual Disability scale [35]
Goal attainment	Method, secondary outcome	Goal attainment scaling [39]
Satisfaction with life	Control for adverse effects	Satisfaction with life scale [52]

Physical Activity

The secondary PA outcome is the number of minutes of moderate PA per day, measured with the commercial accelerometer.

In addition, the International Physical Activity Questionnaire-Short Form, adapted to measure PA using proxy respondents, will be used [53]. The International Physical Activity Questionnaire-Short Form is a 7-item questionnaire that assesses PA in the past 7 days at 4 intensity levels: (1) vigorous-intensity activity, such as aerobics, (2) moderate-intensity activity, such as leisure cycling, (3) walking, and (4) sitting.

Body Mass Index and Blood Pressure

Body mass index will be calculated in kg/m^2 [54]. Blood pressure will be measured using a blood pressure monitor (Welch Allyn Inc). Height will be measured in meters with a stadiometer (Seca GmbH), with the participant wearing no shoes. Weight will be measured in kilograms with an analog floor scale (Seca GmbH), with participants wearing no shoes or outdoor jackets/gear. Waist circumference will be measured 1 cm above the navel.

Physical Performance

The Short Physical Performance Battery (SPPB) will be used to assess physical performance. The SPPB is a screening test designed to evaluate physical performance and predict disability in older adult populations [50]. The SPPB is mainly a measure of lower-extremity function and consists of 3 subtests: static balance, gait speed, and lower limb strength. To measure static balance, the participant is asked to stand with feet in the side-by-side, semitandem, and tandem positions, for 10 seconds each, to his or her best ability. Gait speed is measured with a 4-m (13-ft) walk at the individual´s habitual pace. Lower limb strength is measured by having the participant rise from a chair with arms folded across his or her chest, to his or her best ability. Subtest scores range from 0 (inability perform the test) to 4 (highest level of performance). The SPPB has been validated [55], and reference values have been published [56]. The Norwegian version of the SPPB appears to have acceptable reliability as well as good internal consistency in an older population with and without dementia [57]. The SPPB has been used in people with mild and moderate IDs [58,59].

Behavior Problems

The Aberrant Behavior Checklist—Community (ABC-C) is a questionnaire designed to assess challenging behavior in children, youth, and adults with IDs [51]. The checklist consists of 58 items divided into 5 subscales: irritability, lethargy, stereotypy, hyperactivity, and inappropriate speech. It is a proxy measure requiring knowledge of the person with ID. Each item is scored on a scale of 0 to 3 (3 indicating the highest severity). The ABC-C is a widely used behavioral rating scale used among people with IDs. A Norwegian study [60] examined the construct validity of the Norwegian ABC in a clinical sample of children and youths in Norway and found satisfactory psychometric properties for the ABC, with the exception of the

inappropriate speech factor. The Cronbach coefficients were adequate to excellent, with coefficients ranging from .76 to .95. The ABC subscales were moderately to highly correlated with one another (r=0.41-0.78, P<.001).

Social Support for Physical Activity and Self-Efficacy in a PA Setting

The Self-Efficacy/Social Support for Activity for Persons with Intellectual Disability scale [35] is a questionnaire consisting of 4 subscales. One subscale measures self-efficacy for overcoming barriers to leisure PA. The last 3 subscales measure social support for leisure activity from family members, care staff, and friends for individuals with IDs. The scale has been validated for self-reporting from individuals with mild to moderate IDs and for use by proxy respondents [35]. The questionnaire will be translated into the Norwegian language using standard guidelines [61].

Goal Attainment

Goal attainment scaling [39,62] will be used to identify self-management goals that participants would like to achieve. The questionnaire will be filled out by the researcher, with participants and proxy respondents present. Goal attainment scaling involves several steps. Goals are selected by each individual, and observable behavior that reflects a degree of goal attainment is defined [63]. The participant's pretreatment or baseline levels are defined in terms of the goal. Five different goal attainment levels are used, ranging from "no change" to "much better than expected outcome" (numbered –2 to +2). Follow-up times for participant evaluation are set after 3 months and 6 months. Goal attainment is evaluated after the defined time interval. At the end, the overall attainment score for all goals are calculated. In this study we will define up to 3 goals for PA [64]. The scale has been validated for use in rehabilitations populations [39] and has been used in studies with individuals with IDs [40,65].

Satisfaction With Life

This study will use the satisfaction with life scale developed by Bergström and Hochwälder [52], which was designed to assess satisfaction with the home environment and leisure time in individuals with mild to moderate IDs. The scale has 4 factors: (1) satisfaction with housing environment, (2) satisfaction with life, (3) satisfaction with meals, and (4) satisfaction with recreational activities. Items are read aloud by a researcher and answered by participants with 3 response options: good (happy face=2), in between (neutral face=1), or bad (sad face=0). In the current study, the scale is used to control for adverse effects.

Data Integrity

Patient- or proxy-reported and assessor-reported data are partly captured electronically using Research Electronic Data Capture (REDCap) (Vanderbilt University). REDCap is a web-based system that is compliant with relevant regulations and security requirements. The system has an integrated function for randomization. Questionnaires can be sent electronically to participants or the proxy respondent. Data not captured electronically, such as background information and physical performance test results, are registered at the baseline meeting. The study coordinator will evaluate the data of all participants for completeness. In cases of missing data, respondents will be contacted.

Statistical Analyses

Sample Size

The study will be powered based on the primary outcome of accelerometer-measured steps per day (mean of 4 days) [4,66]. With a 2-group design and effect size of 0.8, power of 80%, and of .05, the expected minimum total sample size is 50 participants (25 participants in each group). The effect size in the current study is estimated based on previous studies, which have reported Cohen d values ranging from 0.29 to 0.91 [14,37,67]. An effect size of 0.8 is considered to be a clinically relevant difference between the 2 groups, corresponding to an increase in steps per day of approximately 2000 in the intervention group, which is also expected to be achievable [14]. To avoid underpowering the study and to prepare for expected dropout, we will recruit 30 participants per group, for a total sample size of 60 (Figure 3). The group size estimated is supported by other randomized controlled study protocols [27,37] and published results [68] of studies to enhance levels of physical activity in individuals with ID.

Data Analyses

The randomized controlled trial includes repeated measures in 2 groups, and linear mixed models will be used in the efficacy analyses of the intervention. In addition to a group variable (treatment or control), follow-up time (3 months and 6 months) and mean steps (with baseline comparison) will be added as covariates. An intention-to-treat approach will be used with a significance level of P<.05 and a secondary per-protocol analysis. All analyses will be performed using SPSS 26 software (IBM Corp).

Results

The project is approved by the Regional Committee for Medical and Health Research Ethics in northern Norway and is registered at ClinicalTrials.gov. Enrollment was planned to start in April 2020 but will be delayed due to the pandemic situation. Participant recruitment for the randomized controlled study will be initiated as soon as practical difficulties due to the pandemic situation are solved. Participants will be recruited, randomized, and administered the intervention individually. The main contribution of this paper is a detailed plan to run our study, which will produce new knowledge about mHealth to support PA in individuals with IDs.

Discussion

The present trial will investigate how modern technology and mHealth can be used in the promotion of PA in individuals with IDs. A tailored PA program is expected to increase levels of PA, and individuals with IDs and low PA have the greatest chances of improving [13]. Throughout our project, we have used an ecological approach, and we are currently developing a theory-based mHealth motivational support system for the promotion of PA, which we believe will increase the probability of improved levels of PA. Focusing on the communication

abilities of each participant and individual goal setting may be particularly important [64]. As previous research has shown difficulties in recruitment and data collection, including missing follow-up data [13], we will be prepared to meet these challenges.

By including individuals with all types of IDs and low levels of PA, we can add to the knowledge on whether mHealth support can be successfully adjusted to individuals with different levels of functioning and whether it can increase levels of PA [5]. There is evidence demonstrating that an mHealth intervention for PA can improve self-efficacy in activities, social support [32], health conditions such as blood pressure [13], and the results of physical performance tests [69]. This study has potentially important implications for both individuals with IDs and their support networks. If successful, the project will provide a simple and accessible solution for promoting PA in individuals with IDs. For widespread clinical implementation, it is necessary to engage stakeholders who support individuals with IDs throughout their lives.

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Conflicts of Interest

None declared.

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Abbreviations

ABC: Aberrant Behavior Checklist
ABC-C: Aberrant Behavior Checklist—Community
ID: intellectual disability
mHealth: mobile health
PA: physical activity
SPPB: Short Physical Performance Battery
WHO: World Health Organization

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Protocol

Sustainability of Community-Based Specialized Mental Health Services in Five European Countries: Protocol for Five Randomized Controlled Trial–Based Health-Economic Evaluations Embedded in the RECOVER-E Program

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Abstract

Background: Community-based recovery-oriented mental health services for people with severe mental disorders have not been fully implemented in Bulgaria, Croatia, Macedonia, Montenegro, and Romania. The RECOVER-E project facilitates the implementation of specialized mental health care delivered by setting up services, implementing the services, and evaluating multidisciplinary community mental health teams. The outcomes of the RECOVER-E project are assessed in a trial-based outcome evaluation in each of the participating countries with a health-economic evaluation linked to these trials.

Objective: The aim of this protocol paper is to describe the methodology that will be used for the health-economic evaluation alongside the trials.

Methods: Implementation sites have been selected in each of the five countries where hospital-based mental health services are available (care as usual [CAU]) for patients with severe mental disorders (severe depression, bipolar disorder, schizophrenia, and other psychotic disorders). The newly implemented health care system will involve community-based recovery-oriented mental health care (CMHC). At each site, 180 consenting patients will be randomized to either CAU or CMHC. Patient-level outcomes are personal and social functioning and quality-adjusted life years (QALYs). Data on participants' health care use will be collected and corresponding health care costs will be computed. This enables evaluation of health care costs of CMHC as compared with CAU, and these costs can be related to patient-level outcomes (functioning and QALY gains) in health-economic evaluation.

Results: Data collection was started in December 2018 (Croatia), February 2019 (Montenegro), April 2019 (Romania), June 2019 (North Macedonia), and October 2019 (Bulgaria). The findings of the outcome evaluations will be reported for each of the five countries separately, and the five trials will be pooled for multilevel analysis on a combined dataset.

Conclusions: The results of the health-economic evaluation of the RECOVER-E project will contribute to the growing evidence base on the health and economic benefits of recovery-oriented and community-based service models for health systems in transition.

Trial Registration: (1) ClinicalTrials.gov NCT03922425 (Bulgaria); https://clinicaltrials.gov/ct2/show/NCT03922425 (2) ClinicalTrials.gov NCT03862209 (Croatia); https://clinicaltrials.gov/ct2/show/NCT03862209 (3) ClinicalTrials.gov NCT03892473 (Macedonia); https://clinicaltrials.gov/ct2/show/NCT03892473 (4) ClinicalTrials.gov NCT03837340 (Montenegro); https://clinicaltrials.gov/ct2/show/NCT03837340 (5) ClinicalTrials.gov NCT03884933 (Romania); https://clinicaltrials.gov/ct2/show/NCT03884933

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KEYWORDS

community-based mental health care; cost-effectiveness analysis; cost-utility analysis; economic evaluation; mental health

Introduction

Many European countries have undergone the process of deinstitutionalization of their mental health care services. Often, this entailed a shift away from hospital-based care toward assertive community treatment (ACT) or ACT-like services for patients, such as flexible assertive community treatment (FACT). Under FACT models, patients live in the community and receive care from community mental health care teams (CMHTs) [1,2]. Typically, these teams consist of psychiatrists, psychologists, social workers, psychiatric nurses, and peers (people with lived experiences of severe mental disorders). The CMHTs focus on evidence-based (ie, guideline concordant) and patient-centered care in those domains where the patient needs recovery the most. This could be treatment directed at symptomatic remission, but could also, and just as importantly, entail support for the patient's personal and social role functioning (eg, independent living, getting along with others, and participating in the community). In brief, the care offered by CMHTs can be described as community-based recovery-oriented models of care.

Community-based recovery-oriented mental health services for people with severe mental disorders are in the early stages of development in Bulgaria, Croatia, Macedonia, Montenegro, and Romania. The RECOVER-E project facilitates the implementation of specialized mental health care delivered by setting up services, implementing the services, and evaluating multidisciplinary CMHTs [3]. This implementation process is flanked by research from start to end. The outcomes of the RECOVER-E project are assessed in a trial-based *outcome evaluation* in each of the participating countries or sites (note that CMHTs will be used at the specified sites and not at the country level). An aspect of this outcome evaluation is the implementation of five health-economic evaluations designed alongside hybrid effectiveness-implementation trials. Finally, this outcome evaluation will result in a series of policy briefs to inform all stakeholders of the *policy dialogues* directed at national scale up of the newly implemented mental health care model and its sustainability.

The aim of this protocol paper is to describe the overall methodology of the five health-economic evaluations that will assess the incremental cost-effectiveness of CMHTs focusing on recovery-oriented care compared with care as usual (CAU). The economic evaluation will be conducted as both a cost-effectiveness analysis (CEA), where treatment response (defined as improvement in global functioning) is the primary outcome, and a cost-utility analysis (CUA) with quality-adjusted life years (QALYs) gained as the main outcome.

Methods

Design

The study is conducted at five sites in the cities of five countries in Central and Eastern Europe (Sofia, Bulgaria; Zagreb, Croatia; Skopje, Macedonia; Kotor, Montenegro; and Siret, Suceava County, Romania). In each country, the study is designed as a health-economic evaluation alongside a pragmatic randomized trial in two parallel groups, comparing newly implemented community-based recovery-oriented mental health care (CMHC) with CAU. Measurements will be performed at baseline (t_0) and at 12 and 18 months after baseline (t_1 and t_2, respectively). A Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the study is shown in Multimedia Appendix 1.

Selected Study Sites

In each of the five countries, one implementation site is selected, using the following criteria: demonstrated a need from stakeholders to scale up community care for people with mental ill health through policy documents, political decisions, or statements made via EU platforms such as the Joint Action for Mental Health and Wellbeing (2012-2015); firm local leadership and support for implementation from local decision-makers; and a selection of sites that reflect the diversity of health systems in Europe, the different stages of transition within the deinstitutionalization process for mental health care, and the different human and technical resources available to start implementation of a community-based mental health project. The selected sites are Mental Health Centre Prof. N. Shipkoveski Ltd. (Sofia, Bulgaria), University Hospital Centre Zagreb

(Zagreb, Croatia), University Clinic of Psychiatry (Skopje, Macedonia), Psychiatric Hospital Dobrota (Kotor, Montenegro), and Siret Psychiatric Hospital (Suceava, Romania).

The trials will not start at the same time across all implementation sites in order to avoid allocating resources to all five trials simultaneously. Instead, a pragmatic approach will be adopted by starting three of the trials at three implementation sites in year 1 of the project (Croatia, Montenegro, and Romania), based on the preparedness to start the trial and the readiness of local authorities and health care professionals to start the implementation. The remaining two sites in Bulgaria and Macedonia will start the trial in year 2.

Eligible Participants

The study participants are consenting adults (aged 18-65 years) with severe mental illness defined as follows: (1) Patients making their first entry into the mental health care system (ie, first admissions without a prior treatment history) with a diagnosis of bipolar disorder, severe major depression, schizophrenia, schizophreniform, and schizoaffective disorder according to the International Statistical Classification of Diseases and Related Health Problems-10 (not in symptomatic remission and in need for continued care) and having severe limitations in personal and social role functioning according to the International Classification of Functioning, Disability and Health (not in functional remission and in need of coordinated care provided by community mental health teams); (2) Readmitted patients who have a treatment history but make a re-entry into the mental health care system (ie, readmissions; patients who make a fresh start with treatment for a new episode or recurrence of their disorder) on meeting the diagnostic criteria for the above-mentioned diagnoses.

Patients will be excluded from participation on presenting with somatic comorbidities (ie, dementia or other severe organic causes of brain damage that can decrease their capacity to consent and participate in the study) that require prolonged medical care in a hospital, undergoing incarceration, or presenting with a terminally ill condition, which makes it impossible to either randomize them to community-based care or precludes long-term follow-up assessments in the context of the study. Patients will preferably be excluded from participation when they have a prior treatment history longer than the past 12 months (ie, from the time of possible inclusion or visit to the participating centers), because a longstanding treatment history may confound or bias the evaluation of patient-level health outcomes.

Recruitment

Patients will be recruited from the population being treated by specialized inpatient and outpatient mental health services participating in the study. Eligible patients expressing interest to participate will receive an introductory letter, a patient information leaflet explaining the study's aims and procedures, and an informed consent form. Patients willing to participate in the study will be asked to sign and return the informed consent form. Patients who decline participation in the study will receive CAU. Each included patient receives a unique identification number for data collection and monitoring of patient flow into and through the trial. At each site, a minimum of 180 patients and a maximum of 200 patients need to be recruited.

In line with ethical requirements, any study participant can decide to withdraw from the study at any time. In addition, responsible clinicians can decide for individual patients to deviate (temporarily or permanently) from the intervention program. Their professional autonomy and responsibility remain. Nonetheless, data analysis will be conducted in agreement with the intention-to-treat (ITT) principle, where all randomized participants are analyzed in the condition to which they were randomized.

Intervention Condition

The CMHTs provide mental health care within a locally adapted version of FACT (thereby still allowing for flexibility due to differences in team compositions and other site-specific practices), an evidence-based service delivery model for providing services to people with severe mental illness, to attain their recovery goals, as well as timely and appropriate psychiatric care in the event of a crisis. FACT provides flexible and intensive home-based treatment to people with severe mental illness and is an adapted form of ACT; the latter approach has been widely implemented in North America, Australia, and Europe [4]. ACT is particularly effective (both clinically and cost-wise) when targeted to high users of inpatient care and has been found to be acceptable in patients [4].

Comparator or Control Condition

Patients randomized to the control condition will be provided CAU by their respective health care organizations and accompanied providers . The constituent of usual care across the implementation sites differs, but it is mostly offered as hospital-based outpatient care (delivered within the psychiatric hospital) and inpatient psychiatric care. None of the current implementation sites have well-functioning CMHTs that provide home treatment or crisis care in the community.

Randomization and Masking

Eligible and consenting patients will be randomly allocated to either the intervention (receiving care provided by CMHTs) or usual care condition consisting of inpatient or outpatient mental health care (described above). An independent statistician, otherwise not involved in the trial, will carry out the randomization at each of the sites, with patients as the unit of randomization. Simple randomization with 1:1 allocation will be applied using a randomization website [5] for true random number generation. In this type of study (a hybrid implementation-effectiveness trial), it is not possible to conceal the randomization status from either clinicians or patients, and masking will therefore not be attempted.

Measures

The primary outcome is disability in personal and social functioning (henceforth referred to as *functioning*). Functioning is measured using the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0), which is directly linked to the International Classification of Functioning, Disability and Health [6,7]. According to the World Health

Organization (WHO), the concept of disability refers to a degree of functional impairment at the bodily, social, and environmental levels, affecting everyday activities and social participation. WHODAS produces standardized disability levels, which are applicable across all diseases, including mental, behavioral, and neurological disorders, in both clinical and general population settings and across cultures. It captures a person's functioning in the following six life domains: (1) *cognition*, understanding and communicating; (2) *mobility*, moving and getting around; (3) *self-care*, attending to one's hygiene, dressing, eating, and staying alone; (4) *getting along*, interacting with other people; (5) *life activities*, domestic responsibilities, leisure, work, and school; and (6) *participation*, joining in community activities and participating in society. The full version of the WHODAS has 36 items. Each item is scored on a 5-point Likert disability scale (0, none; 1, mild; 2, moderate; 3, severe; and 4, extreme). The scores can be summed into an overall functional disability score or presented as six domain-specific sum scores. Alternatively, a more complex scoring algorithm (based on item-response theory) is used (available for SPSS [IBM Corp, Armonk, New York, USA]), which provides an overall score for global functioning on a scale between 0 and 100. In this study, the 36-item self-reported version will be used as a self-administered questionnaire, but trained and supervised interviewers will be available to assist the patients filling in the WHODAS if required. The WHODAS has good psychometric properties and has been designed to monitor the impacts of health and health-related interventions, with a Cronbach α of .86 (range .82-.98) [7].

The secondary patient-level outcome is health-related quality of life, which will be measured using the three-level EuroQoL five dimensions (EQ-5D-3L) [8], which is more commonly used in Eastern Europe. Moreover, a translated version of the newer five-level scale is not available for all countries at the start of the study. The EQ-5D-3L contains the following five dimensions of health-related quality of life: mobility, self-care, daily activities, pain or discomfort, and depression or anxiety. Each dimension can be rated at three levels (from no problems to major problems). The five dimensions can be summed into a descriptive health state with "11111" indicating no problems in any of the five health dimensions and "33333" indicating major problems in all dimensions. In this way, the EQ-5D-3L can describe 243 (3^5) health states. For each of the health states, utility values can be calculated using health state preferences elicited from the Slovenian population [9], as no health state preferences are currently available for any of the five countries included in this study, and out of the available countries, Slovenia is chosen owing to its geographical proximity, as well as similar historical and social environment. For the purpose of sensitivity analyses, utility values will also be elicited using the EuroQoL visual analog scale (VAS). The utility values give weight to the amount of time that a person spends in a certain health state, which is used to compute QALYs. In the CUA, the QALYs will be the outcome of interest.

Data on *resource use* (healthcare uptake, including informal care, travel distances to health services, and productivity losses stemming from functional impairment) will be collected using an adapted version of the Trimbos/iMTA Questionnaire on Costs associated with Psychiatric illness (TiC-P) [10]. We will consider the following three types of costs: (1) health care costs; (2) out-of-pocket costs (from patients and their family members for travel and informal care); and (3) costs stemming from productivity losses due to absenteeism and lesser efficiency while at work (presenteeism). Costs will be estimated using a bottom-up (or microcosting) approach, where units of health service are multiplied by their appropriate unit cost price and summed to provide an overall total cost estimate [11]. Costs will be measured in the local currency, but for the economic evaluation, they will be converted to international euro (Int.€) using purchasing power parity that takes into account exchange rates and the respective buying power in the countries. The reference year for the costs will be 2018.

Data Handling

Data will be handled in accordance with the General Data Protection Regulation [12]. A central Study Protocol and Data Management Plan coordinates all of the five independent trials. In addition, each trial will have a data entry template, a locally adapted version of the study protocol, and a locally adapted version of the central project data safety and management plan.

Sample Size Calculation

Each of the trials is well powered with 90 participants per randomization group (n=180 in total) to detect a clinically relevant effect (mean standardized difference, *d*) of ≥0.33 as statistically significant (at $\alpha \leq .05$, two-tailed) with a power (1-β) of ≥0.80 when the primary outcome (WHODAS personal and social functioning) is evaluated in a baseline-adjusted analysis of variance or similarly specified regression model.

More specifically, the power calculation is carried out with the sample size procedure of Stata (Stata Corp, College Station, Texas, USA) (*sampsi* [13]) assuming that the effect evaluation of functioning would be carried out in a baseline-adjusted analysis of covariance (ANCOVA) with one baseline measurement and two follow-ups. We had to make assumptions about the strength of the correlation of functioning between t_0 and t_1 and between t_1 and t_2 (denoted as $r_{0,1}$ and $r_{1,2}$, respectively). The WHODAS 2.0 has a high 1-week test-retest reliability of $r_{0,1}$=0.98 [14], but the correlation between t_0 and t_1 will be lower when the measurements are further apart (12-month time interval between t_0 and t_1). Hence, we assumed that $r_{0,1}$ would be in the more modest range of 0.30 to 0.50. Regarding the strength of the correlation of personal and social functioning between t_1 and t_2, we made a similar assumption, but expect that this correlation will be weaker still (ie, in the range of 0.20 to 0.40). The size of these correlations is important because they affect the required sample size. For this reason, the sample size calculations were repeated for the likely range of $r_{0,1}$ and $r_{1,2}$. Table 1 shows the required sample size (per arm) for varying $r_{0,1}$ and $r_{1,2}$ values.

Table 1. Required sample size per condition for varying $r_{0,1}$ and $r_{1,2}$ values.

$r_{1,2}$ [a]	$r_{0,1}$ [b]		
	0.3	0.4	0.5
0.2	74	64	51
0.3	81	71	58
0.4	88	78	65

[a]Correlation of functioning between 12 months after baseline (t_1) and 18 months after baseline (t_2).

[b]Correlation of functioning between baseline (t_0) and 12 months after baseline (t_1).

Table 1 shows that in all possible scenarios, the study would be well powered with 88 participants (say 90 participants per condition or 180 in total). In fact, there is a chance that a smaller participant number would suffice, but it is better to be safe. As indicated, the power is based on the idea that the analyses will be conducted with ANCOVA repeated measures or an equivalently specified linear mixed regression model. It was therefore tested if a total sample size of 180 is sufficient for detecting the effect of $d \geq 0.33$ as statistically significant at $\alpha \leq .05$ (two-tailed) with a power of 0.80, when mixed modelling is used. Hence, to determine the sample size required to achieve 80% power, 1000 mixed model simulations were performed, in which baseline measurement and a random effect for individuals were considered. In generating the simulation data, correlations of 0.3 and 0.1 (Pearson r) were assumed between t_0 and t_1 and between t_1 and t_2, respectively. Furthermore, a treatment effect of 0.33 was assumed. In doing so, a sample size of 180 was found to be sufficient.

We will not compensate for dropout by increasing the number of participants at baseline, unless the local research teams identify additional opportunities to recruit more patients than the minimum of 180. As part of the ITT analysis, all participants will be analyzed as randomized, and this will be achieved by either using mixed modelling or imputing missing observations. Imputation is not only required to persevere randomization integrity, but will in addition restore power losses due to dropout. In summary, local teams will have to recruit 180 participants, but can recruit more (up to a maximum of 200) to compensate for dropout when logistically feasible.

It should be noted that the power analysis is directed at the evaluation of the central clinical end-term functioning (ie, the alternative hypothesis predicts that functioning will be at least 0.33 standard units better in the CMHC condition compared with the CAU condition). It is not customary to power a study for testing a health-economic hypothesis, because the large standard errors associated with costs would require extremely large sample sizes. Instead, in health-economic evaluation, a probabilistic medical decision-making approach is used for making inferences about the relative cost-effectiveness of CMHC compared with CAU.

Finally, it is worth mentioning that both the clinical and health-economic evaluations will be based on the pooled dataset of all 900 participants when the data of all five trials are combined.

Analysis

The health-economic evaluation will be conducted as a CEA with health care costs (in euro for the reference year 2018) related to WHODAS treatment response (WHODAS functioning dichotomized) and a CUA of incremental costs per QALY gained. These analyses will be conducted from the health care system perspective and hence will have a focus on health care costs and health-related outcomes. Sensitivity analyses will be carried out and will be directed at the main cost drivers and uncertainty in the outcomes. Sensitivity analyses are conducted to assess the robustness of the main analyses of the CEA and CUA or to enrich the analyses by repeating them in a different way. In one of the planned sensitivity analyses, the CEA and CUA are expanding the health care system's perspective to a wider societal perspective (with changes in productivity included). Finally, the statistical analyses will be based on the pooled dataset of all five trials. Owing to the lack of country-specific guidelines for each of the participating sites, the guidelines of the UK National Institution for Care Excellence will be used [15,16].

Costing

Total costs will be estimated using a bottom-up (or microcosting) approach, where units of health service are multiplied by their appropriate unit cost price and summed to provide an overall total cost estimate [11]. Unit costs will be determined for Croatia and will be extrapolated to the other participating countries based on the purchasing power parity of the respective countries. Cost prices will be estimated using microcosting based on hospital records, financial departments, and national tariffs. Microcosting takes into consideration (if applicable) the initial investment for equipment, other investments, maintenance, number of years of use and discounting, material costs, personnel costs (per hour), and an increase for the overhead of the respective unit price. Costs of medication (and dispensing costs) will be calculated using daily defined dosage (based on clinical practice guidelines) and data from the financial departments of the five participating hospitals, indicating the mean medication usage per adult a day. Productivity losses will only be included in the analyses in which a societal perspective is adopted. Productivity losses will be evaluated using both the friction cost approach (ie, calculation of productivity losses solely for a prespecified "friction period" in which an employee would have been replaced) and the human capital approach (ie, calculation of the productivity losses for the full period of absenteeism) [17,18]. Furthermore, costs of informal care will be based on the shadow prices for unpaid

work in the respective countries. Costs of transport will be calculated as the mean distance per destination to the health care provider multiplied by tariffs of public transport. Total costs will be aggregated over time by calculating the area under the curve (AUC). All costs will be expressed in euro for 2018. If necessary, existing cost prices will be updated to 2018 values using the consumer price index.

All costs will be converted to Int.€ using purchasing power parity, which makes it possible to compare costs between countries with different standards of living (to derive a uniform currency by equalizing the purchasing power of different currencies through the elimination of differences in price levels between countries [19]). Following the National Institute for Care Excellence (NICE) guidelines for health-economic evaluation, both costs and effects will be discounted by 3.5% per annum, because the time horizon of the trials extends beyond 1 year. However, discounting rates will be subject to sensitivity analysis because discounting can have a substantial impact on the outcomes of a health-economic evaluation.

Cost-Effectiveness Analysis

The CEA, with costs and WHODAS functioning as the primary outcomes, will be conducted in several steps.

First, WHODAS global functional disability will be computed using the scoring algorithm based on the item response theory as recommended by WHO [6]. This algorithm provides a per patient functional disability score between 0 and 100, with higher scores indicating greater disability.

Second, the sample characteristics at t_0 will be described to see if despite randomization, some baseline imbalances across conditions have occurred in prognostically relevant variables (ie, variables that are strongly correlated with the outcome). If this is the case, such variables will be used as covariates to make adjustments for the baseline imbalances. In the unlikely scenario where many potential confounders are found, covariate adjustments will be made more efficiently using inverse propensity score weighting, with w=1/p in the control group and w=1/(1-p) in the experimental group, where *w* is the weight and *p* is the propensity score (ie, the likelihood that a participant is in one condition rather than the other), and *p* will be estimated under a logistic model.

Third, dropout will be evaluated, and missing observations in WHODAS functioning at t_1 and t_2 will be imputed to permit ITT analysis. The imputation will be based on the predictors of outcome (for accuracy) and predictors of missing values (to adjust for possibly selective dropout). To handle missing data, single imputation using predictive mean matching embedded in nonparametric bootstraps of seemingly unrelated regression equations (SURE model) will be used. In a recent paper by Brand et al, single imputation nested in the bootstrap percentile method emerged as the method with the best statistical properties [20]. Predictive mean matching will be used to account for nonnormality of the data by imputing "real" observed values from similar cases instead of imputing regression estimates [21,22].

Fourth, in the context of the economic evaluation, WHODAS global functioning must be dichotomized into a binary treatment response outcome. This is done because from an economics perspective, it is meaningless to relate hard currency (euro, which is measured at the interval level) to a health gain (measured at an "elastic" ordinal measurement level). In other words, for a health-economic evaluation, a "tangible" outcome on par with the hard currency required to generate that health outcome is needed in order to merit a meaningful analysis. In this analysis, a binary *treatment response* variable (1, improved; 0, not improved) would constitute such a hard outcome. For the main analysis, treatment response is defined when a patient has improved by 0.33 standard units or more. A change of 0.33 standard units is equivalent to a 6-point change on the WHODAS 0-100 scale. Thus, when a patient has improved 6 points or more, the patient is considered as a treatment responder (ie, treatment response=1 or else 0).

Fifth, to simultaneously evaluate both costs and outcomes, SURE models will be used. The SURE models will be baseline adjusted with baseline WHODAS functioning and cost as covariates or weighted with inverse propensity scores as needed. Because costs are nonnormally distributed, the SURE models will be bootstrapped (2500 times). When bootstrapping, one creates N times (in this case 2500 times) a new sample out of the original sample with replacement. This results in N different samples. Incremental cost-effectiveness ratios (ICERs) will be computed by dividing the between-condition differences in costs by the difference in effects (treatment responders). Thereafter, the scatter of 2500 bootstrapped ICERs will be plotted on the ICER plane. When most simulated ICERs fall into the north-east quadrant of the ICER plane (indicating that better health is achieved at higher costs), an acceptability curve will be graphed for decision-making purposes. The acceptability curve depicts the likelihood that the new health care system has acceptable cost-effectiveness relative to CAU given varying willingness-to-pay ceilings for gaining a QALY [23].

These health-economic evaluations will answer the question, "To what extent the newly implemented community-based recovery-oriented health care system has better patient-level outcomes with regard to WHODAS functioning?"

Cost-Utility Analysis

The methods for the CUA are the same as those for the CEA, with the exception that the incremental costs per QALY gained is the primary outcome. The QALYs will be computed from the EQ-5D-3L and will be based on the Slovenian VAS-based tariffs and the AUC method [9]. The Slovenian tariffs will be used in the absence of local tariffs for the participating countries, and hence, the Slovenian tariffs are deemed most representative. In the sensitivity analyses, alternative strategies for computing the QALYs will be used.

Sensitivity Analyses

The analyses mentioned above will be subject to a series of sensitivity analyses to gauge the robustness of the main findings. Sensitivity analyses will be directed at several uncertainties. First, the health-economic evaluation in the main analysis is restricted to the health care system's perspective, where the

costs are confined to the health care costs incurred by mental health services. In the sensitivity analysis, the health care perspective will be broadened to include the out-of-pocket costs of the patients and their family members for informal copayments, traveling costs for trips to healthcare centers, and informal care. In addition, the costs and benefits stemming from changes in productivity losses will be included. These costs stem from sickness absence (absenteeism) and lesser efficiency while at work (presenteeism). Second, in the main analysis, the valuation of the EQ-5D health states (ie, the tariffs) will be based on the Slovenian tariffs. For the sensitivity analysis, the tariffs will also be based on the study by Greiner et al, which is representative of West European countries, but might be less valid for Central and East European countries [24]. In addition, for each of the participating countries, we will repeat the main analysis using the country-specific EQ-5D VAS. Third, extreme cost outliers in the data may exert a disproportional influence on the economic evaluation. In the sensitivity analysis, we will rerun the economic evaluation while winsorizing cost data (ie, replacing the top 10% highest costs by more modest costs corresponding with the 90th percentile) [25]. Fourth, the choice of the discounting rates may impact the outcomes of the health-economic evaluation and will therefore be varied between 1% and 5% for both the costs and QALY gains. In a sensitivity analysis, the main analyses will be repeated with an annual discounting rate of 3.5% for the effects and 4.0% for the costs, as per the Dutch guidelines for health-economic evaluation [26].

The sensitivity analyses will help to assess the robustness of the findings that were obtained under the main analysis and will enrich the main analysis by taking different perspectives.

Analysis of Pooled Trial Data

One of the secondary goals of the RECOVER-E project is to support and develop on-site research skills and to strengthen collaboration between countries. Therefore, the health-economic evaluations will be carried out locally at each of the sites. Central analysis will also be conducted for the pooled dataset of 900 (5 × 180) participants. The pooled data will be analyzed using mixed linear models with random effects both at the patient and site levels (equivalent to individual participant data meta-analysis) or alternatively with design-based analysis for the data of participants clustered at sites. The pooled data analysis, which has greater statistical power to detect significant effects, will include WHODAS functioning (on the continuous scale), as well as treatment response (dichotomized) and EQ-5D QALY gains. Finally, the pooled data will allow for multilevel modelling of net monetary benefits as the outcome of interest, with net benefits defined as NB = E*λ- C, where NB represents the net benefits, E represents the effects, λ represents a varying willingness-to-pay value (in euro) for gaining one unit of E, and C represents the costs required for generating that one unit health gain.

Reporting

The above evaluations will be reported in agreement with the following pertinent guidelines: the CONSORT statement for randomized trials [27], Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement for trial-based health-economic evaluation [28], and Consolidated Framework for Advancing Implementation Science [29].

Results

Data collection was started in December 2018 (Croatia), February 2019 (Montenegro), April 2019 (Romania), June 2019 (North Macedonia), and October 2019 (Bulgaria). At the time of acceptance of this manuscript, the following numbers of participants were included at each site: 91 in Bulgaria, 165 in Croatia, 180 in Romania, 197 in Montenegro, and 190 in North Macedonia. All procedures are in accordance with the ethical standards of the ethics committees of the participating countries and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent will be obtained from all individual participants included in the study. The five trials have been registered separately for every site. The registration numbers on ClinicalTrials.gov are as follows: NCT03922425 (Bulgaria), NCT03862209 (Croatia), NCT03892473 (Macedonia), NCT03837340 (Montenegro), and NCT03884933 (Romania). The results from the various evaluations will be summarized in policy briefs (a part of the policy influencing strategies developed in each country) using clear and nontechnical wording. The policy briefs will inform decision-makers about the project findings during the final policy dialogue sessions (one per site). Papers reporting primary outcomes will be published in open-access journals and findings will be presented in other academic and scientific fora as per the RECOVER-E research dissemination strategy [30]. The first results describing the follow-up data are expected in 2021.

Discussion

General Considerations

This study will examine the cost-effectiveness of recovery-oriented community mental health care for patients with severe mental disorders (the intervention implemented in the RECOVER-E project) compared with CAU in Bulgaria, Croatia, Macedonia, Montenegro, and Romania. Health-economic evaluations will be conducted alongside hybrid effectiveness-implementation trials at each of the five sites. In addition, a pooled analysis will be performed combining all trial data. It is hypothesized that the shift toward deinstitutionalization using a locally adapted form of flexible assertive community treatment results in the reduction of health care costs by avoiding expensive emergency care or psychiatric hospitalization. At the same time, this intervention has a focus within service delivery on recovery goals, which is hypothesized to contribute to a greater sense of societal role fulfilment and participation in society among people with severe mental illness. It is not unlikely that patients receiving community care will show larger improvements in WHODAS personal and social functioning and EQ-5D health-related quality of life as compared with patients treated in hospital-based mental health care services.

Given the nature of the intervention, a pragmatic approach is chosen to implement and evaluate community mental health services. While this may affect internal validity (eg, due to the lack of allocation concealment and masking), the corresponding

results may be more generalizable and applicable to routine practice settings [31]. Moreover, the proposed methodology includes some methodological solutions to combat threats to the internal validity of the trials (eg, inverse propensity score weighting when randomization appears to be suboptimal).

There are additional limitations that are anticipated and worth noting. Among these, the lack of country-specific EQ-5D tariffs and the difficulty to obtain unit cost prices in lieu of national standard cost prices are relatively important. In an effort to address this lack of tariffs and standard cost prices, the EQ-5D VAS will be used to obtain QALYs and the microcosting technique will be used to obtain reasonably accurate local cost prices. Nonetheless, these approaches may introduce bias in the QALY and cost estimates. It is hoped that these biases occur to the same degree in the CMHC condition as in the CAU condition of the trials and will therefore cancel each other out when computing cost differences and effect differences across the conditions. Moreover, robust statistical techniques will be used, such as nonparametric bootstrapping and inverse propensity score matching. Furthermore, the main analysis will be subject to various sensitivity analyses precisely directed at uncertainties in costs and outcomes in order to ascertain the robustness of the main analysis.

The use of the WHODAS self-report version instead of the interviewer-administered version may cause some reporting bias (eg, due to differences in the literacy level between participants). However, given the randomized nature of the study, we expect this bias to be present equally in both arms. Furthermore, the self-reported version of the WHODAS has been demonstrated to identify improvements in functioning following treatment in people who have certain health conditions (eg, depression, schizophrenia, and alcohol problems) [7]. Regarding the use of the EQ-5D-3L, there is some evidence demonstrating a lack of responsiveness in patients with schizophrenia [32]. However, the EQ-5D-3L is recommended as the preferred utility instrument in most countries worldwide, and in line with the recommendations of Payakachat et al [32], we believe that an appropriate estimate of effectiveness is ensured by also using the WHODAS.

Although the operationalization of the societal perspective is challenging, in this study, we believe the use of the term "societal" is justified, as we include relevant societal costs, such as informal care, travel distances to health services, and productivity losses stemming from functional impairment. However, the educational and criminal justice sectors, which are often overlooked, may also be considered [33]. In this study, we feel that these sectors are relevant to a lesser extent and the substantial efforts in collecting data within these sectors is not justified by the expected impact on total costs (especially for the educational sector as we include adults only).

Lastly, we expect that it will be difficult for some of the participating study sites to recruit 180 participants into the trials and that the trials are likely to experience loss to follow-up. This may deflate the sample size and power. In the event of this occurring, power-efficient statistical techniques will be employed, such as baseline-adjusted ANCOVA (repeated measures) and similarly specified linear mixed models for ITT analysis. It is also worth noting that the economic evaluation will be conducted on the pooled dataset of all five trials combined, which will mitigate power issues, if any.

Conclusions

All five countries included in this project are either relatively new EU members (from 2007 onwards) or EU candidates with per capita GDP far below the EU average. Consequently, their health care budgets are constrained and also face many competing priorities. In this context, scientifically sound health-economic evaluation is a prerequisite for policy makers to decide on wider, possibly national, implementation and scale up of community-based recovery-oriented mental health services. In addition, the results of the health-economic evaluation will contribute to the growing evidence base of effective and cost-effective recovery-oriented and community-based service models for sustainable mental health systems for people with severe and enduring mental ill health in low- and middle-income countries.

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Authors' Contributions

Overall project coordination: IP and LSZ. Co-ordination health economic evaluation: AIU, BFMW, and FS. Writing of the manuscript: FS, BFMW, LSZ, and AIU. Critical appraisal of the manuscript: AI, JD, RD, RN, RV, and MW. All authors have read and approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT 2010 flow diagram for the RECOVER-E program.
[DOC File , 55 KB - resprot_v9i6e17454_app1.doc]

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Abbreviations

ACT: assertive community treatment
ANCOVA: analysis of covariance
AUC: area under the curve
CAU: care as usual
CEA: cost-effectiveness analysis
CHEERS: Consolidated Health Economic Evaluation Reporting Standards
CMHC: community-based recovery-oriented mental health care
CMHT: community mental health care team
CONSORT: Consolidated Standards of Reporting Trials
CUA: cost-utility analysis
EQ-5D: EuroQol five dimensions
EQ-5D-3L: three-level EuroQol five dimensions
FACT: flexible assertive community treatment
ICER: incremental cost-effectiveness ratio
ITT: intention-to-treat
QALY: quality-adjusted life year
SURE: seemingly unrelated regression equations
TiC-P: Trimbos/iMTA Questionnaire on Costs associated with Psychiatric illness
VAS: visual analog scale
WHO: World Health Organization
WHODAS 2.0: World Health Organization's Disability Assessment Schedule 2.0

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Protocol

Interactive Guidance Intervention to Address Sustained Social Withdrawal in Preterm Infants in Chile: Protocol for a Randomized Controlled Trial

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Abstract

Background: Preterm newborns can be exposed early to significant perinatal stress, and this stress can increase the risk of altered socioemotional development. Sustained social withdrawal in infants is an early indicator of emotional distress which is expressed by low reactivity to the environment, and if persistent, is frequently associated with altered psychological development. Infants born prematurely have a higher probability of developing sustained social withdrawal (adjusted odds ratio 1.84, 95% CI 1.04-3.26) than infants born full term, and there is a correlation between weight at birth and sustained social withdrawal at 12 months of age.

Objective: The aims of this study are to compare the effect of the interactive guidance intervention to that of routine pediatric care on sustained social withdrawal in infants born moderately or late preterm and to explore the relationship between sustained social withdrawal in these infants and factors such as neonatal intensive care unit hospitalization variables, parental depression, and posttraumatic stress symptoms.

Methods: This study is designed as a multicenter randomized controlled trial. Moderate and late preterm newborns and their parents were recruited and randomized (1:1 allocation ratio) to control and experimental groups. During neonatal intensive care unit hospitalization, daily duration of skin-to-skin contact, breastfeeding, and parental visits were recorded. Also, a daily score for neonatal pain and painful invasive procedures were recorded. After discharge from neonatal intensive care, for the duration of the study, both groups will attend follow-up consultations with neonatologists at 2, 6, and 12 months of age (corrected for gestational age) and will receive routine pediatric care. Every consultation will be recorded and assessed with the Alarm Distress Baby Scale to detect sustained social withdrawal (indicated by a score of 5 or higher). The neonatologists will perform an interactive guidance intervention if an infant in the intervention group exhibits sustained social withdrawal. In each follow-up consultation,

parents will fill out the Edinburgh Postnatal Depression Scale, the modified Perinatal Posttraumatic Stress Disorder Questionnaire, and the Impact of Event Scale–revised.

Results: Recruitment for this trial started in September 2017. As of May 2020, we have completed enrollment (N=110 infants born moderately or late preterm). We aim to publish the results by mid-2021.

Conclusions: This is the first randomized controlled trial with a sample of infants born moderately or late preterm infants who will attend pediatric follow-up consultations during their first year (corrected for gestational age at birth) with neonatologists trained in the Alarm Distress Baby Scale and who will receive this interactive guidance intervention. If successful, this early intervention will show significant potential to be implemented in both public and private health care, given its low cost of training staff and that the intervention takes place during routine pediatric follow-up.

Trial Registration: ClinicalTrials.gov NCT03212547; https://clinicaltrials.gov/ct2/show/NCT03212547.

International Registered Report Identifier (IRRID): DERR1-10.2196/17943

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KEYWORDS

social withdrawal; preterm; early detection; interactive guidance; emotional stress; social development; postnatal depression; posttraumatic stress

Introduction

Background

In infants in the normal range of development, skills to engage with caregivers such as initiating and maintaining eye contact, vocalizing, using facial expressions, and using body movements, emerge during the first two months after birth [1,2]. The level of synchronization between infants and their caregivers and the capacity of caregivers to detect interactive errors and attune with the infant's emotional state and interactive behaviors appears to be critical for optimal psychological development in the first 18 months of life [3].

Infants can display social withdrawal behaviors as a reaction to minor transient perturbations when interacting with caregivers or when agitated or tired; however, infants are usually able to reengage as soon as they regain the full attention of the caregivers [4-6]. In contrast with this adaptive social withdrawal behavior, sustained social withdrawal is significantly less common and reflects a sustained decrease in engagement during interactions and a sustained decrease in reactivity to the environment [7,8]. Sustained social withdrawal can be assessed by the Alarm Distress Baby Scale [9] and is defined by a score of 5 or higher. Persistent (both repetitive and accumulated) sustained social withdrawal has been shown to be a risk factor for altered emotional development in infants [10].

Sustained social withdrawal has typically been associated with severe pathological conditions in infancy such as posttraumatic stress disorder [4], autism spectrum disorders [11], and child depression [12]. Infants demonstrating sustained social withdrawal have a higher risk of developing attachment disorders [13], emotional or behavioral disorders [14], motor and language delays [15], and altered interactive skills [10,16]. Sustained social withdrawal has also been linked with medical conditions such as intrauterine growth retardation, preterm birth [17], early cardiac surgery [18], Prader-Willi syndrome [19], and cleft lip and palate [20], as well as factors in family medical history such as both parents having mental health problems [2]. Sustained social withdrawal has proven to be an important indicator of infant distress regardless of the cause [10].

The Alarm Distress Baby Scale is a well-validated screening tool designed to assess sustained social withdrawal in infants between 2 and 24 months of age in primary care settings such as routine medical checkups or testing [21]. The infant can be assessed during the interaction with the medical professional which avoids putting pressure on the parents (because of their perception that it reflects their caregiving competence) [22].

Preterm Infants and Mental Health Developmental Risk

Infants born preterm often spend their first days, weeks, or even months in a neonatal intensive care unit where they undergo numerous painful and invasive procedures [23] and can be submitted to various perinatal stresses. During this period, in which both the development and the life of the neonatal infant can be at risk, the infants and their families must adapt to health care unit protocols with respect to visits and care. In addition, the mental health of the parents may be affected increasing the risk of posttraumatic stress and postpartum depression [24].

Several studies have shown that the prevalence of psychopathologies appeared to be significantly higher in infants born preterm than in infants born full term. So far, most studies have focused on infants born very prematurely and have shown high prevalence of autistic spectrum disorders [25], attention-deficit and hyperactivity disorders [26], attachment disorders [13], emotional problems [27], and social withdrawal behavior [28] and growing recognition of behavioral problems [29], lower socioemotional competence [30], and developmental delay [31] relative to prevalence of these in infants born moderately and late preterm. Furthermore, associations between late preterm birth and poor socioeconomic outcomes in adulthood [32] and late preterm birth and poor neurocognitive functioning in late adulthood [33] have been described.

In their first year (corrected for gestational age), infants born preterm have a higher probability of developing sustained social withdrawal (adjusted odds ratio 1.84, 95% CI 1.04-3.26) when compared to that of infants born full term [17] (prevalence was 22.1% and 13.9% for infants born preterm and born full term, respectively). Other studies have found prevalences of sustained

social withdrawal that vary from 11.3% to 22.1% for infants born preterm [6,13,17,34].

Chilean Preterm Infants: Early Detection and Intervention

In Chile, preterm birth rates have been increasing over the last decade. In 2016, 8.3% of live births were preterm (gestational age less than 37 weeks) [35]. Neonatal medical care is provided for these infants (if needed) by a national network of 29 neonatal intensive care units, and follow-up care is provided by interdisciplinary teams in 35 preterm polyclinics. Within the public health system in Chile, all preterm infants are assessed with the Psychomotor Development Assessment Scale [36] between the ages of 0 and 2 years.

Since intervention becomes more challenging as problems in infancy grow more complex or more severe [37], assessing the effectiveness of early sustained social withdrawal detection in preterm infants (using the Alarm Distress Baby Scale) as a precursor to early intervention appears to be an interesting goal.

The Alarm Distress Baby Scale [9] can be used as early as two months of age (corrected age in the case of infants born preterm) and has demonstrated acceptable levels of specificity and sensitivity in several studies (reported in a review study) [10]. In a study with full-term infants, Bonifacino et al [38,39] described a significant difference in sustained social withdrawal in the infants who were followed by Alarm Distress Baby Scale–trained pediatricians compared to sustained social withdrawal in infants who attended routine pediatric follow-up care. Facchini et al [40] investigated the feasibility of a feedback guidance intervention performed by Alarm Distress Baby Scale–trained pediatricians on infants born full term at public well-baby clinics in Italy, and they concluded that these interventions are easily implemented and accepted by patients and their families; however, to the best of our knowledge, there are no reports regarding the effect of an interactive guidance intervention performed by Alarm Distress Baby Scale–trained neonatologists on infants born moderately or late preterm during their first twelve months (corrected age).

The main objective of this study is to compare the effect of an interactive guidance intervention on sustained social withdrawal scores in infants born moderately or late preterm compared to those of infants born moderately or late preterm in routine pediatric care.

Methods

Study Design

The study is designed as a randomized controlled trial (NCT03212547), in order to remove bias in treatment allocation and the effect of possible confounding variables [41]. Chilean infants who were born moderately preterm or late preterm (up to N=110) and their parents will be included and randomized in a 1:1 allocation ratio to an intervention group (up to n=55) and a control group (up to n=55). Both groups will receive routine pediatric care at medical checkups at 2, 6, and 12 months of age. All ages used in this study refer to corrected age. To calculate corrected age, the difference in weeks of gestation at the time of birth and full term (40 weeks of gestation) is subtracted from the infant's chronological age. In addition, the intervention group will receive the interactive guidance intervention, performed by Alarm Distress Baby Scale–trained neonatologists, if the neonatologists detect sustained social withdrawal (a score of 5 or higher in the Alarm Distress Baby Scale) during the routine medical checkups. The interactive guidance intervention will follow a standardized protocol designed by the research team before the start of the recruitment. The control group will not receive the interactive guidance intervention during the first 12 months; however, if any infant in the study receives a score of 5 or higher on the Alarm Distress Baby Scale at the 12-month checkup, they will be offered further assessment and intervention.

Inclusion Criteria

Only preterm infants born from single or twin pregnancy (monochorionic or dichorionic), born between 32 weeks 0 days and 36 weeks 6 days gestation (as determined by neonatologist), hospitalized within the first 48 hours after birth, and remaining at least 48 hours in the neonatal intensive care unit were eligible to participate in this study. Parents of the infants were required to be Spanish speaking and have stable living arrangements to ensure the effectiveness of the interactive guidance intervention (carried out by Spanish-speaking neonatologists). Parents of infants born preterm were recruited from two neonatal intensive care units—Clinica Alemana de Santiago and Hospital San Jose—by a principal investigator or co-investigator of the study or by the neonatal study coordinator. Clinica Alemana de Santiago is a private health center located in a district of Santiago, Chile with a poverty rate of 0.1% whereas Hospital San Jose is a public health center located in a district of Santiago, Chile with a poverty rate of 8.2% [42,43]. At enrollment, socioeconomic variables were recorded using a socioeconomic survey, and pregnancy and postpartum variables were recorded using a perinatal background questionnaire.

Exclusion Criteria

Infants were not eligible for participation in this study if their mother had history of or confirmed exposure to cocaine, marijuana, or other illicit mind-altering substances during pregnancy; if the infant had a neurological disease that impairs development that was confirmed at birth; if the infant had major congenital malformations, suspected or confirmed genetic disorders; and if perinatal asphyxia occurred at birth (defined as an Apgar score less than 3 at 1 minute or an Apgar score less than 5 at 5 minutes, or cord pH less than 7.0 at birth).

Protocol

For this study, in 2017, Bonifacino et al [38] conducted Alarm Distress Baby Scale training in Chile over 4 days which consisted of 30 hours and 12 training modules. The program featured 2 central theoretical modules which covered early interactions and emotional development, emotional deprivation and its consequences, social withdrawal behaviors as an early alarm sign, and the Alarm Distress Baby Scale fundamentals. Subsequently, 10 modules of video training were presented featuring material with infants between 2 and 24 months of age. These infants had attended medical checkups with Alarm

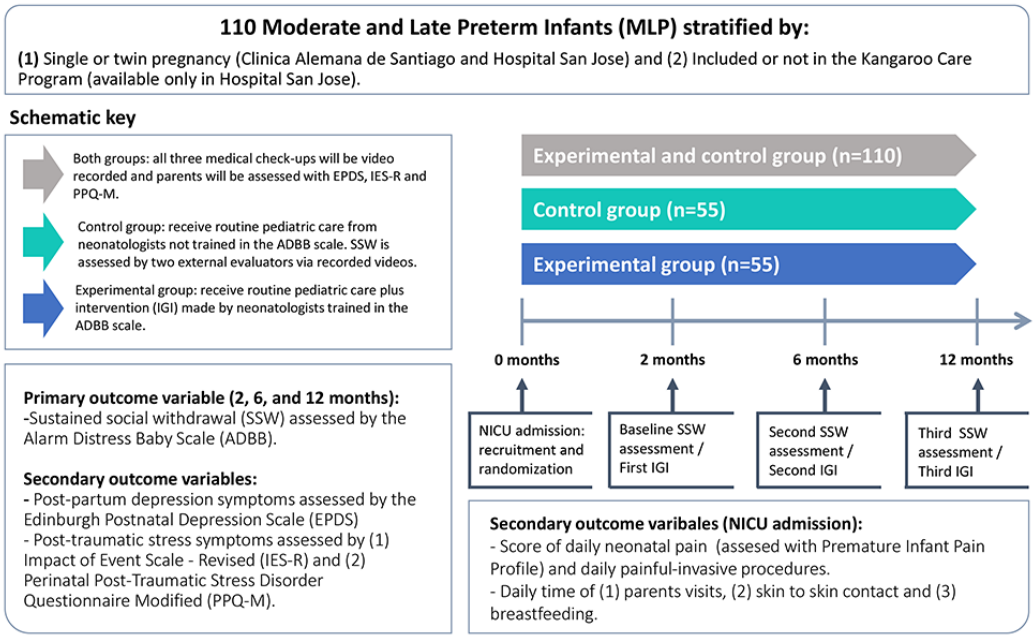
Distress Baby Scale–trained and untrained pediatricians. Following the videos, there was an exam to certify the professionals in the use of the Alarm Distress Baby Scale. Fleiss kappa was used to determine if there was agreement between the 11 evaluators regarding diagnosis (normal behavior or sustained social withdrawal). There was a substantial agreement [44] between evaluators (κ=0.794, 95% CI 0.676-0.913; *P* .001). Individual kappa values for normal and sustained social withdrawal categories were κ=0.795 and κ=0.794, respectively.

One fundamental element of the training was that the professionals learned not only to detect the sustained social withdrawal behaviors (and to score these behaviors using the Alarm Distress Baby Scale), but also to meaningfully show the parents how—in terms of communication or contact—their infants seek interaction, with the objective of reducing sustained social withdrawal behaviors.

Participants of the study will be recruited during their admission to the neonatal intensive care units by members of the researcher team and enrolled and randomized by a study coordinator to either the intervention or the control group. The infant will be randomized in a 1:1 allocation using SPSS Statistics (version 25.0; IBM Corp), stratified by hospital center (Clinica Alemana de Santiago or Hospital San Jose) in blocks of four. Also, infants will be stratified into two groups, single or twin pregnancy, in order to isolate the intervention effect from that of other covariables (such as mother of twins learning). The Hospital San Jose sample will also be stratified into two groups, whether the infant is included or is not included in the Kangaroo Care program, since only Hospital San Jose currently offers this program that aims to promote mother infant bonding, and which could potentially act as a confounding variable.

As shown in Figure 1, all infants will receive routine pediatric care during the medical checkups at 2, 6, and 12 months of age, but in addition, infants in the intervention group will also receive the interactive guidance intervention if the Alarm Distress Baby Scale–trained neonatologists detect sustained social withdrawal during these medical checkups. All medical checkups will be video-recorded, and the videos will be assessed by external Alarm Distress Baby Scale–trained evaluators, and at every medical checkup, parents will fill out the Edinburgh Postnatal Depression Scale, the modified Perinatal Posttraumatic Stress Disorder Questionnaire, and the Impact of Event Scale–revised.

Figure 1. Interactive Guidance Intervention plan for infants born moderately or late preterm with primary and secondary outcome variables recorded during NICU admission and during medical checkups at 2, 6, and 12 months of corrected age. ADBB: Alarm Distress Baby scale; EPDS: Edinburgh Postnatal Depression scale; IES-R: Impact of Event scale–revised; IGI: Interactive Guidance Intervention; NICU: neonatal intensive care; PPQ-M: modified Perinatal Posttraumatic Stress Disorder Questionnaire; SSW: sustained social withdrawal.



Blinding

Participants

The families of the infants born moderately or late preterm, randomly assigned to intervention or control group, will remain blind to which group they belong. Families will receive feedback on their infant's Alarm Distress Baby Scale score by telephone after the final assessment at the 12-month medical checkup and will be offered further assessment and intervention, if needed.

Care Providers

Neonatologists who care for participants during the trial will be aware of whether the infant is in the intervention or control group. The Alarm Distress Baby Scale–trained neonatologists will only perform follow-up for the intervention group, and neonatologists who provide routine pediatric care will only perform follow-up for the control group.

Investigator

The principal investigator (JBL) will also be an external evaluator. Though, an Alarm Distress Baby Scale–trained psychologist, JBL will not participate in the follow-up of any of the infants and will be blind to the Alarm Distress Baby Scale scores of the Alarm Distress Baby Scale–trained neonatologists. Scores will be entered into the database by an independent agent who is blind to the group category.

Outcome Assessment

The Alarm Distress Baby Scale–trained neonatologists will be blind to the Alarm Distress Baby Scale scores of the external evaluators and to those of the other Alarm Distress Baby Scale–trained neonatologists. Once they record an Alarm Distress Baby Scale score, this data will be collected by a study coordinator, who is blind to the group category.

Data Collection Assessors

Data collection assessors will collect all study data (all variables) and upload the data into the database. They were not trained in the Alarm Distress Baby Scale, are blind to the group category, and do not have contact with the infants or their families.

Sample Size

We used the G*Power 3 software (Psychonomic Society Inc) to determine the minimum sample size required for obtaining a significant medium effect size (an effect size of 0.25), given α=.05 and a statistical power of 0.80 (β=.20), using the results presented in Bonifacino et al [37]. In Bonifacino et al's study [37], the dependent variable was assessed in 4 different stages, with 3 of them involving the total sample. Also, between the second and third assessments, the control group received the intervention. Because of this, we considered the observed differences between the first and second assessments in order to compute our sample size (postintervention difference in prevalence of 57% for the control group and 13% for the intervention group). The resulting sample size estimate was 23 per group; however, in order to ensure a sufficient effect size and taking attrition into consideration, a sample size of 55 infants per group will be used.

Assessment Instruments

Alarm Distress Baby Scale [9] reliably (Cronbach α=.83) assesses sustained social withdrawal behavior in infants from 2 to 24 months of corrected age during routine physical examination. It consists of 8 items (lack of facial expression, eye contact, general movement, self-stimulation gestures, vocalization, liveliness in response to any stimulation, ability to establish and maintain a relationship, and ability to attract and catch the attention of others) each scored from 0 (normal behavior) to 4 (massively abnormal behavior). A total score of 5 or more indicates sustained social withdrawal behavior. The assessment can be done during routine pediatric checkup by a trained professional, or by assessment of an 8 to 12-minute video of recorded infant behavior during a pediatric checkup.

Edinburgh Postnatal Depression Scale [45] reliably (Cronbach α=.77) assesses the probability of postnatal depression in women. It consists of 10 questions with 4 possible answers for each. Each answer is given a score of 0, 1, 2, or 3 according to the severity of the symptom. The maximum score is 30. A total score of 12 or higher suggests the presence of a postnatal depression disorder. The Edinburgh Postnatal Depression Scale can be administered from 2 months onward, after delivery.

Impact of Event Scale–revised [46] reliably (Cronbach α=.98) assesses symptoms associated with posttraumatic stress disorder. It is composed of 22 items and three subscales: intrusion, avoidance, and hyperactivation. It employs a 5-point Likert scale from 0 (not at all) to 4 (extremely), to assess the intensity of the symptoms. The Impact of Event Scale–revised can be applied from six weeks onward, after the occurrence of a stressful or traumatic event. Scores higher than 24 indicate significant clinical relevance.

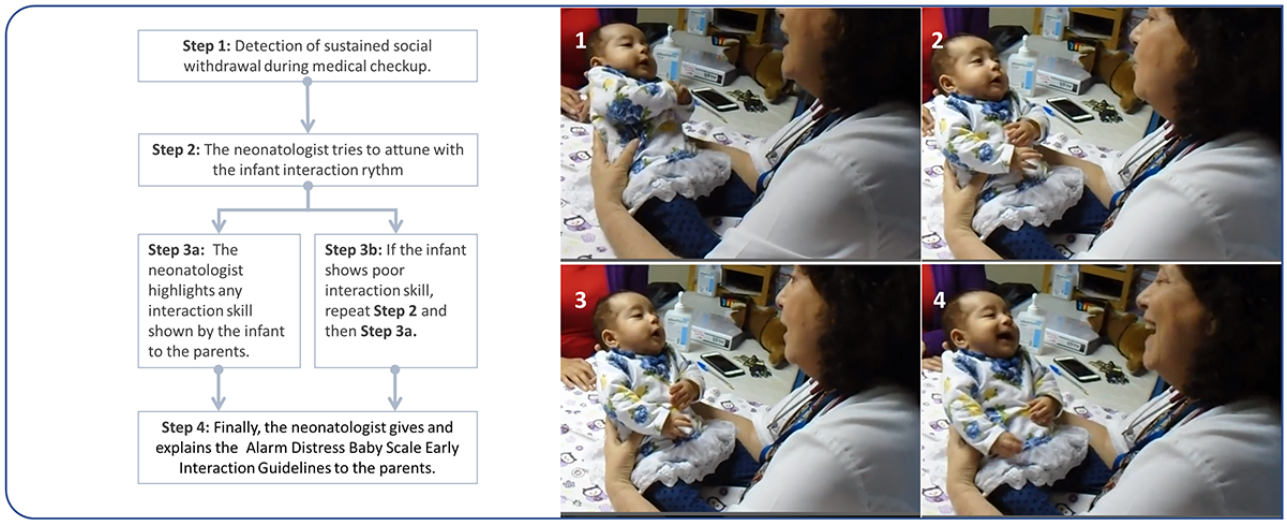
Modified Perinatal Posttraumatic Stress Disorder Questionnaire [47] reliably (Cronbach α=.90) assesses posttraumatic stress symptoms in parents including intrusiveness or reexperiencing, avoidance behaviors and hyperarousal, or numbing of responsiveness. It consists of 14 items, which are measured using a 5-point Likert scale from 0 to 4. Parents are instructed to provide responses that reflect their experience during the 4th and 18th month after delivery. The total score can range from 0 to 56. The clinical range for a high-risk parent is set at 19 or higher.

Premature Infant Pain Profile [48] is a reliable (Cohen $\kappa \geq 0.85$, consistently) 7-indicator composite measure developed to assess acute pain in preterm and term neonates . The 7 indicators are gestational age, behavioral state, heart rate, oxygen saturation, brow bulge, eye squeeze, and nasolabial furrow. Each indicator is numerically scored using a 4-point Likert scale from 0 to 4, and total scores can range from 0 to 21. Higher total scores indicate greater pain. Premature Infant Pain Profile scores below 6 means no pain, 6 or higher indicates pain, and 12 or higher indicates moderate to severe pain.

Intervention

As shown in Figure 2, this interactive guidance intervention consists of a brief, nonintrusive, behaviorally focused intervention performed during medical checkup and which follows a simple protocol that is based on the intervention proposed by Bonifacino et al [38].

Figure 2. Summary of the steps of the interactive guidance intervention during medical checkup.



The main objective of this intervention is to reduce sustained social withdrawal behaviors in moderately and late preterm infants by (1) detecting sustained social withdrawal behaviors during medical checkup, (2) becoming attuned with the interaction rhythm of the infant, (3) meaningfully showing parents how their infant seeks to interact by pointing out specific interactive behaviors (every interaction skill displayed by the infant), and (4) inviting parents to engage in the interaction.

Infants born preterm have a higher probability of developing sustained social withdrawal, and withdrawn infants show poor performance during interaction [17,49]; therefore, by facilitating parental understanding of the development of their infant, by involving them in the observation of and interaction with their infant [50], and by reinforcing every seeking interactive behavior displayed by the infant during medical checkups, we can reduce sustained social withdrawal in these infants.

In the intervention group, this interactive guidance intervention will be performed if the trained neonatologist detects sustained social withdrawal during the 2, 6, and 12-month medical checkups. The interactive guidance intervention will be performed during the 20 to 30-minute medical checkup and will not require any extra time. The interactive guidance intervention will be supplemented with a written guide for parents called Early Interaction Guidelines. The objective of this written guideline is to enhance the effect of interactive guidance intervention.

In the control group, infants will receive routine pediatric care. At the 2, 6, and 12-month medical checkups (also lasting 20 to 30 minutes), parents will be given a Development Stimulation Guide which has been adapted from Ministry of Health of Chile Guidelines for the Stimulation of Development [51,52].

If any infant in the study (in either the intervention or the control group) shows sustained social withdrawal (a score or 5 or higher on the Alarm Distress Baby Scale) at the 12-month medical checkup, they will be offered additional interventions by the researcher team.

Outcomes

Primary Outcome Measure

The primary outcome is sustained social withdrawal assessed using the Alarm Distress Baby Scale. The Alarm Distress Baby Scale categorizes the level of sustained social withdrawal according to the sum of the score—scores from 0 to 4 indicate no sustained social withdrawal, scores from 5 to 9 indicate moderate sustained social withdrawal, and scores equal to or higher than 10 indicate severe sustained social withdrawal. Infants born moderately or late preterm will be assessed with the Alarm Distress Baby Scale during medical checkups at 2, 6, and 12 months of age.

Secondary Outcome Measures

The secondary outcomes measured during neonatal intensive care unit admission are neonatal pain and daily duration of parental visits, skin-to-skin contact, and breastfeeding; and the secondary outcomes measured after medical discharge are postpartum depression symptoms and posttraumatic stress symptoms which will be assessed at the 2, 6, and 12-month medical checkups. A socioeconomic survey, a substance-use survey, and a perinatal background questionnaire will be used to obtain additional information from the parents of the infants.

Statistical Analysis

Two-tailed paired *t* tests will be used to compare covariates and dependent variables from the infant groups. A one-way analysis of covariance will be used to determine the effects of covariates (sociodemographic and neonatal intensive care unit hospitalization variables, postpartum depression, and posttraumatic stress) on the comparisons between groups (control and intervention) and between times (2, 6, and 12 months of corrected age medical checkups) regarding the dependent variable (sustained social withdrawal). Other statistical techniques such as matching, odds ratios, and logistic regression will also be used.

Ethics

The study was approved by the *Comité Ético Científico de la Facultad de Medicina* (Scientific and Ethics Committee of the

Faculty of Medicine), Universidad del Desarrollo (approval record 2017-05) on April 25, 2017. The clinical trial was registered at the United States National Institutes of Health (clinicaltrials.gov; NCT03212547) and approved on July 7, 2017. Informed oral and written consent were obtained from the accompanying parent of each infant included in the study.

Results

The clinical trial is ongoing. It was funded in December 2016, approved by institutional review board on April 25, 2017. Data collection started on September 19, 2017. As of May of 2020, enrollment has been completed (N=110 infants born moderately or late preterm). We aim to publish the results by mid-2021. The data sets from this study will be available by request from the corresponding author, once results have been published.

Discussion

Summary

This project is a logical continuation of the work in Bonifacino et al [38] and aims to contribute to the early detection of alarm signs in emotional development and early intervention to help infants born moderately or late preterm. Neonatologists have a central role to play in this regard, and based on the findings of both Bonifacino et al [38] and Facchini et al [40], we hypothesize that implementing interactive guidance intervention will reduce sustained social withdrawal in infants born moderately or late preterm compared to those who receive routine care. Also, we hypothesize that this interactive guidance intervention will be easily implemented and accepted by patients and their families.

This is the first randomized controlled trial that will be performed with infants born moderately or late preterm at follow-up pediatric checkups. The implementation of an interactive guidance intervention will allow Alarm Distress Baby Scale–trained professionals who use this interactive guidance intervention as a model to intervene for infants at risk.

Study Limitations

One of the limitations of this study is the possibility that the parents of infants included in the intervention group will share information with parents of infants included in the control group. For this reason, twins are randomized together (both either in the control or in the intervention group). Additionally, all parents included in the study will be asked to refrain from sharing the written guides used in the study with others until the study is finished.

Another limitation is the pain protocol established at each institution. Clinica Alemana de Santiago has had a standardized pain protocol since 2012 that includes administering the Premature Infant Pain Profile every 3 hours while, in Hospital San Jose, the standardized pain protocol does not include the Premature Infant Pain Profile. Before the start of study recruitment, training was performed by nurses of Clinica Alemana de Santiago in order to teach the midwives in Hospital San Jose how to administer the Premature Infant Pain Profile. At Hospital San Jose, this is only done for the infants included in the study.

Ethical Considerations

The interactive guidance intervention does not involve any risk to the participating infants and parents. The neonatologists will follow routine medical care protocols at medical checkups and will only perform the interactive guidance intervention (verbally) if they detect sustained social withdrawal. Currently, the neonatologists on the investigation team are the only follow-up neonatologists trained in the Alarm Distress Baby Scale in Chile, so these infants will receive an evaluation and an intervention that is otherwise not currently available in either the public or in the private health system. Finally, if any infant scores 5 or higher on the Alarm Distress Baby Scale at the 12-month medical checkup (final assessment), they will be offered further assessment and intervention.

Acknowledgments

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Authors' Contributions

JBL conceived and designed the study, drafted the manuscript, and coordinated the Clinica Alemana de Santiago and Hospital San Jose research teams. MPR participated in the study design, provided critical review, and coordinated the Clinica Alemana de Santiago research team. AG, PPS, and SS participated in the study design and provided critical review. MMN coordinated Hospital San Jose research team and provided critical review. HC, JGM, LM, and LL provided critical review. AM and RSG participated in the manuscript and provided critical review. AMS planned the statistical analysis and provided critical review. All authors read and approved the final manuscript.

Conflicts of Interest

This study is funded by the Academic and Scientific Department of Clinica Alemana de Santiago, and the study protocol has undergone peer review by the funding body. Clinica Alemana de Santiago is part of a nonprofit Chilean-German charity corporation and adheres to the Good Clinical Practices and the requirements of the Instituto de Salud Pública de Chile (Public Health Institute of Chile) in accordance with their current Guide of Inspection of Clinical and Pharmacological Studies.

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Protocol

A Clinical Trial to Increase Self-Monitoring of Physical Activity and Eating Behaviors Among Adolescents: Protocol for the ImPACT Feasibility Study

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Abstract

Background: Severe obesity among youths (BMI for age≥120th percentile) has been steadily increasing. The home environment and parental behavioral modeling are two of the strongest predictors of child weight loss during weight loss interventions, which highlights that a family-based treatment approach is warranted. This strategy has been successful in our existing evidence-based pediatric weight management program, Brenner Families in Training (Brenner FIT). However, this program relies on face-to-face encounters, which are limited by the time constraints of the families enrolled in treatment.

Objective: This study aims to refine and test a tailored suite of mobile health (mHealth) components to augment an existing evidence-based pediatric weight management program.

Methods: Study outcomes will include acceptability from a patient and clinical staff perspective, feasibility, and economic costs relative to the established weight management protocol alone (ie, Brenner FIT vs Brenner FIT + mHealth [Brenner *m*FIT]). The Brenner *m*FIT intervention will consist of 6 mHealth components designed to increase patient and caregiver exposure to Brenner FIT programmatic content including the following: (1) a mobile-enabled website, (2) dietary and physical activity tracking, (3) caregiver podcasts (n=12), (4) animated videos (n=6) for adolescent patients, (5) interactive messaging, and (6) in-person tailored clinical feedback provided based on a web-based dashboard. For the study, 80 youths with obesity (aged 13-18 years) and caregiver dyads will be randomized to Brenner FIT or Brenner *m*FIT. All participants will complete baseline measures before randomization and at 3- and 6-month follow-up points.

Results: This study was approved by the Institutional Review Board in July 2019, funded in August 2019, and will commence enrollment in April 2020. The results of the study are expected to be published in the fall/winter of 2021.

Conclusions: The results of this study will be used to inform a large-scale implementation-effectiveness clinical trial.

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KEYWORDS

physical activity; obesity; adolescence; adult; therapy, family; mobile phone

Introduction

Severe obesity among youths (BMI for age ≥120th percentile) has been steadily increasing. Declines in physical activity over the last four decades have been accompanied by concurrent declines in dietary quality [1], increased sugar consumption [2], and increased energy intake [3]. The combination of these factors has contributed to the increased prevalence of overweight/obesity in youths during this period, particularly severe childhood obesity [4]. Clinical interventions to treat obesity through healthy eating and physical activity show that improvements in these behaviors are linked to modest, positive weight outcomes [5] and improvement in cardiometabolic risk factors [6]. However, pediatric weight loss programs have relied on in-person visits, creating difficulties for parents' work schedules and the need to travel. A US Preventive Task Force panel noted that intensive clinical programs are effective but require ≥26 hours of contact to achieve positive results, which is difficult for the youths and their families to do [7]. Mobile technology supporting health practices (mobile health [mHealth]) can reduce these barriers by delivering theoretically based content, facilitating self-monitoring, and connecting families to enhance treatment adherence and improve weight status [5].

Involving family members in the treatment of adolescents with obesity can be effective, but adherence is suboptimal [6]. Few studies have targeted youths and their families with an mHealth approach to supplement a clinical weight loss intervention [8] despite evidence for its acceptability and feasibility in adolescents and adults [8,9]. Parent-child interventions are more effective than treatment programs that focus primarily on the child, and mHealth strategies are ideally suited for intervention targets identified in previous conceptual models (eg, increasing parental competence, self-efficacy, parent-child communication, and parents' support of the adolescent's autonomy) [10]. Engaging parents or other caregivers in treatment plans can be challenging, but mHealth strategies can potentially increase the caregivers' exposure to and engagement with intervention strategies by providing caregivers with more easily implemented tools to monitor youth behaviors and facilitate communication between caregivers and adolescents.

Self-monitoring is the cornerstone of behavioral treatment for weight loss [11], and both adherence to self-monitoring [12] and tailored feedback on self-monitoring behaviors [13] are associated with weight loss. mHealth technologies can be used to deliver the behavioral content of a weight loss intervention and provide participants with ways to self-monitor and receive feedback. Moreover, mHealth can deliver efficacious approaches for weight loss as phone ownership is pervasive in both adults [14] and children [15]. mHealth has the potential to make monitoring of healthy eating and physical activity less burdensome, although limited tools exist for parents and children. Therefore, there is an opportunity to develop and test mHealth tools to augment clinical practices. This paper describes the study design and conceptual approach of developing mHealth tools that will then be formally evaluated in a full-scale randomized trial to assess their effectiveness. The current project will randomize 80 youths with obesity (aged 13-18 years) and caregiver dyads to a pediatric weight management program or the same program plus a suite of mHealth tools. This study will establish the acceptability, feasibility, and costs of the mHealth program relative to the standard of care (ie, family-based, multidisciplinary weight management), and the proposed sample of 80 dyads will give sufficient power for the estimation of retention rates and confidence intervals to inform a large-scale implementation-effectiveness clinical trial (see Trial Sample Size section).

Methods

Study Setting

Brenner Children's Hospital is a 160-bed children's hospital, which is part of the Wake Forest Baptist Medical Center (WFBMC). Located at the WFBMC, Brenner Families in Training (Brenner FIT) is an interdisciplinary, family-based pediatric weight management program [16-18] that focuses on the treatment of obesity in children aged 2 to 18 years. A physician referral is required, and treatment involves the entire family. The Brenner FIT team includes physicians, family counselors, dietitians, social workers, an activity/play specialist, and a physical therapist. Brenner FIT materials are available in English and Spanish. Brenner FIT also offers free nutrition and face-to-face parenting classes to all members of the community. Given that Brenner FIT provides care for a diverse patient population, it will serve as the base of the study. The average patient is clinically obese, as indicated by a BMI of 35.9 kg/m^2 (SD 8.6) and a BMI z-score of 2.6 (SD 0.5). Half of the patient population is in their teenage years (13-18 years). Brenner FIT is successful in enrolling a diverse population of families into research studies [19,20]. Approximately 66% of those enrolled in Brenner FIT improve their weight status [21], and the children who are successful display a decrease in BMI z-score of 0.07 to 0.1, with an average BMI z-score decrease of 0.11 at 8 months. A 0.1 to 0.15 decrease in BMI z-score is linked with healthy changes in cardiometabolic biomarkers [21].

Study Design: Inclusion/Exclusion Criteria and Recruitment

Caregiver/adolescent dyads referred to the Brenner FIT program are invited to participate. Dyads are eligible if the adolescent under treatment is aged 13 to 18 years, a caregiver who lives in the house (eg, a parent or grandparent) agrees to participate, both members of the dyad (the adolescent and caregiver) own a smartphone or tablet, and the adolescent has no contraindications for physical activity as indicated by their physician. Research suggests that smartphone ownership is greater than 95% in the target population [22]. The youth will

be excluded from participation in the study if they have functional limitations that preclude engaging in physical activity as directed by the program because of our inability to tailor the mHealth materials for those requiring adaptations. Those deemed eligible initially are informed of the study following their intake visit by Brenner FIT clinical staff. Those who express interest receive an in-person *warm handoff* to a research team member who confirms eligibility, reassesses interest, and performs or schedules an intake visit.

Informed Consent and Intake

Following the clinical visit, caregivers and patients are informed of the study and are invited to learn more from the research staff. At this orientation session, the research staff describe the study and administer consent/assent forms to those who wish to enroll. Participants complete the consent/assent forms, then complete all baseline survey measures, have their weight/height assessed, and are oriented to the procedure for physical activity measurement via an accelerometer. ActiGraph accelerometers are affixed to all youth participants via a wrist strap, and the family is given a self-addressed, padded envelope to return the accelerometer in after 7 days of wear. Once participants return the monitor and complete dietary assessments, they are contacted to learn their group assignment (ie, Brenner FIT or Brenner FIT + mHealth [Brenner *m*FIT]). Follow-up visits are scheduled by the clinical staff in coordination with the research staff who complete assessments at 3 months (a subset of measures), and at 6 months, with the participating dyads following their clinical appointments at both time points.

Study Design: Randomization

This study is registered in ClinicalTrials.gov (NCT03961061). The study will be a two-group, randomized controlled superiority trial design. Dyads will be block randomized by our statistician to 1 of 2 groups. The 2 groups are (1) Brenner FIT (standard care: n=40 dyads) and (2) Brenner *m*FIT (standard care plus mHealth features: n=40 dyads). Owing to the nature of the study, it is impossible to blind the clinical staff or participants, but all data will be collected by an independent evaluator who is blind to the condition and not involved in the delivery of the intervention.

Control Condition: Brenner Families in Training (Standard Care)

Brenner FIT is an interdisciplinary, family-based pediatric weight management clinic. Treatment teams comprised a pediatrician, counselor, dietitian, and physical activity specialist, with others (eg, social workers, physical therapists) as needed. The entire family is encouraged to attend all aspects of the treatment program, although only 1 caregiver is required. As recommended with tertiary care stage 3 to 4 weight management programs [23], treatment is guided by an established protocol that is monitored using a clinical database.

After referral to Brenner FIT, families attend an orientation, following which they are scheduled for an initial introductory 2-hour intake group session; these occur within 2 to 4 weeks of the orientation. Monthly 1-hour-long visits with the dietitian, counselor, and physical activity specialist are held for 6 months, after which the child and caregiver see the pediatrician. During the 6 months of treatment, they attend 4 group classes, choosing from topics such as meal planning, physical activity, and parenting. Specialized visits with the physical activity specialist or physical therapist are scheduled when pertinent issues arise. Clinic visits include individualized goal setting (for behaviors that the family/clinician have jointly agreed to address), healthy eating and physical activity education, and behavioral counseling to implement changes at home. Motivational interviewing, modified by Brenner FIT for use with families [24], is key to treatment; family counselors are trained in cognitive behavioral therapy as well as parenting support and education, nonrestrictive approaches to dietary modification, and mindfulness and employ these approaches to assist families in developing healthy habits. Self-monitoring is part of the intervention: parents and children complete handwritten paper diet and physical activity logs and return them to clinicians.

Intervention Condition: Brenner Families in Training Plus Mobile Health

Brenner *m*FIT includes all components of the standard Brenner FIT program and 6 mHealth components that are designed to target theoretically supported constructs (Table 1). The 6 mHealth components are (1) a mobile-enabled website, (2) dietary and physical activity tracking and a physical activity tracker, (3) caregiver podcasts (n=12), (4) animated videos (n=6) for adolescent patients, (5) interactive messaging (between the participants and clinical staff), and (6) tailored clinical feedback. All Brenner *m*FIT components are delivered by the clinical staff. The components are outlined individually as follows.

Table 1. Components of the Brenner Families in Training plus Mobile Health condition and associated theoretical constructs.

Component	Use/Content	Theoretical construct
Mobile-enabled website	The mobile-enabled website will serve as the central hub of the mHealth components and will enable easy access to study materials and feedback	Facilitation (SCT[a])
Diet and physical activity tracking	Tracking physical activity via the Fitbit wearable and behavioral food goals tracked via the mobile-enabled website	Facilitation (SCT); self-regulation (SCT)
Caregiver podcasts	A 12-part episodic story about caregivers who are working with their adolescent children to help them to be active, eat healthy, and achieve a healthy weight. The podcasts will deliver theoretically informed content around emotional regulation, proper use of incentives, and providing support for their child to gain autonomy over their weight loss program	Outcome expectations (SCT); self-efficacy (SCT); incentive motivation (SCT); autonomy support (SDT[b])
Youth-animated videos	A 6-part series of short videos about teenagers who are struggling but succeeding with commonly encountered challenges to weight loss. Each episode will take on a different scenario that youth face successfully. The brief videos will use a compelling story and humor to address tough situations that the youths may find themselves in, such as navigating the holidays, being active despite barriers (eg, rain, inactive friends), shopping/cooking for oneself, or lack of motivation to be active	Observational learning (SCT); outcome expectations (SCT); autonomy (SDT); relatedness (SDT)
Peer and professional support	Secure platforms will be created so that caregivers can give and receive encouragement and feedback from peers and the clinical staff. The clinical staff will also give direct feedback regarding goal progress via directs texts and emails with families based on personalized reports provided to the clinical staff	Relatedness (SDT); self-efficacy (SCT)
Tailored clinical feedback	Personalized reports from each dyad will be provided to the clinical team on a weekly basis, which will give insight into successes and challenges related to self-monitoring, goal setting, goal attainment, and engagement with intervention materials	N/A[c]

[a]SCT: social cognitive theory.

[b]SDT: self-determination theory.

[c]N/A: not applicable.

Component 1: A Mobile-Enabled Website

A mobile-enabled website (Multimedia Appendix 1) developed for the project and accessible via a telephone, tablet, or personal computer serves as a central hub for the materials. Podcasts, animated videos, tracking summaries (for the parent and child), goal setting, and messages are delivered via the website utilizing an application program interface that integrates data from a commercial app (Fitbit) with data entered by participants.

Component 2: Dietary and Physical Activity Tracking

A wearable tracking device, chosen by the study team after consultation with caregivers and patients from previous work, is utilized for physical activity self-monitoring. Caregivers and adolescents are instructed to download the Fitbit app to their mobile devices, and adolescents are given a Fitbit Inspire HR activity tracker which synchronizes with the Fitbit app. Mobile phone apps have been shown to facilitate increased self-monitoring [25], which supports tracking of progress on behavioral goals (a component of Brenner FIT) by the youth and reporting to the caregiver and clinical team. Tracking app data are integrated into the mobile-enabled website.

Dietary behavioral tracking is supported by the mobile-enabled website. This strategy was chosen over the use of commercially available apps because no commercially available apps are congruent with the goals of the Brenner FIT program. The mobile-enabled website lets caregivers and youths track their goals in a manner that is appropriate for their role in the weight loss journey. For example, parents are asked to set goals related to providing a healthy food environment (eg, provide 5 family dinners this week), whereas youths are asked to set goals related to their behaviors (eg, eat 5 dinners with my family).

Component 3: Caregiver Podcasts

Caregiver podcasts tell a story of a caregiver of an adolescent Brenner FIT patient helping his/her child achieve a healthy weight. Through an engaging story, podcasts will help caregivers deal with the emotions that come with raising an adolescent in treatment for a medical condition (ie, obesity), provide strategies and encouragement to caregivers to help their adolescent build autonomy for healthy behaviors, engage in age-/ability-appropriate physical activity with their child, cook healthy family meals, and provide healthy snacks. Podcasts additionally focus on positive communication, interactions, and challenges often encountered in parenting. Podcasts have been used successfully in 4 previous studies by the team [26-30] and target several constructs from the self-determination theory and social cognitive theory, including (1) outcome expectations, (2) self-efficacy, (3) incentive motivation, and (4) autonomy support. Podcasts will be 5 to 10 mins long each and downloadable via the mobile-enabled website. Caregivers can download and listen to 1 podcast each week in weeks 1 to 12.

Component 4: Animated Videos

Animated videos were created based on feedback from adolescents previously enrolled in the Brenner FIT program. In this study, youths are given access to these animated episodic videos in six 30-second episodes. Animated videos are available to the youth biweekly for the first 12 weeks. Animated videos introduce scenarios encountered by adolescents who are part of a program like Brenner FIT. Each episode follows the youths

as they deal with the negative and positive emotions of their weight loss journey and the difficult social situations in which they find themselves engaged. The stories and scenarios contain elements of humor and drama while targeting several constructs from the self-determination theory and social cognitive theory, including (1) observational learning, (2) outcome expectations, (3) autonomy, and (4) relatedness. Similar to the podcasts, the videos are accessible from the mobile-enabled website. The scenarios were developed based on feedback provided by the clinical staff with input from a panel of families enrolled in the Brenner FIT program. Audio for the videos is available in English with subtitles available in English and Spanish.

Component 5: Interactive Messaging

Peer support is associated with weight loss [31]. Therefore, opportunities are created for peer social support among caregivers and youths on the mobile-enabled website. As many adults do not have social media accounts, we also created a private, secure, moderated message board on the mobile-enabled website. Participants (caregivers and adolescents) are encouraged to (1) post questions to the clinical staff, (2) participate in group discussions and challenges (eg, *post a picture of your healthiest meal today*), (3) post about physical activities, and (4) share their success stories and challenges. Participants on social media are encouraged to follow each other as well as a curated list of health professionals on social media.

Component 6: Tailored Clinical Feedback

Tailored feedback is provided at regularly scheduled clinic visits by the clinical staff based on a web-based dashboard generated from self-monitoring data. The clinical staff have access to the web-based dashboard that provides a summary of the level of self-monitoring, level of physical activity, and progress on behavioral/weight loss goals for the adolescent and their caregiver. The staff use this information to engage with dyads via regularly scheduled face-to-face meetings and emails to give feedback based on behavioral progress, encouragement to engage in greater self-monitoring, and/or theoretically informed messages to promote self-efficacy, positive outcome expectations, and self-regulatory behaviors.

Primary Outcomes

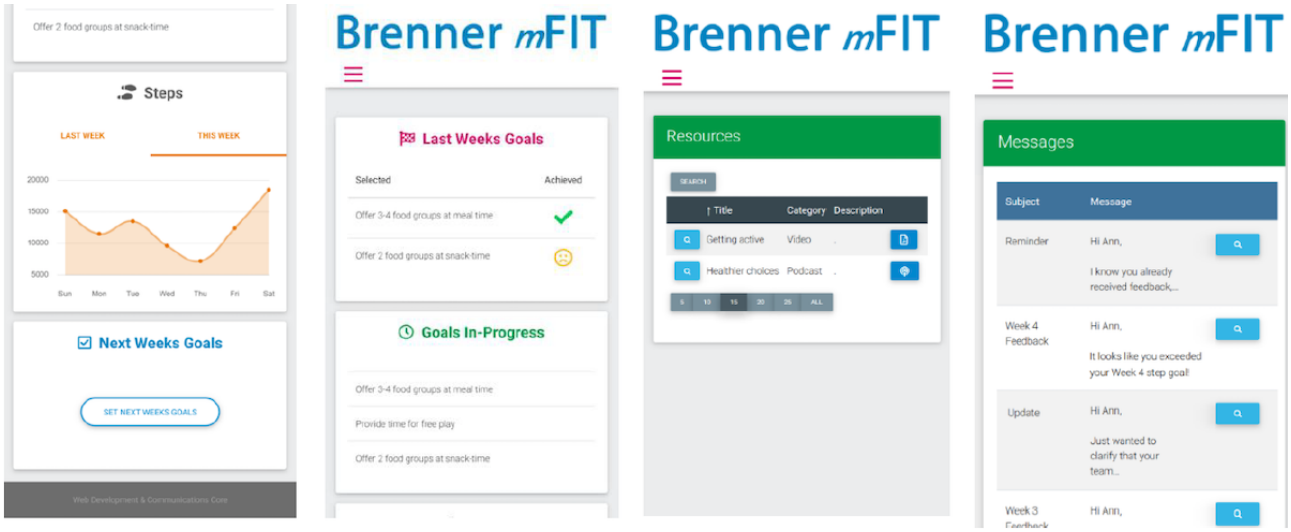
Primary Aim: Pilot the Intervention in Dyads Recruited From a Pediatric Weight Loss Clinic to Establish Acceptability and Feasibility of the Intervention Relative to Standard Care

Acceptability is measured using a brief survey from caregivers and youths to gain insight into their reception of the 6 mHealth components following the completion of the 6-month assessment (ie, completion of the study). Surveys include the system usability scale [32] to inquire about the usability of the mobile-enabled website, tracking apps, Fitbit tracking device, podcast format and content, animated video format and content, and web-based interactions with other participants and the clinical staff.

Feasibility is assessed consistent with the recommendations of Leon et al [33]. Specifically, the team examines screening, recruitment, randomization, retention, adherence, fidelity, and the assessment process. The number of patients screened per month, the number enrolled per month, the proportion of those enrolled who are eligible, and the number who remain enrolled in the study by condition are all tracked. Retention rates (completion of at least 75% of monthly sessions through 6 months) are tracked for each intervention condition. The time needed for assessments is monitored, and feedback on participant burden is recorded. Examples of clinical staff data include increases in clinical staff time interacting with patients and families, costs of delivering clinical staff training (eg, orientation to the technology), time spent in technical support with families related to mHealth components, and hosting/maintenance of the mobile-enabled website. The team developed a brief survey for the clinical staff to gain insight into the benefits and challenges of using the mHealth components and suggestions for improvements. Previous publication documents from the study group have demonstrated good engagement, retention, feasibility, and acceptability of a mobile tracking intervention in youths and their families [34].

Implementation fidelity is assessed to inform a future implementation-effectiveness study. Specifically, activity by the clinical staff and participants is compared against what has been directed (staff) or prescribed (participants). For example, the number of downloads of podcasts/videos, frequency of dietary and physical activity self-monitoring, goal setting, and open rates for web-based messaging from the clinical staff are recorded (Figure 1). The logs of participant engagement with website components are utilized rather than using self-reporting to remove recall bias. In addition, the participant retention rate is considered as a measure of fidelity (the criterion for retention rate has been detailed in the Trial Sample Size section). These data give indicators of fidelity and dose and highlight areas for improvement in future studies.

Figure 1. Screenshots showing (left to right) physical activity monitoring, goal setting, resources, and message board.



Procedures and Measures

Youth Measures Only: Physical Activity and Diet

Accelerometer data are collected at a 7-day interval at baseline and again at 6 months using ActiGraph GT3X+ accelerometers. The accelerometers are set to collect data in the *raw* format and analyzed by converting the data to 1-second epochs to account for the intermittent and sporadic nature of children's physical activity [35] and to improve the ability to capture the transitory physical activity patterns of children. During each 7-day data collection period, these monitors are affixed to a wrist strap on the participant's nondominant hand. Research by our team and others suggest that compliance is greater when the accelerometer is worn on the wrist, and this placement also allows for comparison with the National Health and Nutrition Examination Survey normative data collected at the wrist beginning in 2011 [36-38]. The cut points are distilled in a manner consistent with emerging research that allows for comparability with waist-based estimates [39]. Participants are instructed to wear the monitor continuously over the next 7 days except during bathing and sleeping. Once an accelerometer is received, data from the accelerometer are downloaded using the manufacturer's software and a USB computer interface. The accelerometer data are reduced, cleaned, and processed using custom scripts in Stata (StataCorp). The accelerometers are initialized and set to record beginning at 5 AM the day following their distribution. This provides 7 days of data for analysis, from which 4 or more complete (>10 hours) days will be extracted. Participant's accelerometer data are included in the analyses if 4 days with 10 hours of data are available.

Diet is assessed using the National Cancer Institutes' automated self-administered 24-hour (ASA24) dietary assessment tool (version: ASA24-2016) on 3 nonconsecutive days (including 1 weekend day). The ASA24-2016 is available on both computers and mobile devices and takes approximately 25 min to complete. All youth participants complete one ASA24 at their baseline orientation and at 6-month follow-up office visits to encourage compliance while allowing youths and caregivers to ask questions and gain comfort with using the system. The project coordinator contacts participants within 6 days (on a randomly selected day) following the office visits to inform participants that they should complete the second/third dietary recall and offers to conduct the recall over the phone if the youths need assistance (the ASA24 has been shown to perform equally well as a self-administered or interviewer-administered questionnaire) [40,41]. A series of follow-up reminder messages and/or phone calls are made by the coordinator to encourage completion of the second/third of the two recalls if not completed within 24-hours following the first contact after the clinic visit. Dietary data are collected at baseline and 6-month follow-up.

Caregiver and Youth Measures: Psychosocial Variables, Sociodemographic Variables, and Weight Status

Family and individual (youth and caregiver) constructs are assessed to identify potential mediators or moderators of observed effects of the intervention; these are incorporated into a larger trial in the future. Brenner FIT uses the family systems theory as a guiding model to address child and parent behaviors within the context of their family [42] and presently uses a number of scales to assess families participating in Brenner FIT. Specifically, Brenner FIT families complete the Family Assessment Device General Functioning subscale (capturing family function) [43], Olson's Family Communication Scale [44], perceived stress [45,46], self-efficacy for physical activity, impulsivity, and health behaviors of the family [47]. In addition, the team administers scales to capture social cognitive theory and self-determination theory constructs targeted by the intervention that are not captured as part of the intake process. These include outcome expectations, autonomy, autonomy support, and relatedness [48]. All psychosocial data are collected at baseline (before randomization), at 3 months, and at 6 months. Details regarding the variables collected, their theoretical rationale, and measurement instrument are presented in Table 2.

The caregiver and youth participants' age, sex, race, and ethnicity are collected via a parental self-report upon enrollment in Brenner FIT. The youth participants will also self-report their gender, race, and ethnicity during baseline data collection. The weight status of caregivers and youths are quantified through the calculation of BMI derived from the measurement of height and weight at the intake and follow-up visits. Both height (SD

0.1 cm) and weight (SD 0.5 kg) are recorded twice, and the values are averaged to produce the final value. BMI is calculated as kg/m^2. Height and weight are measured without shoes in normal clothing. The BMI z-score and percent of the 95th percentile BMI are calculated using the Centers for Disease Control and Prevention growth charts.

Table 2. Intervention-targeted constructs to be measured, participant providing data, theory, and instrument or method used.

Construct	C/Y[a]	Theory	Instrument or method
Weight status	Y	N/A[b]	Measured height and weight: used to calculate the BMI (weight in kg/height in m^2) and calculate the BMI z-score and percent over the 95th percentile
Physical activity	Y	N/A	Accelerometry (7 days of monitoring): used to estimate minutes of moderate-to-vigorous physical activity per day
Dietary intake	Y	N/A	Automated self-administered 24-hour (ASA24-2016) dietary assessment tool: used to estimate dietary composition
Perceived autonomy support	Y	SDT[c]	Perceived parental autonomy support scale: produces a continuous score
Autonomy support	C	SDT	Motivators' Orientations Questionnaire: produces a continuous score
Impulsivity	C	SDT	Abbreviated impulsiveness scale: produces a continuous score
Autonomy	C/Y	SDT	Subscale of the basic needs satisfaction in general scale: produces a continuous score
Competence	C/Y	SDT	Subscale of the basic needs satisfaction in general scale: produces a continuous score
Relatedness	C/Y	SDT	Subscale of the basic needs satisfaction in general scale: produces a continuous score
Self-efficacy for physical activity	Y	SCT[d]	Self-efficacy for physical activity: produces a continuous score
Self-efficacy for healthy eating	Y	SCT	Self-efficacy to make healthy food choices: produces a continuous score

[a]C/Y: caregiver/youth.

[b]N/A: not applicable.

[c]SDT: self-determination theory.

[d]SCT: social cognitive theory.

Secondary Outcome: Establish Costs Associated With Implementation of Mobile Health Components When Delivered With the Brenner Families in Training Program

Economic costs of delivery (ie, resource use) associated with implementing the two conditions are collected over the duration of the program. These costs allow for calculation of the full economic cost of delivering each condition, which includes direct, indirect, and opportunity costs. Examples of these may include utilization of supplies and materials (eg, the printing of materials for participants), training costs (eg, hourly wages for employees), costs associated with the actual delivery of the mHealth components, and opportunity costs (eg, volunteer time, donated materials). Net costs associated with delivering the mHealth strategies will be calculated by subtracting the costs for Brenner FIT from the costs of Brenner mFIT. Costs related to the evaluation of these strategies/conditions are excluded to capture the true economic cost of replicating the strategies across other clinics. Of the ways to express cost, one is cost per child enrolled. The more money caregivers pay for enrollment, the lower the likelihood of participation, especially when patients are from lower socioeconomic categories. Willingness and the ability to pay are assessed, as demonstrated in previous work examining the cost-effectiveness of interventions in youth [49]. However, for the proposed study, there are no additional costs for participants beyond those associated with the standard Brenner FIT program (eg, co-pays).

Analysis Plan for Pilot Data

To inform future effectiveness of the trial, a quantitative data analysis strategy is developed as part of the proposed study to provide parameter estimates for future power calculations. For the pilot data to be collected in this study, the analysis relies on a mixed linear model to accommodate repeated assessments of BMI. This approach is anticipated to be at least as powerful as the two-sample *t* test. At each follow-up visit, the change in BMI z-score is calculated as the difference between the current and baseline z-scores. However, as some studies suggest using variations of relative BMI [50,51] or BMI for longitudinal data [52], and there continues to be a debate about the best measure to use to detect change particularly in children greater than the 97th percentile for BMI [53,54], the study group assesses the BMI, BMI z-score, and percent over 95th percentile BMI for youths with obesity [55] and secondary outcomes. These are modeled as the dependent variable, with the baseline value, assessment time point (in weeks), treatment group, and treatment by visit interaction modeled as fixed effects and subject as a random effect, with an unstructured variance-covariance matrix. Contrasts are used to test the difference between treatment groups at each visit, and the contrast for the 6-month visit forms the primary effectiveness test. Age, race, ethnicity, and sex are included in the model. Restricted maximum likelihood estimation is used to incorporate missing data under a missing

at random assumption. Model assumptions are evaluated using standard diagnostics. Transformations and nonparametric alternatives are considered as needed. Sensitivity analyses to examine the impact of missing data mechanisms on our results are performed using a combination of multiple imputations, pattern mixture, and inverse probability weighting analyses, as appropriate.

Although sex as a biological variable is not believed to play a substantial role in the weight-related behaviors of adolescents, gender as a social variable is salient to this study, as girls, for example, display different age-related patterns of physical activity than boys [56], lower overall physical activity [57], and greater declines in physical activity during early adolescence (8-14 years) [58]. Thus, the team considers gender in the intervention components and in all analyses via the inclusion of gender as a dichotomous predictor and potential moderating variable.

Trial Sample Size

Sample size was determined relying on guidance from Eldridge et al [59] and Whitehead et al [60]. Specifically, we based our sample on a feasibility outcome (retention) and the ability to estimate parameters that will inform future trial power calculations. Given a sample size of 40 (per group), there is an anticipated range of possible precision for the retention probability estimates (CIs) as follows: a true retention rate of 60% yields a 95% CI of 55% to 75%; for a retention rate of 90%, the CI is 81% to 99%. The observed CIs provide a plausible range for the true retention rate in our population and trial conditions. If the CIs exclude values <80%, this would be an acceptable retention rate to plan a large-scale trial of Brenner *m*FIT; regardless, these estimates (CIs) are weighed heavily and, together with many other components of the trial experience, are used to determine overall acceptability and feasibility, and along with estimates of effect size, these estimates will assist with the design aspects of any future trial.

Scalability

This study will be informed by emerging literature on the scalability of health promotion programs [61,62]. Specifically, the several scalability considerations identified by Milat et al [61] are evaluated, such as (1) reach and adoption, (2) organizational resources required (including costs), (3) intervention delivery (eg, acceptability, fidelity), (4) contextual factors (eg, interaction of the intervention with organizational contexts), and (5) evaluation approach. For example, we will characterize the features of the clinic and its operations (eg, equipment, staffing, costs, reimbursement) to identify areas of potential variability to inform future rollout. The data collected provide answers to crucial questions suggested by Klingner et al [63]: (1) Under what conditions and with whom does Brenner *m*FIT work? (2) What is necessary to support clinical staff implementation of Brenner *m*FIT? (3) What is necessary to enhance the capacity of clinics to support staff in implementing Brenner *m*FIT under different conditions? (4) What is necessary to support broad, deep, sustained implementation of Brenner *m*FIT? This information is crucial in helping us to scale the intervention.

Results

This study was approved by the Institutional Review Board in July 2019, funded in August 2019, and will commence enrollment in April 2020. The results of the study are expected to be published in the fall/winter of 2021.

Discussion

Study Goal

This study seeks to establish an effective way to boost adolescent weight loss by implementing a suite of mHealth tools in conjunction with an established pediatric weight loss clinic, Brenner FIT. The design is based on a strong theoretical background from the social cognitive theory and self-determination theory, which have been shown to be influential in adolescent weight loss. All the mobile materials are developed to be inclusive of adolescents/caregivers from different backgrounds and accessible through multiple ways. The study is designed to test the acceptability and feasibility of the mHealth intervention and compare it with the standard treatment of Brenner FIT alone. The study design attempts to minimize potential pitfalls and limitations that have plagued prior research in this realm. The results have the potential to change the current approach and clinical methodology to address adolescent weight loss through mobile technology and apps in a potentially cost-effective fashion.

Study Limitations and Addressing Potential Concerns

Although all efforts have been made to minimize threats to validity and other potential pitfalls, a few limitations still exist related to the reduction of bias and contamination. One of the limitations is the inability to mask the conditions from the clinical staff or their assignment from the participants as it represents a potential threat to internal validity. However, the independence of the research staff from the clinical staff should protect against any expectancy effects biasing the data. Steps to prevent bias are outlined next. First, all assessments and analyses are conducted by the research staff or clinical administrative staff who are not involved in patient care and who are blinded to participant allocation. Second, data that are not normally collected during routine clinical practice will not be shared with the clinical staff who are in direct contact with patients. For example, although the clinical staff working with dyads randomized to the Brenner mFIT condition receive personalized reports based on mobile self-reporting of food consumption and physical activity, they do not receive data from the 24-hour dietary recalls, research accelerometers, or any questionnaires not normally administered as these tools are rarely available to the clinical staff in standard practice. Lastly, we will monitor the number and duration of sessions to ensure that the clinical staff are not scheduling more or longer sessions with intervention participants.

In addition, the baseline data collection concludes before group assignment is made, which will help to ensure that reactivity (if any) to being assigned to the intervention group has time to dissipate before the 3-month follow-up assessments. Meeting recruitment goals is often a concern with any clinical trial

involving a finite population. However, the Brenner FIT program sees a large number of families per year that should meet the criteria, and referrals are increasing from within the Family Medicine and Pediatrics clinics of the WFBMC through targeted advertising. This increases the number of people eligible to join the proposed study.

Although participants will be recruited from and treated within the same clinic, group activities or classes are separated based on group assignment. The mobile-enabled website is password-protected, making it unlikely that the control group could access it. As we cannot blind the clinical staff to group assignment, we assess contamination via the participant report (posttest) to control for potential contamination.

Conclusions

The ImPACT study attempts to improve on adolescent weight loss by supplementing a weight loss clinic curriculum with an mHealth curriculum. The study not only develops the extra curriculum but subsequently compares the combined treatment (Brenner FIT + *m*Health) with the standard of care (Brenner FIT) in a randomized controlled trial to assess feasibility and acceptability of the intervention. The results can help inform future research and improve clinically meaningful weight loss in adolescents.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
National Institutes of Health Peer Review Comments.
[PDF File (Adobe PDF File), 139 KB - resprot_v9i6e18098_app1.pdf]

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Abbreviations

ASA24: automated self-administered 24-hour
Brenner FIT: Brenner families in training
Brenner mFIT: Brenner FIT + mHealth
mHealth: mobile health
WFBMC: Wake Forest Baptist Medical Center

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Protocol

A Mobile Game (Safe City) Designed to Promote Children's Safety Knowledge and Behaviors: Protocol for a Randomized Controlled Trial

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Abstract

Background: Children have high levels of curiosity and eagerness to explore. This makes them more vulnerable to danger and hazards, and they thus have a higher risk of injury. Safety education such as teaching safety rules and tips is vital to prevent children from injuries. Although game-based approaches have the potential to capture children's attention and sustain their interest in learning, whether these new instructional approaches are more effective than traditional approaches in delivering safety messages to children remains uncertain.

Objective: The aim of this study is to test the effectiveness of a game-based intervention in promoting safety knowledge and behaviors among Hong Kong school children in Grades 4-6. It will also examine the potential effect of the game-based intervention on these children's functioning and psychosocial difficulties.

Methods: This study comprises the development of a city-based role-playing game Safe City, where players are immersed as safety inspectors to prevent dangerous situations and promote safety behavior in a virtual city environment. The usability and acceptability tests will be conducted with children in Grades 4-6 who will trial the gameplay on a mobile phone. Adjustments will be made based on their feedback. A 4-week randomized controlled trial with children studying in Grades 4-6 in Hong Kong elementary schools will be conducted to assess the effectiveness of the Safe City game–based intervention. In this trial, 504 children will play Safe City, and 504 children will receive traditional instructional materials (electronic and printed safety information). The evaluation will be conducted using both child self-report and parent proxy-report data. Specifically, child safety knowledge and behaviors will be assessed by a questionnaire involving items on knowledge and behaviors, respectively, for home safety, road safety, and sport-related safety; child functioning will be assessed by PedsQL Generic Core Scales; and psychosocial difficulties will be assessed by the Strength and Difficulties Questionnaire. These questionnaires will be administered at 3 time points: before, 1 month, and 3 months after the intervention. Game usage statistics will also be reviewed.

Results: This project was funded in September 2019. The design and development of the Safe City game are currently under way. Recruitment and data collection will begin from September 2020 and will continue up to March 1, 2021. Full analysis will be conducted after the end of the data collection period.

Conclusions: If the Safe City game is found to be an effective tool to deliver safety education, it could be used to promote safety in children in the community and upgraded to incorporate more health-related topics to support education and empowerment for the larger public.

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International Registered Report Identifier (IRRID): PRR1-10.2196/17756

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KEYWORDS

serious game; safety training; mobile game; mobile phone; injury prevention; randomized controlled trial; game-based intervention

Introduction

Background

Injury is the leading cause of death and disability among children in many parts of the world [1,2]. Despite the decreasing trend of injuries around the world, the burden of injury remains high in Hong Kong. Cross-cultural research showed that the rate of unintentional transport-related injury was higher in Hong Kong than in other developed countries [3,4]. Between 2001 and 2012, 742,552 children and adolescents in Hong Kong were treated for injuries including unintentional injuries attributable to home accidents (39%), sports (18%), and road traffic (4%), resulting in an annual direct medical cost of HK $230 million (US $29.4 million) and an indirect cost of up to 2-3 times higher [5]. Although traffic injuries were more common in younger children, domestic and sport injuries were among the top 3 leading causes of injury in the age groups of 5-9 years, 10-14 years, and 15-19 years, respectively [5]. Furthermore, during the same study period, more than 753 children died from injuries, with traffic injury as the most frequent cause (0.69 deaths per 100,000 people) [5]. These findings suggest that injuries can substantially cost society and should be prevented as early as possible.

Despite the potentially severe and unplanned nature of unintentional injury, these problems are largely predictable and preventable. In Hong Kong, some preventive efforts have been made by the government and health care professionals. For example, the Road Safety Town and Bus were developed to provide a simulated road environment to increase local children's awareness of road safety [6]. Online resources and smartphone apps for prevention of children's sport and domestic injuries are also available in Hong Kong [7]. Nonetheless, these programs and resources are often time bound and designed to guide mainly parents or teachers to minimize the injury hazards for children. Local Hong Kong children lack opportunities to learn safety and apply the safety knowledge by themselves in real-life situations. There are also limited resources for children to learn safety outside of school. Traditional classroom-based education often uses one-way instructional approach from the instructor to the students, which can make learning dull and ineffective [8].

In recent years, game-based learning has become increasingly popular. Some evidence shows that game-based learning can enhance student motivation and engagement and critical thinking skills [9]. It can also trigger curiosity and fantasy in students, thereby increasing their intrinsic motivation and enjoyment in learning [10]. For example, serious games, defined as computerized games produced for educational or training purpose [11], can provide a platform for children to learn and explore the materials at their own pace. After gameplay, teachers can conduct in-class discussions on students' gaming experiences to reinforce the new knowledge gained from the gameplay. Teachers can also make use of the in-game point and ranking system to develop healthy competition between students to make learning more interesting. Several meta-analyses have shown support for the positive effects of video games with elements such as immersive stories and interactive game environment on health-related behavior including diet, physical activity, and symptom management [12,13]. By contrast, there has been inconsistent evidence on the association between time spent playing games and psychosocial difficulties such as social, emotional, and behavioral problems in children [14,15]. Several studies have shown a relationship between violent video game use and aggressive behavior and poor performance in school [14,16]. However, little is known about the impact of serious games on children's functioning and psychosocial difficulties.

Based on the experiential gaming model proposed by Kiili [17], positive user experiences are reinforced through the use of immediate feedback, clear goals, and developmentally appropriate challenges. Experiential learning is also known as the process of learning through experience, which has demonstrated effectiveness in enhancing student reasoning and critical thinking skills [18]. Most of the existing safety training studies were conducted through virtual reality (VR) games, which allow children to learn and practice safety techniques in realistic simulated situations. A meta-analysis published in 2014 identified 19 articles on child pedestrian safety behavioral interventions and found that repeated practice in vivo at street-side locations or in game-based VR environments was the most effective strategy [19]. Although VR techniques are increasingly used for education and training purposes, game-based VR training requires expensive production, and young children without adequate safety knowledge may find it difficult to navigate the virtual environments alone [20]. To overcome these VR game limitations, another popular genre of video and computer games introduced is role-playing games (RPGs). As with VR game, RPG allows players to strategize and interact with in-game objects and resources, thereby increasing their motivation, critical thinking, and problem-solving skills [21,22]. Instead of training players in realistic simulated hazard situations, RPG players can create their own avatar/character customized with unique attributes, skills, and traits to play and advance in the cyber world. However, no trials have been conducted to evaluate the effectiveness of RPG-based intervention for injury prevention.

To our knowledge, only few digital safety games are available on the market, all of which have high usage and download rates but are developed for Western child populations and in English language [9,23]. Although there has been positive user feedback

on these games, including better safety knowledge and behaviors [23], cultural and language differences could undermine non–English-speaking children's interest in these games. Hence, we would like to design and develop a Chinese digital safety game for Hong Kong children.

Aims of This Study

This paper describes the protocol for a study that will test the effectiveness of an intervention using a mobile city game, Safe City, to improve the safety knowledge and behaviors of Hong Kong Chinese children in Grades 4-6 by a randomized controlled trial. Our hypotheses are as follows: (1) children in the intervention group (ie, those who receive the Safe City game intervention) will have higher levels of correct safety knowledge and behaviors than children in the control group (ie, those who receive electronic and printed safety information) at 1- and 3-month follow-ups. (2) We expect a change in the children's functioning and psychosocial difficulties. At 1- and 3-month follow-ups, we expect that children in the Safe City intervention group will show better functions and fewer psychosocial difficulties than those in the control group. (3) We expect that those who play the game more frequently will show greater improvement in safety- and health-related outcomes.

Methods

Research Strategy

This study will follow the analysis, design, development, implementation, and evaluation model of instructional design [24] to design, produce, and test a mobile safety game–based intervention for improving safety knowledge and behaviors in Hong Kong Chinese children.

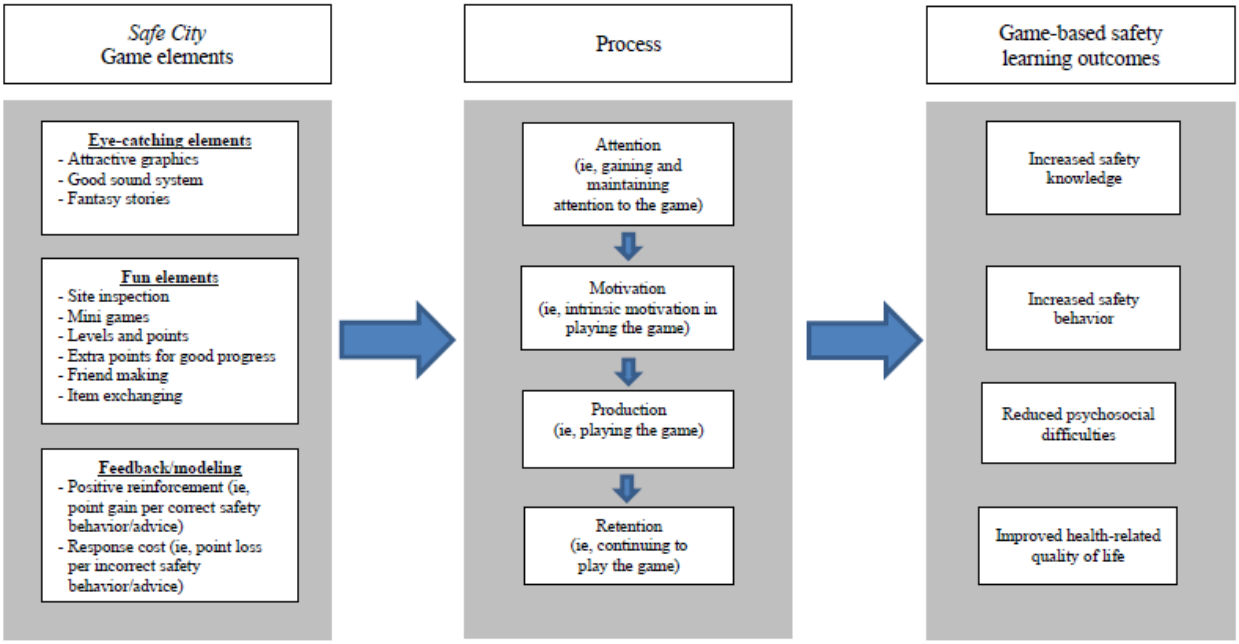
Game Design

The mobile game, Safe City, will be co-designed by our project team (pediatricians, psychologists, safety experts, and experienced health promotion researchers) and the game development team (programmers, artists, and sound designers). The model of learning used in the Safe City game will be guided by the social cognitive theory [25] and elaboration likelihood model [26]. The elaboration likelihood model proposes that capturing attention is the first step in motivating people to process information [26], whereas the social cognitive theory proposes that behavioral change is a function of improved skills and confidence through repeated modeling, feedback, or both [25]. Hence, the Safe City game will be packaged as an RPG with multiple components to teach players how to recognize and minimize injury hazards to prevent injuries in a real-world environment.

In the game, players will start by indicating their preferred gender, hairstyle, facial features, and clothing for their human avatar who will assume the role of safety inspector in the virtual city. This avatar-creation approach is to engage the player in the game as if he or she is exploring the game city using the first-person perspective. As a safety inspector, the player will use the city map provided in the game to identify safe routes to navigate between potentially dangerous checkpoints (homes and athletic areas) and assess the safety level of the checkpoints in the busy and lively land of Safe City. The gameplay will feature mini games (eg, multiple choice questions, spot the danger, and matching items to reinforce safety messages) with fun elements such as game points and in-game ranking to encourage daily play of the game plus engagement strategies such as positive reinforcement (ie, point addition for each correct response) and response cost (ie, point deduction for each incorrect response) to promote safety behavior.

Figure 1 illustrates the gaming process by which the Safe City game–based intervention may influence the students' target outcomes. All these game concepts and technical specifications of the game will be stated in the game design document for guiding the development of prototypes of the game. To create an effective and developmentally appropriate learning product, a multiple-phase study approach (collaboration, prototyping, and evaluation) will be employed to produce design prototypes that are developmentally appropriate, comprehensible, and attractive for the end users (children in Grades 4-6) [27]. Collaboration will involve working with game designers and exploring ideas for design prototypes. The prototype game will be played by a group of 4-8 children from the target age group and a debriefing session will be arranged to review their gameplay experiences. The gameplay will be further adjusted based on these end users' feedback. During the evaluation phase, a 4-week, 2-arm randomized intervention trial will be conducted with 3 data collection periods (baseline and 1- and 3-month follow-ups). Participants will be randomized into 2 groups (the Safe City game intervention group and a traditional health education group) in a 1:1 allocation ratio (Figure 2).

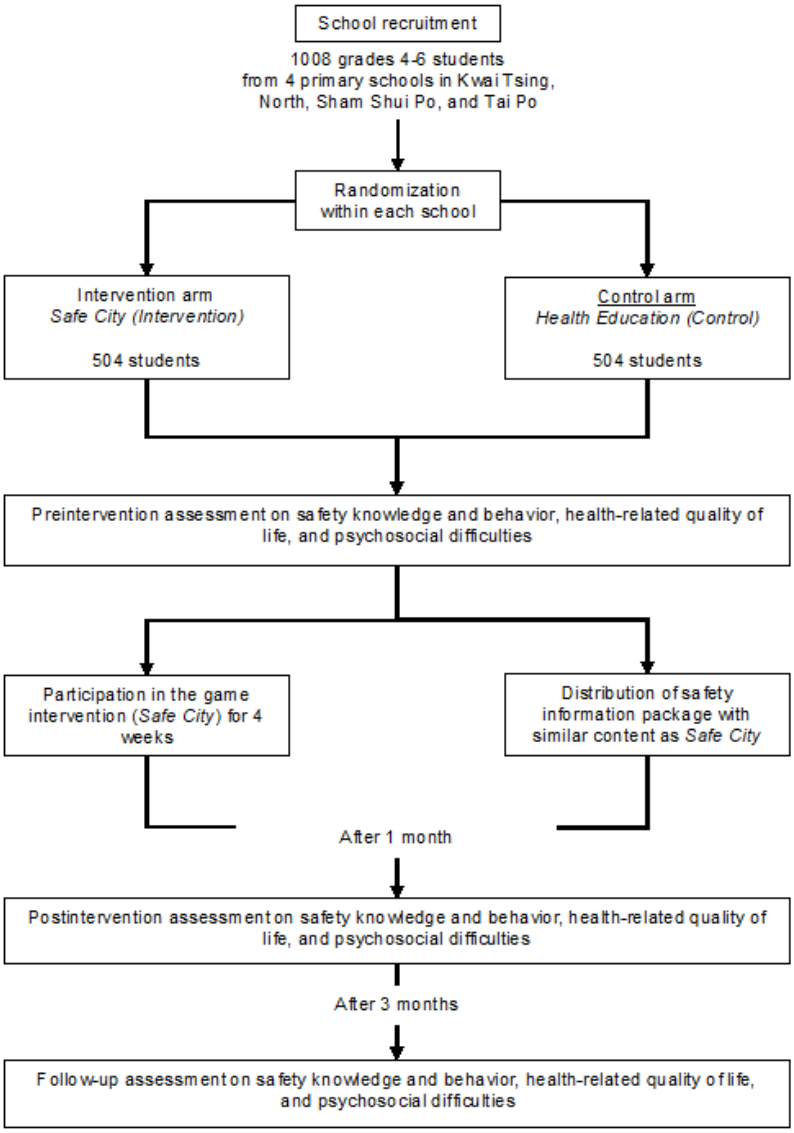
Figure 1. The Safe City gaming process.



Participants

Four districts, including Kwai Tsing, North, Sham Shui Po, and Tai Po, were found to have the highest rates of traffic, domestic, and sport injuries in Hong Kong [5]. All nonspecial, local (noninternational) primary schools in the selected districts will be eligible for participation in the evaluation. Among them, we will recruit 4 schools. Assuming an average of 30 students per class and a participation rate of 70%, the trial will have 4 schools × 3 forms × 4 classes × 30 students × 70% = 1008 participants. Primary schools will be a blocking factor in randomization. All students in Grades 4-6 will be invited to join the trial. Participating students within each school will be randomized with a 1:1 allocation ratio into the intervention or control group. Because the intervention materials will be designed in traditional Chinese, students who are not able to comprehend the Chinese questionnaires at baseline will be excluded from this study. An invitation letter will be sent to all schools in the selected districts. Upon obtaining school consents, informed written consents will be collected from parents of participating students before randomization.

Figure 2. Study flowchart.



Sample Size Calculation

A previous intervention study reported a small-to-medium effect on road crossing behaviors (Cohen *d*=0.258) [23]. Assuming a conservative effect of 0.181 (70% of the previous study), 1008 participants (504 in each group) should be recruited to detect this effect size with 80% statistical power at 5% significance level.

Intervention

A total of 1008 Hong Kong Chinese children studying in Grades 4-6 will be recruited and randomly allocated to the intervention (ie, the Safe City game) and control (ie, promotional leaflets on safety information) groups. The participant recruitment and randomization process will be independently carried out by different research assistants. Outcome assessors will be blinded to the allocation of participants in each group. To avoid contamination between groups, unique login credentials will be provided to each participant. The participant will need to enter these login credentials when accessing the game. This strategy is designed to prevent students in the control group from getting the same intervention. At follow-ups, a questionnaire item will ask whether the participant has used the Safe City game to inform subsequent analyses.

Students in the intervention group will be given a manual containing instructions to play the Safe City game. A research assistant will provide a briefing session on the game in each participating school. A unique username and password set will be created for each user to log in the game. These login credentials will be provided to the student participants in a sealed envelope after the briefing session and can be retrieved from the research team anytime during the intervention period. The participants will be permitted to play the game as many times as desired within a 4-week timeframe. The players ranked in the top 20 will receive a reward in the form of book coupon after the intervention ends.

All students in the control (ie, health education) group will receive a comprehensive package on safety information. The information package includes both printed and electronic promotional materials regarding safety and a comprehensive list of relevant website and information sources. The information

from these relevant websites and information sources is similar to that used in developing the safety case scenarios for the Safe City game. Consequently, both intervention and control arms will have comparable accessibility to safety-related information, and the major contrast between the two groups will be the method of presentation (game-based learning vs traditional health promotion approach, ie, unidirectional information package).

Outcomes

Primary Outcomes: Safety Knowledge and Behaviors

Child safety knowledge and behaviors will be measured by a questionnaire involving items adopted from the existing literature and questionnaires under the 3 contexts: home safety [28], road safety [23], and sport-related safety [29]. Some item wordings will be modified to ensure their relevance to local environments. Child participants will be asked to indicate their level of involvement in the said behavior (eg, home safety: *use sharps without the presence of my parents*; road safety: *forget to look properly because you are thinking about someone else*; sport-related safety: *play while injured*) on a 5-point Likert scale ranging from "Never" to "Very Often." They will also be asked to indicate their agreement on safety-related statements (eg, home safety: *never leave food or water unattended on the stove*; road safety: *stop at red lights and stop signs*; sport-related safety: *do warm-up exercise before having any sports activities*) on a 4-point Likert scale ranging from 1=Strongly disagree to 4=Strongly agree. A total score will be generated for each safety context by summing the relevant items. These items will be self-completed by the children at baseline and 1- and 3-month follow-ups. At each follow-up, their parents will also be asked to rate the degree to which children have shown changes in safety knowledge and behavior after the intervention on a 5-point Likert scale ranging from 1=Much worse to 5=Much better.

Secondary Outcomes

PedsQL Generic Core Scales

Child functioning will be measured by both child self-report and parent proxy-report versions of the Chinese PedsQL Generic Core Scales which are suitable for use in ages 8-12 [30]. It has 4 scales with 23 items measuring child physical (eg, I hurt or ache), emotional (eg, I feel afraid or scared), social (eg, I have trouble getting along with other kids), and school functioning (eg, I miss school because of not feeling well). Each item is rated on a 5-point scale from 0 (never) to 4 (almost always). A higher score indicates better functioning. Its Chinese version has been validated in Hong Kong with good psychometric properties [31].

Strength and Difficulties Questionnaire

Both child self-report and parent proxy-report versions of the Chinese Strength and Difficulties Questionnaire (SDQ) will be used to measure children's psychosocial behavior. The SDQ has 5 subscales, including emotional symptoms (5 items; eg, often unhappy, depressed, or tearful), conduct problems (5 items; eg, often loses temper), hyperactivity/inattention (5 items; eg, restless, overactive, cannot stay still for long), peer relationship problems (5 items; eg, rather solitary, prefers to play alone), and prosocial behavior (5 items; eg, considerate of other people's feelings). Each subscale has a score, and the first 4 subscales generate a total score of difficulties (20 items) [32]. The parent proxy-report version of SDQ in traditional Chinese has been validated and demonstrated satisfactory reliability and validity [33]. The self-reported version has also been used in younger children (aged 8-13 years) with satisfactory results [34].

Game Usage Statistics

The user account system will capture all in-app/task-specific actions taken by the player, including login time, gameplay duration, total game points, the number of correct and incorrect responses in each safety domain (ie, home safety, road safety, and sport-related safety), and the number of attempts needed to reach the correct answer. The account system will only be accessible to the members in the research team, and all user data will be encrypted with a unique password generated by the research team. The usage data will be retrieved from the account system for process evaluation as well as for guiding award reimbursement.

Data Analysis

Results will be reported from intention-to-treat analysis, where outcome variables of the dropouts will be assumed to be unchanged from the previous assessments to provide a conservative estimate. A complete-case scenario will also be considered as a sensitivity analysis. The effectiveness of the intervention in achieving the proposed targets will be estimated using linear mixed models. Group allocation will be included as dummy independent variable. School will be controlled as random intercepts, whereas covariates, such as child's age and sex and family socioeconomic status, will be adjusted as fixed independent variables. The linear model will be used for continuous outcomes, whereas logistic and Poisson models will be used for binary and count variables, respectively. The association between total game points and pre–post changes in outcomes will also be analyzed using the linear mixed models among students in the intervention group. Students in the control group will not be considered in this analysis because they will not be able to access the game. Game usage statistics will be added to the model as independent variables.

Ethical Issues

This trial is registered on the ClinicalTrials.gov database (NCT04096196) and has been approved by the Institutional Review Board of Hong Kong University and Hospital Authority Hong Kong West Cluster (Reference number: UW 19-028).

Results

Safe City is currently at the initial stages of development and programming of its prototype version. Acceptability and usability tests on target participants will subsequently be conducted to detect and correct occasional bugs or problems and refine the design. Participant recruitment will commence in September 2020. Completion of data collection is anticipated to occur in March 2021, and analysis of results will be undertaken by December 2021.

Discussion

Childhood injury is a major public health problem. Although it is the leading cause of disability and death for children in many parts of the world [1,2], prevention strategies to tackle this public health problem are still inadequate. Health education is an important part of health promotion, and middle childhood is the ideal time for health education. In Hong Kong, safety training and programs often take place in formal education settings such as classroom. Although simulated road facilities such as Road Safety Town and Bus are available in the local community for children to learn road safety, this type of community-based learning has limitations such as short visit time and inconvenient location. Recent advances in technology allow students to learn with more opportunities to explore real-world problems and challenges in a virtual environment [9]. Evidence suggests that game-based learning may enhance positive learner experiences, feelings of empowerment and self-efficacy, and positive psychological outcomes including enjoyment and confidence [12,35,36]. Several safety games have been developed for Western children with high usage and download rates [9,23]. This will be the first report of a safety promotion game developed for Hong Kong child population. We are hopeful that the game can be a valuable tool for prevention of childhood injury in the community in the long run. Moreover, the resulting city game platform can be used for general health education purpose, so other health topics such as mental health and substance use can also be incorporated into the game in future development phases. Moreover, this is the first known research trial assessing the effectiveness of a mobile serious game in teaching children about safety knowledge and behaviors. Findings from this study will be made available to the public, local schools, news media, education groups, and safety organizations working to improve injury prevention in Hong Kong and beyond, as they could inform future innovative strategies for injury prevention.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-reviewed reports of the funding agency.
[PDF File (Adobe PDF File), 262 KB - resprot_v9i6e17756_app1.pdf]

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Abbreviations

RPG: role-playing game
VR: virtual reality

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Protocol

A Web-Based Intervention to Reduce Decision Conflict Regarding HIV Pre-Exposure Prophylaxis: Protocol for a Clinical Trial

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Abstract

Background: HIV pre-exposure prophylaxis (PrEP) is recommended for populations at high ongoing risk for infection. There are noted racial disparities in the incidence of HIV and other sexually transmitted infections (STIs) for African, Caribbean, and Canadian Black (ACB, black) populations in Ontario, Canada. Although blacks represent only 4.7% of the Ontario population, they account for 30% of HIV prevalence and 25% of new infections in the province. The existing clinical public health practice toolkit has not been sufficient to optimize PrEP uptake, despite the overwhelming evidence of PrEP's efficacy for reducing HIV transmission risk. Since its establishment as an effective HIV prevention tool, the major focus in behavioral research on PrEP has been on understanding and improving adherence. To date, there is no known formalized intervention in place designed to support ACB men and women at high risk of making high-quality decisions regarding the adoption of PrEP as an HIV prevention practice.

Objective: We propose 2 aims to address these gaps in HIV prevention and implementation science. First, the Ottawa Decision Support Framework (ODSF) for use in the PrEP decisional needs of black patients was adapted. Second, the decision support intervention to estimate effect size compared with control conditions in reducing decision conflict and predicting adherence over 60 days was pilot tested.

Methods: In aim 1, we propose a cross-sectional qualitative descriptive study using data collected from key informant interviews with eligible PrEP patients (n=30) and surveys with health professionals (n=20) involved in HIV PrEP management. Data obtained from aim 1 will be used to develop a decision support intervention based on the ODSF. In aim 2, the adopted decision support intervention using a block-randomized design to estimate effect size compared with control conditions in reducing decision conflict and predicting adherence over 60 days was pilot tested. Hypothesis testing will be de-emphasized in favor of generating effect size estimates.

Results: A research award was funded on March 25, 2017 (Multimedia Appendix 1). Ethical approval was received on March 25, 2019 (with supplemental approval received on May 10, 2019). Data collection started on April 9, 2019. As of September 30, 2019, we enrolled 29 patients and 24 health care providers for aim 1. We are currently analysing the data collected for aim 1. Aim 2 is scheduled to start in May 2020.

Conclusions: This study will provide evidence-based information on the decisional needs of black patients who are at risk of HIV and have been offered PrEP. The study will also test the effect of decision support intervention in reducing decision conflict, adoption of PrEP, and adherence to PrEP.

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KEYWORDS

pre-exposure prophylaxis; PrEP; HIV; blacks; prevention; smartphone; mobile phone

Introduction

Background

HIV preexposure chemoprophylaxis (PrEP) is recommended for populations at high ongoing risk of HIV infection [1]. There are noted racial disparities in the incidence of HIV and other sexually transmitted infections (STIs) in African, Caribbean, and Canadian Black (ACB) populations in Ontario. Although blacks represent only 4.7% of the Ontario population, they account for 30% of the HIV prevalence and 25% of new infections in the province. There are also especially high rates of HIV in black individuals with a history of STI diagnosis [2,3]. Significant scientific gaps remain regarding the best strategies for supporting PrEP scale-up among blacks. Research evidence on self-determination theory (SDT) indicates that informed and autonomous decision making is a central component in facilitating motivation for long-term maintenance of health behaviors, such as orally taking PrEP daily. This concept has been demonstrated in clinical trials across various populations and health domains [4-9] but has only recently received attention in HIV prevention [10-12]. Considering that decisions regarding whether to start and continue using PrEP can be complex, there are no known studies that have investigated the decisional needs of black patients who are asked to consider taking PrEP. Furthermore, there is no known intervention that provides decisional support to blacks making choices concerning PrEP initiation. There is also a gap in evidence on how the quality of black patients' decisions to initiate PrEP is related to PrEP adherence.

The existing clinical public health practice toolkit has not been sufficient to optimize PrEP uptake [13-28], despite the overwhelming evidence showing PrEP's efficacy in reducing HIV transmission risk [29-33]. Since its establishment as an effective HIV prevention tool, the major focus in behavioral research on PrEP has been in understanding and improving adherence [34-40]. To date, there is no known formalized intervention in place designed to support ACB men and women at high risk of making high-quality decisions regarding the adoption of PrEP as an HIV prevention practice. We define *adoption* as an internally endorsed commitment to integrating PrEP into one's personalized risk reduction plan. This is distinguished from the important concept of *adherence*, which refers to compliance with a medication administration schedule.

Objectives

We propose 2 aims to address these gaps in HIV prevention and implementation science:

1. Adapting the Ottawa Decision Support Framework (ODSF) for use in the PrEP decisional needs of black patients (Multimedia Appendix 2).
2. Pilot testing the decision support intervention using a 2-arm randomized design to estimate effect size compared with the control condition in reducing decision conflict and predicting adherence over 60 days.

Methods

Characteristics of the Research Population

Number of Subjects

We will enroll a maximum of 90 (aim 1: n=50, 30 patients, 20 service providers; aim 2: n=40) participants in the study. We expect that 1 in every 3 persons that we screen will enroll in the study; thus, we anticipate screening 140 individuals to reach our enrollment goal.

Age of Subjects

We will enroll subjects ≥18 years of age. We excluded children under the age of 18 years because we assessed that the risk of a confidentiality breach was heightened for the youth under the legal age of emancipation. Furthermore, the youth in this age range may require parental/guardian consent for research participation and medical procedures. Complying with such requirements may increase the risk of inadvertent disclosure of information that the youth may have wanted to remain private. With these complexities in mind, we cannot justify the risk of enrolling people aged younger than 18 years as our primary research aim can reasonably be addressed without their inclusion. We are also restricting the enrollment of individuals aged older than 65 years to minimize the potential for confounding due to aging-related neurocognitive factors.

Gender of Subjects

We will include both men and women (cisgender and transgender inclusive). We will monitor participant enrollment for aim 1 and aim 2 to ensure that there is an equitable gender distribution in the study. We will not apply gender enrollment targets to the recruitment of health care professionals.

Racial and Ethnic Origin

The sample will consist only of individuals who are racially categorized as black. The research questions addressed in this proposal are specific to blacks. The focus on blacks in Canada is due to their disproportionate representation in Canada's HIV epidemic. Given this, black racial homogeneity is essential to the internal validity of the study, and thus, it is inappropriate to enroll nonblacks into this study. Owing to generations of

immigration coming into Canada from countries in Africa and the Caribbean, the black population is ethnically and culturally heterogeneous. We, therefore, expect considerable ethnocultural diversity in the sample; however, we will not set enrollment targets based on culture or ethnicity. We will not apply race/ethnicity criteria to the recruitment of health care professionals.

Inclusion Criteria

A subject will be eligible for study participation if they (1) are aged at least 18 years, (2) identify as an African, a Caribbean, and/or a Canadian black, (3) currently live in the Greater Toronto Area (GTA), (4) can speak and understand English, and (5) are assessed by the referring health care provider as being a good candidate for starting HIV PrEP.

A health care professional will be eligible for study participation if the following conditions are fulfilled:

1. Are employed at a participating clinical or community-based agency.
2. Have a health care role involved in any component of the PrEP care continuum including the following:
    - Identifying individuals at the highest risk for contracting HIV
    - Increasing HIV risk awareness among these individuals
    - Enhancing PrEP awareness
    - Facilitating PrEP access
    - Linking to PrEP care
    - Prescribing PrEP
    - PrEP clinical management
    - Supporting PrEP adherence
    - Retaining individuals in PrEP care

Subject identification, Recruitment, and Consent

Subject Identification

A venue-based nonprobability sample will be used to identified 12 clinical and community-based agencies. The 12 participating agencies located in downtown Toronto and suburban areas of the GTA with high concentrations of black residents include the following:

- St. Michael's Family Practice Unit
- Sumac Creek Health Centre
- St. James Town Health Centre
- St. Lawrence Health Centre
- Health Centre at 80 Bond Street
- Health Centre at 410 Sherbourne
- Women's Health in Women's Hands Community Health Centre
- Africans in Partnership Against AIDS
- Church Wellesley Health Centre
- Taibu Community Health Centre
- Black Coalition for AIDS Prevention
- Committee for Accessible AIDS Treatment

Staff employed at the participating clinical and community-based sites will identify prospective participants that meet basic study-defined eligibility criteria for HIV PrEP as described in the inclusion and exclusion criteria of this protocol. Once it is determined that a potential participant meets the eligibility criteria, the staff will inform the patient about the study's existence and inquire if they want to be contacted by a research assistant (RA). If the person agrees to be contacted, then the staff will ask the patient (potential study participant) to provide written consent to release their information to the research team. Once written consent is obtained, the staff will relay the person's contact information to the study office. An RA will follow up with the patient by phone to further explain the study and to conduct a confirmatory eligibility screen. Eligible participants will be invited (with assistance if necessary) to visit the study office at 209 Victoria Street for informed consent and enrollment.

Some participants identified through the participating clinical and community-based agencies may elect to receive the study's contact information and call the study office, in lieu of (or in addition to) authorizing site staff to release their personal contact information to the RA. Participants who contact the study office will be given a brief overview of the study and asked if they wanted to learn more details. If the person is interested in knowing more about the study, then the RA will further explain the study and conduct an eligibility screen. Eligible participants will be invited (with assistance if necessary) to visit the study office at 209 Victoria Street for informed consent and enrollment.

Subject Recruitment

We will recruit primarily from community-based and clinical providers. Personnel at the selected participating clinical and community-based agencies will assist with recruitment. RAs will be available by phone during the same operating hours as the participating clinical and community-based agencies in order for them to (1) be reached by phone by someone attempting to make a referral and (2) initiate contact with a potential participant within the same business day. The RA's role in the recruitment process is to screen for initial interest and, if the person is interested, to then screen the potential participant to determine if they are a match to the eligibility criteria. The RA will then initiate informed consent procedures and enrollment into the study.

Process of Consent

The RAs will be responsible for obtaining and ensuring informed consent from study participants. The RAs will fully explain the study and answer all questions regarding the participants will be asked to do as part of the study. RAs will receive training on informed consent so that during outreach activities, they can tell potential participants what to expect. In most cases, the RAs will perform the informed consent procedures as a contiguous process with recruitment. We will ensure that all participants know that their participation is completely voluntary and that they can withdraw at any time without repercussions. Once a participant verbally indicates to the RA that all their questions have been satisfactorily answered, we will document that the person has given informed consent to participate by having them sign an informed consent form. The paper copy will be stored in a locked filing cabinet. The informed consent does not end at this phase but continues throughout the entire time that the participant is engaged with the study. In service of this

critical point, the RAs are responsible for ensuring that the participant understands what it is that they are being asked to do as part of the study throughout the time that the subject is enrolled, so that their participation always remains informed and volitional.

Illiterate and Visually Impaired Participants

Participants who are unable to read in English (defined here as illiterate) or who are visually impaired will have the possibility to select a witness who is literate and has no connection to the research team. The witness should be an adult who can confirm the accurate reading of the consent form to the participant and that the participant has given consent freely. The participant will still sign the informed consent document, and the witness will also sign attesting they understand what the participant is being asked to undertake in the study. Alternatively, participants will be given the option of having a second staff member, (a research staff who does not work on this particular research study or a staff member from the St Michael's Hospital Family Health Team (SMH FHT) or community agency), witness the consent portion of the interview. Participants can choose the option they prefer.

Aim 1: Methods and Study Procedures

Aim 1: Adapt Ottawa Decision Support Framework for the HIV Pre-Exposure Prophylaxis Decisional Needs of Black Patients

Under this aim, we will investigate 2 research questions: (1) what factors do black patients consider when deciding if to adopt HIV PrEP? and (2) How do SDT constructs of autonomy, competence, and relatedness influence black patients' decision-making experiences regarding PrEP adoption?

Overview and Theoretical Basis of Self-Determination Theory Principles for the HIV Pre-Exposure Prophylaxis Decisional Needs of Black Canadians

SDT is a social psychological theory of motivation that contends that humans are naturally inclined toward health-protecting activities. These natural inclinations are optimized through the support of a human's basic psychological needs for autonomy (volition and freedom), competence (perceived ability to attain a desired goal), and relatedness (connection to and caring from others). SDT also articulates how sociocultural factors can either facilitate or undermine volition. In this study, we will qualitatively investigate the ways in which autonomy, competence, and relatedness are present in (or absent from) PrEP decision-making experiences of black patients and use this to adapt the ODSF.

Evidence for Adaptation of the Ottawa Decision Support Framework for HIV Pre-Exposure Prophylaxis Decisional Needs of Black Patients

Decision support tools are a best evidence strategy in health care and improve the quality of decision making by (1) improving the accuracy of HIV risk assessment, (2) creating realistic outcome probabilities for each decision option, (3) resolving decisional conflict and increasing confidence when choosing among options, and (4) increasing satisfaction with the chosen decision. However, decision support tools have received little attention in HIV prevention and increased uptake of PrEP. Studies show that those at increased risk of HIV seroconversion underestimate their risk of HIV infection and thus may not appreciate the personal relevance of PrEP. For example, in 1 study of 7 public health clinics, 67% of people newly diagnosed with HIV rated their risk for infection as *low* or *no* risk. Studies on PrEP adoption intentions also found that self-assessing one's behavior as *low risk* was associated with decreased intentions and the likelihood of using among men who have sex with men (MSM). Moreover, using a web-based decision aid is congruent with SDT as it promotes autonomy by eliminating perceived pressure for patients to make immediate decisions during their clinical appointment.

Design and Setting

We propose a cross-sectional qualitative descriptive study using data collected from key informant interviews with PrEP eligible patients (n=30) and surveys with health professionals (n=20) involved in HIV PrEP management. The study will take place in the GTA (population. 2.5 million). Over half (59%) of Canada's black population is settled in the province of Ontario. Moreover, the majority (70%) of black people in Ontario live in GTA, making it the ideal location for this study. The trial procedures will be conducted at sites within the St. Michael's Hospital (SMH) system, including the SMH Li Ka Shing Knowledge Institute.

Procedures

Using the Centers for Disease Control and Prevention guidance for emtricitabine/tenofovir (Truvada) for PrEP and/or the approved generic equivalent, we will identify prospective subjects through SMH FHT sites and community-based agencies. Staff will assess all black patients for PrEP eligibility and interest in initiating PrEP. We will purposively select subjects who want to start PrEP (n=10), do not want to start PrEP (n=10), and remain undecided (n=10) for one-on-one qualitative interviews. We will monitor sexual orientation to ensure MSM are represented in the sample. In the interviews, we will inquire about their (1) concerns about PrEP and barriers to PrEP initiation, (2) normative beliefs about PrEP, and (3) decision-making processes regarding PrEP use. We will also conduct surveys with SMH FHT staff and staff at community-based agencies who assess patient risks and make clinical recommendations for PrEP as well as those that may prescribe and/or support clinical PrEP management. We will use these qualitative findings to guide the adaptation of the ODSF for use in supporting the decisional needs of black patients who are considering PrEP. Patients will receive Can $30 (US $22) for completing the interviews. Providers will receive a Can $40 (US $29) gift card to Amazon on the web for filling in the survey tool as their participation will occur over the course of their work.

Data Collection

We will use several sources of data in this study. The data sources are explained as follows.

Demographic Surveys

We will administer a brief demographic survey to participants using the Snap Professional software (Snap Surveys). An RA will be present for this administration, although it is possible for the survey to be self-administered if this is what the participant chooses.

Semistructured Key Informant Interviews

We will use a semistructured interview guide for participants that includes items designed to address research questions 1 and 2 of aim 1. We will include items that are shown in the literature to impact decision-making quality. For example, we will address aim 1's question 1 by including items that explore the perceived relevance of PrEP to their clinical situation, decisional conflict, and clarity regarding risk-reduction options and potential outcomes. We will address aim 1's question 2 by exploring autonomy (eg, Were you told about the choices and effective options that were available to you when you were discussing PrEP?), competence (eg, What are some examples of how you were encouraged to ask questions during the discussion? How did you feel about the responses you received?), and relatedness (eg, Describe how your values were/were not understood during the discussion about PrEP?). The interviewers will also take brief field notes during the interview and will further develop more detailed notes within 24 hours.

Structured Surveys

We will administer a structured survey on *Facilitators and Barriers to Decision Support* using the Snap Professional software. An RA will be present to administer the survey, although it is possible for the survey to be self-administered if this is what the health care provider chooses.

Ottawa Decision Support Framework Adaptation

We will use inputs from the qualitative findings in aim 1, public health guidelines on PrEP, and the emtricitabine/tenofovir product monograph to tailor the ODSF for use in the Client-Centered Care Coordination (C4) PrEP decision support web-based app.

Aim 2: Methods and Study Procedures

Aim 2: Pilot Test of the Adapted Decision-Support Intervention Using a 2-Arm Randomized Controlled Design

Hypothesis testing will be deemphasized in favor of generating effect size estimates. This aim will investigate 3 research questions. Preliminary hypotheses include the following:

- H1: PrEP decision support reduces decision conflict in both low decisional conflict (LDC) and high decisional conflict (HDC) groups.
- H2: LDC + decision support group will be more likely to initiate PrEP than LDC control.
- H3: LDC PrEP initiators are more likely than HDC PrEP initiators to have serum levels consistent with adherence at 60 days.

Randomization

A block randomization strategy will be used to randomize patients in aim 2 into the experimental or control groups. Random blocks of 2, 4, and 6 are used.

Pilot Procedures

We will use C4 decision support tool, which is an HTML-5 mobile web-based app that does not require device-specific configurations. Staff will provide participants with a web link to the decision-support app. When possible (ie, when a participant has a smartphone or other applicable device), staff will help participants preprogram the decision support app as both a bookmark and an icon on the participant's device and the RA will give participants a brief tutorial on its use. Patients assigned to the experimental condition (High Decision Conflict + Decision Support and Low Decision Conflict + Decision Support) will be asked to use the bookmarked link to the decision-support website within the first 14 days (and thereafter as needed) during the study period. The routine care control group will be asked to use a bookmarked link to the frequently asked questions website on emtricitabine/tenofovir for PrEP. All groups will be compared on decision readiness and decision conflict at 14 days, self-reported PrEP initiation at 30 days, and PrEP adherence at 60 days postenrollment.

Data Collection

Data on decision conflict and PrEP initiation will be generated by the participant from self-administered assessments via the decision-support web-based app. We will also collect finger-stick blood drops to measure adherence to HIV PrEP at 60-days postenrollment. We will use several sources of data in this study. The data sources are structured survey and blood draw.

Patient Surveys

RAs will send participants an email with the link to access the web-based structured survey, which will be programmed in Snap Professional software. All data were entered into Snap Professional software. Once the survey is complete (ie, the submit button is selected), the survey is uploaded automatically to the Snap web host. As soon as this transfer is complete, the survey and its data are automatically removed from the device. We will collect whole blood using a finger-stick procedure and use the microfluid sample for dried blood spot analysis.

Measures for Aim 2

In addition to basic demographic data that will be used to describe the sample (eg, age, gender, relationship status), we will use the measures summarized below to assess key variables necessary to address aim 2:

1. The sure test indicates *the probability that a patient experiences clinically significant decisional conflict.*
2. The stage of decision making is a 4-6 item instrument. *Stage of decision making refers to the individual's readiness to engage in decision making, progress in making a choice, and receptivity to considering or re-considering options.*
3. The Decisional Conflict Scale is a 16-item tool. *The Decisional Conflict Scale (DCS) measures personal perceptions of: (1) uncertainty in choosing options, (2)*

modifiable factors contributing to uncertainty such as feeling uninformed, unclear about personal values and unsupported in decision making; and (3) effective decision making (in full version) such as feeling the choice is informed, values-based, likely to be implemented and expressing satisfaction with the choice.

4. The Decision Preparation Scale is a 10-item scale. *The scale assesses a patient's perception of how useful a decision aid or other decision support intervention is in preparing the respondent to communicate with their practitioner at a consultation visit and making a health decision.*
5. The Health Care Climate Questionnaire (HCCQ) is a 15-item questionnaire. *The HCCQ was designed to be used by patients to report their perceptions of their doctors or their team of health care providers*
6. The PrEP Self-Regulation Questionnaire is a 15-item questionnaire that elicits information regarding why an individual may initiate and/or maintain PrEP usage.
7. The PrEP Use Perceived Competence Scale is a 4-item scale for individuals who elect to use PrEP regarding their perceived confidence to adhere to their decision to use PrEP.

Payment for Participation

We will implement a modest, modular incentive structure to be applied to participants who enroll and attempt to participate in the study (Table 1). In aim 1, a Can $30 (US $22) cash gratuity will be offered for a 1-hour interview. Health care providers will receive Can $40 (US $29) for the health care provider survey. Participants can receive up to Can $120 (US $86) in aim 2. Participants will be provided with 2 Toronto Transit Commission transit tokens for in-person interviews (enrollment interview and 60-day visit for the finger-stick blood drop). The baseline in-person survey and registration process are expected to take approximately 45 min. The subsequent web-based surveys are expected to take about 15 min; thus, participants in aim 2 are committing to participating for about 1.5 hours of their time. Participants will receive the incentive for enrolling in and completing the study and will also receive it even if they decide (at any point) that they do not wish to continue completing the study activities. If participants know that they will receive the incentive even if they do not complete the procedure (eg, follow-up assessments), then this will reduce the risk that participants are financially coerced to complete any component of the study. These gratuities are also culturally accepted gestures of appreciation for the participants' generosity in contributing their time and knowledge to the study. Participants will receive incentives immediately after the completion of data collection.

The data collected in this study will not be made available to participants. The data are for exploratory research purposes and are not appropriate for participants to use for medical self-management.

Table 1. Participant incentive schedule.

Study procedures	Incentive amount
Aim 1 study procedures	
Key informant review	Can $30 (US $22)
Health care provider survey	Can $40 (US $29)
Aim 2 study procedures	
Baseline survey	Can $20 (US $15)
14-day follow-up	Can $30 (US $22)
30-day follow-up	Can $30 (US $22)
60-day follow-up	Can $40 (US $29)

Subject Withdrawals

We will advise all study participants that their involvement in the study is completely voluntary and that they are free to withdraw at any time, for any reason, without penalty or prejudice. This will be emphasized during the process of obtaining initial informed consent from participants and again during each of the data collection points of the study. Participants who withdraw from the study will be provided with an opportunity to indicate if they also want any data collected up to that point to be used in the study analysis. If a participant does not wish to have their data included in the study analysis, then we will identify the specific data in our database and mark it as *999=not for use in analysis.* We will also keep a record of reasons for participant withdrawals (if the participant wishes to disclose such reasons), to monitor patterns and use these in our research team training sessions to better identify strategies to support retention.

Risk/Benefit Assessment

Risks to Subjects

Participation in the study does not involve more than minimal risk. Potential risks of study participation are outlined as follows.

Frustration With Assessments

Potential risks of participation in the study include the frustration that may be encountered in completing assessments, scales, and questionnaires. Subjects are carefully counseled that they may discontinue testing at any time if they find it frustrating or embarrassing. There is also a potential risk of breaching patient confidentiality.

Risk for Financial Coercion

We will also implement a modest, modular gratuity structure to be applied to participants who enroll and attempt to participate in the study. A Can $30 (US $22) cash gratuity will be offered

for participation in the key informant interview. Health care providers who participate in the structured survey will receive Can $40 (US $29) cash gratuity. Subjects who participated in the pilot trial will receive a modest gratuity at enrollment when they register on the decision aid app via their smartphone device (Can $25 [US $18]), at day 30 when they complete the midpoint survey (Can $30 [US $22]), and at day 60 (Can $45 [US $32]) when they provide a blood sample for adherence assessment. Although the gratuity is very modest, it is possible that some individuals experiencing severe material and financial deprivation may be compelled to participate against their own volition in order to receive the modest gratuities offered.

Risks of Unintentional Disclosure of Private Health Information

The greatest potential risk in this study was the potential for a breach of confidentiality which is most likely to occur in situations where the participant has opted to have the RA perform study procedures (eg, study description, informed consent, data collection) outside of one of the participating agencies, such as in their private home. The clinic sites are all equipped with private examination rooms that allow the participant and RA to discuss private health information without the risk of unauthorized persons overhearing protected information. To support participant autonomy and comfort, we will also designate the SMH Li Ka Shing Knowledge Institute as an alternative site for data collection. This site also has private spaces where study procedures can be performed. If a participant desires to complete study procedures in a nonclinic location, the RA cannot guarantee that what is discussed cannot be overheard by others who may be in the immediate vicinity either at a fixed distance away or moving around nearby.

Legal Implications of Unintentional Disclosure of Private Health Information

It is possible that the participants in this study could be engaged in social and/or legal contractual arrangements with others that may presume mutual monogamy, such as marriage. An unintentional disclosure of sexual behavior information, including same-sex behavior, could provide material evidence for litigation against the study participant by an allegedly injured party. This could have both legal and financial consequences for the study participants. This risk is more likely to occur during a visit outside of the clinical setting where others who are not bound by privacy regulations may be in close enough proximity to hear clinical discussions between the participant and the RA.

Protections Against Risk and Minimizing Risk of Unintentional Disclosure of Private Health Information

Emphasis on Voluntary Nature of the Study

We will emphasize to all study participants that their involvement in the study is completely voluntary and that they are free to withdraw at any time, for any reason, without penalty. This will be emphasized during the process of obtaining initial informed consent from participants and again before enrollment and data collection. Participants who withdraw from the study will be provided with an opportunity to indicate whether they also want any data collected up to that point to be used in the study analysis. We will also keep a record of reasons for participant withdrawals (if the participant wishes to disclose such reasons), such that we can try to monitor patterns and use these in our research team training sessions to better identify strategies to support study retention.

Use of Emergency Protocols for Patients Experiencing Psychological Distress

During the course of the study, it may become apparent that a participant is experiencing psychological distress of some sort that warrants further clinical assessment and possibly intervention. This distress could be experienced at any time during the course of the study. However, there is very little evidence to support that behavioral and psychosocial surveys trigger acute episodes of psychological distress for study participants in behavioral research studies; nonetheless, it is remotely possible. If a participant appears to be in psychological distress during the interview, the RA will bring the interview to a close. After that, they will sensitively engage the individual to determine if they wish to talk about what causes them distress. The RA will also ask questions to ascertain if the participant is receiving any support for their distress (eg, friends, family, or professionals), and if not, whether they feel they would benefit from support. If they wish to receive support, the RA will provide them with a list of professionals to talk to.

It is more likely that a participant may experience distress upon receiving an HIV diagnosis. After initiating contact with the RA, participants will be provided with the Canadian AIDS Treatment Information Exchange (CATIE)'s contact information, including their website. CATIE is a nationally respected Non Governmental Organization funded federally and provincially that provides evidence-informed, sex-positive, plain language HIV and Hepatitis C resources in French and English, in print, via phone, and through collect calls. We do not know how many (if any) participants will HIV seroconvert during the course of their participation in the study. All participating clinics have many years of experience in planning for and responding to situations in which patients are unable to manage their psychological distress and require support from clinical staff. We will use clinical site-specific security and emergency protocols to handle potential situations that arise at the site.

Reminder About Risks of Disclosures Outside of Clinic Environments

If a participant wishes to provide informed consent and survey procedures outside of the SMH FHT's, SMH Li Ka Shing Knowledge Institute, or community agency study sites, we will remind them of the limitations this poses for maintaining confidentiality. We will further inform the participant that even if no one is physically present at the location they choose, we cannot guarantee the degree to which the discussion of any clinical information is *private*. We will remind participants that they are not compelled to share any information about which they do not feel comfortable. We will also advise participants of the advantages of study procedures to take place in the preapproved study sites. We want participants to be forthcoming with their information; however, they will be reminded that they are not compelled to share any information that they feel may jeopardize their health or social status.

Benefits to Subjects

Direct Benefits to Participants

There are no direct benefits to the participants for enrolling in this research study.

Benefits to Others

This study has important potential benefits to the community and to primary HIV prevention science. The study will generate knowledge that will be used to inform the development of a decision support intervention to help participants make more informed choices about their engagement in clinical HIV prevention. Furthermore, this proposed study will form a foundation to support more studies of program and implementation science that aims to make scientific advances through research while at the same time making gains and improvements in health outcomes in real-world practice environments.

Important Knowledge to Be Gained

Results from this pilot will generate data for the preliminary studies section of a research grant application. The results will also help us determine how providing decision-support and improving decision quality can enhance local health department efforts to link and support black patients' maintenance of HIV PrEP.

Alternatives to Participation

In this study, participants chose to withdraw their participation at any time. To our knowledge, there are no alternatives for PrEP-related decision support available in the GTA. There are several clinic-based and web-based resources that provide information regarding HIV PrEP. Participants can make use of any available sources of PrEP information via the agency from which they were referred. Any participant who wishes to discontinue participation in the study will be offered a leaflet that lists HIV PrEP informational resources.

Confidentiality of Data and Information Storage

We will only collect the minimum contact information necessary to be able to reach participants for scheduling and reminders about the study visits and data collection. We will collect a participant's first name (or alias), cell phone number, and email addresses. We will not collect information such as home address and work phone number so as to avoid the risk that unauthorized persons can apprehend and use it to identify study participants. We will also ask participants to provide the number of 1-2 trusted family members or friends that we can call in the event of a medical or legal emergency, or if we are unable to reach the participant for a follow-up. We will not provide family or friend contacts with any information about the study to maintain participant confidentiality.

The study team will use electronics-based surveys using the Snap Professional software for data collection. Please note that the Snap Professional Software has been reviewed and approved for use by St. Michael Hospital's: Peter Lambert, Manager of Privacy and Security and Rino La Grassa, Research Applications Support Specialist (Information Communication Technology). The Snap server utilized is owned by the Centre for Urban Health Solution Survey Research Unit and is located inside the SMH network.

No identifiable participant information or de-identified participant information will be stored locally. The RA will not record any client contact information in the Snap Professional software. Original lab reports (source documentation) will be stored onsite at the SMH lab and maintained by the site principal investigator (LN) at SMH when the study concludes.

All survey data were entered into Snap Professional software. Once the survey is complete (ie, the submit button is selected), the survey is uploaded automatically to the Snap web host. Before it reaches the web host, it must first travel through a secure socket layer (SSL), which is where the data is encrypted. Any partially completed surveys will undergo the same process and can be retrieved from the web host to complete at a later date. As soon as this transfer is complete, the survey and its data are automatically removed from the device. Data stored on the secure web host server will be deleted after study completion. Before deletion, the research team will confirm that all completed surveys have been downloaded to the SMH secure server. Once confirmed, the surveys will be deleted from the Snap webhost, and this will be documented in an Excel file. Again, both the Snap web host and SSL tunnel have undergone a TRA to ensure that the data transferred and stored remains encrypted and secure.

No identifying information (eg, name, address, phone number, place of employment) was collected in the behavioral survey. The behavioral survey data is maintained separately from the data file, which includes participants' contact information to reduce the risk that survey responses are linked to participant identities. No identifying information is listed on the blood samples of the dried blood spots. The dried blood spot transport media will be labeled only with participant identification codes. ID codes will be used to match the emtricitabine/tenofovir concentration with the self-report data variables for each participant.

Research Information in Medical Records

No information generated during the study will become part of the participant's medical record, unless requested by the participant. If such a request is posed by the participant, they will be advised of the potential risks and benefits to doing so. The request will be honored, provided it does not transgress the privacy and confidentiality requirements of Ontario.

No one outside of the principal investigator, RA, research manager, study medical director, and a medical provider with a clinical *need to know* will have access to any identifiable data. The RA will need access to basic identifying data such as name and phone number for follow-up contact purposes to aid in recruitment, enrollment, and data collection. If an urgent clinical issue arises (such as a participant experiencing acute psychological distress), it may be necessary to link a participant's contact information to the subject's identity in order to provide clinical follow-up. No data will be shared without the participant's written informed consent to release medical information. It is in keeping with the principle of beneficence to ensure continuity of care by making it possible

(not mandatory) for participants to share information with the medical provider.

Data Analysis and Data Monitoring

Planned Statistical Analysis

Aim 1: Analysis Plan

Interview data will be transcribed verbatim and subjected to qualitative content analysis. After uploading the transcripts into NVivo, we will read each transcript and use *in vivo* (open) coding function to bracket text segments that describe factors that influence decision-making regarding PrEP adoption. We will also develop *a priori* codes based on SDT constructs and use these, along with open codes, to investigate research questions. We will use data display tables to arrange codes by decision-group (adopted vs declined vs undecided) and examine the text associated with each code, consolidating overlapping codes and clustering codes that fit together. The code clusters will be reviewed within and across decision groups to interpret and describe how they address our research questions. We have successfully used these analytic strategies in previous qualitative research.

Aim 2: Analysis Plan

To compare conditions, we will use analysis of covariance procedures. When we compare the 4 conditions, our primary interest will be the tests of participants who received the decision-support intervention versus the information-only control. We will test whether the decision quality, PrEP initiation, and PrEP adherence differ between conditions controlling for baseline decision-quality score. We did not conduct a power analysis to calculate sample size because we de-emphasized hypothesis testing in favor of generating effect size estimates to inform the development of a larger study.

Data Handling

The statistical analyses for the study will be performed at McMaster University by LM. Once all self-report surveys and biological data have been entered into Snap Professional software, LN will download a complete database with no identifying information and provide it to LM for analysis. No identifiable information was included in the downloaded database.

Data and Safety Monitoring

LN and Dr Jesleen Rana will review patient data biweekly, commencing 14 days after the first participant is enrolled in the trial of the decision support intervention. Dr Rana will chair the patient safety review team. The research manager will prepare routine safety data reports for review by the research team. The study team will meet monthly or as needed throughout the study implementation to review safety data as well as discuss and address any potential safety concerns. The study team will agree on the content and format of safety data reports before study implementation. Furthermore, as this study does not have data safety monitoring board oversight, the SMH Institutional Review Board may also review aggregate or individual level−safety data.

The data and safety monitoring responsibilities of the study team will include the following:

1. Maintain confidentiality of the data and results of the monitoring.
2. Review the research protocol and plans for data safety and monitoring.
3. Review monthly (or more frequently as needed).
4. Participant recruitment:
   - Retention between recruitment and data collection
   - Participant risk-benefit ratio
   - Unanticipated adverse effects
5. Monitor reports of related studies to determine if this study needs to be changed or terminated.
6. Review proposed modifications to the study before implementation.
7. Determine if the study should continue as designed, modified, or terminated based on the data available at the review meeting.

In addition to the routine safety data reviews, the study team will convene on an ad hoc basis to make decisions regarding the handling of any significant safety concerns. If necessary, experts external to the study representing expertise in the fields of community-based research, biostatistics, or medical ethics may be invited to join the safety review. A recommendation to stop the study may be made by the study team at any such time that the team agrees an unacceptable type and/or frequency of adverse events has been observed. In the unlikely event that the study team has serious safety concerns that lead to a decision to permanently discontinue the study for all participants and stop accrual into the study, the principal investigator will immediately notify the SMH Institutional Review Board.

Results

A research award was funded on March 2017. Ethical approval was received on March 25, 2019 (with supplemental approval received on May 10, 2019). Data collection started on April 9, 2019. As of September 30, 2019, we enrolled 29 patients and 24 health care providers for aim 1. We are currently analyzing the data collected for aim 1. Aim 2 is scheduled to start in May 2020.

Discussion

This study will provide evidence-based information on the decisional needs of black patients who are at risk of HIV and have been offered PrEP. The study will also test the effect of the decision support intervention in reducing decisional conflict, adoption of PrEP, and adherence to PrEP.

Conflicts of Interest

LN, the principal investigator of this study is a shareholder of tuliptree systems, LLC—the company that owns the decision support aid that is used in this trial. As such, LN has a direct financial interest in the success of the decision support aid and its continued use as an intervention. LN has accepted a conflict of interest (COI) management agreement with Unity Health Toronto St. Michael's Hospital to minimize any potential undue influence on the study's outcomes. The COI management plan stipulates that LN will neither be involved in the recruitment of participants nor in obtaining informed consent.

Multimedia Appendix 1
SON peer review letter.
[PDF File (Adobe PDF File), 131 KB - resprot_v9i6e15080_app1.pdf]

Multimedia Appendix 2
Ottawa Decision Support Framework (ODSF).
[PDF File (Adobe PDF File), 45 KB - resprot_v9i6e15080_app2.pdf]

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Abbreviations

ACB: African, Caribbean, and Canadian Black
C4: Client-Centered Care Coordination
CATIE: Canadian AIDS Treatment Information Exchange
GTA: Greater Toronto Area
HCCQ: Health Care Climate Questionnaire
HDC: high decisional conflict
LDC: low decisional conflict
MSM: men who have sex with men
ODSF: Ottawa Decision Support Framework
PrEP: pre-exposure prophylaxis
RA: research assistant
SDT: self-determination theory
SMH FHT: St Michael's Hospital Family Health Team
SSL: secure socket layer
STI: sexually transmitted infection

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Protocol

A Multilingual, Culturally Competent Mobile Health Intervention to Improve Treatment Adherence Among Women Living With HIV: Protocol for a Randomized Controlled Trial

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Abstract

Background: Adherence to HIV care is complex, as barriers to care are multidimensional, particularly for ethnic minority women. Mobile health (mHealth) solutions are supportive in improving HIV health care outcomes. In the United States, however, mHealth interventions are not widely implemented in public HIV clinics and have not been customized for women. There is an unmet need for culturally and linguistically appropriate mHealth interventions that address the health care needs of minority women living with HIV.

Objective: This study aims to describe a protocol investigating the feasibility of an mHealth intervention for treatment adherence among women living with HIV. This is a two-phase, mixed methods, pilot randomized controlled trial that begins with qualitative patient interviews to inform the system design. Participants will be block randomized by language (English, Spanish, and Haitian Creole) to 1 of 2 study arms.

Methods: Women (age ≥18 years) who were followed up at the women's HIV clinic of an academic medical center, with a recent history of nonadherence to HIV care (missed appointments, unsuppressed viral load, or not taking medications as prescribed), will be enrolled. The experimental arm will receive the intervention, which includes health reminders and psychoeducational messaging, plus clinical standard of care reminders. The psychoeducational messaging will target patient-level barriers of HIV stigma and medical mistrust and resilience as a patient-level strength. The control arm will receive standard of care reminders only (ie, mailed appointments and automated telephone calls). All aspects of the study and intervention will be offered in the participants' preferred language. The primary outcome is the feasibility and acceptability of the study. The secondary outcomes are changes in self-reported medication adherence, depression symptoms, HIV stigma, medical mistrust, resilience, and clinic attendance and viral suppression extracted from the participants' medical records. Data will be assessed at baseline (T0) and 2 subsequent clinic visits—approximately 3 to 4 months from the baseline (time 1; T1) and 6 to 9 months from the baseline (time 2; T2). Qualitative data will be transcribed and analyzed iteratively. Bivariate analyses will compare data by the study group (chi-square, odds ratios, and t tests). Exploratory analyses will be conducted for each outcome variable—T1 and T2 values will be compared with values at T0 by the study group.

Results: As of March 2020, baseline quantitative data were collected on 54 participants (28 English speakers, 14 Spanish speakers, and 12 Haitian Creole speakers). The first 3 focus groups (1 in each of the 3 languages) were completed, with a total of 20 participants. The findings are currently being integrated into the beta version of the mHealth texting system.

Conclusions: The findings of this novel HIV adherence intervention may shed light on the barriers and facilitators of HIV health care and the mechanisms of an mHealth intervention that is customized for ethnic minority women living with HIV.

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KEYWORDS

telemedicine; HIV; acquired immunodeficiency syndrome; women; adherence; clinical trial protocol; barriers; facilitators; text messaging; mHealth; SMS/texting

Introduction

Background

Adherence to care (eg, visit adherence) is the single most important factor projected to improve health outcomes for persons living with HIV and reducing communal HIV viral load, relieving both the individual and public health burden of HIV [1]. Adherence to care is complex, as barriers are multidimensional. Barriers are experienced at the individual or patient level (ie, mental health and psychosocial) or can occur as a result of structural issues (ie, insurance coverage) [2]. In the United States, barriers to regular HIV care disproportionally affect women and ethnic minorities [3,4]. Metropolitan Miami has the highest HIV transmission rate in the United States; however, only 61% of women living with HIV are engaged in HIV care [5,6]. In Miami, a multicultural and multilingual region, two-thirds of the residents are foreign born and speak a language other than English. Specifically, 60% of the residents speak Spanish or Haitian Creole at home [7]. Mobile health (mHealth) technology, such as texting, has shown promise in improving HIV care adherence, both globally and domestically, in a variety of settings [8].

Rationale

mHealth solutions, which range from texting to full-blown apps, are supportive in improving HIV health outcomes [8]; however, in the United States, where 95% of the residents own a mobile phone, mHealth is not widely implemented in public HIV clinics. Furthermore, most mHealth interventions in the United States for HIV care adherence are designed for specific populations such as sexual minority men or adolescents. Interventions tested among ethnic or linguistic minorities have focused on a single ethnic group and were monolingual. Furthermore, only a few have been designed for women [8]. Women access health care at specific life stages—pregnancy, primary, and gynecological care; these stages are opportunities to engage women in HIV care and address barriers to regular care. Among women, the frequency of engaging in care depends on their life stage. Postnatal women, who may be adequately engaged in HIV care, for example, fall out of care after the birth of their child [9]. Effective solutions need to reach all sectors of the population. Taken together, there is an unmet need for culturally and linguistically appropriate mHealth interventions that address the health care needs of women living with HIV.

Individual barriers to HIV care adherence are often interrelated and affect individuals differently. In the literature, HIV stigma (eg, discrimination experienced because of an HIV diagnosis) and medical mistrust (ie, distrust of providers or a medical system) often co-occur—a combination that directly affects HIV health outcomes among minorities [2]. In a recent study, medication mistrust was found to be directly related to HIV care adherence among African Americans [10]. HIV stigma is also known to be related to depression [2]. In examining strengths or coping mechanisms, resilience, which is defined as adaptation in the face of adversity, mitigates the negative barriers to positive health outcomes for minority women living with HIV [11].

In a public clinic in Miami, serving a predominantly minority population, a significant correlation was demonstrated between HIV care barriers and HIV care adherence. Depression and low patient-physician relationship ratings correlated significantly with low adherence. Moreover, patients who endured multiple barriers were more likely to have detectable viral loads [12]. HIV stigma, medical mistrust, and depression can be used to measure barriers to health care access. The relationship among these previously identified barriers, combined with a person's resilience, may inform interventions to improve HIV care adherence.

Objective

The overall goal of this innovative intervention is to develop a patient-centered mHealth system tailored to individual patients that addresses their unique HIV barriers. The system will deliver different text messages and will be designed for a cohort of multicultural and multilingual women living with HIV, who were followed up at a large, public academic medical center in Metropolitan Miami.

Study Comparators

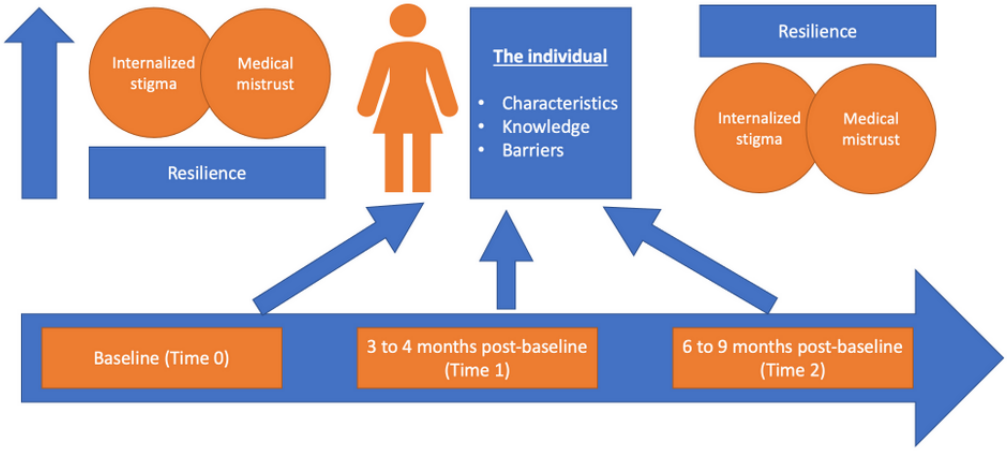
The control arm for this study are enrolled participants who will receive the hospital's standard of care, as it relates to the reminders for clinical appointments. The hospital system mails reminder letters 7 to 10 days before the appointment. Patients also receive automated reminder telephone calls, approximately 2 working days before the appointment.

Theoretical Foundation

Conceptually, the design of the intervention is consistent with the Health Belief Model (HBM) [13,14]. The HBM considers individual-level characteristics, strengths, and barriers to influence health behavior change. The mHealth system includes health reminders and psychoeducational (behavioral) messaging to reduce nonadherence, internalized stigma (one's own negative perceptions about HIV), and medical mistrust while strengthening resilience. Behavioral messaging is adapted from the Dale and Safren's Striving Towards Empowerment and Medication Adherence (STEP-AD) intervention, which aims to reduce nonadherence and the experiences of stigma and to

improve resilience for women living with HIV [15]. The conceptual framework of the protocol is depicted in Figure 1.

Figure 1. Protocol conceptual framework based on the Health Belief Model.



Trial Design

This is a concurrent, two-phase, mixed method, pilot randomized controlled trial. Both the qualitative and quantitative components collect data from the target population women living with HIV. The trial begins with the qualitative component.

Phase 1

The qualitative component comprises interviews in the form of participant focus groups and participant key informant sessions.

Phase 2

The quantitative component is a short-term longitudinal intervention, where participants will be randomized to 1 of 2 study arms (parallel group). The allocation ratio is set at 1:1. The control arm will receive the standard of care for reminders, and the experimental arm will receive the intervention, in addition to the standard of care for reminders (see Study Comparators section). Data will be collected at baseline (T0), 3 to 4 months postbaseline (time 1; T1), and 6 to 9 months postbaseline (time 2; T2) after the launch of the intervention (exploratory trial).

Methods

Study Setting and Population

The study site is a women's HIV clinic, located within an academic medical center in Metropolitan Miami, United States. Participants will be enrolled from various services of the clinic, including prenatal care, primary care, and gynecological specialty care.

Eligibility Criteria

The following are the eligibility criteria for the study: (1) women aged ≥18 years; (2) confirmed HIV diagnosis (per the clinic's standard); (3) active patient (ie, not withdrawn, transferred, or dismissed); (4) 2 or more previously scheduled visits 12 months before the study enrollment; and (5) nonadherence, based on 1 or more of the following criteria: missed 1 or more visits, having a viral load >20 copies/mL, or not taking HIV antiretroviral medications as prescribed.

Participants will have to confirm at the time of enrollment that they possess a working mobile phone number (to receive text messages). We will exclude women with serious psychiatric diagnoses, who are cognitively impaired or are not able to consent for themselves.

Study Consent Process

Participants will give consent in person with the institutional review board (IRB)–approved paper copies of forms and an ink signature. First, clinic providers and staff will inform the patients of the study, including the purpose of the study and participation criteria. Second, patients who express interest in participating will be referred to a research team member who will be on site to provide further information. Potential candidates for the study will be read the informed consent form and the Health Insurance Portability and Accountability Act (HIPAA) form in their preferred language (English, Spanish, or Haitian Creole). A trained and IRB-approved study team member will explain the different aspects of the study in simple words and answer the study candidates' questions. Interested candidates will then be asked 3 to 4 questions to assess the understanding of the project, purpose, procedures involved, and the voluntary nature of participation. Those who cannot successfully answer the questions will have the study re-explained by the research staff, with an opportunity for clarification on the areas that they did not understand. Only participants demonstrating an understanding of the study and voluntary agreement to participate will be invited to sign the forms. To accommodate low written literacy in the participants' respective languages (Spanish or Haitian Creole), bilingual study team members will be on hand to ensure that the participants understand the questionnaires.

Before the beginning of each focus group, participants will be rebriefed on the purpose of the study and informed that the focus group will be recorded. Moreover, the participants will be informed of their right to remove themselves from the study or withdraw their responses at any time, without penalty. The respondents will also have the opportunity to ask questions before the session begins.

Intervention Components

Qualitative Component

The qualitative component comprises 6 focus groups of 5 to 8 participants in each of the 3 different languages (English, Spanish, and Haitian Creole). Overall, 3 focus groups (focus groups before baseline; FG1), 1 per language, will occur before T0—the launch of the intervention. The second set of focus groups (focus groups at the end of the intervention; FG2) will occur at the end of the intervention (T2). The FG1s, conducted before T0, will inform the customization of the mHealth system; the FG2s, conducted after T2, will elicit the participants' experiences with the intervention. The focus group participants will also complete the quantitative questions described in Table 1.

Table 1. Summary of assessments and data collected for primary and secondary study outcomes.

Study outcomes	Study measures: description	Variable type and values	Data source (time point)
Primary outcomes			
Rates of enrollment			
	The proportion of participants enrolled out of the total number of participants approached. The proportion of participants who declined enrollment or failed the screening out of the total number of participants approached	Continuous; range 0-1	Study logs (T0[a])
Acceptability of the mobile health app			
	The proportion of messages opened out of the number of messages received	Continuous; range 0-1	Data usage logs (T0, T1[b], and T2[c])
Secondary outcomes			
Clinical outcomes			
Adherence to medication	Wilson 3-item self-report measure for medication adherence (self-administered) [16]	Continuous (score); range 1-100	Participant (T0, T1, and T2)
Clinic attendance (change)	Number of missed visits 1 year before assessment (T0), between T0 and T1, and between T1 and T2	Continuous (number)	Electronic medical record
Viral suppression	Viral load	Categorical; ≥20 copies/mL or <20 copies/mL	Electronic medical record or measured through a blood test (T0, T1, and T2)
Behavioral outcomes			
Depressive symptoms	Patient health questionnaire-9 (self-administered) [17-19]	Continuous (score); range 0-27	Participant (T0, T1, and T2)
Internalized stigma	HIV stigma scale (self-administered) [20,21]	Continuous (score); range 40-160	Participant (T0, T1, and T2)
Medical mistrust	12-Item group-based medical mistrust scale (self-administered) [22,23]	Continuous (score); range 12-60	Participant (T0, T1, and T2)
Resilience	25-item Connor-Davidson resilience scale (self-administered) [24-26]	Continuous (score); range 0-100	Participant (T0, T1, and T2)

[a]T0: baseline.

[b]T1: time 1 (3 to 4 months postbaseline).

[c]T2: time 2 (6 to 9 months postbaseline).

The qualitative component will also comprise 6 sets of key informants, where 2 to 3 participants will represent each language. The first group of key informants (KI1) will be drawn from the FG1, approximately 1 month after FG1 for each language. KI1s will be invited to be interviewed based on their interaction with the mHealth system. The second group of key informants (KI2), who will be sampled from the intervention group, will be interviewed after T1. KI1 and KI2 will provide interim feedback to fine-tune the design of the mHealth system.

Quantitative Component

Mobile Health Messaging System Prototype: Delivery of Text Messages

An English-version prototype of the mHealth messaging system using commercially available software for mobile texting has been designed. A basic user front end populates the system with data from an Excel (Microsoft Corp) spreadsheet, including mobile phone numbers, message types (medication reminder or behavioral messages), message frequency (weekly or daily), start/stop data, and message content. The communication is

bidirectional, in that participants can respond with preselected codes (eg, *1* and *2*), responding to prompts such as "Press '1' if you received this message."

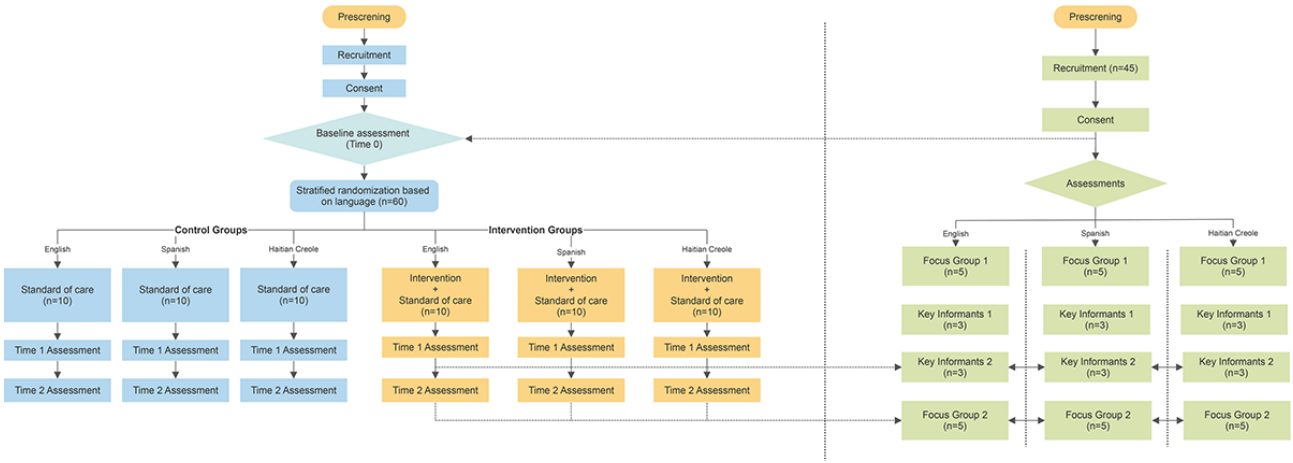
Mobile Health Messaging System Prototype: Privacy and Security

The system will not transmit personal health information (PHI). Exact names of clinics or terms such as "HIV" or "AIDS" will not be transmitted. The patients' phone numbers are the only identifiers that will be stored in the system. Twilio is HIPAA, International Organization for Standardization 27001, and General Data Protection Regulation Privacy Shield compliant. Twilio is password-protected, and programmers use a two-factor authentication process to access the programming environment.

Connection Between the Qualitative and Quantitative Components

This is a parallel, mixed methods study, where the results from the qualitative component will inform the design of the intervention (quantitative component). As depicted in Figure 2, the qualitative and quantitative components will connect at 3 time points: before T0, at T1, and T2 (study end). FG1, KI1, and KI2 will provide insights into the messaging preference (reminder and behavioral) for the customization and refinement of the mHealth prototype and also pilot the mHealth prototype. All messaging will be piloted with focus groups by language.

Figure 2. Data flow diagram for the study quantitative components (left) and the qualitative components (right).



Intervention: Personalization of Reminders and Behavioral Messages

Text messages set for medication reminders will be customized based on timing, frequency, and exact content per participant preference. Behavioral messages address the barriers of internalized stigma, medical mistrust, and resilience at the individual/personal level. Participants will be blinded to their survey results. The baseline scores of participants (high internalized stigma, high medical mistrust, or low resilience) will determine the behavioral message content. At T0, participants will provide their customizations for the system. At T1 or T2, and any other time the participants choose, updates will be entered into the system. Behavioral messages have been adapted from the STEP-AD intervention aimed at decreasing internalized stigma and medical mistrust while improving adherence and resilience for women living with HIV. Suggested text messages will be presented to participants at FG1, conducted in the 3 different languages, to test for acceptability in the population of interest.

Intervention Fidelity

Laboratory Data

If participants miss their scheduled clinical appointment, they will be asked to come to the clinic's research wing, where a blood sample will be drawn by a clinical research staff member to obtain the viral load. Quantitative data will be collected as well. This procedure will ensure adherence to study data points T1 and T2.

Texting System

For the mHealth system, participants will be prompted to respond to predefined responses such as "Press '1' if you received this message" and "Press '2' if you would like us to call you." Downloadable data usage logs will track messages that are opened and the participants' responses. Periodically, participants will receive text surveys regarding the usefulness of a message immediately upon opening the message. These data will further guide messaging development and gauge intervention adherence.

Intervention: Concomitant Care

At the discretion of the principal investigator (PI), participants who are concurrently enrolled in another intervention with overlapping objectives may be excluded from the data analysis. The proposed intervention will supplement the standard of care provided by the hospital, as it relates to appointment reminders.

Study Outcomes

The primary and secondary outcomes are summarized in Table 1. Data will be collected either from the electronic medical record (EMR), the HIV database, or directly from the participants' responses to questionnaires. For analysis, all outcomes (Table 1) will be reported as a change from baseline. As this is a pilot study, our intention is to determine the most sensitive measures. We will explore the data to determine the

most suitable categorizations for a future study; therefore, the total scores will be reduced to categories once all data have been compiled. To report on the participant characteristics, sociodemographic data, including age, race/ethnicity, HIV or AIDS status, socioeconomic status, pregnancy status, substance use, and mental health history (past year), will be collected at T0.

Clinical outcomes (at T0, T1, and T2) that will be examined include a comparative history of self-reported medication adherence, visit attendance, and viral suppression reported as the biological marker of HIV viral load (copies/mL). Psychological and behavioral data include depressive symptoms, internalized stigma, resilience, and medical mistrust (Table 1).

Power Analysis

This study aims to develop and measure the feasibility of a pilot system. Therefore, a power analysis is not appropriate for this study. The plan is to estimate the expected effect sizes and determine the sensitivity of the measures at the conclusion of the study.

Target Sample Size

For the qualitative component, approximately 15 participants per language will be enrolled to ensure that 5 to 7 participants (per language) will convene for the FG1; therefore, a total of 45 participants will be enrolled to prepare for FG1. As a feasibility trial, this study is descriptive in nature, with the ability to test the study hypotheses. For the quantitative component, approximately 20 participants will be recruited per language, of which half will be randomized to the control group.

Recruitment Strategy

Participants will be enrolled from a women's HIV service in an academic medical center where approximately 900 individual women are seen annually. An estimated 50 patients are seen weekly. The women's HIV service is made up of a variety of clinics, including prenatal, primary care, and gynecological specialty care. The women's HIV service collects sociodemographic information, appointments, and laboratory/pathology results in its database (Ryan White Care Ware system) to comply with the reporting and quality requirements of its various funding sources. Information such as missed appointments, adherence to medication, viral load, primary language spoken, and ethnic/racial background will be extracted from the Ryan White Care Ware system for all potential study participants with a confirmed appointment.

Assignment to Study Arms

Participants will be randomized 1:1 to 1 of the 2 treatment arms. Randomization will be stratified by language, where approximately 10 participants per language group will be enrolled in each study arm. This ensures that approximately equal numbers of participants by language groups are represented in each study arm. A randomization schedule will be created by the study statistician based on the Excel function of random number generation. The randomization schedule will be of a randomized block nature to ensure relative equality of assignment across conditions and to prevent the potential of study staff guessing the next assignment. Randomization will take place upon the completion of baseline assessments. The study group assignment will be communicated back to the study team member who consented the patient within 24 hours of enrollment.

Data Collection, Management, and Analysis

Data Collection Plan

Qualitative Component

Audio recordings gathered from all qualitative data (FG1, FG2, KI1, and KI2) will be transcribed using a commercially available transcription software available in English and Spanish. In addition, 2 study team members will review the entire transcription and make changes manually through the software. The Haitian Creole audio will be transcribed manually. The transcripts, along with other information (see Instrumentation), will be entered into a software package designed for mixed methods analyses [27].

Quantitative Component

Unless stated otherwise, all data will be collected at T0, T1, and T2. Participants will complete their paper forms. All questionnaires are meant to be self-administered, but a research team member will be present at all times to answer any questions that the participant may have.

Quantitative Data Sources

Data will be collected from the clinic's EMR, the women's HIV service database, and directly from the participants.

Instrumentation

Sociodemographic, Clinical, and Behavioral Data

Demographic, behavioral and mental health history, and clinical data outcomes, including viral suppression and visit history, will be extracted from the EMRs for each participant. Demographic data will be collected at the time of consent for both the qualitative and quantitative studies.

Background, Financial Information, and Viral Suppression (Self-Reported)

Self-reported sociodemographic information, including age, race/ethnicity, place of birth, marital status, relationship status, highest level of education completed, employment status, annual income, adherence to medication, viral load, and CD4 count, will be collected.

Three-Item Self-Report Measure for Medication Adherence

Medication adherence will be measured using the 3-item self-report measure for medication adherence, which examines *days taken*, *frequency*, and *rating of medications* over the past 30 days. This questionnaire has been validated using an electronic drug monitoring device (Cronbach α=.84 for HIV antiretroviral medications) [16]. The questionnaire was translated into Spanish and Haitian Creole and will be piloted with FG1 participants.

HIV Stigma Scale

Internalized stigma will be measured using the HIV-related stigma scale, a 40-item measure validated in both English (Cronbach α=.96) [20] and Spanish (Cronbach α=.91) [21].

Individuals rate statements such as "Some people act as if it's my fault I have HIV" on a 4-point Likert-type scale (*1=strongly disagree* to *4=strongly agree*). The scale will be translated into Haitian Creole and then piloted with the FG1.

Group-Based Medical Mistrust Scale

Medical mistrust will be measured by the group-based medical mistrust scale, which comprises 12 items (Cronbach α=.64-.70), with statements such as "I have personally been treated poorly or unfairly by doctors or health care workers because of my ethnicity" rated by patients on a 5-point Likert-type scale (*1=do not agree at all* to *5=completely agree*) [22]. It has been translated and validated into Spanish (Cronbach α=.80) [23]. A Haitian Creole version has been created and will be piloted with FG1 participants.

Resilience

The Connor-Davidson resilience scale (CDRISC-25) is a validated 25-item questionnaire (Cronbach α=.89), including statements such as "When things look hopeless, I don't give up," and responded to on a 5-point Likert-type scale (*0=not true at all* to *4=true nearly all of the time*) [24]. The CDRISC-25 has been translated and validated in Spanish (Cronbach α=.89) [25] and in Haitian Creole (Cronbach α=.80) [26].

Patient Health Questionnaire-9

Depressive symptoms will be measured using the Patient Health Questionnaire-9. Participants will rate the questionnaire on a 3-point Likert-type scale based on how often they have been bothered by any of the symptoms stated (*0=not at all* to *3=nearly every day*). It has been validated in English (Cronbach α=.89) [17], Spanish (Cronbach α>.89) [28], and Haitian Creole (Cronbach α=.78) [19].

Data Management

The completed questionnaires will be stored in a secured cabinet in a locked room inside the PI's office. Only the PI and study team members will have access to the data forms and electronic versions of the collected data. Data will be extracted from the paper surveys and entered into an HIPAA-compliant database. Deidentified data will be exported into file formats appropriate for analysis. Authorized team members will use their unique password-protected accounts to access the database. A master spreadsheet will be available to all study team members, uploaded into a *cloud* document manager, and the participant's study ID number will be recorded. This spreadsheet will be encrypted and will be the only database that contains identifying information. All data collection forms, consent forms, and the study log will be stored for 3 years after the closure of the study. The audio and transcription files will also be stored in the *cloud* document manager.

Study Outcomes

Qualitative Data Analyses

Recordings from FG1, FG2, KI1, and KI2, for both the English and Spanish languages, will be processed using a commercially available transcription software and reviewed by a study team member fluent in that language. Haitian Creole will be transcribed manually. All transcriptions will be reviewed a second time by a different study team member fluent in the language. Spanish and Haitian Creole language texts will be first translated into English. The English texts will be analyzed iteratively for thematic content (major themes). Themes pertaining directly to the research questions will inform the mHealth system customization. Dedoose [27] mixed methods analysis software will facilitate data analysis. Overall, 2 study team members will review, enhance, and categorize the software-generated codes. A codebook will document each iteration of the data analysis.

Quantitative Data Analysis

Data Preparation

Sociodemographic and Clinical Data

Participants' mobile numbers will be matched to the mHealth texting system logs; participants' medical record number (MRN) will be matched to the Ryan White Care Ware database and the hospital's EMR. Inconsistent data and outliers will be reviewed. Missing data and unresolved data discrepancies will be considered and recorded as *missing data* and excluded from the analyses.

Study Measures

Questionnaires will be evaluated and compared with the expected response ranges. Participant-level records with incomplete responses will be considered missing for all instruments.

Descriptive Statistics

Groups (intervention vs control) will be compared by baseline characteristics to detect significant group differences, (eg, chi-square values and odds ratios for frequency tables and *t* tests for continuous variables). Cutoffs at $P<.05$ will determine 2-tailed significance. If needed, an alternate (Fisher exact test) or a nonparametric analysis will be conducted.

Exploratory Analyses

We will conduct exploratory analyses, where analysis of variance (ANOVA) models will be constructed for each outcome variable. Statistically significant baseline characteristics, mHealth usage, clinically relevant characteristics, and total instrument score will be entered as covariates. The ANOVAs will compare T1 and T2 outcomes to values at T0 by the study group. At T1 and T2, clinical and behavioral outcomes will be compared with values at T0 for both study arms.

Statistical Analysis: Missing Data

For individual statistical tests, only records with complete data will be included in the analyses.

Data, Safety, and Confidentiality

Data and Safety Monitoring Plan

A data and safety monitoring plan was developed and registered with the funding agency. We anticipate that the largest risk in this study is a breach of confidentiality. Breaches of confidentiality will be reported to the IRB, where action at the institutional level will take place. In addition, the study procedures will be stopped, and we will re-evaluate our procedures.

Potential Harms

Potential unexpected events include a breach in confidentiality, as some participants would not have disclosed their HIV status to their intimate partners, family members, or friends. Some participants may be sharing their mobile devices, and so a potential risk exists. Adverse events and serious adverse events may be reported spontaneously by the participant. If a potential adverse event is identified, the PI will report the adverse event directly to the IRB. Events that are psychosocial in nature and that meet the criteria for reporting to the IRB (unexpected, related, and serious) will be reported in the 10-day timeframe established. Other events will be reported annually.

Confidentiality

A breach of confidentiality is still a possible risk, but measures will be taken to minimize this risk. The study team will have to collect names and contact information to schedule a participant for a focus group or contact as a key informant and conduct the chart review; therefore, complete anonymity is not possible.

Participants will be assigned an ID number, and only the ID number will identify the data collected on all questionnaires. The questionnaires will not be linked to the consent forms and contact information forms and will not record any identifying information such as name, date of birth, or contact information. The only protected health information that will be stored in the mHealth system is the participants' cell phone numbers. No PHI will be transmitted to the participants. Only the study team members will have access to the data. A study log, which includes MRN, study identification number, and date consented, will be kept in an electronic file, secured with an encrypted password. Only the study team members will know the passwords. The contact information forms and recordings will be destroyed upon the completion of the study. The consent forms and logs will be destroyed after 3 years. The participants' names or personal identifiers will never be transmitted or be part of the study publication of its findings.

The participants' audio recordings, study records, and survey results will be kept private and will not be identified in any publication. Data will be presented in aggregate only. The completed questionnaires, contact information forms, consent forms, and recording devices will be kept in a locked cabinet in the office of the PI. The data collection form, along with the electronic files of the focus group and key informant recordings and their transcriptions will be stored in a university-approved HIPAA-compliant database and in cloud-based storage. Only the study team members will have access to the data. Data collection forms and transcriptions will be kept for analysis. The completed questionnaires will be destroyed after 3 years.

Research Ethics Approval

The PI obtained IRB approval to conduct the study. The IRB approved the study personnel, consent forms, recruitment materials, instruments, and all other materials given to the participants. Changes to the study protocol will be submitted in writing to the IRB, and only IRB-approved modifications will be implemented.

Results

The study was funded in December 2018. IRB approval for the English language version of the protocol was attained in January 2019. As of March 2020, baseline quantitative data have been collected on 54 study participants (28 English speakers, 14 Spanish speakers, and 12 Haitian Creole speakers). The first 3 focus groups (1 in each of the 3 languages) have taken place, with a total of 20 participants. The findings from these data are currently being integrated into the design of beta version of the mHealth texting system.

Discussion

Overview

As of April 2020, 54 participants have been enrolled. Based on the number of subjects enrolled, we anticipate continued participation and enrollment, where we will further test the system and launch the intervention.

Strengths and Limitations

The most significant strength of this study is that, to our knowledge, it is the first HIV adherence intervention in the United States that is designed for minority women across multiple cultural and linguistic contexts. We recognize that the most significant limitation of the study is that there may not be sufficient power to test complex interaction models for the quantitative arm of the analyses. Furthermore, because the intervention is being tested among a cohort of women with a history of nonadherence, study retention may be negatively impacted.

Conclusions

This study aims to determine the feasibility of a mobile intervention on adherence to HIV health care among ethnic minority women living with HIV across multiple linguistic and cultural contexts. The beta version of the mHealth texting system is currently being designed. One limitation is that the study may be underpowered for higher order statistical analyses of the quantitative findings. Nevertheless, the proposed intervention is unique, and the findings of the study may shed light on the barriers, facilitators, and mechanisms of a novel intervention customized for the needs of ethnic minority women living with HIV. Furthermore, the findings of this study were carried out successfully and will serve as the basis for a clinical trial with a larger sample size to fully test the intervention's effectiveness.

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Authors' Contributions

LD researched the literature and conceptualized the study protocol, and AM refined the study protocol. AS wrote the initial manuscript draft, and LD completed the manuscript. JP provided clinical expertise for the protocol design. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review reports from Miami CTSI KL2 Awards FY19.
[PDF File (Adobe PDF File), 166 KB - resprot_v9i6e17656_app1.pdf]

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Abbreviations

ANOVA: analysis of variance
CDRISC-25: Connor-Davidson Resilience scale
EMR: electronic medical record
HBM: Health Belief Model
HIPAA: Health Insurance Portability and Accountability Act
IRB: institutional review board
mHealth: mobile health
MRN: medical record number
PHI: personal health information
PI: principal investigator
STEP-AD: Striving Towards Empowerment and Medication Adherence

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Protocol

Remote Monitoring Telemedicine (REMOTE) Platform for Patients With Anxiety Symptoms and Alcohol Use Disorder: Protocol for a Case-Control Study

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Abstract

Background: Monitoring mental health outcomes has traditionally been based on heuristic decisions, often based on scarce, subjective evidence, making the clinical decisions made by professionals, as well as the monitoring of these diseases, subject to flaws. However, the *digital phenotype*, which refers to the analysis of data collected by measuring human behavior with mobile sensors and smart bracelets, is a promising tool for filling this gap in current clinical practice.

Objective: The objectives of this study are to develop the digital phenotyping of patients with alcohol use disorder and anxiety symptoms using data collected from a mobile device (ie, smartphone) and a wearable sensor (ie, Fitbit) and to analyze usability and patient satisfaction with the data collection service provided by the app.

Methods: We propose to conduct a study among a group of 60 participants split into two subgroups—experimental and control—of 30 participants each. The experimental group will be recruited by physicians from the Hospital Clínic de Barcelona, and the control group will be recruited on a volunteer basis through fliers and social media. All participants will go through pretraining to ensure technological capability and understanding of tasks, then each participant will download the HumanITcare app and will be given a wearable sensor (ie, Fitbit). Throughout the 4-month period, participants will be monitored on a range of factors, including sleep cycle, heart rate, movement patterns, and sociability. All data from the wearable sensors and the mobile devices will be saved and sent to the HumanITcare server. Participants will be asked to complete weekly questionnaires about anxiety, depression, and alcohol use disorder symptoms. Research assistants will ensure timely responses. The data from both sensors will then be compared to the questionnaire responses to determine how accurately the devices can predict the same symptoms.

Results: The recruitment phase was completed in November 2019 and all the data were collected by the end of December 2019. Data are being processed; this process is expected to be completed by October 2020.

Conclusions: This study was created and conducted as a pilot study with the Hospital Clínic de Barcelona, with the purpose of exploring the feasibility of our approach. The study is focused on patients diagnosed with anxiety and alcohol use disorder, but participants were also monitored for depressive symptoms throughout the trial, although these were not part of the initial inclusion criteria. A limitation to our study was the exclusive use of Android smartphones over iOS devices; this could result in a potential selection bias, due to the accessibility and affordability of Android phones as opposed to iOS-based phones. Another limitation might be that reviews of usability and satisfaction could be confounded by factors such as age and familiarity. An additional function that we might add in future studies is the ability for patients to manage their own data.

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KEYWORDS

digital health; digital biomarkers; digital phenotype; mental health

Introduction

Background

In the European Union (EU), approximately 165 million people suffer from mental health disorders, namely anxiety, mood disorders, and substance abuse. These mental health disorders have resulted in both direct and indirect global economic costs estimated at US $2.5 trillion in 2010, with the indirect costs (US $1.7 trillion) being significantly higher than the direct costs (US $0.8 trillion), contrasting the trends of other key diseases, such as cardiovascular disease and cancer [1]. Concurrently, problematic alcohol consumption is considered the causal factor of more than 200 diseases, leading to 5.1% of all global diseases and damages being attributed to alcohol abuse. In addition to the health risks this poses, the social and economic damages involved not only for individuals suffering from alcohol abuse but for society in general must be taken into consideration [2].

Monitoring mental health outcomes has traditionally been based on heuristic decisions, often based on scarce, subjective evidence, making the clinical decisions made by professionals, as well as the monitoring of these diseases, subject to flaws [3]. However, the *digital phenotype*, which refers to the analysis of data collected by measuring human behavior with mobile sensors and smart bracelets, is a promising tool for filling this gap in current clinical practice, offering objective evidence in an otherwise subjective field of diagnosis, namely through the utilization of digital biomarkers [4].

Biomarkers are physiological, pathologic, or anatomic characteristics measured objectively and used to evaluate a patient's health in the status quo by comparing their current biomarkers to ideal, healthy biomarkers. In the wake of advancing technology, *digital biomarkers* are emerging as a new form of tracking patients' health. Digital biomarkers are considered digital as they utilize sensors and computational tools to collect data. These measurements can be taken outside of a traditional clinical environment using sensors such as mobile devices and wearable sensors [5].

Numerous studies have shown that information collected from behavioral and physiological sensors can be used to improve conventional evaluations of patients with symptoms of anxiety. In addition, patients who use these platforms show higher levels of consistency with their treatment plans than those involved only in conventional practice [6]. There are various examples of the effectiveness of digital phenotype data collection in analyzing anxiety disorders:

1. There exist significant patterns between the time spent in certain places and presence of depression and anxiety, although these relationships were not consistent [7].
2. It has been shown that sensors integrated into smart bracelets measuring conductance and skin temperature can be utilized to reach 78.3% (148/189) accuracy in classifying students into groups of high or low stress levels. Furthermore, the sensors provided a 79% (37/47) accuracy rate for classifying students' states of mental health [8].
3. Furthermore, analysis from sensors tracking GPS location and incoming and outgoing text messages and calls collected from 54 college students over a 2-week period indicated that levels of social anxiety can be predicted with an accuracy of up to 85% by tracking these variables [9].

Alongside digital tracking of anxiety symptoms, there also exist various apps designed to facilitate the monitoring of alcohol consumption in patients with alcohol use disorder [10-12]. Although more research is needed, these apps have been shown to be effective in increasing patients' abilities to manage their conditions [10], leading to reduced days of consumption risk [11]. In addition, these tools allow for patients' usual professional caretakers to monitor their conditions, allowing for more informed care [10]. Therefore, with the REMOTE (Remote Monitoring Telemedicine) Study, we aim to provide valuable insights and knowledge about digital biomarkers in alcohol use disorders and anxiety disorders.

Study Objectives

Due to emerging research on digital biomarkers and the accuracy of passive monitoring of data in patients with mental health disorders, we propose to conduct the REMOTE Study among a group of 60 participants split into two subgroups of 30 participants each This study will be conducted in the Addictions Unit at the Hospital Clínic de Barcelona. The primary objective of this study is to analyze the digital physiological patterns of two groups of participants—one group with symptoms of anxiety disorder and alcohol use disorder and one healthy control group without these disorders—using data collected from a mobile device (ie, smartphone) and a wearable sensor (ie, Fitbit). The data will be collected from the sensors through the HumanITcare platform. The data will then be compared with the symptoms validated in clinical questionnaires, which participants will complete four times over the course of the study, in order to determine whether the use of sensor data is an efficient and accurate means of presenting objective diagnoses rather than the subjective diagnoses of the status quo.

The secondary objective of this study is to analyze usability and patient satisfaction with the data collection service provided by the app and to explore the feasibility of this approach in clinical practice.

Methods

Design

Overview

This study is a case-controlled, prospective study consisting of two groups: one group of healthy control individuals who do not have symptoms of alcohol use disorders or anxiety and one experimental group that meets the selection criteria described in the Study Population and Setting section. Participants in both groups will be matched for age and sex, since both can be confounding factors regarding usage patterns of electronic devices. Both groups will receive mobile and wearable sensors that will track their physiological and behavioral activity over the course of 1 month. Both groups will also take the State-Trait Anxiety Inventory (STAI) [13], the Beck Depression Inventory-II (BDI-II) [14], and the Alcohol Use Disorders Identification Test (AUDIT) [15] once per week through the HumanITcare app downloaded on their phones. Participants will be instructed on the use of the app during the initial visit, along with receiving their wearable sensors (ie, Fitbits). The data will be monitored by the research team through an online, encrypted compilation of participants' data.

The HumanITcare platform allows for the collection of data from the participants; the platform also provides a source of data for the researchers to verify that each participant's data are being collected appropriately and that the Fitbit devices are working properly. The HumanITcare app that participants download to their phones collects data from the phones and sends them to the HumanITcare platform. As stated above, the app sends notifications to the participants once a week to remind them to complete the questionnaires. Also, it provides a *help* button so they can contact the researchers if needed (see the HumanITcare App section below).

Study Population and Setting

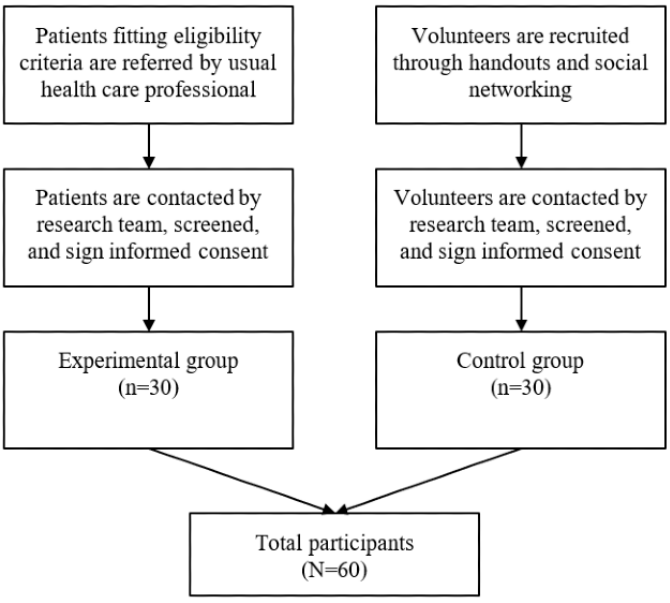
The study will be conducted at the Hospital Clínic de Barcelona and is a single-center national study. Experimental participants will be drawn from the outpatient clinic at the Addictions Unit of the Hospital Clínic de Barcelona, and control group participants will be drawn from random volunteers recruited through fliers and social media.

The research team members at the Hospital Clínic de Barcelona Addictions Unit will be tasked with finding eligible subjects for the experimental group. The inclusion criteria for the experimental group participants are as follows: must be between the ages of 18 and 70 years; must have knowledge and daily use of new technologies; must have an alcohol use disorder, based on the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) [16]; must have significant anxiety symptoms (STAI score >33rd percentile); and must have been informed about the study and signed the data processing consent form. Potential experimental group participants are not eligible if they meet any of the following criteria: their mobile device is not compatible with the Android mobile operating system (OS); they have a diagnosis of affective disorder, based on the DSM-5; they have cognitive deficits that prevent proper participation; or they actively consume other substances, in addition to alcohol, except nicotine.

Recruitment

There will be a total of 60 participants split between the experimental and control subgroups (see Figure 1).The recruitment of the 30 experimental patients, conducted by psychiatrists and clinical psychologists, will take place in the outpatient clinic and day hospital of the Addictions Unit of the Hospital Clínic de Barcelona. The usual health care professionals for patients with anxiety symptoms will refer the selected patients to the research team who will assess whether the selected patients meet the eligibility criteria. The 30 healthy control participants will be recruited using brochures distributed by the Faculty of Medicine at the University of Barcelona, as well as through social media.

Figure 1. Study recruitment diagram.



Patients deemed eligible for the study will be contacted by the research team and will have the study explained to them. They will be given a sheet with instructions for proper usage of the Fitbit device (ie, how to load it, how to connect to the app, etc). Informed consent will be given after a full explanation of the trial, including the trial's use of data assets and potential liabilities.

Study Procedures

Participants will complete the study phases as described in the following sections.

Initial In-Person Visit: First Visit

Once deemed eligible by the research team, participants who meet the requirements for the experimental group, as well as the volunteer control participants, will be called to the Hospital Clínic de Barcelona. The first visit will last approximately one hour and will include an explanation of the project to the participants with time for them to ask questions and clarify any doubts. We will explain to the participants' their rights and obtain their informed consent in the presence of the research team. We will also explain the measurement of the following variables: age, gender, education level, marital status, symptoms of anxiety (measured with the STAI), symptoms of depression (measured with the BDI-II), evaluation of alcohol use disorder (measured with the AUDIT), use of medication, medical comorbidities, and substance use. Those experiencing current medication or substance abuse will not be considered for the healthy control group.

Once the variables are profiled, each participant will be instructed to download the HumanITcare platform app and will receive their data encryption code and password. The app will use the participants' mobile phone sensors to collect and consolidate data, which are then sent to the research team for evaluation. A Fitbit device will also be provided and each participant will be informed of their obligation to return the device once the study is completed. For proper operation of the Fitbit, participants will be instructed to access the Fitbit app through their personal email and to specify their age, sex, weight, height, and date of birth. This app complies with data protection laws.

Physiological and behavioral data from the participants' smartphone devices will be compiled in the HumanITcare servers and will be transmitted, along with the data collected in the Fitbit servers, to a separate server available to the research team, which assigns each participant a unique, randomized character code that functions as a profile name (eg, mt1e45al). The data collected through the HumanITcare app and servers and the Fitbit servers for each participant will be represented by this 8-digit code in order to protect each participant's privacy.

Weekly Assessment of Depression and Anxiety Symptoms

Patients will receive a notification from the HumanITcare app once per week reminding them to respond to the three questionnaires—STAI, BDI-II, and AUDIT [15]—available on the HumanITcare app. This will result in a total of four evaluations throughout the duration of the 1-month study period.

Noncontact Visits

Research assistants will perform supervision of participants' data and will monitor whether participants are answering the three weekly questionnaires through the HumanITcare platform. Research assistants will make reminder calls to participants if they are not responding to the questionnaires, in which case the factors that have influenced nonresponse will be explored. All of this data will be recorded.

Final In-Person Visit: Second Visit

The investigator shall summon each participant to the Hospital Clínic de Barcelona to return the borrowed Fitbit device. For participants in both groups, data will be collected regarding user experience with the app through an adaptation of the System Usability Scale (SUS) [17] and the Post-Study System Usability Questionnaire (PSSUQ) [18].

Once the study has been completed, data analysis and data processing will follow. After the statistical analysis is complete, we will proceed to the discussion and interpretation of the results and the writing of a scientific article that outlines the findings.

HumanITcare App

HumanITcare is a Spanish company that has developed an Internet of Things (IoT) platform (HumanITcare platform) as well as a mobile app (HumanITcare app) for the collection and analysis of the daily data of the participants. The HumanITcare app is an Android and iOS app developed by HumanITcare with the intent of collecting mobile phone sensor data for clinical use. The app continuously collects and stores users' sensor data within the HumanITcare app servers, automatically uploading the data collected by the sensors to the HumanITcare servers when connected to Wi-Fi. This allows for constant gathering of sensor data regardless of the quality of network service available at the time; this also ensures that mobile data fees are not charged to users.

The HumanITcare platform ensures anonymity for users by utilizing the SHA (Secure Hash Algorithm)-256 hashing algorithm to encrypt the data collected by users' mobile phone sensors. Furthermore, all of the data collected for each participant are only recognizable by a randomized 8-character code (eg, mt1e45al) assigned to each participant, ensuring that the data are anonymous. The data collected by the HumanITcare app will be evaluated in tandem with data collected by a Fitbit wearable device; however, the app offers a wider breadth of sensors. The passive data types collected by the app and the Fitbit wearable device are represented in Textbox 1.

Textbox 1. Passive sensor data collected by the HumanITcare app and the Fitbit device.

Mobile phone sensors utilized in the HumanITcare app:

- Accelerometer
- Bluetooth
- Call log
- Text log
- Mobile phone identifier
- GPS
- Power state: battery level
- Power state: charging event
- Power state: screen on or off
- Wi-Fi connection

Fitbit sensors utilized:

- Heart rate monitor
- Sleep monitor
- Accelerometer

Outcomes

Primary Outcome: Sensor Data Accuracy and Efficiency

The symptoms of anxiety and alcohol use disorder presented to the research team will be derived from the algorithm calculated from data collected by the HumanITcare platform (ie, app) and the Fitbit devices. These symptoms will be compared with the diagnoses provided by the status quo, *gold standard* questionnaires—the STAI [13] and the DSM-5 [16]—to determine the feasibility and efficiency of using objective sensor data in place of the current subjective methods of diagnosing mental health disorders. This will be done in a two-step process: first, by determining the relationship between the individual types of data tracked by sensors (eg, distance traveled and sleep schedule) and levels of anxiety and alcohol use disorder symptoms as presented by the questionnaires; and second, by using a mathematical model to estimate questionnaire scores by solely using the data collected by sensors (see Table 1). The primary outcome will be the efficiency of the developed algorithm's ability to predict disorder symptoms.

Table 1. Data collection by sensors compared with questionnaires.

Type of data being collected	Method of data collection
Sensor data: to be used to calculate estimation algorithm	
Sleep pattern	Monitored using a cardiac activity sensor and the Fitbit watch given to participants at the initial visit
Rapid eye movement (REM) sleep time	Monitored using the Fitbit motion sensor and cardiac activity sensor
Heart rate	Monitored using the Fitbit sensor
Step count	Monitored by compiling each participant's daily step count using an accelerometer, smartphone GPS services, and Fitbit motion sensor
Distance travelled	Monitored using the GPS services of each participant's smartphone via the HumanITcare app
Mobile device usage	Monitored by determining the time frames in which there was a presence or absence of signals from each participant's device via the HumanITcare app
Sociability: number of incoming and outgoing calls and text messages	Monitored by the number of incoming and outgoing calls and text messages from each participant's smartphone via the HumanITcare app
Questionnaire data: to be tested against estimation algorithm	
Self-reported anxiety symptoms	Assessed via the State-Trait Anxiety Inventory (STAI); participants receive STAI scores ranging from 0 (lowest number of symptoms) to 60 (greatest number of symptoms), which are then transformed into percentiles according to age and sex
Self-reported depression symptoms	Assessed via the Beck Depression Inventory-II (BDI-II); participants receive BDI-II scores ranging from 1 to 63: a score of 0-13 indicates minimal depression, 14-19 indicates mild depression, 20-28 indicates moderate depression, and 29-63 indicates severe depression
Self-reported alcohol use symptoms	Assessed via the Alcohol Use Disorders Identification Test (AUDIT); participants receive AUDIT scores ranging from 0 to 40: a score of ≥8 is associated with harmful or hazardous drinking and a score of ≥13 in women or ≥15 in men is likely to indicate alcohol dependence

Secondary Outcome: System Usability

Satisfaction with and usability of the data collection app will be evaluated after the trial period in order to determine the practicality of the user interface and to determine the practical feasibility of widespread usage of similar apps:

1. Satisfaction with the app will be scored using the PSSUQ [18]. Scores range from 0 (least satisfactory) to 100 (most satisfactory). Participants will be asked to complete the PSSUQ after the data collection period is over.
2. Usability of the mobile app will be scored using the SUS [17]. Scores range from 0 to 100, with a score of ≥68 being considered above average. Participants will be asked to take the SUS after the data collection period is over.

Data Collection, Management, Security, and Ethics

Treatment, communication, and transfer of personal data of all participants will be adjusted to compliance with the EU Regulation 2016/679 of the European Parliament and of the Council of 27, April 2016, on the protection of individuals with regard to the processing of personal data and the free movement of data. The legal basis that justifies the processing of data is the consent hereby given, pursuant to the provisions of Article 9 of EU Regulation 2016/679.

The data that will be collected from each participant are identified only by a randomized 8-digit code, so they will not include any information that could identify participants. Only the research team members with the right of access to the source data (ie, medical history) may relate the data collected in the study with the clinical history of the patient. The identity of participants will not be available to any other person except for a medical emergency or legal requirement. The Ethics Committee for Research, health authorities, and the personnel authorized by the study sponsor will have access to identifiable personal information when necessary to check data and study procedures but will always maintain confidentiality in accordance with current legislation. Moreover, the project will be conducted in accordance with the Declaration of Helsinki (2013).

Risk Management Protocol

Stage 1: Recruitment

Table 2 shows the factors and challenges associated with participant recruitment, for both the experimental and control groups.

Stage 2: Initial In-Person Visit

Table 3 shows the factors and challenges associated with activities of the in-person visit.

Stage 3: Monitoring

Table 4 shows the factors and challenges associated with activities during the study duration and symptom monitoring.

Stage 4: Second In-Person Visit

Table 5 shows the factors and challenges associated with activities of the second in-person visit.

Stage 5: Analysis and Results

Table 6 shows the factors and challenges associated with study analysis and results.

Table 2. Difficulties associated with participant recruitment and their correction measures.

Study activity and associated difficulties or risks	Measures to correct or mitigate
Patient recruitment	
Low number of patients recruited or low involvement by health care professionals	Send weekly reminders
Adult Mental Health Care Center professionals have little familiarity with the questionnaire	Attach the questionnaire in reminder emails for health care professionals
Delay in the schedule due to slow recruitment	Expand to the maximum period of recruitment
Control participant recruitment	
Low access to paired patient controls	Create database of potential candidates who wanted to participate as controls
Dependence on the pace of patient recruitment	Provide informative brochures

Table 3. Difficulties associated with activities of the in-person visit and their correction measures.

Study activity and associated difficulties or risks	Measures to correct or mitigate
Presentation protocol and signing informed consent	
Participants decide not to participate	Summarize by phone so that they can assess whether to participate (avoid visit if uninterested)
Participants do not understand the function	Explain in a simple and clear way the protocol and benefits (eg, “measure your sleep...”)
Patient questionnaires	
Patients do not meet the inclusion criteria	Clearly specify the criteria and instruments when explaining the protocol and review medical history
Download of the app	
Lack of storage space on phone	Forewarn the participant before the visit that an app will need to be downloaded
Instructions of use	
Misuse of the app or device	Deliver a clear, visual instruction notebook in the first session Rehearse app use during the visit with patient Provide contact information to call in case of difficulties
Explaining the follow-up	
Participants forget to respond to questionnaires	Prepare a specific calendar for the patients, showing schedule of days to respond to the questionnaires, and schedule a date for the second in-person visit
Participants forget to wear the device daily	Send weekly reminders

Table 4. Difficulties associated with monitoring during the study and related correction measures.

Study activity and associated difficulties or risks	Measures to correct or mitigate
Correct use of the device	
No use	Send notifications encouraging use of the device Call to remind participants and stress the use of the device
Problems with the server in recording of the data	Perform maintenance of the platform Call to record the daily use if more than 7 days without use
Defective Fitbit	Provide contact number for technical problems Test devices in advance
Forget username and/or password	Provide contact number in the instruction book for technical concerns Create database of patients and log-in data Configure the app so that it does not log out the participants
Problems uploading the Fitbit data	Explain that Bluetooth needs to be enabled for uploading of data; participants should synchronize data every day
Response to the weekly questionnaires	
No response	Send reminders in the form of notifications Review responses from the platform Consider a percentage of 30% as possible dropouts in recruitment
Loss of the patient from the study	
No response to the calls	Consider a percentage of 30% as possible dropouts in recruitment
Patients reject follow-up	Follow-up call to all patients in the middle of the study to explore difficulties and problems, to encourage, etc

Table 5. Difficulties associated with activities of the second in-person visit and their correction measures.

Study activity and associated difficulties or risks	Measures to correct or mitigate
Visit	
Forget to visit	Send reminder call before visit
Satisfaction and usability evaluation	
Validity of questionnaires	Select valid instruments
Bias	Aside from the general questions, include questions according to the number of uses of the bracelet and app
Delivery and retrieval of wearables	
No return of the device	Stress the necessity of returning the device Communicate that the patient must pay the cost of the device
Return in bad condition	Instructions of use Damage will be assessed and, based on impact, the device will be paid for if it is in bad condition

Table 6. Difficulties associated with activities of study analysis and results and their correction measures.

Study activity	Difficulties and risks	Measures to correct and mitigate
Data analysis	Problems with sample variability	Perform preliminary analysis with half of patients Control patients according to degree of use (ie, group according to involvement: a lot, moderate, low, and null)
Dispersion of the results	Scientifically irrelevant data	Assess the usability and satisfaction with the intervention and degree of use Determine association between severity of symptoms and degree of use

Data Analysis

Overview

For each participant, we will collect data through a Fitbit and smartphone device, as well as written data through the form of questionnaires. The devices will offer insight into the physiological responses and changes within participants, which provides a more objective side of the data. For example, the heart rate monitor will report the intensity of one's heartbeat and could suggest symptoms of anxiety. Additionally, the smartphone GPS will report a participant's movement and, therefore, insight into one's daily energy or lethargy.

The written responses through questionnaires will give a subjective account of the participants' anxiety or alcohol use disorder symptoms. An example of this is the STAI, which asks for a scalar rating on one's feeling of lethargy. Using the data from the Fitbit and smartphone devices, plus the data from the questionnaires, we will determine any correlation.

Statistical Methods

The statistical analysis will be carried out as described in this section. Data collected from Fitbit devices, smartphones, and surveys from both groups will be interpreted with descriptive statistics. For the entire group, including all experimental and control participants, the mean and median will be calculated to determine the central tendencies. Next, we will find the standard deviation and range of the data to determine the variability within the dataset. The same process will be done for each group—experimental and control—individually, for the purpose of between-group comparison. The data will also be split and compared based on the source of the data: device information versus survey information.

Results

The recruitment phase was completed in November 2019 and all the data were collected by the end of December 2019. Data are being processed; this process is expected to be completed by October 2020.

Discussion

The study is focused on patients diagnosed with anxiety and alcohol use disorder, but participants are also monitored for depressive symptoms throughout the trial, although these were not part of the initial inclusion criteria. Including this data while interpreting results could be a potential confounding factor. However, we would like to emphasize that while we recognize that anxiety disorders and depressive disorders are not clinically synonymous, major studies strongly support the finding that there are high rates of comorbidity between the two. In one study, results showed that 67% of patients with a depressive disorder also had a current anxiety disorder and 75% had a lifetime anxiety disorder [19]. Harvard researchers Jukka-Pekka Onnela and John Torous conducted a similar study using participants diagnosed with major depressive disorder and reported "Patients in this study were not excluded due to comorbidity of additional illnesses," such as anxiety [6]. Due to this evidence, we believe there is justification for using participants who have symptoms of both. To avoid confusion, future research should prescreen for anxiety as well as depression, and standardize the initial sample. Researchers may also decide to use anxiety and depression interrelated questionnaires, such as the Depression Anxiety Stress Scales (DASS), that take into account the comorbidity of the two disorders, rather than primarily depression-related (ie, the BDI-II) or primarily anxiety-related (ie, the STAI) surveys, in order to improve reliability and validity of patient measures.

A limitation to our study is the exclusive use of Android smartphones over iOS devices. This study was conducted at the beginning stages of our company's development. At that stage, we did not have the iOS version of the HumanITcare app available. There exists a potential selection bias due to the accessibility and affordability of Android phones as opposed to iOS-based phones. Research shows that Android phones are generally more affordable and financially available to those with a lower socioeconomic status (SES) [20] and that there are higher rates of anxiety and depression present among lower SES populations, possibly due to inferior or limited medical treatment [21]. Thus, this technological criterion may create a biased sample based on SES and the subsequent mental health disorders precipitated by the living conditions of those within this SES. Future research should include a sample of both Android and iOS users to eliminate any confounding variables related to the accessibility of each smart device. Additionally, statistics given by GlobalStats StatCounter show that the mobile OS market-share ratio between Android and iOS is approximately 80:20 [22]. Future research might include a sample that uses Android and iOS devices proportionate to the use in the country to eliminate any confounding variables and to be more accurately representative of the population.

Another limitation might be reviews of usability and satisfaction confounded by factors such as age and familiarity. Prior to the start of the study, researchers ensured that participants understood the tasks and they supplied hard copies of instructions. Researchers from the Hospital Clínic de Barcelona were also present during the training for quality assurance. Nonetheless, it is possible that younger cohorts within the sample are more likely to positively review the usability and satisfaction based on the technological fluency of their generations.

An additional function that we might add in future studies is the ability for patients to manage their own data. We plan to eventually employ an open-database system in which patients can access their own stats and measurements. This may or may not influence the success of the intervention by allowing participants to take notice of their own behavior.

This study was created and conducted as a pilot study with the Hospital Clínic de Barcelona, with the purpose of exploring the feasibility of our approach. The small sample size could be used to calculate the sample size necessary for the most citable outcomes in a follow-up study. Future research will use a larger sample to improve ecological validity. The study experienced one dropout from the experimental group. All original participants remained from the healthy control group.

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Authors' Contributions

AG, SM, HLP, EC, US, and NPH were responsible for the study conceptualization and methodology. EK and DM wrote the draft of the protocol. AG, HLP, SM, and EC provided clinical expertise, whereas NPH and US provided expertise in technological monitoring of symptoms. All authors contributed to the review of the study protocol and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Evaluation from Comité de Ética de la Investigación con medicamentos del Hospital Clínic de Barcelona.
[PDF File (Adobe PDF File), 507 KB - resprot_v9i6e16964_app1.pdf]

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Abbreviations

AUDIT: Alcohol Use Disorders Identification Test
BDI-II: Beck Depression Inventory-II
CERCA: Centres de Recerca de Catalunya
DASS: Depression Anxiety Stress Scales
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EIT: European Institute of Innovation and Technology
EU: European Union
FEDER: Fondo Europeo de Desarrollo Regional
HS: Headstart
IDIBAPS: Institut d'Investigacions Biomèdiques August Pi i Sunyer
IoT: Internet of Things
OS: operating system
PoC: Proof of Concept
PSSUQ: Post-Study System Usability Questionnaire
REMOTE: Remote Monitoring Telemedicine
RETICS: Red Temática de Investigación Cooperativa en Salud
SES: socioeconomic status
SHA: Secure Hash Algorithm
STAI: State-Trait Anxiety Inventory
SUS: System Usability Scale

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Protocol

Determining the Impact of a School-Based Health Education Package for Prevention of Intestinal Worm Infections in the Philippines: Protocol for a Cluster Randomized Intervention Trial

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Abstract

Background: Repeated mass drug administration (MDA) of antihelminthics to at-risk populations is still the main strategy for the control of soil-transmitted helminth (STH) infections. However, MDA, as a stand-alone intervention, does not prevent reinfection. Accordingly, complementary measures to prevent STH reinfection, such as health education and improved sanitation, as part of an integrated control approach, are required to augment the effectiveness of MDA for optimal efficiency and sustainability.

Objective: The aim of this study is to determine the impact and generalizability of a school-based health education package entitled *The Magic Glasses* for STH prevention in the Philippines.

Methods: We conducted a cluster randomized controlled intervention trial, involving 2020 schoolchildren aged 9-10 years, in 40 schools in Laguna Province, Philippines, to evaluate the impact of the school-based health education package for the prevention of STHs. The trial was conducted over the course of 1 year (June 2016 to July 2017). A total of 20 schools were randomly assigned to the intervention arm, in which *The Magic Glasses Philippines* health education package was delivered with the standard health education activities endorsed by the Philippines Department of Health (DOH) and the Department of Education (DepEd). The other 20 schools comprised the control arm of the study, where the DOH/DepEd's standard health education activities were done.

At baseline, parasitological assessments and a knowledge, attitude, and practice survey were carried out in all schools. In addition, height, weight, and hemoglobin levels were obtained from each child (after parental consent), and their school attendance and academic performance in English and mathematics were accessed from the school records. The baseline and 2 follow-up surveys were completed using the same study measurements and quality-control assessments.

Results: Key results from this cluster randomized intervention trial will shed light on the impact that *The Magic Glasses* health education package will have against STH infections in schoolchildren in the province of Laguna, located on the Island of Luzon, in the Calabarzon Region of the Philippines.

Conclusions: The results of the trial will be used to assess the generalizability of the impact of *The Magic Glasses* health education package in different epidemiological and cultural settings, providing evidence for translation of this health education package into public health policy and practice in the Asian region and beyond.

Trial Registration: Australian New Zealand Clinical Trials Registry number ACTRN12616000508471; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=368849

International Registered Report Identifier (IRRID): DERR1-10.2196/18419

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KEYWORDS

soil-transmitted helminths; school-based health educational intervention; Magic Glasses; integrated control; randomized controlled trial; Philippines

Introduction

Soil-transmitted helminth (STH) infections, including roundworms (*Ascaris lumbricoides*), whipworms (*Trichuris trichiura*), and hookworm (*Necator americanus* and *Ancylostoma duodenale*), affect more than a quarter of the world's population, particularly inhabitants of poorer regions [1]. The highest STH prevalence occurs in Central and South America, the People's Republic of China, Southeast Asia, and sub-Saharan Africa [1]. STH infections are commonly associated with poverty, where access to satisfactory sanitation, adequate waste disposal, clean water, hygiene, and health care is poor and knowledge of preventive measures through health education is inadequate [2-5]. The public health importance of STH infections is widely recognized, as they are associated with malnutrition, poor growth and development, iron-deficiency anemia, diminished physical fitness, and impaired cognitive development [3-7]. These features are of particular concern in schoolchildren, who have the highest infection prevalence and intensity of *A. lumbricoides* and *T. trichiura* and are at risk of a high burden of hookworm-associated morbidity [3,5,8]. The most recent estimate (2015) of disability-adjusted life years lost to STH infections is about 3.38 million years worldwide [9].

The World Health Organization (WHO) recommends preventive chemotherapy as a means to control STH infections. This strategy is implemented through mass drug administration (MDA) with benzimidazoles, compounds which are cheap and safe but have variable efficacy depending on the STH species and location. The main feature of this strategy is to administer MDA regularly to at-risk populations with a target of treating at least 75% of preschool-aged children (pre-SAC) and school-aged children (SAC). The WHO recommends annual MDA of pre-SAC and SAC in areas where the prevalence of STH is between 20% and 50% and semiannual if above 50% are infected [10]. The London Declaration on Neglected Tropical Diseases (NTDs) included a pledge from pharmaceutical companies to continue their donations of antihelminthic drugs until 2020 [11,12]. With this commitment, the worldwide deworming coverage has greatly increased over the past years, but the deworming coverage target of 75% has yet to be reached [12]. As a stand-alone intervention, the MDA strategy decreases the intensity and severity of infection and improves the health and nutrient uptake of children [1,10], but it does not prevent reinfection [13-15]. Repetitive treatment is required as the eggs or larvae of intestinal worms continuously contaminate the external environment for many months, and poor hygiene and sanitation favor recurrent exposure [16]. Although WHO advocates repeated rounds of chemotherapy in areas where MDA programs have stopped, infection prevalence and intensity have rapidly rebounded to pretreatment levels [14,17-19]. This lack of sustained benefit substantially lessens the effectiveness of MDA.

Recent mathematical modeling studies of STH transmission show that MDA programs targeting pre-SAC and SAC alone cannot eliminate STH infections; adults must also be treated at high coverage levels [13,20,21]. Other studies have shown that in areas with high STH transmission, high coverage and frequency of treatment [22], with health education and water, sanitation, and hygiene (WASH) efforts are required [14]. To sustain MDA as a stand-alone strategy, an uninterrupted supply of antihelminthic drugs is essential. Whether large-scale drug donations will continue beyond 2020 remains unclear [12], but without continuous donor support, MDA may not be sustainable in the long run. Another concern with MDA includes the potential development of drug resistance as a result of continued treatment pressure on the parasites [14,23]; indeed, there have been reports of decreased drug efficacy against hookworms [24-26] and *T. trichiura* [17,27,28]. With the continual threat of drug resistance, developing complementary interventions for preventing STH reinfection, such as improvements in personal hygiene through health education, as part of an integrated approach, are required to complement chemotherapy to treat and prevent STH infections. This will reduce the number of treatment rounds necessary, consequently lessening the treatment

burden and thus creating a more sustainable long-standing approach to STH control.

In 2013, we reported the successful development and testing of a health education package featuring a 12-minute animated narrative cartoon video entitled *The Magic Glasses* to prevent STH infections in Chinese primary school children [29]. The cluster randomized controlled intervention trial, conducted in Linxiang City District, Hunan Province, People's Republic of China, and involving 1718 children in 38 rural schools showed that the video-based health education package increased students' knowledge about STH and led to behavior change and a 50% efficacy in preventing STH infections [29]. To evaluate the potential for up-scaling this video-based health educational package as a universal school-focused educational tool to form part of a multicomponent sustainable STH control program, we assessed the generalizability of the earlier findings in different geographical settings with a greater force of infection and in different sociocultural groups. This is to provide an evidence base for the translation of the package into public health policy and practice in the Asian region and beyond.

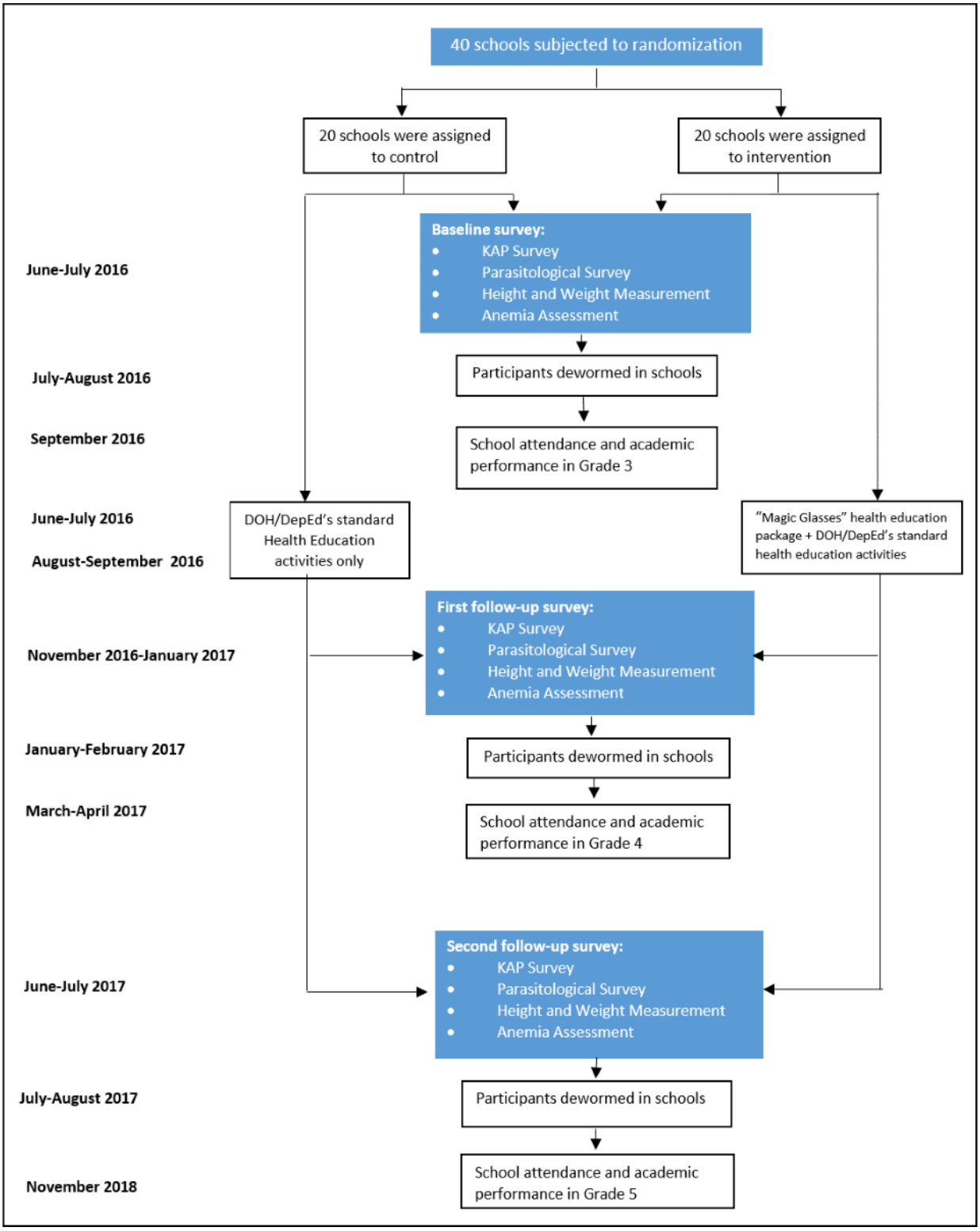
In June 2016, we commenced a new trial to assess the impact of the video-based educational package, culturally adapted for the Philippines. This report describes the protocol of *The Magic Glasses Philippines* (MGP) trial, which has been developed using the Standard Protocol Items: Recommendations for Intervention Trials 2013 guidelines (see Multimedia Appendix 1) [30].

Methods

Study Design

Our overarching hypothesis is that a video-based health educational package (for use in schools) targeting STH will increase students' knowledge of intestinal worms, their transmission, symptoms, treatment, and prevention and improve self-reported hygiene behavior. We addressed this hypothesis by conducting an unmatched cluster randomized intervention trial, targeting schoolchildren aged 9 to 10 years, in 40 schools in Laguna province, the Philippines. The trial study design is shown in Figure 1. The trial was conducted over the course of 1 year (June 2016 to July 2017). A total of 20 schools were randomly assigned to the *intervention* arm, in which the *MGP* health education package was delivered in combination with the standard health education activities (focused on WASH) endorsed by the Philippines Department of Health (DOH) and the Department of Education (DepEd). The other 20 schools comprised the *control* arm of the study, where the DOH/DepEd's standard health education activities were implemented. At baseline, parasitological assessments and a STH-related knowledge, attitude, and practice (KAP) survey were carried out in all schools. In addition, height, weight, and hemoglobin levels were obtained from each consenting child; school attendance and academic performance were accessed from the school records. Only those children who had matched data on KAP and at least one stool sample at baseline were deemed eligible for assessments in the 2 follow-up surveys. The baseline (June-July 2016), first follow-up (Nov 2016-Jan 2017), and second follow-up (June-July 2017) surveys were completed using the same study measurements and quality-control assessments. The baseline survey was conducted immediately before the semiannual mass administration of albendazole in all schools, and follow-up surveys were conducted 5 months before the MDA [31].

Figure 1. Trial study design and timelines. DepED: Department of Education; DOH: Department of Health; KAP: knowledge, attitude, and practice.



Study Setting

Approximately 43 million children are at risk of STH infection in the Philippines (2016 figures, calculated using the Preventive Chemotherapy Databank, maintained by the WHO); of these, about 24% are pre-SAC, whereas 76% are SAC [32]. The burden caused by STH infections remains high according to the results of several studies conducted in the country. A nationwide survey performed in 2001 and reported in 2005 found that the STH prevalence among schoolchildren was as high as 67% [33]. A subsequent study in 2006 showed a prevalence of 54% for at least one type of STH infection and a prevalence of 23.1% for heavy-intensity infections [34]. In a follow-up survey in 2009, a decrease in the overall prevalence (44.7%) and heavy-intensity STH infections (19.7%) among SAC (aged 6-12 years) was reported [35]. Although the prevalence had decreased, it still exceeded the 20% target for morbidity control set forth by the WHO.

The current Philippines national control program for STHs involves semiannual MDA for schoolchildren aged 6-12 years in all public elementary schools (ESs), as advocated by the WHO. This has been implemented since 2007 by the DepEd in collaboration with the DOH through its Integrated Helminth Control Program (IHCP) [36]. As part of the long-term strategy, the IHCP also incorporates health education/promotion and WASH interventions through the DepEd [37,38]. However, the persistently high prevalence of STH reported across the country suggests that the impact was lower than expected [39,40]. In 2014, we conducted a cross-sectional pilot survey in the province of Laguna (located on the Island of Luzon, in the Calabarzon Region of the Philippines). The survey was undertaken to confirm the appropriateness of the study site for the MGP trial by quantifying the prevalence of STH among ES children, particularly before the first implementation of the National School Deworming Day program on July 29, 2015 [41]. The results of the survey showed a prevalence of 33.3% by the Kato-Katz (KK) thick fecal smear microscopy technique for at least one type of STH infection [40]. Overall, the pilot survey indicated that Laguna satisfied the criteria as a study site to test the MGP and that STH continues to be a significant public health concern in the Philippines despite several years of MDA implementation.

Ethics Approval and Consent to Participate

The study protocol was submitted to and approved by the institutional review board of the Research Institute for Tropical Medicine (RITM) with approval number 2013–16, the QIMR Berghofer Medical Research Institute (QIMRB) Human Ethics Committee (approval number: P1271), and the Australian National University Human Ethics Committee (approval number: 2014/356). Permission was sought from the DepEd and DOH before the conduct of the study. With the permission obtained, we provided an orientation about the study to the principals of each school involved, and their oral consent was sought to participate in the study. Written informed consent was obtained from the parents or legal guardians of the students invited to participate in the study. The purpose and procedures of the study were also explained to the participating children, and their oral assent was sought.

Intervention Program: Magic Glasses Philippines

The existing educational video *The Magic Glasses*, originally for Chinese schoolchildren [42], was culturally adapted for the Philippines setting. The cultural adaptation of the video involved 3 major steps: formative research, production and pilot testing, and revision.

Formative Research

The formative research was carried out in selected schools (outside the main trial study area) in 3 municipalities of Los Baños, Pagsanjan, and Victoria in the province of Laguna from August to September 2014. It included an initial assessment of the previous KAP of the schoolchildren using a quantitative questionnaire, qualitative drawing assessment, field observations, and interviews to identify risk factors and drivers for behavior change to translate them into key messages for the video. The formative research comprised the following data collection procedures:

1. A household survey was conducted involving 30 households with Grade 4 children from 3 randomly selected municipalities mentioned above (involving 10 households in a selected village per municipality). The survey involved household observations, in-depth interviews with the head of the household, and infrastructure assessments.
2. A KAP questionnaire was administered to Grade 4 and Grade 5 schoolchildren (aged 9-10 years) in 10 randomly selected schools in the same 3 municipalities (N=616) to assess their KAP associated with intestinal worm infections. Information on the cartoon preferences of schoolchildren was also collected in this survey.
3. Qualitative *draw and write* assessment and semistructured interviews with 30 schoolchildren in 3 selected schools in the same municipalities (10 schoolchildren per school) were conducted to assess their previous knowledge on intestinal worms.
4. Key informant interviews were conducted with teachers (n=6; 1 district supervisor, 2 principals, 2 language teachers, and 1 mathematics teacher), doctors (n=2; 1 municipal health officer and 1 pediatrician), and nurses (n=2; 2 health education promotion officers).

Production of the Video

The cartoon video was developed from October 2014 to May 2015. First, a review of the history of Philippines animation and popular Philippines cartoons was conducted. This information and the results from the formative research were then used to adapt the script and storyboard from the original video to the Philippines culture. Behavioral theories such as the Health Belief Model [43], Integrated Behavioral Model [43,44], and Social Cognitive Theory [43,44] were explored to ensure that the final cartoon was both engaging and informative. Following the script and storyboard adaption, the concept art was developed, and the animation process was finalized using Adobe Creative Suite (Adobe Systems Incorporated), Autodesk 3DS Max (Autodesk, Inc), and Motion-builder software (Autodesk, Inc). The audio for the video was recorded and dubbed by Filipino university students from the University of the Philippines Los Baños.

Pilot Testing of the Video

In 2015, the beta version of *The Magic Glasses Philippines* video was piloted in 2 schools in Laguna Province, again located outside the main trial area: one rural area (San Isidro ES in Calauan) and one urban area (Sampaloc ES in Pagsanjan). The cartoon was shown twice to an audience of schoolchildren (n=124) and teachers (n=7) in the 2 schools. The schoolchildren completed a short questionnaire during the second viewing session to assess whether the key messages of the video were understood. Subsequently, a classroom discussion was conducted to take note of any existing questions and comments. A total of 10 randomly selected schoolchildren in each school (n=20) were also invited to a focus group discussion (FGD) to identify comprehension problems and to seek feedback in a smaller group. Teachers from both schools (n=3 for San Isidro ES and n=4 for Sampaloc ES) were also asked to answer questions related to the content of the video, visual and audio

aspects, and its cultural acceptability. The answers in the questionnaire were discussed in the FGDs for both groups (schoolchildren and teachers), and participants were asked to comment on the cartoons and make suggestions for its improvement.

To ensure that the cartoon had been appropriately adapted and technical issues had been rectified, the revised version of the cartoon was piloted again in 2 schools (outside the radius of 3 km from the main trial sites): one in a rural municipality (Dayap ES in Calauan) and the other in an urban municipality (Platero ES in Biñan). The revised version of the video was shown to an audience of 113 schoolchildren, 18 parents, and 4 teachers in the 2 schools. FGDs were conducted with 10 schoolchildren in each school (n=20) and parents (n=8 for Dayap ES and n=10 for Platero ES), whereas individual interviews were conducted with the teachers in each school (n=2 for Dayap ES and n=2 for Platero ES).

Delivery of the Intervention Program (Within the Trial)

The intervention schools received the video-based health educational package, which was administered by the research staff. The presentation of the cartoon was supplemented by a classroom discussion, a pamphlet summarizing the key messages delivered in the cartoon, and a drawing and essay-writing competition to reinforce the messages. Details of the implementation of the health education package are shown in Table 1. The front cover of the cartoon *The Magic Glasses Philippines* is shown in Figure 2.

Table 1. Details of the implementation of the health education package for soil-transmitted helminths in the intervention schools.

Date and education component	Aim
May 2016	
Research staff training	The research staff were oriented on how to deliver the health education package
June 2016	
Baseline survey	N/A[a]
June-July 2016	
Video shown twice	Inform about STH[b] transmission and prevention
Student questions	Repeat key messages and answer students' questions
Distribution of pamphlet (comic)	Key messages as take-home message
July-August 2016	
Participants received treatment at school (as part of the National Deworming Month program)	N/A
August-September 2016	
Video shown twice	Reinforce knowledge about STH transmission and prevention
Student questions 10-15 min classroom discussion based on student questions	Repeat key messages and answer students' questions
August-September 2016	
Essay competition; write story about own actions taken to prevent worm infection	Practice and reinforce new knowledge
November 2016-January 2017	
First follow-up survey	N/A
January-February 2017	
Participants received treatment at school (as part of the National Deworming Month program)	N/A
June-July 2017	
Second follow-up survey	N/A
July-August 2017	
Participants received treatment at school (as part of the National Deworming Month program)	N/A

[a]Not applicable.

[b]STH: soil-transmitted helminth.

Figure 2. Cover of the cartoon "The Magic Glasses Philippines".

Standard Intervention Approach

Both the intervention and the control schools received the standard health education activities as part of the WASH in Schools (WINS) Program for the promotion of correct hygiene and sanitation practices among schoolchildren endorsed by DepEd and DOH. This program covers the following provisions in schools: (1) provision of safe water, hand washing, toilet, and proper drainage facilities; (2) proper hand washing; (3) oral hygiene; (4) food sanitation; (5) deworming; (6) environmental sanitation; (7) menstrual hygiene management; (8) solid waste management; (9) capacity building for program implementation; and (10) health education focused on hygiene and sanitation. The key concepts of the WINS program are incorporated into the kindergarten to Grade 12 curriculum (ie, in the case of the study participants included in the trial, it was integrated under the Health Education subject in Grade 4) [45]. Teachings included in the Health Education subject are correct knowledge and understanding of the importance of proper hygiene and sanitation practices.

Mass Drug Administration

Following the baseline survey, the recruited students across both control and intervention schools were treated with the WHO recommended dose (400 mg) of albendazole as part of the National Deworming Month program. In the intervention schools, MDA occurred simultaneously with the delivery of *The Magic Glasses* intervention. Follow-up surveys were scheduled to occur just before the semiannual National Deworming Month program.

Study Outcomes

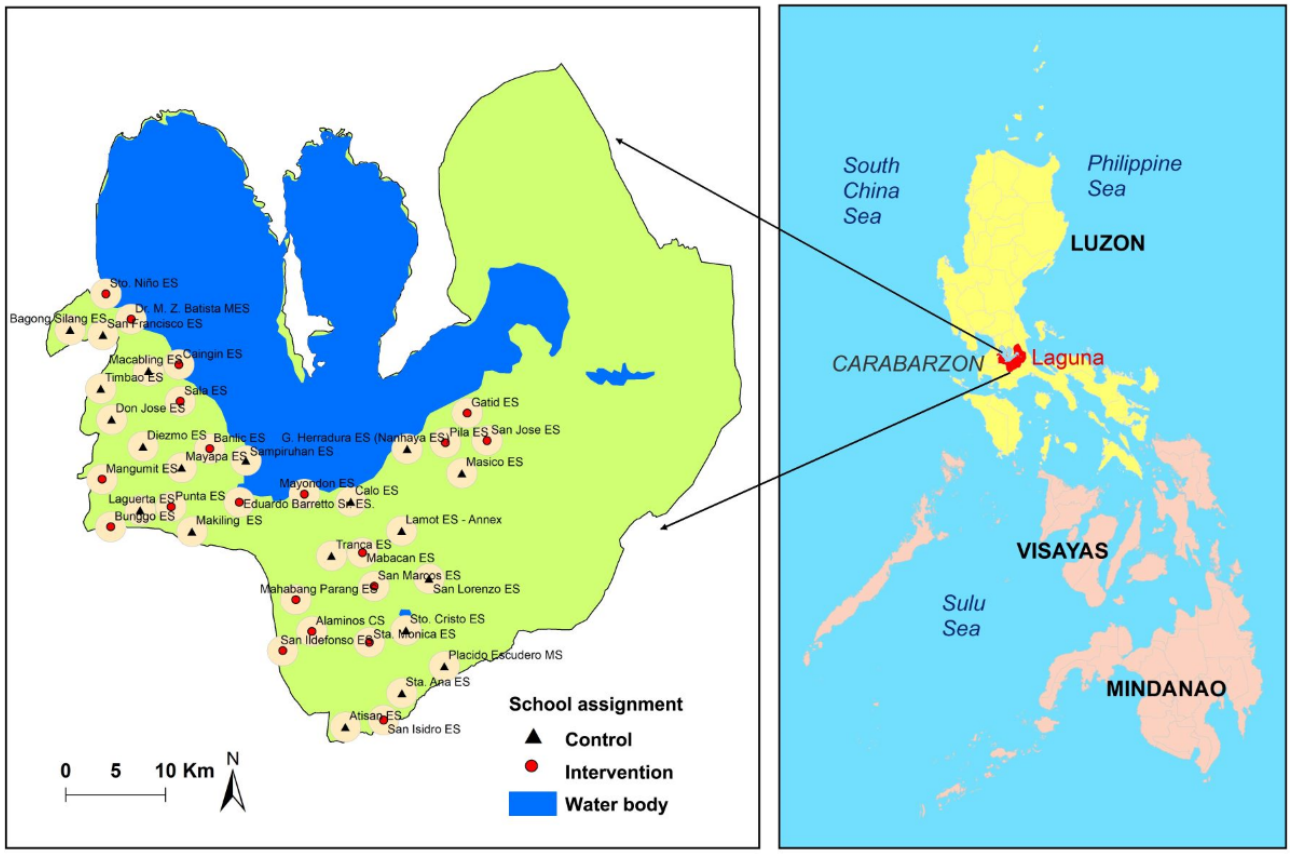
The primary outcomes of the study are STH infections rates and knowledge of intestinal worms and their transmission, symptoms, treatment. Secondary outcomes are changes in self-reported behavior (hand washing, use of toilets, and food hygiene). Tertiary outcomes comprised measures of morbidity (hemoglobin levels to assess anemia; height and weight for stunted growth and malnutrition) and school academic performance and attendance for impact on education. All outcomes are compared between the control and intervention schools.

Selection of Clusters/Schools

Sample size calculations were performed according to the study by Hayes and Bennett [46]. With an infection incidence of 18% and an intervention efficacy of 30%, the study had 80% power with a sample size of 20 intervention clusters (40 in total) and 38 students per cluster at the end of the trial, with a predicted annual 10% loss to follow-up.

Participating public ESs were selected using a spatial sampling technique to eliminate contamination between the intervention and control schools. From the list of schools that fit the criteria of 3 km radius distance from each other, 40 schools were randomly selected and assigned either to the intervention (MGP health education package) group or to the control group (no MGP health education package). Thus, 20 schools were randomly assigned to the intervention group, leaving the remaining 20 as controls. Figure 3 shows a map of the school locations.

Figure 3. Study site and school locations. Map generated through ArcGIS program (ESRI Inc, Redlands, CA, USA).



Recruitment of Study Participants

Study participants were Grade 4 students (aged 9-10 years) from the selected schools. To ensure that all parents were engaged and informed about the study, the research team, with the assistance of the village or barangay health workers (BHWs), organized parents and caregivers' meetings at the catchment barangays of the schools included in the MGP trial before the commencement of classes in June 2016. The BHWs who assisted in the parents/caregiver's meeting were oriented by the research staff on STH and the MGP study. The STH orientation aimed to empower the BHWs about intestinal worms and relate these with preventive measures in other DOH programs, such as sanitation and hygiene. The orientation about the MGP study provided the BHWs with the information necessary to invite and ask the parents or caregivers to attend the meetings. The research staff were responsible for obtaining parental informed consent after the parents and caregivers' meeting. Caregivers who were not reached through the caregiver's meetings were located and oriented by the BHWs in their homes; the research staff validated the information provided to these parents and caregivers during home visits and obtained written consent.

One week before the baseline survey, the Grade 4 students in both the intervention and control schools were oriented about the study and the different study procedures to be conducted on them. However, information regarding cartoon viewing was provided only in the intervention schools. An informed consent document was also distributed to the students whose parents were not present during the parents and caregivers' meeting in the barangay. These students were asked to return the signed informed consent form to the research staff on the day of the survey. The inclusion criteria for schoolchildren were as follows: (1) enrolled in Grade 4 and (2) had parental informed consent.

Data Collection

Field Organization, Training, and Field Schedule

Four teams were set up and organized to carry out the data collection procedures in the 40 participating schools before the commencement of the National Deworming Month. Each team, composed of 1 supervisor from the Department of Epidemiology and Biostatistics from the RITM in the Philippines, 1 team leader, and 6 medical technologists, was responsible for collecting data from 2 to 3 schools per week.

Before the start of the survey, the research staff had undergone a 2-week training. The first week was a microscopy proficiency training conducted by the National Reference Laboratory for Parasitology of RITM, whereas the second week focused on data collection procedures, filling out of forms, and administration of the data collection tools.

Four visits were made at each school at baseline and during the 2 follow-up surveys to allow the children with multiple opportunities to participate in all the data collection procedures, if they were absent during previous visits. On the fifth day, a review of the data collection forms was done to ensure accuracy, consistency, and completeness of the information collected before the departure of each team from the schools and moving to the next set of schools.

Stool Surveys

Stool samples were collected at baseline and at 2 follow-up surveys. A week before the survey week, the participating children, following their orientation to the study, were requested to provide 2 stool samples as part of their involvement in the project. Each child was given a stool collection kit that included a stool container, gloves, an applicator stick, and instructions on how to collect a stool sample. Children were instructed to collect 2 stool samples on any morning of the 4 collection days. They were asked to submit only 1 sample per day (normally in the morning of the same day of collection) to the research staff in the school. The samples were collected, processed at the school site within 2 hours after collection, and read the same day using 3 KK thick smears (41.7 mg of stool/smear) prepared per sample [47]. A team of trained microscopists read the slides. The microscopists worked independently of each other on the samples assigned to them, with 1 sample examined by 1 microscopist only. The number of STH eggs was counted and recorded separately for each helminth species. To ensure the validity and accuracy of the results, 10% of all slides were randomly selected and reexamined by a reference microscopist on each collection day.

Knowledge, Attitude, and Practices Survey

All study participants were administered a questionnaire on STH-related KAP at baseline and at the 2 follow-up surveys. The KAP questionnaire consisted of multiple-choice and open-ended questions regarding demographics, health characteristics, medical history, and previous health education; knowledge about intestinal worms, how they are transmitted, and the symptoms and treatment of STH infection; the student's attitude toward STH; self-reported hygiene practices with respect to hand washing, handling of food, using the toilet, and wearing of shoes; and household characteristics relating to household water source and household assets. The questionnaire was translated into Tagalog and back-translated to English to ensure accuracy. It was piloted in March 2015 in 2 schools outside the main trial area on a total of 83 schoolchildren from San Andres ES in the municipality of Alaminos (n=26) and Gulod ES in the municipality of Calauan (n=57).

Two research staff members were responsible for administering the questionnaire. One gave instructions to the children and read the questions one-by-one in front of the class, whereas the other moved around the room to check whether the children were able to follow the instructions and to ensure that each question was answered.

Students were considered to have a positive (or correct) attitude toward STH if they were aware of the risk of infection and intended to change their behavior to prevent an infection. Students were considered to have a negative (wrong) attitude if they did not recognize the health risk of STH and the importance of correct behavior (eg, good hygiene). A higher score in the questionnaire was considered indicative of a more positive attitude.

Anthropometric and Hemoglobin Measurements

Using a height scale chart (paper beam chart) and calibrated digital weighing scale (Tanita HD-383, Tanita Corporation, Japan), all participating children underwent measurement of height (to nearest 0.1 cm) and weight (to nearest 0.1 kg), respectively, obtained as a single measurement at baseline and at the 2 follow-up surveys. Fingerprick blood samples for hemoglobin measurement (using a portable hemoglobin analyzer [HemoCue Hb 301 System, HemoCue Sweden]) were also collected from 2000 randomly selected children with matching data on the KAP and at least one stool sample at baseline and at the 2 follow-up surveys. Using the height and weight measurements collected from the children, anthropometric values indicative of their nutritional status were calculated. Indicators for malnutrition included stunting (height-for-age), thinness (BMI-for-age), and being underweight (weight-for-age). These anthropometric indicators were calculated as Z scores (the number of SDs from the mean of the standard population, with malnutrition and severe malnutrition defined as values 2 and 3 SDs, respectively, below the mean score of the standard population [48,49]), employing the 2007 WHO growth standards for SAC and adolescents [49]. Anemia was defined according to the WHO classification guidelines, adjusted for altitude in communities more than 1000 m above sea level [50].

Collection of Attendance and Academic Performance

The attendance for the school year and academic performance based on grades or end-of-quarter marks in English and mathematics for each of the 4 grading periods of the participating children while they were in Grades 3, 4, and 5 were accessed from the school records and were obtained in September 2016, March 2017, and November 2018, respectively. The end-of-school-term marks were defined as the arithmetic mean of the 4 grading periods in each school year. The attendance rate was defined as the number of days the children had attended school over the total number of days in 1 school year.

Treatment

Upon completion of each survey (ie, baseline and first and second follow-up), parasitological and hemoglobin results were communicated to all parents in an enclosed envelope, with a recommendation for treatment (if necessary) at the local health center or a request to participate in the deworming activity at school. All participating children were encouraged to take the deworming drug (albendazole [400 mg], as recommended by the WHO) provided free of charge. The school principal, teachers, and/or assisting health professionals (nurses) at each school monitored the students for treatment compliance. In collaboration with the school principals and teachers, the research staff collected the data on the deworming status of the participating students, any side effects experienced, and the reason why any student failed to take the drug.

School Facility Survey

In 2015, before the main trial, a school facility survey was conducted, whereby Grade 4 classrooms in all 40 schools included in the MGP trial were visited and assessed for the presence of toilets, water facilities, and hand washing area, and their functionality.

Household Survey

A household survey was conducted by trained interviewers on a subset of randomly selected students (n=400; households of 10 schoolchildren from each of the 40 participating schools) between October 23 and November 22, 2017, to assess the household support and facilities that promoted STH preventive behavior among the participating schoolchildren. Informed consent was obtained from each student's parent or caregiver, and a structured interview was administered to them. The structured interview covered questions related to knowledge on STH and health education, household assets, and household infrastructure related to WASH. Rapid assessments of the hand-washing facilities and toilets available in the selected households were also conducted.

Data Quality Assurance and Processing

Quality Assurance of the Field Data Collection

Field data quality was monitored through quality assurance by research investigators. All questionnaires and data collection forms were reviewed for accuracy, consistency, and completeness. This review was undertaken immediately after data collection, before the respective research teams had left the area.

Management and Processing of Qualitative Data

All qualitative FGDs and interviews were conducted in English and Tagalog. Informed consent was obtained from all study participants (teachers and from the parents of children involved). All FGDs and interviews were audio recorded, transcribed verbatim, coded, and analyzed.

Data Management and Confidentiality

All results collected from the study respondents were kept confidential. Stool samples were labeled using each participant's assigned study ID number, with no identifying information. Reports that had been generated from this study only contained a summary of the data collection without the names of the respondents.

Results of parasitological assessments, KAP surveys, school attendance information, academic performance, deworming data, height, weight, and hemoglobin measurements were entered twice by 2 different data encoders in a customized password-protected data entry system developed using Microsoft Access [51]. The data entry system contained validation codes and built-in range checks for appropriate variables. The final study datasets were accessible only to the study investigators. All study forms were placed in a locked cabinet in a study office at RITM.

Study End Point Analyses

Models for infection will use generalized estimating equations (GEEs), and a logistic regression model will be used to estimate odds ratio and, therefore, intervention efficacy against infection, accounting for clustering within schools, repeated measures, and baseline infection. Stratification by school-based baseline prevalence will be undertaken to evaluate intervention efficacy at low and high endemicity. Analyses of changes in knowledge and self-reported behavior scores will be analyzed with the use of a linear regression model and GEE to take into account clustering within schools and repeated measures. Potential confounders such as age, sex, and rural or urban status of schools will be incorporated. Spearman correlation coefficients will be used to estimate correlations among self-reported behavior, knowledge, and incidence.

Dissemination

The progress and key results of the study were communicated to and discussed with the Philippines DOH, DepEd, other key decision makers and local stakeholders, including community members of the province of Laguna, at several workshops over the course of the trial.

Results

The study enrollment was carried out in June 2016. Baseline, follow-up 1, and follow-up 2 surveys were completed between June and July 2016, November 2016 and Jan 2017, and June and July 2017, respectively. Data analysis is currently underway, and the first results are expected to be submitted for publication in 2020.

Discussion

The current global context for the elimination of common NTDs is focused on chemotherapy-based control. With the limitations of stand-alone MDA approaches [24], the potential added benefits of including health education and WASH interventions in treatment programs for the prevention of STH infections (as part of an integrated multicomponent approach) for sustainable control must be emphasized. It has been repeatedly shown that to create an enabling environment for both chemotherapy and sanitation to thrive, additional public health measures, including novel, effective, simple, and low-cost health educational interventions, are needed [52-55].

The effective health education package *The Magic Glasses*, previously developed and successfully tested in schools in People's Repblic (PR) of China [29], complements the current approach to control STH infections advocated by the WHO. The trial in PR China established proof of principle that the health education package increased the knowledge and changed the behavior of students, resulting in a significant decrease in their intestinal worm infections.

To demonstrate the generalizability of the approach, we culturally adapted *The Magic Glasses* video for the Philippines audience and applied the health education package in a single-blinded cluster randomized intervention trial to evaluate its impact on STH infection in schoolchildren in Laguna province. The goal was to establish proof of principle that the package is effective and applicable in a different geographical area with a greater prevalence of STH infection and in a different ethnic group. Furthermore, the sensitive cultural adaption of this tool provides an evidence base for a health educational package for use in schools that can be readily integrated into the school curriculum.

A more integrated comprehensive control strategy—combining MDA with improvements in hygiene through health

education—has the potential to result in the sustainable control of STH infections among schoolchildren. This trial was designed to provide additional evidence supporting the inclusion of this health education package into public health policy and practice in the Asian region and beyond.

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Authors' Contributions

DJG, DPM, GMW, RO, and YL conceived the study. DJG, DPM, GMW, RO, MLSM, VT, ACAC, DES, PS, and KH designed the study. DJG, MLSM, VT, FAAB, EA, PA, MDR, CMD, JL, MPD, EDS, and TAB conducted the fieldwork. MLSM and DJG drafted the manuscript. All authors edited the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT Checklist.
[PDF File (Adobe PDF File), 139 KB - resprot_v9i6e18419_app1.pdf]

Multimedia Appendix 2
Existing Peer-Review Reports from Funding Agencies.
[PDF File (Adobe PDF File), 260 KB - resprot_v9i6e18419_app2.pdf]

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Abbreviations

BHW: barangay health worker
DepEd: Department of Education
DOH: Department of Health
ES: elementary school
FGD: focus group discussion
GEE: generalized estimating equation
IHCP: Integrated Helminth Control Program
KAP: knowledge, attitude, and practice
KK: Kato-Katz
MDA: mass drug administration
MGP: Magic Glasses Philippines
NTD: neglected tropical disease
pre-SAC: preschool-aged children
RITM: Research Institute for Tropical Medicine
SAC: school-aged children
STH: soil-transmitted helminth
WASH: water, sanitation, and hygiene
WHO: World Health Organization
WINS: WASH in Schools

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Protocol

Enhanced Enrollment in the National Diabetes Prevention Program to Increase Engagement and Weight Loss for the Underserved: Protocol for a Randomized Controlled Trial

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Abstract

Background: Type 2 diabetes affects 9.4% of US adults with higher rates among racial and ethnic minorities and individuals of low socioeconomic status. The National Diabetes Prevention Program (NDPP) is an evidence-based and widely disseminated behavioral intervention to reduce diabetes incidence through modest weight loss. However, retention in the yearlong NDPP is problematic and leads to suboptimal weight loss, especially among diverse, underserved populations. Strategies to improve NDPP engagement and weight loss are needed urgently. Pilot results of the pre-NDPP, a novel enhancement to enrollment in the NDPP based on the Health Belief Model, were highly successful in a nonrandomized cohort study among 1140 racially diverse, predominately low-income participants. A total of 75 presession participants had doubled attendance and weight loss as compared with earlier participants who did not receive presessions. On the basis of these promising results, we are conducting a randomized controlled trial (RCT) to determine whether pre-NDPP reliably improves NDPP outcomes, as reported on ClinicalTrials.gov.

Objective: This study aims to (1) conduct an RCT comparing NDPP attendance and weight loss outcomes between participants who receive pre-NDPP versus direct enrollment into the NDPP (usual care), (2) examine potential effect mediators (perceived risk for developing diabetes and self-efficacy and readiness for weight control) and moderators (race and ethnicity; income level), and (3) evaluate implementation factors, including cost and projected return on investment.

Methods: This two-arm RCT will compare outcomes among diverse, predominately low-income participants who receive pre-NDPP versus direct enrollment into the NDPP (usual care). This is a type 1 hybrid effectiveness-implementation design to determine clinical effectiveness through an RCT, while assessing factors that may impact future pre-NDPP dissemination and implementation, including cost. Our primary research question is whether pre-NDPP improves NDPP attendance and weight loss compared with standard NDPP delivery.

Results: This project was funded in April 2019. Recruitment is underway as of July 2019. Initial participants began the intervention in October 2019. Data analysis and results reporting are expected to be completed in 2024.

Conclusions: This RCT of pre-NDPP may lead to future dissemination of a scalable, evidence-based strategy to improve success of the NDPP, reduce disparities in NDPP effectiveness, and help prevent type 2 diabetes across the country.

Trial Registration: ClinicalTrials.gov NCT04022499; https://clinicaltrials.gov/ct2/show/NCT04022499.

International Registered Report Identifier (IRRID): PRR1-10.2196/15499

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KEYWORDS

type 2 diabetes; prevention; weight loss; diabetes mellitus, type 2; cohort studies; self efficacy; vulnerable populations

Introduction

Background

Type 2 diabetes (T2D) affects 9.4% of US adults with higher rates among racial and ethnic minorities and individuals of low socioeconomic status [1]. The Diabetes Prevention Program was a successful clinical trial demonstrating that intensive lifestyle support for weight loss initially reduced diabetes incidence by 58% [2]. The intervention was translated into the National Diabetes Prevention Program (NDPP) and disseminated by the Centers for Disease Control and Prevention (CDC) as a yearlong group-based program since 2012 [3]. Despite successes, a 2017 report found that retention in the NDPP is problematic and leads to suboptimal weight loss [4]. Attendance and weight loss are especially low among Hispanic, non-Hispanic black (NHB), and low-income non-Hispanic white (NHW) participants [4-6]. Strategies to improve NDPP outcomes among these disadvantaged populations are urgently needed.

We previously developed and pilot tested an NDPP enrollment protocol, the pre-NDPP, that provides a *presession* with three main components: (1) education about diabetes risks, (2) motivational interviewing (MI) to encourage participation in the NDPP, and (3) problem-solving of barriers to engagement [7]. The Health Belief Model [8] is the theoretical model underlying pre-NDPP, which posits that perceived risk, benefits of, barriers to, and cues to action, and self-efficacy are factors determining health behavior. As such, interventions to prevent T2D should focus on increasing risk awareness and exploring pros and cons of available interventions, including the NDPP. Studies have demonstrated that increasing awareness of diabetes risks may lead to risk-reduction behavior [9,10]. MI [11] may further facilitate action-oriented decision-making about NDPP engagement with its empathic coaching style and evocation of *change talk*. Multiple systematic reviews support the intended use of MI in a brief, group-based intervention to improve NDPP effectiveness [12-15].

The presession enhancement showed highly successful results upon initial dissemination in a diverse, predominately low-income population and may be a viable strategy to address suboptimal NDPP outcomes [7]. In a longitudinal cohort study among a diverse and underserved population, outcomes of 75 pre-NDPP participants who enrolled in the NDPP were compared with 1065 prior participants using the analysis of covariance and multivariable logistic regression. Presession participants stayed in the NDPP 99.8 days longer (P<.001) and attended 14.3% more sessions (P<.001) on average than those without a presession. Presession participants lost 2.0% more weight (P<.001) and were 3.5 times more likely to achieve the 5% weight loss target (P<.001).

Objective

As reported on ClinicalTrials.gov (ID NCT04022499), we are now conducting a large intent-to-treat (ITT) randomized controlled trial (RCT) to test effects of the pre-NDPP enhancement on NDPP attendance and weight loss among a diverse, predominately underserved population with elevated diabetes risks. The primary outcome is percent weight loss. Additional aims include the examination of mediators and moderators of pre-NDPP outcomes and evaluation of the implementation factors of pre-NDPP.

Methods

Overview

We are recruiting 500 participants at risk for developing T2D from a large safety net health care system. Eligible, consenting participants are randomized 1:1 to either the usual care control group who are enrolled directly into the NDPP or the intervention condition who receive a presession prior to the NDPP (pre-NDPP). NDPP classes are held separately for the intervention and control groups to prevent contamination of pre-NDPP effects. Outcomes are NDPP attendance and weight loss. New NDPP classes are staggered to commence quarterly over 2.5 years. In addition to measuring main outcomes and potential mediators and moderators of treatment effects, we are collecting data related to program implementation to inform future dissemination. This RCT includes pragmatic research elements to support comparison to current NDPP outcomes and facilitate future dissemination, including (1) recruiting diverse individuals who meet CDC-established eligibility criteria for the NDPP with no further exclusions, (2) identifying eligible individuals through referrals from health care providers according to best practices [16], (3) providing the NDPP to both treatment conditions without altering its core structure, apart from the inclusion of a presession prior to the first NDPP class (for the pre-NDPP arm), (4) implementation in health care settings in which the NDPP is routinely available, and (5) using standard measurement of NDPP outcomes. The Colorado Multiple Institutional Review Board (18-2542) approved study procedures, and all participants will provide written informed consent before enrollment.

Setting

Denver Health (DH) is an academic medical center and integrated health care system that is nationally recognized for

its model of care for the underserved. DH serves 1 in 4 residents of Denver, Colorado, with a patient population that is 50% Hispanic, 15% NHB, and 30% NHW. In addition to a tertiary-care hospital and trauma center, DH operates 10 primary care clinics across the region. DH was an early adopter of the NDPP and to date has launched 61 yearlong NDPP classes across its network of primary care clinics with over 1400 participants to date.

Eligibility

As a pragmatic trial, we are recruiting English- and Spanish-speaking adults who meet CDC-established NDPP eligibility criteria, including BMI≥25 kg/m^2 (≥23 kg/m^2 if Asian) and history of recent prediabetes or former gestational diabetes mellitus (GDM) diagnosis [17]. Prediabetes is based on a laboratory test within the past year in the individual's electronic health record (EHR) that indicates a fasting blood glucose of 100 to 125, blood glucose of 140 to 199 measured 2 hours after a 75 gm glucose load, or hemoglobin A_{1c} of 5.7 to 6.4. GDM is based on past diagnosis in the medical record or self-reported. Patients without known prediabetes or past GDM may also be eligible based on a risk-screening tool [18], as administered by Lifestyle Coaches during recruitment. Participants are excluded if pregnant at enrollment or known to have T2D.

Recruitment

We are identifying potential participants through referrals from health care providers at DH, which is known to support initial enrollment in the NDPP [16]. Providers refer through the EHR per usual practice. We also identify participants from a risk registry based on EHR data as needed to meet recruitment goals. The enrollment process after initial identification is as follows: (1) Lifestyle Coaches contact referrals by phone to verify interest, eligibility, and schedule eligible individuals for an initial screening visit, (2) consenting individuals are randomized to receive pre-NDPP or usual care NDPP and (3) complete an initial assessment (behavioral and anthropometric assessments), (4) the pre-NDPP group completes a presession 1 to 2 weeks before NDPP classes start, (5) both groups complete a follow-up behavioral assessment 1 to 2 weeks before NDPP classes start (after presessions are completed for the pre-NDPP arm), and (6) both groups commence yearlong NDPP classes.

We will enroll 500 participants, with a goal of 400 randomized participants (allowing for 20% attrition) across both groups attending ≥1 NDPP session as based on statistical power estimates presented below. From previous experience, we expect approximately 50% of referred patients to express interest in participating upon initial outreach. Then, after initial assessment, we expect early attrition of approximately 20% of consenting participants. We seek to recruit 50 individuals every 3 months, for a total of 500 participants recruited over 2.5 years (ie, 200 participants annually). Demographic characteristics of individuals in this study are expected to approximately match characteristics of all previous NDPP participants at DH: 78.0% female, 58.2% Hispanic, 19.5% NHB, 21.0% NHW, 61.4% low income (including a majority of low-income individuals within each racial and ethnic group), and a mean age of 48.4 (SD 12.7) years.

Randomization

We are randomizing eligible, consenting participants to receive either the enhanced intervention (pre-NDPP + standard NDPP) or usual care control group (standard NDPP only) in a 1:1 ratio. Specifically, at the conclusion of the initial recruitment visit, consenting participants receive a preprepared *randomization packet* that denotes their group assignment and relevant details (eg, all class dates and times, Lifestyle Coach contact information). Packets are prepared in advance in a random order using a random number generator and sealed, such that research staff and participants are blinded to condition until the time of assignment.

Retention

For generalizability, we are delivering NDPP with only customary retention methods, including offering classes at clinics where participants receive their primary care, facilitating transportation (eg, providing free parking and information about insurance-provided transportation benefits), offering make-up sessions as needed, and updating participant contact information often. To accommodate additional data collection required of participants in both arms of the trial (above and beyond routine care in the NDPP), we are providing compensation of US $25 for completing each of two research assessments at the time of initial recruitment and immediately prior to attending the NDPP. We are also providing an additional US $25 for all participants to complete a final weight measurement at 12 months.

Description of the National Diabetes Prevention Program (for Both Conditions)

The yearlong NDPP promotes modest weight loss through diet and physical activity. The curriculum is published by the CDC [3]. We follow the CDC guidelines for implementing the standard group-based NDPP [17], including 16 weekly to biweekly sessions, followed by ≥6 monthly sessions over a total of 1 year. The objective of NDPP is achieving ≥5% weight loss. Attending more sessions is associated with greater weight loss [4,19], and guidelines allow NDPP sites to offer more than the minimum 22 sessions to support this goal. We offer 25 total NDPP sessions (16 in months 1-6; 9 in months 7-12), held at the same time, day, and location in group visit rooms available at 6 to 8 neighborhood primary care clinics. Two new NDPP classes commence quarterly over 2.5 years. To minimize potential contamination, participants in the two study arms are enrolled in separate NDPP classes. Trained, bilingual lay health educators lead NDPP classes as Lifestyle Coaches and provide make-up sessions as needed. They are observed by the research coordinator for fidelity and to assess for potential bias in NDPP delivery. Weight is measured at each session on a high-capacity, medical-grade scale. As required by the NDPP curriculum, participants are encouraged to achieve a weekly goal of ≥150 min of moderate to vigorous intensity physical activity (beginning gradually as needed). Participants are instructed to track start and stop times and report total weekly activity minutes at the following session. The most recent CDC curriculum also encourages a low-fat diet but does not require

monitoring of dietary adherence [3,17]. Lifestyle Coaches conduct support calls between sessions to support engagement and health behavior change, address individual questions and concerns, and remind participants about upcoming sessions.

Description of the Pre-National Diabetes Prevention Program Protocol

The pre-NDPP protocol was previously developed in a pilot study funded by the Colorado Department of Public Health and Environment. The protocol is based on the Health Belief Model [8] and extensive stakeholder engagement, including feedback from previous NDPP participants and Lifestyle Coaches. Presessions are intended to increase motivation and readiness to engage in the NDPP, while helping participants become comfortable with the group class format. Content was developed for a fourth grade reading level. Presessions focus on the following: (1) education on diabetes risks, (2) MI to participate in the NDPP, and (3) problem solving of barriers to engagement, following a standardized intervention manual. Presessions are delivered in a group format and scheduled for 1 hour to minimize burden, but are flexible in practice, lasting 60 to 90 min to address participant questions and needs. Presessions are held 1 to 2 weeks before NDPP classes start, at the same day, time, and location to facilitate transitions to the NDPP. To minimize bias, Lifestyle Coaches are alternatingly assigned each quarter to deliver pre-NDPP versus usual care NDPP, with accompanying fidelity observations.

Pre-NDPP participants first receive education on diabetes risks and information about available resources to reduce risk, including a description of the NDPP. Education is informed by the Health Belief Model [8] in which perceived risk, severity, benefits of and barriers to action, and cues to action determine health behavior. Topics include (1) an overview of T2D (eg, prevalence and common complications) and risks for developing T2D (eg, prediabetes, sedentary lifestyle, and overweight and obesity), (2) rates of T2D onset, (3) guidance that modest weight loss can reduce risk, and (4) evidence-based resources to prevent T2D, including a detailed overview of the NDPP. Guidance is intended to normalize the experience of being at-risk for T2D to reduce anxiety, while focusing on instilling hope that T2D is preventable and making calls to action.

Following the pre-NDPP manual, coaches then use MI techniques (eg, reflective listening, evoking ambivalence, rolling with resistance, and eliciting change talk) [11] to help participants identify their preferred plan of action to reduce risk, encouraging participation in NDPP sessions. For example, to create discrepancy, coaches acknowledge the difficulty of making changes in health behavior and probe for typical experiences of weight loss followed by weight regain or other similar challenges. To counterbalance these challenges, coaches will encourage participants to describe why preventing T2D is important to them (eg, wanting to live a long and healthful life or setting a positive example for their children and grandchildren). Coaches also nonjudgmentally acknowledge that while the NDPP works well for those who attend regularly, it may be challenging for some individuals to attend a yearlong class, and that it is okay to opt out or choose other risk reduction resources.

Finally, to plan behavior to reduce diabetes risk, participants are guided toward developing a personalized SMART (Specific, Measurable, Achievable, Realistic, and Timebound) strategy for attending the NDPP. Coaches help participants identify their anticipated barriers to attendance (eg, need for child care) and possible solutions that would enable participation (eg, finding other caregivers or bringing children to class on occasion if needed). Participants are also encouraged that more frequent attendance is associated with greater weight loss, but overall benefits can be achieved despite missing some sessions: attending ≥15 sessions is associated with achieving the ≥5% weight loss goal on average (ie, each session is associated with 0.31% weight loss [4]). Scaling questions are used to help individuals identify an appropriate initial goal. For example, although some participants may have limited confidence to make a commitment to attend the yearlong NDPP without having tried it before, they may report a 10 of 10 in confidence to attend at least the first NDPP session. Finally, participants complete an individualized action plan that includes their SMART goal and anticipated problem-solving strategies. Coaches also conduct brief calls after presessions are completed to follow up and address remaining questions or concerns.

Data Collection

The RCT focuses on comparing NDPP outcomes between participants who receive pre-NDPP versus direct enrollment into the NDPP. The assessment schedule is shown in Table 1.

Demographic characteristics are extracted from EHR databases and verified as needed during the first study visit, including age, gender, race and ethnicity, preferred language, income (above or below 133% of federal poverty level), and education (highest level completed). Body weight is measured on a high-capacity medical-quality scale at study visits and NDPP sessions. The primary outcome is percent weight change from baseline to 12 months by ITT analysis (without regard to whether participants declined NDPP or had early dropout). We also calculate percent weight change from the first to last NDPP sessions attended (ie, last observation carried forward), per CDC guidelines [17]. CMS standards for NDPP reimbursement also emphasize achieving ≥5% weight loss at any point in the program [24], assessed as a dichotomous outcome. Attendance in the NDPP is measured as ≥1 session attended, total number of NDPP sessions attended (including make-up sessions), and duration of participation in the yearlong program. Rates of completing between-session support calls are also assessed as an additional indicator of engagement and treatment dose. Per the CDC's NDPP curriculum, participants self-report weekly minutes of moderate to vigorous physical activity since the last session [3]. Baseline BMI is also be assessed at the initial study visit as kg/m^2.

We are assessing potential mediators of perceived risk and self-efficacy, key constructs of the Health Belief Model [8], and readiness for weight loss as an indicator of motivation. Perceived risk for developing diabetes is assessed with the Risk Perception Survey for Developing Diabetes, a 43-item Likert scale measure with four subscale scores on Comparative Disease Risk, Environmental Risk, Personal Control, and Optimistic Bias [20]. Self-efficacy for weight control is measured with the

Weight Efficacy Lifestyle Questionnaire–Short Form, an 8-item measure of confidence (on a 10-point scale) managing five situational factors related to weight management behavior: negative emotions, availability, social pressure, physical discomfort, and positive activities [21]. We use validated Spanish-language versions of both measures [25,26]. Weight loss readiness is assessed with the Stages of Change in Overweight and Obese People (S-Weight), a 5-item survey developed concurrently in English and Spanish by expert consensus [22,23]. Mediators are measured during an initial assessment at the time of enrollment and 1 to 2 weeks before the first NDPP session (ie, immediately after presessions are completed for the pre-NDPP arm, and shortly before NDPP classes begin for the usual care NDPP arm). This is intended to determine whether pre-NDPP results in increased perceived risk, self-efficacy, and readiness compared with the usual care NDPP, and whether changes in these variables mediate outcomes.

We are also evaluating implementation factors regarding pre-NDPP using the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) planning and evaluation framework for implementation research [27]. RE-AIM constructs will be assessed through a combination of recruitment data, intervention outcomes, staff logs, observations, and interviews with Lifestyle Coaches, clinic personnel, and patients, as well as cost records (Table 1).

Observations and interviews with Lifestyle Coaches and clinic personnel will focus on how pre-NDPP implementation works in practice and where gaps in care processes may be. Interviews will seek to understand the context of intervention delivery and mindsets and belief systems that drive thoughts and actions regarding pre-NDPP. External influences such as financial demands and staff turnover will also be explored as potential challenges. Both Lifestyle Coaches and 3 personnel per each of 8 clinics (focusing on high- and low-referring providers and clinic directors) will be interviewed. The qualitative research assistant will shadow presessions using the observation template and field notes to determine fidelity to core features of the pre-NDPP protocol. Patient interviews will focus on discerning similarities and differences in perspectives about the pre-NDPP and NDPP across 6 groups: those (1) randomized to pre-NDPP and (2) randomized to usual care, and within these groups, those (1) who initially decline to enroll in the NDPP, (2) who enroll but complete <6 months of the NDPP, and (3) who complete ≥6 months. We will begin with 5 interviews per group and continue until the thematic saturation is achieved (ie, not eliciting new information). Key interview questions include the extent to which pre-NDPP sessions increase motivation, relieve uncertainty about participating in the NDPP, address practical barriers to engagement, support autonomy, and other emergent factors that may influence participation. Patients and clinic personnel will be provided gift-card incentives. Interviews will be recorded with consent and transcribed for analysis.

We will measure pre-NDPP costs using principles of time-driven, activity-based costing [28,29], accounting for Lifestyle Coach and supervisor time (including salaries and benefits), supplies and other direct costs, and indirect costs (eg, facilities and general administrative expenses). To focus on the cost of delivering the pre-NDPP, we will exclude costs associated with standard NDPP delivery and research-related costs (eg, data collection solely for research purposes). To facilitate accurate estimates of personnel costs, coaches and their supervisor will track the time spent on pre-NDPP activities (eg, training, outreach, preparing for, and conducting pre-NDPP) and report total hours for each pre-NDPP activity quarterly. Supplies and other direct costs will also be reported quarterly.

Table 1. Measures for randomized controlled trial of Pre-National Diabetes Prevention Program

Measure	Description	Method of collection	Timeframe
Characteristics			
Demographics	• Age, gender, race and ethnicity, primary language, income, education	• Collected from EHR[a] and during first study visit	• BL[b]
BMI	• Baseline BMI (kg/m^2)	• Collected during first study visit	• BL[b]
Main outcomes			
Initial NDPP[c] attendance	• ≥1 NDPP session attended	• Collected during NDPP delivery	• Ongoing collection
Number of sessions attended	• 1-25 NDPP sessions attended	• Collected during NDPP delivery	• Ongoing collection
Duration in NDPP	• 1-365 days of NDPP participation	• Collected during NDPP delivery	• Ongoing collection
Number of between-session calls completed	• 1-25 between-session support calls completed	• Collected during NDPP delivery	• Ongoing collection
Physical activity	• Average self-reported weekly minutes at each NDPP session	• Collected during NDPP delivery	• Ongoing collection
Percent weight change	• Based on (1) BL to 12 months (primary outcome), and (2) first to last NDPP sessions attended	• Collected during NDPP delivery; note weight is also measured at an initial study assessment and at a final 12-month study visit (we are setting up a time for all randomized individuals to have their weight measured at these study visits, for which they will receive gift cards)	• Ongoing collection
≥5% weight loss	• Achieved at any point in the NDPP	• Collected during NDPP delivery	• Ongoing collection
Mediators			
Risk perception	• Risk Perception Survey for Developing Diabetes [20]	• Administered by Lifestyle Coaches during first study visit and repeated prior to start of NDPP classes to assess pre-post change	• BL and 1-5 days prior to start of NDPP classes
Self-efficacy	• Weight Efficacy Lifestyle Questionnaire [21]	• Administered by Lifestyle Coaches during first study visit and repeated prior to start of NDPP classes to assess pre-post change	• BL and 1-5 days prior to start of NDPP classes
Readiness	• Stages of Change in Overweight and Obese People [22,23]	• Administered by Lifestyle Coaches during first study visit and repeated prior to start of NDPP classes to assess pre-post change	• BL and 1-5 days prior to start of NDPP classes

Measure	Description	Method of collection	Timeframe
Implementation factors using Reach, Effectiveness, Adoption, Implementation, and Maintenance			
Reach—Absolute number, proportion, and representativeness of individuals who participate	• Number and characteristics of patients referred, outreached, and expressed interest, consented, completed pre-NDPP (intervention group), and attended NDPP (both groups); reasons for not enrolling or dropout	• Demographics and referral data from EHR; enrollment and participation data collected by coaches; reasons for participating or declining collected by QRA[d] interviews with select participants	• Ongoing collection
Effectiveness—Intervention impact on key outcomes	• Based on main outcomes listed above	• Based on main outcomes listed above	• Based on main outcomes listed above
Adoption—Absolute number, proportion, and representativeness of settings and agents willing to initiate intervention	• Number and characteristics of participating Denver Health clinics; NDPP referrals; Lifestyle Coach participation • Factors influencing adoption	• Study documentation; EHR data • QRA interviews with Lifestyle Coaches and select clinic personnel	• Monthly abstraction analysis • BL; 6 months after start of pre-NDPP
Implementation—Fidelity to intervention protocol, including consistency of delivery (eg, bias) and time and cost of intervention	• Completion of pre-NDPP and NDPP protocol components • Acceptability of pre-NDPP components, processes, and tools; any adaptations made by coaches • Process, barriers, facilitators to implementing pre-NDPP • Pre-NDPP cost	• Coach documentation; presession shadowing by QRA; fidelity checks • Survey by QRA to Lifestyle Coaches, select clinic personnel and select patients • QRA interviews with select participants, select clinic personnel and Lifestyle Coaches • Lifestyle Coach time and resources survey	• Ongoing collection • 6 months after start of pre-NDPP • 12 months after start of pre-NDPP • Quarterly after each presession
Maintenance (potential)—Extent to which intervention becomes routine practice and long-term participant benefits	• Plans and intent to continue, or modify and adapt, pre-NDPP after study; ROI[e] as an indicator of potential sustainability; 12-month weight loss outcomes	• QRA interviews with Lifestyle Coaches and select clinic staff; document review and abstraction of NDPP payment schedules (eg, Medicare); above outcome data	• Study completion

[a]EHR: electronic health record.

[b]BL: baseline.

[c]NDPP: National Diabetes Prevention Program.

[d]QRA: qualitative research assistant.

[e]ROI: return on investment.

Analysis Plan

General Quantitative Approaches

Differences in characteristics between study arms will be assessed using chi-square and *t* tests to examine potential sampling bias. Percent weight change is the primary outcome, which has a well-documented association with T2D incidence [2,30]. ITT analyses will include all randomized participants regardless of NDPP participation, including those lost to follow-up. Weight loss data for women who become pregnant during the study will be excluded from analyses. Patient-level covariates will be screened in bivariate analyses and included

in multivariate analysis if related to the outcome at $P<.20$, differ between treatment arms, or associated with dropout. Covariates and potential moderators will include age, gender, race and ethnicity, primary language, comorbidities, and other demographic and clinical variables. Although primary analyses examine a single outcome per patient (eg, percent weight loss), for longitudinal analyses (eg, perceived risk), we will determine whether missingness patterns are ignorable or nonignorable [31-34]. If so, we will employ likelihood-based methods that use all available data, adjusting for covariates associated with missingness. If missingness is nonignorable, we will use pattern mixture models [35]. If normality assumptions are not met, we will use transformations to normalize distributions, ordinal or Poisson regression where appropriate, and/or the appropriate link function and distribution (eg, logit link and gamma distribution). We will use general (generalized) linear mixed models to incorporate data structures that may be both hierarchical (patients within groups) and longitudinal (repeated observations over time) [36,37]. Hypothesis tests will be two-sided with $\alpha=.05$ or P values reported. Goodness of fit statistics and model fitting diagnostics will be used to assess for influential points, outliers, overdispersion, and heteroscedasticity and to evaluate alternative model specifications [37]. Analysts will be unblinded to condition but will not conduct preliminary analyses to minimize potential of biasing other project staff. Further, while Lifestyle Coaches record individual participant weights and minutes of physical activity at each NDPP session (per standard CDC guidelines for NDPP delivery), they will not calculate aggregate outcomes at the cohort level. SAS version 9.4 (SAS Institute Inc) will be used for analyses.

Aim 1: To Evaluate Clinical Effectiveness of the Pre-National Diabetes Prevention Program Intervention

Hypothesis 1.1

Pre-NDPP participants will experience greater weight loss than those directly enrolled into NDPP. The primary outcome for this analysis will be percent weight change among all randomized participants. As study participation includes groups of individuals in the same study arm, the data structure will be hierarchical, with patients nested within groups. Statistical models are shown in hierarchical notation below. Likelihood of achieving ≥5% weight loss in the NDPP will also be evaluated (using generalized linear mixed models with logit link), as well as percent weight change from first to last NDPP sessions attended.

Hypothesis 1.2

Pre-NDPP participants will have greater engagement in the NDPP than those who are directly enrolled into the program. The outcome variables, number of sessions attended and days of participation, will be analyzed using similar approaches. If the distribution of outcomes is nonnormal, we will use generalized linear mixed models with the appropriate distribution and link function, as described earlier. We will also examine the dichotomous outcome of ≥1 NDPP session attended using multilevel logistic regression (generalized linear mixed model with logit link and random effect for group).

Aim 2: To Examine Mediators and Moderators of Pre-National Diabetes Prevention Program Outcomes

Hypothesis 2.1

The Pre-NDPP intervention will increase perceived risk for developing diabetes and self-efficacy and readiness for weight management. Outcomes for these analyses will be patients' perceived risk, self-efficacy, and readiness scores over time. We will use longitudinal models to determine if trajectories differ for patients in control versus intervention groups.

Hypothesis 2.2

Perceived risk, self-efficacy, and readiness will mediate relationships between pre-NDPP treatment and outcomes. Outcomes will be weight loss and session attendance, using similar approaches as described earlier for hypotheses 1.1 and 1.2. We will include baseline perceived risk, self-efficacy, and readiness as covariates and change in these constructs as primary independent variables to determine if the intervention effect is partially or fully explained by these hypothesized mediators [38].

Hypothesis 2.3

Pre-NDPP effects will differ for participants with the moderator condition (eg, Hispanic and low-income) compared with those without the moderator (non-Hispanic and higher income). The effects of moderator analyses involve the inclusion of an intervention × moderator fixed effect for models that are not longitudinal (eg, percent weight loss and number of sessions attended). For longitudinal models (eg, self-efficacy over time), models will include a main effect for time, arm, moderator variable, time × arm, time × moderator, arm × moderator, and time × arm × moderator interaction term. The 3-way interaction term tests for differential intervention effectiveness in subgroups identified by the moderator variable.

Sample Size and Power

Pre-NDPP pilot data indicate a 0.36 effect size for percent weight change in the NDPP with an intraclass correlation coefficient (ICC) of 1.44%. To be conservative for our primary outcome of percent weight loss among all randomized participants regardless of NDPP participation, we estimate minimum effect sizes detectable for various sample sizes and ICCs (Table 2), with effect sizes of approximately 0.28 to 0.35 for analyses of the primary outcome with a type 1 error rate of .05. Consequently, we expect that 500 randomized participants will provide adequate power while accounting for 20% potential attrition. Note that mediation and moderation analyses are considered exploratory, as estimated power is unknown.

Table 2. Estimated power to detect treatment differences in percent weight loss.

Groups per arm	Patients per group	Intraclass correlation coefficient (%)	Effective sample size	Detectable difference (effect size)	Power (%)
10	18 (180 per arm)	1	154	0.32	80
10	18 (180 per arm)	2	134	0.35	82
10	20 (200 per arm)	1	168	0.31	81
10	20 (200 per arm)	2	145	0.33	80
12	20 (240 per arm)	1	201	0.28	80
12	20 (240 per arm)	2	174	0.31	82

Secondary Analyses

Secondary analyses will be used to inform future applications of pre-NDPP. We will examine whether pre-NDPP participants only benefit if they attend NDPP thereafter (vs no benefit for those not attending NDPP after presessions), which would suggest potential utility as a screening process to identify individuals likely to engage in and benefit more from the NDPP. Additional secondary analyses will be conducted to determine whether patient characteristics that are associated with poor outcomes (ie, lack of retention and little or no weight loss) differ between control and intervention participants. If so, this information can be used to better target the intervention to individuals who could benefit from the presession.

Aim 3: To Evaluate the Implementation Factors of Pre-National Diabetes Prevention Program

Qualitative analyses will evaluate pre-NDPP implementation from a Lifestyle Coach, clinic provider and leadership, and patient perspective. Interviews and observation data will be cleaned and entered into the qualitative software program ATLAS.ti (version 8; Scientific Software Development GmbH) for analysis. Analyses will begin as a small group process for data triangulation to occur and use a grounded hermeneutic editing approach [39]. Qualitative researchers will read 5 to 10 interviews and together determine key themes and their definitions and labels (*codes*). Codes will be vetted with the larger study team and stakeholder representatives. After establishing initial codes, analysts will code the data (first together, then independently) as outlined by Addison [39] and will compare and reconcile coding until a high degree (≥80%) of conceptual interrater reliability is achieved. Specifically, data from interviews with Lifestyle Coaches and clinic personnel will examine themes related to adoption, feasibility, and acceptability of pre-NDPP. This analysis will determine key underlying characteristics, such as belief systems or mindsets, and/or practical reasons that make pre-NDPP effective or not, and to what extent. We expect that data from patient interviews will more thoroughly explain engagement in the NDPP. We will examine emergent codes across study groups by comparing group-level quotations to determine differential experiences. Finally, perceived reasons for participation (or nonparticipation) will be examined alongside actual engagement data to corroborate and explain quantitative results. In ongoing meetings with the larger study team, we will further consider existing literature and associated experiences for corroboration and seek out additional data as needed to confirm or refute results. After initial analysis has identified data to support one theme or interpretation, effort will be devoted to finding negative or disconfirming evidence. Clinic personnel and Lifestyle Coaches will be selected for member checking and revision of thematic groupings before final coding. The final phase consists of preparing interpretive summaries detailing the findings of prior phases. All phases of data processing and analysis will be cross-checked to ensure consistency in application of coding and classification procedures. Observation data will be analyzed similarly.

Pre-National Diabetes Prevention Program Cost and Return on Investment

We will calculate pre-NDPP cost as the average expense of each presession delivery based on personnel time, supplies and other direct costs, and indirect costs. We will then determine the projected return on investment (ROI) of pre-NDPP from both provider and payer perspectives. For NDPP providers, ROI will be calculated as the additional payment expected from payers as a result of potentially improved retention and weight loss of pre-NDPP participants minus the average presession cost and divided by presession cost. For common reference, payments will be based on the Medicare reimbursement schedule for achievement of NDPP attendance and weight loss milestones [24]. We will compare the average expected reimbursement for participants in both study arms to measure additional payments that may be attributed to pre-NDPP. We will also conduct a sensitivity analysis by calculating the projected ROI for varying numbers of pre-NDPP participants with varying demographic characteristics (eg, race and ethnicity and income) and with other available NDPP payment schedules (eg, Maryland Medicaid) [40]. Sensitivity analysis results will inform pre-NDPP sustainability by identifying the number of participants needed per presession to achieve a positive ROI, the extent to which moderators identified in hypothesis 2.3 affect ROI, and the extent to which different payment models affect ROI. From the perspective of NDPP payers, ROI will account for the expected reduction in direct health care expenditures as a result of covering pre-NDPP through an additional payment to NDPP providers, as calculated over a 3-year horizon. ROI will be the reduction in projected expenditures minus the average presession cost and divided by presession cost. Estimates of change in direct health care expenditures will be based on the impact of pre-NDPP on weight loss from hypothesis 1.1, the known relationship between weight loss and T2D incidence [30], and the difference in expenditures for individuals with prediabetes or T2D over a 3-year horizon

[41]. This timeline requires discounting of expected reductions in years 2 and 3 expenditures for which we will apply a standard 3% discount rate. We will also conduct a sensitivity analysis by varying the number of pre-NDPP participants, their characteristics, and the discount rate. To be conservative, cost and ROI are based on all pre-NDPP participants, regardless of NDPP attendance.

Results

Recruitment is underway as of July 2019. Initial participants will begin the intervention in October 2019. Data analysis and results reporting is expected to be completed in 2024.

Discussion

NDPP Outcomes

NDPP outcomes are suboptimal, especially for disadvantaged populations, which involves the risk of further widening of health disparities if not addressed. Pilot data show feasibility and promising results of pre-NDPP among diverse, underserved patients with elevated diabetes risks, but are limited by small sample size of the intervention group and no concurrently randomized control group. To address the research gap, we are now conducting an RCT to compare NDPP attendance and weight loss among diverse, predominately underserved participants who receive pre-NDPP versus direct enrollment into NDPP (usual care).

The primary hypothesis is that presessions improve NDPP engagement and weight loss, which will be confirmed if those randomized to pre-NDPP have better outcomes than those receiving usual care NDPP. A secondary analysis will examine whether only pre-NDPP participants who go on to NDPP benefit (vs no benefit for those declining NDPP), which would suggest that presessions screen for individuals likely to participate adequately, and thus benefit from, the NDPP. Screening via presessions may yet be an efficient population health strategy to (1) increase risk awareness for the estimated one-third of US adults with prediabetes [1], (2) offer informed decision-making, and (3) maximize performance-based reimbursement for suppliers, which supports access [42]. In either case, a brief group model may be optimal as (1) individual presessions appear cost-prohibitive, while longer sessions may also be more taxing on vulnerable populations; (2) uptake by NDPP suppliers likely depends on establishing efficacy in a low-cost, high-reach model; and (3) a key goal is supporting engagement in the yearlong NDPP for continued intervention, and thus increasing familiarity with its hour-long, group class format may be important.

If effective, greater uptake is expected if NDPP providers and payers can understand how pre-NDPP achieves an effect and whether their populations are likely to benefit, which will be addressed via mediation and moderation analyses. To prepare for future dissemination, we will also evaluate implementation factors, including cost of adding presessions to NDPP delivery and estimated RO. If effective, this approach may reduce disparities in NDPP effectiveness. It can also be disseminated to all NDPP providers, including more than 1700 suppliers [43], and may be supported by current NDPP payers such as Medicare, commercial insurers, and employer groups [24,44,45]. Thus, pre-NDPP has potential for high impact on the burden of T2D and related health disparities across the country.

Limitations

This study is powered on percent weight loss; more limited power is expected to evaluate pre-NDPP effectiveness among demographic subgroups and mediators and moderators. Although we do not anticipate difficulty meeting recruitment goals from provider referrals, we can identify additional eligible participants as needed from DH's EHR. Recruitment is limited to a single health care system, yet in a variety of different clinics and following CDC standards for NDPP delivery. Our study requires initial contact by phone to proceed with enrollment, thus we may be systematically missing especially under-resourced individuals who lack sufficient connectivity. Further, participants are initially assigned to pre-NDPP or usual care NDPP, yet some pre-NDPP participants may not attend the presession prior to beginning NDPP classes, which may result in a lower effect size than observed in our pilot study of outcomes following presession completion.

Lifestyle Coaches are necessarily unblinded to condition, thus introducing potential to bias their delivery of pre-NDPP and usual care NDPP interventions. While Lifestyle Coaches follow a standardized intervention manual for pre-NDPP, exact delivery of components like MI techniques may vary among presessions, as coaches must be responsive to the unique presentation of each group of pre-NDPP participants. Similarly, variability may occur for delivery of the NDPP curriculum across cohorts.

Economic analysis limitations include reliance on the literature-derived estimates of projected cost savings and the relationship between weight loss and T2D incidence. It is possible that there will be limited or no effect of pre-NDPP in an RCT, but pilot results are strong, and any clinically meaningful benefit may be worthwhile given pre-NDPP is expected to be a relatively low-resource intervention. Financial incentives may in fact lead to better outcomes than obtained in previous observational study but are only offered for study-related assessments and appropriately sized.

In summary, this RCT of pre-NDPP may lead to future dissemination of a scalable, evidence-based strategy to improve success of the NDPP, reduce disparities in NDPP effectiveness, and help prevent T2D across the country.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-reviewer report from NIH.
[PDF File (Adobe PDF File), 179 KB - resprot_v9i6e15499_app1.pdf]

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Abbreviations

CDC: Centers for Disease Control and Prevention
DH: Denver Health
EHR: electronic health record
GDM: gestational diabetes mellitus
ICC: intraclass correlation coefficient
ITT: intent-to-treat
MI: motivational interviewing
NDPP: National Diabetes Prevention Program
NHB: non-Hispanic black
NHW: non-Hispanic white
pre-NDPP: presession prior to the NDPP
RCT: randomized controlled trial
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
ROI: return on investment
SMART: Specific, Measurable, Achievable, Realistic, and Timebound
T2D: type 2 diabetes

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Protocol

Pragmatic Strategy Empowering Paramedics to Assess Low-Risk Trauma Patients With the Canadian C-Spine Rule and Selectively Transport Them Without Immobilization: Protocol for a Stepped-Wedge Cluster Randomized Trial

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Abstract

Background: Each year, half a million patients with a potential neck (c-spine) injury are transported to Ontario emergency departments (EDs). Less than 1.0% (1/100) of these patients have a neck bone fracture. Even less (1/200, 0.5%) have a spinal cord injury or nerve damage. Currently, paramedics transport all trauma victims (with or without an injury) by ambulance using a backboard, cervical collar, and head immobilizers. Importantly, prolonged immobilization is often unnecessary; it causes patient discomfort and pain, decreases community access to paramedics, contributes to ED crowding, and is very costly. We therefore developed the Canadian C-Spine Rule (CCR) for alert and stable trauma patients. This decision rule helps ED physicians and

triage nurses to safely and selectively remove immobilization, without x-rays and missed injury. We successfully taught Ottawa paramedics to use the CCR in the field in a single-center study.

Objective: This study aimed to improve patient care and health system efficiency and outcomes by allowing paramedics to assess eligible low-risk trauma patients with the CCR and selectively transport them without immobilization to the ED.

Methods: We propose a pragmatic stepped-wedge cluster randomized design with health economic evaluation, designed collaboratively with knowledge users. Our 36-month study will consist of a 12-month setup and training period (year 1), followed by the stepped-wedge trial (year 2) and a 12-month period for study completion, analyses, and knowledge translation. A total of 12 Ontario paramedic services of various sizes distributed across the province will be randomly allocated to one of three sequences. Paramedic services in each sequence will cross from the control condition (usual care) to the intervention condition (CCR implementation) at intervals of 3 months until all communities have crossed to the intervention. Data will be collected on all eligible patients in each paramedic service for a total duration of 12 months. A major strength of our design is that each community will have implemented the CCR by the end of the study.

Results: Interim results are expected in December 2019 and final results in 2020. If this multicenter trial is successful, we expect the Ontario Ministry of Health will recommend that paramedics evaluate all eligible patients with the CCR in the Province of Ontario.

Conclusions: We conservatively estimate that in Ontario, more than 60% of all eligible trauma patients (300,000 annually) could be transported safely and comfortably, without c-spine immobilization devices. This will significantly reduce patient pain and discomfort, paramedic intervention times, and ED length of stay, thereby improving access to paramedics and ED care. This could be achieved rapidly and with lower health care costs compared with current practices (possible cost saving of Can $36 [US $25] per immobilization or Can $10,656,000 [US $7,335,231] per year).

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International Registered Report Identifier (IRRID): DERR1-10.2196/16966

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KEYWORDS

cervical spine injury; Canadian C-Spine rule; immobilization; paramedic; trauma

Introduction

Background

Problem

Ontario paramedic services annually transport half a million patients with a potential neck (cervical/c-spine) injury from falls or motor vehicle collisions to local emergency departments (EDs). Of these patients, 95.0% (95/100) are alert and stable and at low risk of c-spine injury. Less than 1.0% (1/100) have a c-spine fracture, and even less (1/200, 0.5%) have a spinal cord injury. Spinal cord injuries result from moderate-to-severe blunt traumas and not from minor movements occurring during transport to hospital. Regardless, current paramedic practice is to transport all such trauma victims (with or without c-spine injury) by ambulance using backboards, collars, and head immobilizers. These patients stay fully immobilized until an ED bed is made available, sometimes for as long as 3 hours. This prolonged immobilization is often unnecessary and increases patient discomfort, contributes to ED crowding, prolongs paramedic intervention times, and adds a heavy financial burden to our health care system.

Why C-Spine Immobilization of Low-Risk Patients May Be Unwarranted

Not only is immobilization often unnecessary, but its potential for clinical adverse effects and discomfort are also well documented [1]. Chest straps used in immobilization can have a pulmonary-restrictive effect, even in healthy nonsmokers. Immobilization on a board leads to progressively worsening pain in the head, neck, and back area, often resulting in the necessity to perform diagnostic imaging on an otherwise normal spine in the ED. The presence of a c-spine immobilization collar has been associated with hyperextension, causing spinal cord injury in patients affected by ankylosing spondylitis. In addition, c-spine collars can cause neck vein compression and increased intracranial pressure for patients with head injury, difficulty swallowing, and local skin necrosis.

We have identified three systematic reviews relevant to c-spine immobilization. A review published by Abram and Bulstrode in 2010 (comprising 32 studies) suggested there was a growing body of evidence documenting the “risks and complications of routine spinal immobilization” and that there was a “possibility that immobilization could be contributing to mortality and morbidity in some patients” [1]. A more recent review by Sundstrom et al (220 studies) concluded that there is limited evidence supporting current c-spine immobilization practices and that large definitive randomized trials are lacking. It further concluded that the benefit of c-spine immobilization on neurological injury and spinal stability is uncertain and that there is a growing body of opinions against the use of c-spine collars [2]. The International Liaison Committee on Resuscitation (ILCOR) provides international guidelines on cardiac arrest and trauma resuscitation. In November 2015, ILCOR published a recommendation not to use routine application of c-spine collars for adults and children with blunt suspected traumatic c-spine injury (based on very low quality of evidence from 29 studies) [3].

Effect on Overburdened Paramedic Systems and Crowded Emergency Departments

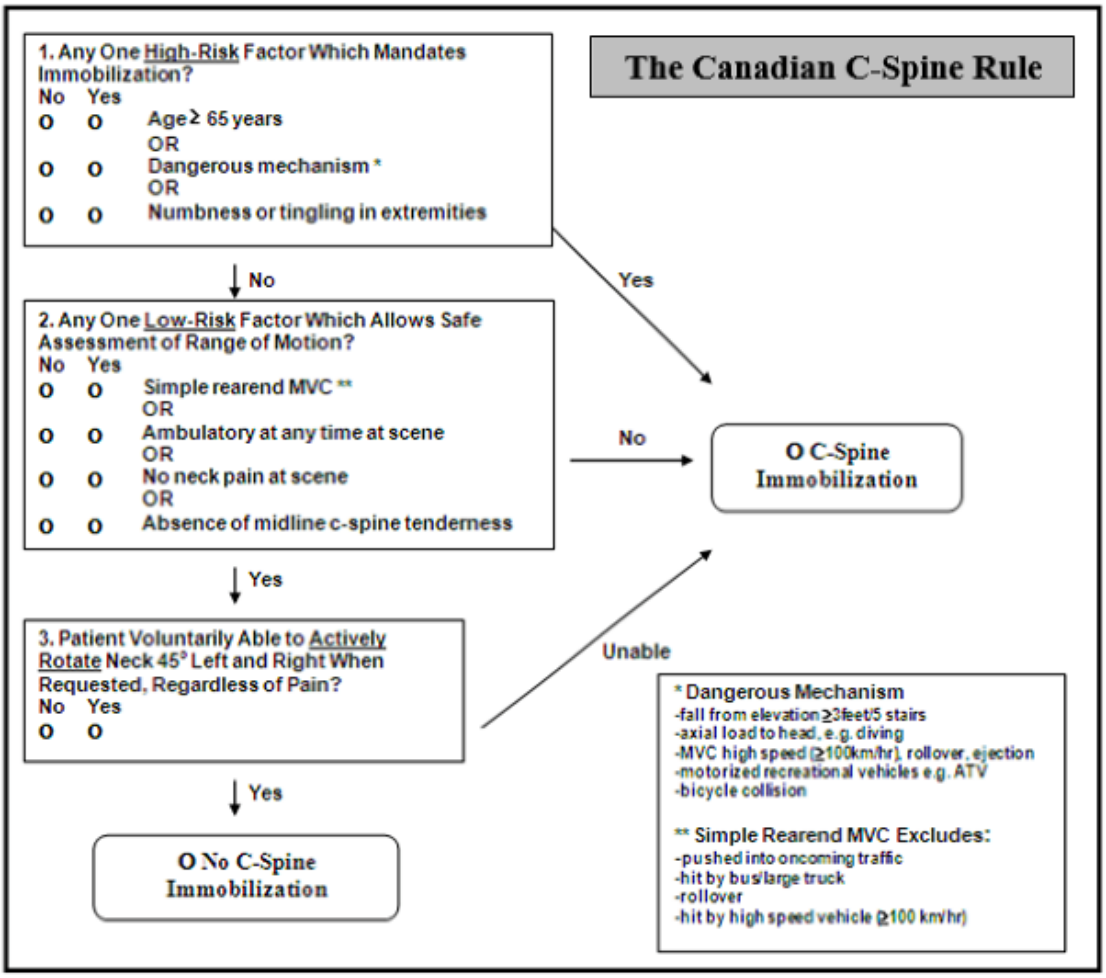
As trauma victims need to be seen rapidly at the hospital, paramedics are given only 15 to 20 min to evaluate and treat them in the field before transport. Even for minor trauma victims, c-spine immobilization takes more than 5 min to apply, or up to 30% of the allotted field time. Unlike minor trauma victims coming to the ED by their own means of transport and commonly triaged to the waiting room area, minor trauma victims immobilized and transported by paramedics may have to wait up to 3 hours until an ED stretcher becomes available, in turn holding up the paramedic crew who then become unavailable for the next community emergency. In 2013, the US National Association of Emergency Medical Services Physicians took a position in favor of a judicious immobilization strategy [4].

Once on an ED stretcher, it is not unusual for these patients to remain fully immobilized for several hours until physician assessment and c-spine diagnostic imaging can be performed and interpreted. This consumes valuable time for physicians, nurses, and radiology technicians and distracts them from other urgent responsibilities. These delays compound the burden of our crowded Canadian EDs in an era when they are under unprecedented pressures. The median length of stay for a patient evaluated in the stretcher area is approximately 8 to 12 hours, whereas similar minor trauma victims arriving without immobilization can be evaluated and discharged in less than 4 hours.

Canadian C-Spine Rule

We have derived, validated, and implemented the Canadian C-Spine Rule (CCR) to be used by physicians [5-7], triage nurses [8], and paramedics [9] in more than 40,000 alert and stable trauma patients. The CCR (Figure 1) directs that immobilization is unnecessary if the patient has no high-risk criteria, has at least one low-risk criterion, and can voluntarily rotate their neck 45° left and right. Physicians and nurses already use the CCR in the ED to safely remove immobilization devices without the need for imaging and with no documented adverse outcomes. We recently completed a pilot implementation study with Ottawa paramedics, where selective patients were transported without immobilization. We have recruited 3854 patients, and paramedics have identified all clinically significant injuries (100% sensitivity) without negative consequence when the CCR determined that immobilization was not required (68% specificity). Approximately 60% of immobilizations were avoided.

Figure 1. The Canadian C-Spine Rule adapted for use by paramedics.



C-Spine Evaluation in Children

The National Emergency X-Radiography Utilization Study (NEXUS) decision instrument for use in adults and children was validated in 2160 children aged 8 to 17 years and identified all significant injuries [10]. The CCR's performance was superior to that of the NEXUS decision instrument when prospectively compared in an adult population [6] but is yet to be implemented for use in children. A case-control study of children younger than 16 years with c-spine injuries identified 8 risk factors for significant injuries, 7 of which are included in the CCR [11].

On the basis of information provided by our paramedic stakeholders, we estimate that there are 4000 or more children aged 8 to 16 years transported with immobilization each year in Ontario. In a survey of physicians, 85% stated they would use the CCR if it were properly evaluated for use in the pediatric population [12].

Rationale for This Study

Minor trauma is very common, and these patients are usually transported to the ED by paramedics, but rarely do they have a fracture or spinal cord damage. Current immobilization and transport practice guidelines are not evidence-based, and there is a growing body of evidence testifying to the deleterious effects and consequences of this practice on patients, paramedic systems, EDs, and the health care system. We have successfully derived, validated, and implemented the CCR for use by physicians, nurses, and, more recently, by paramedics in a pilot project. Patient groups, paramedic stakeholders, ethics board members, and the Medical Advisory Committee for the Ontario Ministry of Health and long-term care Emergency Health Services Branch (EHSB) are all supportive of this multicenter implementation evaluation study. We now need a large pragmatic study to evaluate the feasibility, benefits, and safety of implementing the CCR in geographically and socially diverse prehospital communities. It is encouraging that most paramedic services would only participate in the study if we adopted a design that would guarantee, at some point, an opportunity for them to be assigned to the intervention arm and expand the scope of their paramedics' practice.

Objectives

The overall goals of this study are to improve patient care and health system efficiency and outcomes by allowing paramedics to assess eligible low-risk trauma patients with the CCR and selectively transport them *without* immobilization to the ED. We therefore sought to answer the following study question: Does allowing paramedics to assess selective low-risk trauma patients with the CCR and transporting them without immobilization result in *significant and immediate* health service benefits for patients, paramedic services, and EDs in a safe cost-effective manner?

Methods

Trial Design

The multicenter implementation of the CCR by paramedics is designed as a stepped-wedge cluster randomized trial with three sequences, involving a total of 13 Ontario paramedic services. Our 36-month study will consist of a 12-month setup and training period (year 1), followed by the stepped-wedge trial (year 2) and a 12-month period for study completion, analyses, and knowledge translation and exchange (see Table 1). Paramedic services in each sequence will cross from the control condition (usual care) to the intervention condition (CCR implementation) at intervals of 3 months until all communities have crossed to the intervention. Data will be collected on all eligible patients in each paramedic service for a total duration of 12 months.

Table 1. Diagram of the study and stepped-wedge design.

Year	Months 1-9	Months 10-12
Year 1	• Study set-up • ePlatform programming-paramedic data collection • Preparation of study material and site visits	Paramedic training
Year 2		
Sequence		
1 (4 sites)	• Months 1-3: Usual Care • Months 4-6: CCR • Months 7-9: CCR	CCR[a]
2 (4 sites)	• Months 1-3: Usual Care • Months 4-6: Usual Care • Months 7-9: CCR	CCR
3 (4 sites)	• Months 1-3: Usual Care • Months 4-6: Usual Care • Months 7-9: Usual Care	CCR
Year 3	• Months 1-6: Study completion; data linkage with IC/ES[b] • Months 7-9: Data cleaning; data analyses	Reports and manuscripts writing; KTE[c]

[a]CCR: Canadian C-Spine Rule.

[b]IC/ES: Institute for Clinical Evaluative Sciences.

[c]KTE: Knowledge Translation and Exchange.

Study Setting

The study will take place in the province of Ontario. Up to 12 new Ontario paramedic services will participate. Ottawa will also participate but only provide data for the pediatric cohort as the CCR has already been implemented within their practice. The 12 new paramedic services vary in terms of size, population served, and geographical location. Each paramedic service in Ontario is affiliated with a base hospital. There are eight regional base hospitals in Ontario that provide medical direction, leadership, and advice in the provision of prehospital emergency care. Although the base hospital programs will not be participating directly in the study as separate sites, they will be assisting with start-up, implementation, and follow-up.

Population

All consecutive, alert (able to follow commands), stable patients (normal vital signs) will be evaluated by the paramedics employed by a participating paramedic service for potential cervical spine injury after sustaining acute blunt trauma (within 48 hours). These are patients for whom standard Ontario prehospital trauma protocols usually require immobilization. As in prior CCR studies, patients will be excluded if they do not require immobilization as per the standard Ontario paramedic trauma protocol, have a Glasgow Coma Scale score of less than 15 or are intubated, or have unstable vital signs (systolic blood pressure <90 mm Hg; respiratory rate <10 or >24 breaths/min). Patients will also be excluded if their injury occurred more than 48 hours earlier, if they have penetrating trauma from a stabbing or a gunshot wound to the neck, acute paralysis, or known vertebral disease (specifically ankylosing spondylitis, rheumatoid arthritis, spinal stenosis, or previous cervical spine surgery), if they were referred from another hospital and transported between facilities, or if they are younger than 8 years.

Research Ethics Approval Process

The study protocol and all study-related documents (paramedic CCR and study data collection) have been approved by the Ottawa Health Sciences Network Research Ethics Board (OHSN-REB). The OHSN-REB has recently become a board of record for Clinical Trials Ontario. As a result, and because this is a multicenter study, the study protocol was submitted to the OHSN-REB through Clinical Trials Ontario. All participating sites that have existing agreements in place with Clinical Trials Ontario were included in the REB submission approval. We identified a local site investigator and helped coordinate REB submission, review, and approval for those sites that do not have agreements with Clinical Trials Ontario.

Consent and Permissions

We obtained a waiver of patient-informed consent from the OHSN-REB, Clinical Trials Ontario, and all other participating research ethics boards. This was the case in the previous multicenter prehospital validation of the CCR and the single-center prehospital implementation study. The study protocol has been reviewed by the Medical Advisory Committee for the Ontario Base Hospitals Group (MAC-OBHG). The Medical Advisory Committee provides advice to the EHSB of the Ontario Ministry of Health and Long-Term Care. Paramedics employed by paramedic services participating in the study will be allowed via a medical directive to use the CCR to evaluate eligible patients instead of the usual immobilization protocols. The medical directive was drafted by the MAC-OBHG and authorized by the EHSB for the duration of the study.

Paramedic Training

Paramedics will be trained in the use of the CCR before the start of the trial. We have conducted an Ottawa paramedic CCR implementation pilot study and have designed our training program to address barriers identified in the pilot. The training entails 1 hour of education: 30 min of self-review of a teaching video addressing the background and scientific development of the CCR and a 30-min in-class teaching video reviewing the specific steps involved in using the CCR, complete with a demonstration and question and answer period with a certified trainer. Paramedics will be *certified* to clear the cervical spine by medical directive if they have (1) successfully completed the initial training sessions and (2) successfully completed (score of ≥80%) a written quiz. Paramedics failing the written quiz would be required to attend a remedial session and review all wrong answers with their certified trainer. It should be noted that Ottawa paramedics all successfully completed their training.

During the study setup period (Table 1), each participating service will designate a local paramedic study champion. These individuals will be in close contact with staff at the study coordinating center and will receive further information about the study, methodology, and implementation of the CCR. These individuals will be heavily involved in delivering the study training material at their particular location and will serve as a first point of contact throughout the implementation. Paramedics with questions about specific aspects of the CCR or the application of the CCR for unusual scenarios will be able to communicate directly with a peer in an effort to promote adherence to the protocol. Paramedics will be encouraged to ask questions during the training sessions, speak directly with their study champion, add comments to study forms, or communicate with study staff via the study website or through social media. These questions and concerns will be compiled and distributed back to study champions to disseminate to local staff. Staff at the study coordinating center will regularly provide updates and reminders to study champions.

Intervention

The stepped-wedge trial will begin after paramedic training has been completed (see Table 1). During the usual care phase, paramedics will complete the CCR data collection form for all eligible patients but will continue to immobilize them all before transport to the receiving hospital. Once a community has crossed to the intervention CCR phase, paramedics will be permitted by a medical directive to implement the CCR. Paramedics will then transport selected patients without immobilization according to the CCR. Although following the medical directive will be mandatory for paramedics, they will be encouraged and allowed to immobilize patients if they are uncomfortable with the CCR's recommendation to not immobilize them.

Outcome Measures

The outcomes of interest are divided into three categories: measures of patient and health system benefit, measures of patient benefit, and measures of health system benefit. These were supported and ranked by patients and paramedic stakeholders.

Measures of Patient and Health System Benefit

The measure of patient and health system benefit included the proportion of patients transported with immobilization (primary outcome).

Measures of Patient Benefit

The measures of patient benefit included the following:

1. Proportion of patients feeling comfortable (score ≤4 on a 10-point Likert scale; coprimary outcome)
2. Proportion of patients with a pain score ≤4 on a 10-point Likert scale upon transfer of care to the ED
3. Time from paramedic arrival to ED discharge or admission to hospital
4. Patient radiation exposure (in millisieverts) from diagnostic imaging of the spine
5. Number of skin pressure injuries
6. Number of missed clinically important c-spine injuries. A clinically important c-spine injury includes any injury other than the following defined unimportant injuries that require neither specialized treatment nor follow-up: isolated avulsion fracture of osteophyte, isolated fracture of the transverse process not involving the body or facet joint, isolated fracture of the spinous process not involving the lamina, isolated simple compression fracture less than 25% of body height.

Measures of Health System Benefit

The measures of health system benefit included the following:

1. Time spent in the field by paramedics before arrival to hospital
2. Time spent in the hospital by paramedics before transfer of care to the ED team
3. ED length of stay until discharge or admission to hospital
4. Number of subsequent ED visits or admission to hospital within 30 days of ED discharge
5. Number of subsequent clinic/family physician visits within 30 days of ED discharge
6. Frequency of c-spine diagnostic imaging performed within 30 days of ED discharge
7. Incremental cost per 1 immobilization avoided (including cost of training, equipment, paramedic time, ED utilization, diagnostic imaging, and follow-up visits)

Data Collection and Data Sources

Once training of paramedic staff has been completed, paramedics will begin evaluating eligible patients with the CCR. Each time an eligible patient is assessed using the CCR, the paramedic treating that patient will complete and submit an electronic CCR. The paramedic will also record patient-reported comfort level and pain level on this form. Staff at the study coordinating center will receive the electronic paramedic-completed CCR and a copy of the electronic paramedic care record (ePCR). Study staff will review the paramedic documentation to assess compliance with the study protocol and application of the CCR. Information on patient age, gender, mechanism of injury, field time, offload time, and immobilization status are contained in the ePCR and will be recorded from there.

We will link the information obtained from paramedic care records to provincial administrative databases housed at the Institute for Clinical Evaluative Sciences (IC/ES). This linkage will allow us to obtain information related to the initial ED visit, c-spine diagnostic imaging, hospitalization, and subsequent ED or clinic or family physician visits within 30 days of injury.

Confidentiality and Data Linkage

Paramedics will evaluate eligible patients using the CCR. They will complete an electronic form that will capture information on the elements of the CCR and pain, patient comfort, and paramedic comfort with using the CCR. The electronic form will not include any information that can identify a patient. Upon receipt of the electronic form, study staff will assign a unique study number. We will also receive the corresponding paramedic documentation electronically that will allow us to capture the remainder of the prehospital data required. The paramedic documentation will also be transmitted electronically, stripped of patient identifiers.

To link the prehospital information with the data housed at IC/ES, we will need to maintain a list of eligible enrolled patients, including first name, last name, date of birth, sex, postal code, and health card number (where available). This list will be generated and maintained by staff at each base hospital, or paramedic service if base hospital staff are unable to access this information. The information will be stored in a password-protected, encrypted spreadsheet. When this information is required by IC/ES for linkage purposes, it will be transmitted securely according to their protocols. The linked information that we receive back from IC/ES will be stripped of personal identifiers before we receive it. All paper study files will be stored in locked filing cabinets in a locked office. All electronic files will be stored on limited-access network folders that are backed up regularly. Any information shared with the study committees will not include any identifiable information.

Data Management

Data will be entered centrally at the study coordinating center by trained study staff. Staff will receive training on the study protocol, definition of data elements, application of the CCR, and elements of the ePCR. A complete list of data points and definitions will be compiled and included in a study manual for reference. The data will be entered electronically. The data entry screens will resemble the paper study forms approved by the steering committee. Where possible, the study database will be designed to ensure that each given variable can only be entered in a certain format, thereby limiting the number of errors in data entry. A certain percentage of cases will be entered in duplicate to ensure accuracy. A small percentage of cases (10%) will also be pulled and compared with the source documents to independently verify the accuracy of the data. We will regularly run range and logic checks to previously entered data to locate and fix any errors or discrepancies in the data set. We will work closely with the staff at the participating base hospitals and our local paramedic study champions to promptly identify and locate missing data. Queries about particular cases and situations will be flagged for review by the research coordinator. If the research coordinator is unable to determine the appropriate course of action, the flagged issue will be brought to the attention of the principal investigator who will review the issue and advise. Any resulting changes to data definitions will be noted and dated in the study manual.

The study database will be designed and located on servers housed at the Ottawa Hospital Research Institute. All electronic study documents will be saved on network folders with limited access. The network folders are backed up nightly by the Ottawa Hospital Research Network Information Technology team. Paper files will be stored in locked cabinets in locked offices.

Auditing

We plan to conduct regular site visits with all participating sites. The initial visit will be primarily to go over training material with local study staff, go over study requirements, and ensure local study staff have all the necessary study documentation. The intervention duration is 12 months. We will conduct one subsequent visit to each site during the invention phase to ensure that study documentation is accurate and up to date, all study material is accurate and up to date, and local study procedures are being conducted as per the study protocol. If concerns are noted, we will work individually with each site to address the concern and rectify the situation.

Sample Size

Our sample size for this study is determined mainly by pragmatic considerations: we need a large number of sites from across Ontario to evaluate the safety and generalizability of the implementation in this multicenter setting while accounting for between-site differences such as size and setting. Power calculations were carried out for the stepped-wedge trial. Using data from a previous study in these communities, we expect approximately 600 patients per paramedic service per year (or 150 patients per 3-month time interval). A total of 12 paramedic services (7200 patients in total) evaluated across four time intervals in a stepped-wedge design will provide adequate power to detect minimally important differences of 10% in our two coprimary outcomes using two-sided tests at the 2.5% level of significance. In particular, for our *primary outcome*, we will have greater than 99.9% power to detect a minimally important absolute reduction of 10% in the proportion of patients immobilized, assuming a control arm proportion of 1. For our *coprimary outcome*, we will have 80% power to detect a minimally important increase of 10% in the proportion of patients feeling comfortable assuming a conservative control arm proportion of 0.5. In these calculations, we have assumed a commonly used within-period intracluster correlation coefficient of 0.05, and an exponential decay with a decay parameter of 0.85 (ie, a 15% decay per period).

Recruitment Feasibility

On the basis of the volume of immobilized patients transported in each of the 12 new proposed participating centers, we expect there could be 8129 eligible cases over the proposed 12-month evaluative period (required sample size is 7200). We are confident that the required sample size can be obtained with the participation of the proposed centers, and we have accounted for unlikely attrition in our study design and sample size calculation.

We also plan to employ a number of strategies during the enrollment phase of the study to meet our recruitment goals. We have specifically approached Ontario paramedic services that have previously and successfully participated in prehospital research. These paramedics will be familiar with completing specific study paperwork. We will be approaching the vendors of the software used by paramedic services to develop a study form that is easy to access, complete, and submit. We will employ a local study champion at each paramedic service who will be accessible to the frontline paramedics to answer questions, deliver updates and reminders, and provide feedback regarding certain cases or applications of the CCR. Finally, we will develop a study website and utilize social media to keep the participating paramedic services and their staff engaged in the study.

Randomization and Allocation

The 12 new participating paramedic services will be randomized using the technique of covariate constrained allocation to protect against chance imbalances in the following prognostic factors: catchment area (km^2), number of immobilizations per month, average response time, and staff makeup (advanced care paramedics and primary care paramedics). Owing to the relatively small number of allocation units, it is particularly important to use an allocation technique that minimizes the risk of chance imbalances. In the stepped-wedge design, randomization is with respect to the timing of implementation of the intervention. Effective randomization is essential to protect the internal validity of the trial, including the ability to obtain a valid estimate of any secular trend and a valid estimate of the intervention effect. Covariate constrained allocation was selected as it was found to be superior to simple stratification and matching in a recent simulation study [13]. In covariate constrained allocation, all possible allocations of sites will be considered (a total of 34,650 possible allocations) and those that are acceptable, in that they meet a set of balance constraints, will be identified. One of the allocations will then be randomly selected from among the set of acceptable allocations. To protect the validity of the randomization, the number of times that any given pair of sites receives the same allocation will be counted, and constraints will be relaxed if the design is found to be overly constrained. The allocation will be performed using a SAS macro developed for this purpose, by an independent statistician not associated with the trial [14]. Allocations will be securely kept by the independent statistician and will be concealed from the study investigators and all participating sites until 1 month before the allocated start time of a particular site.

Statistical Analyses

Analyses will be conducted at the level of the individual patient using generalized linear mixed-effects regression, with random effects to account for clustering by paramedic service and over time and fixed effects for treatment and time interval to account for the stepped-wedge design. The analysis will adjust for sex, age, and the need for immobilization according to the CCR. The primary and coprimary outcomes will be analyzed using binomial distribution with identity, log, or logit link, and the effect of intervention will be expressed as absolute differences, relative risk, or odds ratios with 97.5% CIs. Secondary outcomes will be similarly analyzed using binomial distribution and identity or logit link for dichotomous variables, normal distribution and identity link after log transformation or gamma distribution and log link for continuous variables with a skewed distribution, or Poisson or negative binomial distribution with log link for count variables. The effect of the intervention on each secondary outcome will be described using absolute difference, relative risk, or odds ratio with 95% CI. Subgroup analyses (described in the following sections) will be conducted by including interactions with time interval and treatment in the regression model.

Our *health economist* will perform a cost-effectiveness analysis from the perspective of the Ministry of Health and Long-Term Care. Trial data will be used to populate the relative costs and outcomes of the use of the CCR by paramedics with usual care (100% immobilization). Resource use will be collected during the trial and obtained from IC/ES, whereas unit costs will be obtained from appropriate Canadian sources, such as Schedule of Benefits for Physician Services. The total cost for each patient includes the costs of the intervention and costs of health services, including the follow-up period of 30 days post-ED discharge. The cost of intervention covers the cost of training and operation. Costs of operating paramedic services include personnel cost (eg, salaries and employee benefits), service cost (eg, fuel and maintenance), medical supplies (eg, an onboard liquid oxygen system, medications, and single-use patient care supplies). The costs of health care services will be obtained from IC/ES and will be estimated by multiplying the unit costs by the volume of health care used. We will use mixed-effects regression analyses to estimate the difference in expected health care costs and outcomes between the intervention and control groups. The incremental cost-effectiveness ratio will be estimated by dividing a difference in cost by a difference in the number of immobilizations. The 95% CI will be calculated using a nonparametric bootstrapping method. Results from the bootstrapping exercise will also be used to depict a cost-effectiveness acceptability curve (CEAC), which links the probability of a treatment being cost-effective to a range of potential threshold values (lambda) that the health system may be willing to pay for an additional unit of effect [15]. A CEAC is a graphical representation of the probability that the CCR may be cost-effective given the alternate dollar values placed on an outcome. This will allow estimation of the probability that the CCR can be considered cost-effective given the available data. In addition, sensitivity analysis will be undertaken to examine the effect of conducting a complete case-only analysis and of varying the cost of the intervention. We will also conduct a budget impact analysis to estimate the financial consequences of implementing the CCR by paramedics in Ontario. All analyses will be conducted using STATA version 13.0 and Microsoft Excel and Visual Basic for Applications.

Prespecified subgroup analyses will be conducted to examine the differential effects (possible inequity) of the intervention on the following groups, defined by the following:

1. Sex
2. Language barrier present vs not present (collected by paramedics on data collection form)
3. Long transport times (longer vs shorter than 15 min)

4. Age (adult ≥16 years vs children <16 years)
5. Socioeconomic status and education level (IC/ES data)
6. Type of backboard used (full board, open-back scoop, or trunk and neck Kendrick extrication device)

Results

We received study funding in 2015 and institutional research ethics approval in 2016. Recruitment and data collection took place between March 2017 and May 2018 and included a total of 6049 patients at the time of submission. Data linkage and analyses are under way, and the final results are expected in the spring of 2020. If this multicenter trial is successful, we expect that the Ontario Ministry of Health will recommend that paramedics evaluate all eligible patients with the CCR in the Province of Ontario.

Discussion

We conservatively estimate that in Ontario, more than 60% of all eligible trauma patients (300,000 annually) could be transported safely and comfortably, without c-spine immobilization devices. This will significantly reduce patient pain and discomfort, paramedic intervention times, and ED length of stay, thereby improving access to paramedic and ED care. This could be achieved rapidly and with lower health care costs compared with current practices (possible cost saving of Can $36 [US $25] per immobilization or Can $10,656,000 [US $7,335,231] per year).

In addition, this project will facilitate a new paradigm in prehospital research by integrating paramedics and patients actively into the research and knowledge translation process. It will offer the added benefits of consolidating a network of paramedic research partners and of facilitating future collaborative projects. It will also make innovative use of data provided by the IC/ES to streamline and decrease the cost of conducting prehospital research, and, with the help of our new partners, foster collaborative efforts to measure and possibly correct health inequities in prehospital care. Finally, this project could lead to the use of the CCR by paramedics from across Ontario and Canada and to immediate health care benefits/savings on a national scale.

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Authors' Contributions

CV and IS completed the foundational work using the CCR and secured funding for this study. CV played a leadership role with all aspects of the study and chaired the steering committee, whereas MC drafted the study protocol and coordinated and oversaw all aspects of study implementation, budget, and monitoring. All authors significantly contributed to the scientific merit and design of the study. Specifically, MT and KT provided input on design, sample size requirement, and proposed statistical and cost-analyses; EH provided insight and guidance with the choice and ranking of study outcomes as a person with lived experience; BM chaired the paramedic committee, in addition to PK and SC who provided guidance with study operations and implementation; DF, JB, IG, and TR provided methodological support and expertise; LC provided expertise with patient safety; PT offered guidance on measuring patient inequities; RF contributed expertise with large database linking and analyses; AP, MO, and CM contributed to the pediatric implementation of the CCR; SS provided knowledge translation expertise; PR offered guidance on measuring sex-related inequities; DP and SD offered guidance on measuring language-related inequities, and SM offered expertise with the Clinical Trials Ontario ethics application process. All authors have read and contributed to this protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review and Responses to reviewers.
[PDF File (Adobe PDF File), 210 KB - resprot_v9i6e16966_app1.pdf]

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Abbreviations

CCR: Canadian C-Spine Rule
CEAC: cost-effectiveness acceptability curve
ED: emergency department
EHSB: Emergency Health Services Branch
ePCR: electronic paramedic care record
IC/ES: Institute for Clinical Evaluative Sciences
ILCOR: International Liaison Committee on Resuscitation
KTE: Knowledge Translation and Exchange
MAC-OBHG: Medical Advisory Committee for the Ontario Base Hospitals Group
NEXUS: National Emergency X-Radiography Utilization Study
OHSN-REB: Ottawa Health Sciences Network Research Ethics Board

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Protocol

Simulation-Based Education for Staff Managing Aggression and Externalizing Behaviors in Children With Autism Spectrum Disorder in the Hospital Setting: Pilot and Feasibility Study Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: Children with autism spectrum disorder (ASD) frequently demonstrate aggression and externalizing behaviors in the acute care hospital environment. Pediatric acute care nursing staff are often not trained in managing aggression and, in particular, lack confidence in preventing and managing externalizing behaviors in children with ASD. High-fidelity simulation exercises will be used in this study to provide deliberate practice for acute care pediatric nursing staff in the management of aggressive and externalizing behaviors.

Objective: The purpose of this study is to conduct a pilot and feasibility cluster randomized controlled trial (RCT) to evaluate the effectiveness of simulation-based education for staff in managing aggression and externalizing behaviors of children with ASD in the hospital setting.

Methods: This study has a mixed design, with between-group and within-participant comparisons to explore the acceptability and feasibility of delivering a large-scale cluster RCT. The trial process, including recruitment, completion rates, contamination, and completion of outcome measures, will be assessed and reported as percentages. This study will assess the acceptability of the simulation-based training format for two scenarios involving an adolescent with autism, with or without intellectual disability, who displays aggressive and externalizing behaviors and the resulting change in confidence in managing clinical aggression. Two pediatric wards of similar size and patient complexity will be selected to participate in the study; they will be randomized to receive either simulation-based education plus web-based educational materials or the web-based educational materials only. Change in confidence will be assessed using pre- and posttraining surveys for bedside nursing staff exposed to the training and the control group who will receive the web-based training materials. Knowledge retention 3 months posttraining, as well as continued confidence and exposure to clinical aggression, will be assessed via surveys. Changes in confidence and competence will be compared statistically with the chi-square test using before-and-after data to compare the proportion of those who have high confidence between the two arms at baseline and at follow-up. The simulation-based education will be recorded with trained

assessors reviewing participants' abilities to de-escalate aggressive behaviors using a validated tool. This data will be analyzed using mean values and SDs to understand the variation in performance of individuals who undertake the training. Data from each participating ward will be collected during each shift for the duration of the study to assess the number of aggressive incidents and successful de-escalation for patients with ASD. Total change in Code Grey activations will also be assessed, with both datasets analyzed using descriptive statistics.

Results: This study gained ethical approval from The Royal Children's Hospital Melbourne Human Research Ethics Committee (HREC) on November 1, 2019 (HREC reference number: 56684). Data collection was completed in February 2020. Data analysis is due to commence with results anticipated by August 2020.

Conclusions: We hypothesize that this study is feasible to be conducted as a cluster RCT and that simulation-based training will be acceptable for acute care pediatric nurses. We anticipate that the intervention ward will have increased confidence in managing clinical aggression in children with ASD immediately and up to 3 months posttraining.

Trial Registration: Australian New Zealand Clinical Trials Registry (ANZCTR) ACTRN12620000139976; http://www.ANZCTR.org.au/ACTRN12620000139976.aspx

International Registered Report Identifier (IRRID): DERR1-10.2196/18105

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KEYWORDS

feasibility studies; autism spectrum disorder; intellectual disability; high-fidelity simulation training; pediatric nursing; child; adolescent; aggression

Introduction

Background and Rationale

Autism spectrum disorder (ASD), a neurodevelopmental disorder identified in childhood, is characterized by persistent deficits in social communication and social interaction across multiple contexts and restricted, repetitive patterns of behavior or interests [1]. Children diagnosed with ASD, with or without an intellectual disability, have an increased risk of hospitalization [2-5]. They also have longer and more frequent outpatient visits and medications prescribed than children in general [6]. Intellectual disability, one of the most prevalent comorbidities occurring in approximately 40%-70% of individuals with ASD [7-9], has been associated with greater autism symptomology with increased difficulties in communication and social functioning [10].

Exposure to the hospital environment can provide a sensory overload to children with ASD as it is often noisy and brightly lit, with people moving quickly, many unfamiliar people, and long wait times [11]. The surroundings are unfamiliar and usual home routines are not able to be maintained. The hospital environment necessitates that children must communicate with many more people, mostly unfamiliar, than usual. This is particularly challenging and stressful for children with ASD as they innately prefer less social interaction and have more difficulty identifying social cues and understanding the expressed emotions of others. Externalizing behaviors are common in children with ASD when exposed to these stressors and can result in difficult or delayed treatment, increased anxiety for the parent and child, prolonged procedure times, increased health care costs, and poorer health outcomes [2,6,11,12].

The Code Grey procedure is one of a series of emergency response codes used in some Australian hospitals. Code Grey refers to *unarmed aggression* and is called when an individual fails to respond to initial defusing mechanisms undertaken by staff [13]. At The Royal Children's Hospital (RCH) Melbourne, the numbers of Code Grey activations are rising each year. In 2016, there were 611 recorded Code Grey activations, 1050 in 2018, and 1682 in 2019. In 2016-2017, 36% of Code Grey activations were due to aggression demonstrated by children and young people with ASD, with or without an intellectual disability [14].

Need for a Trial

Staff training programs designed to teach best practice principles in the management of clinical aggression in pediatric acute care settings is warranted; however, evidence on training effects in general hospital settings is scant [15]. There are a number of reviews of aggression management training programs in psychiatric and mental health settings [16,17]; however, the results cannot be generalized to the acute setting or further extrapolated to the pediatric setting due to the different types of care provided in each facility and prior training of staff [18,19]. In addition, aggression management training programs designed for nursing staff working with children with neurodisabilities are rarely described in the literature. Simulation training may be an effective educational tool to practice de-escalation skills in a high-fidelity situation. Simulation-based education for communication skills has been shown to improve patient safety in a number of studies [20-22]. There is a paucity of literature in the use of simulation-based education to teach de-escalation communication techniques to staff working with children and young people, particularly those with ASD, in the acute care setting.

Choice of Comparator

A purpose-designed and purpose-built web-based learning package for working with children and young people with ASD and aggression or externalizing behaviors was chosen as the comparator. An online learning package was chosen as it is convenient and flexible in time to complete, yet provides consistent information and allows self-paced learning. The online resource includes an opportunity for learner-determined

revision of concepts, promotion of active and independent learning, and ability to link to and explore relevant resources.

Study Purpose and Trial Design

The purpose of this study is to conduct a pilot and feasibility cluster randomized controlled trial (RCT) to evaluate the effectiveness of simulation-based education for staff in managing aggression and externalizing behaviors of children with ASD in the hospital setting.

This study has a mixed design, with between-group and within-participant comparisons to explore the acceptability and feasibility of delivering a large-scale cluster RCT and to assess trial processes, including recruitment, completion rates, contamination, and outcome measures. Randomization of two hospital wards will be performed with 1:1 sample size per cluster.

Study Objectives

Primary Objective

The study objectives are to conduct a pilot and feasibility study and assess features of the acceptability and feasibility of our pilot design.

Population, Intervention, and Comparator

Our study population will include clinical nurses working in an acute care pediatric hospital. The study intervention will be comprised of simulation-based education plus web-based education resources on the management of clinical aggression and externalizing behaviors in children with ASD, with or without an intellectual disability. The study comparator will be web-based educational materials on the management of clinical aggression and externalizing behaviors in children with autism.

Outcomes

The following criteria will have to be met to indicate that an RCT is feasible and acceptable as planned:

1. Randomization: more than 10% recruitment rate from ward staff. A total of 160 staff members from the two selected wards will be eligible to participate in the study. We aim to recruit 10 staff members to each arm of the study.
2. Completion: less than 20% attrition rate with survey completion rate of at least 80%; focus group participation rate of at least 50% of total participants.
3. Acceptability: high acceptability of the intervention among participants as indicated by 80% of scores being 4 (good) out of 5 or higher in survey data.
4. Data collection: follow-up survey response rate of at least 30% with acceptability and confidence levels maintained; ward data-collection rate of at least 80% of total shifts during study time in each ward.
5. Low contamination from intervention participants as evidenced by participant report.

Secondary Objectives

The secondary objectives and their outcomes are as follows:

1. Confidence and competence: 80% of participants reporting increased confidence levels and positive qualitative comments.
2. Data collection: 80% reporting of the number of Code Grey activations and the number of successful de-escalation episodes not requiring a Code Grey activation with description of context and outcome for each incident; participant use of de-escalation skills during simulations using the English Modified version of the De-escalating Aggressive Behaviour Scale (EMDABS).

Summary

In summary, the aim of this study is to conduct a pilot and feasibility cluster RCT to evaluate the effectiveness of simulation-based education for acute care hospital staff in managing aggression and externalizing behaviors of children with ASD. We hypothesize that a multisite cluster RCT to evaluate this training format is feasible.

Methods

Participants, Interventions, and Outcomes

Study Setting

The study setting is a tertiary pediatric hospital, the RCH Melbourne, Australia. Recruitment will be performed from nursing staff from one general medical ward and one general surgical ward, both of similar size and patient complexity. Hospital data indicate that children and young people with autism, with or without intellectual disability, are admitted with similar frequency to these wards. The two included wards also experience similar numbers of aggressive incidents per year requiring a hospital Code Grey response.

Eligibility Criteria

Clinical nurses who work in the general medical and surgical wards will be invited to participate in the study. Eligible nurses will be those who are responsible for providing direct clinical care for ward patients. Nurses from these wards are excluded if they are not responsible for direct patient care (eg, care coordinators, advanced practice nurses, and nurses in charge of the shift).

Interventions

Overview

The training intervention will consist of two components:

1. A web-based learning package, developed using Articulate software (Articulate Global), for the management of aggression and externalizing behaviors in children and young people with autism, with or without intellectual disability, in the hospital setting as prereading.
2. Prereading will be followed by a 1.5-hour simulation-based group education session to manage aggression and externalizing behaviors in an adolescent with autism; this will include two separate simulation exercises, each followed by a facilitated reflective debrief, which explores what the participants did well, what the challenges were, and what they will do differently next time. The first scenario involves an adolescent with autism and aggressive and externalizing behaviors. The second scenario increases in complexity and involves a nonverbal adolescent who has autism and intellectual disability who also demonstrates

aggressive and externalizing behaviors. The training will be conducted in the Simulation Centre, conducted by the Simulation Faculty and Code Grey Coordinator, with an actor playing the role of the patient. The parent role in each of the scenarios will be played by a member of the Simulation Faculty. The simulation exercises will be recorded using Sportstec (also known as Studiocode) software.

Web-Based Education: Comparator

A web-based learning package is being developed using Articulate software. Content will be written by a study investigator with significant experience working with children with ASD and intellectual disability and their families. The content will be reviewed by autism experts within the Department of Neurodevelopment and Disability, RCH; the Murdoch Children's Research Institute; and the Department of Paediatrics, University of Melbourne. A consumer representative will also review the content. Modifications will be made from the feedback received. The content will be succinct and will be designed for the learner to complete within 30 minutes. A small number of short multiple-choice questions will be included in the education package to test understanding and application of knowledge.

Simulation-Based Education: Training Intervention

A 1.5-hour simulation-based education session, focusing on managing aggression and externalizing behaviors exhibited by a young person with autism in the inpatient setting, is being developed by the study investigators in conjunction with the Simulation Faculty. The RCH Simulation Program curriculum and simulation sessions are designed according to the concepts described by Dieckmann et al [23], utilizing the debriefing framework by Rudolph et al [24]. The simulation scenarios will be reviewed and trialed by members of the Simulation Faculty, with modifications to improve the learning experience made prior to conducting the sessions. The training sessions will be delivered by the Simulation Faculty in the Simulation Centre with assistance from the Code Grey Coordinator. Two separate simulation exercises will be delivered within this 1.5-hour simulation training session.

Participants will be required to complete pre- and posttraining surveys and a follow-up survey 3 months posttraining. Each participant will be asked to create a unique identifier for use in all the surveys, using the first three letters of their first street name followed by the first two numbers of their mother's birth date.

Nurses randomized in the ward to receive the training intervention will receive the simulation-based training intervention plus web-based training resources. They will be sent an email with instructions on how to access the surveys and the training and the requirements of the study. Participants in this arm will be instructed to complete the web-based training prior to attending the simulation-based education.

Nurses working in the ward randomized to receive the comparator will receive the web-based training resources only. They also will receive an email outlining the requirements of the study with links to the surveys and the training materials.

The intervention arm will be sent an electronic link to reserve their place in one of two simulation training sessions. Each session will have capacity for 5 participants. The comparator arm will be sent a link to access the web-based training. It is expected that the participants will confirm with their Nurse Unit Manager (NUM) whether they are able to be released from ward duties for the duration of the training. Participants will also be instructed via email to complete the pretraining survey prior to commencing the training. The time commitment to complete the web-based education will be 30 minutes, with the simulation education involving a 1.5-hour commitment within working hours.

Staff will complete the simulation training during double staff time; during this time, there are more nurses available to attend training while not compromising patient care. The principal investigator will liaise with the relevant nurse education team members to ensure that nurses have the capacity to complete the simulation-based training and the online training during double staff time. This is the time that education is often scheduled for nurses working on wards. The training was scheduled for late Spring 2019, when it was anticipated that ward activity levels would be lower than during the winter period. The nursing executive and the NUMs of the study wards have agreed to support this study, as have the RCH Simulation Program and the Department of Neurodevelopment and Disability.

Training Intervention

A researcher who is not involved with this study will explain the study design to the participants prior to commencement of the prebrief to the simulation training. The researcher will explain that participants will complete a short electronic survey at the completion of the simulation education program. The survey will be completed anonymously with no personal details recorded. The researcher will explain that the simulation sessions will be recorded to enable researchers to view the recordings at a later date to assess the impact of the training on participants' performances in de-escalating aggressive situations. Only the study investigators will have access to the recordings, which will be deleted once analyzed. The assessment of the recordings will not include any participant identification details. Participants in the simulation-based education intervention will be asked to maintain and hold confidential all information regarding the performance of specific individuals and the details of the specific scenarios. The researcher will check that all participants have completed the pretraining survey. For those who have not, time will be provided for them to complete it in a nearby room with computer access prior to commencing the simulation training.

The Simulation Faculty member facilitating the simulation session will then brief the participants on the objectives of the two simulation exercises. The roles and expectations of both the participants and the instructors will be discussed. The structure of the session and the purpose of the postsimulation debrief will be explained. The participants will be informed that the same professional actor will play the role of the patient in each of the simulation exercises. The second simulation scenario will be more complex than the first, giving the participants the

opportunity to extend their skills and build on knowledge learned from the first scenario. Participants will be asked to volunteer for the different roles in each simulation scenario. The Simulation Faculty technologist will orient the participants to the Simulation Centre and simulation equipment prior to commencement of the first simulation scenario.

Outcomes

The primary and secondary outcome measures for assessing the acceptability and feasibility of conducting the training intervention are detailed in the Study Objectives section above.

Two simulation scenarios involving an adolescent with autism, intellectual disability, aggression, and externalizing behaviors will be assessed. Study participants will be asked to complete three surveys: a pretraining survey, a posttraining survey, and a follow-up survey.

The purpose of the pretraining survey is to determine participants' self-perceptions of confidence and competence in managing aggressive and externalizing behaviors in a young person with autism. The pretraining survey incorporates the Confidence in Coping with Patient Aggression Instrument [25], short-answer questions, and free text to assess self-perceived levels of confidence and competence in managing aggression in a young person with autism and intellectual disability as well as acceptability of the simulation- and web-based education. The Confidence in Coping with Patient Aggression Instrument is a one-dimensional, 10-item instrument demonstrating a high degree of internal consistency (Cronbach alpha=.92) and precision (SE 1.5) [25].

The purpose of the posttraining survey is to determine if the training had an impact on participants' self-perceptions of confidence and competence in managing aggression and externalizing behaviors in a young person with autism. The posttraining survey also incorporates the Confidence in Coping with Patient Aggression Instrument [25], short-answer questions, and free text to assess self-perceived levels of confidence and competence in managing aggression and externalizing behaviors in a young person with autism and intellectual disability as well as acceptability of the simulation- and web-based education. The purpose of the follow-up survey is to determine if the training had a continued impact on participants' self-perceptions of confidence and competence in managing aggression in young people with ASD.

Each of the simulation training scenarios will be recorded. The recordings will be analyzed by two clinicians, who are experienced in clinical aggression management, using the EMDABS to assess the influence the training had on participants' performances in de-escalating aggressive situations. A study investigator will train the clinicians in the use of the tool using the training materials provided by Mavandadi et al [26], providing a clear definition of terms and items and the scoring system. Both clinicians will use the tool on a recording of a practice simulation involving only members of the Simulation Faculty and the study investigator and will discuss decision-making processes to ensure consistency and interrater reliability [27].

Knowledge retention by study participants 3 months posttraining, as well as continued confidence and exposure to clinical aggression, will be assessed via surveys similar in content to the pre- and posttraining surveys. Results from the pretraining, posttraining, and follow-up surveys will be linked using the unique identifiers that the participants created prior to completing the pretraining survey.

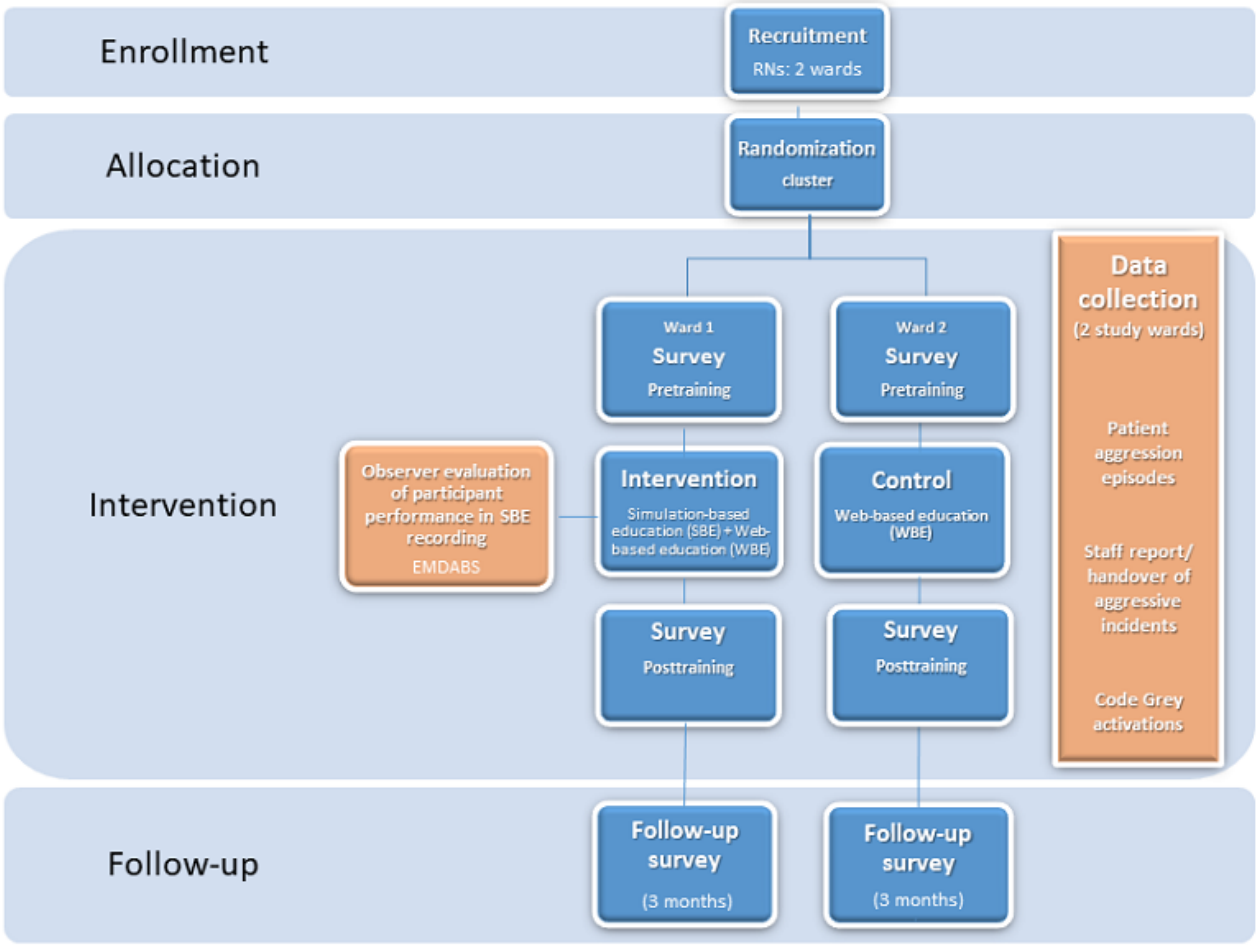
Data will be collected at the ward level at each shift for the duration of the study to assess the number of aggressive incidents and rates of successful de-escalations for patients with ASD. A short survey will be emailed to Associate Nurse Unit Managers (ANUMs), as well as to any additional nurses who acted in the roles of ANUM or *nurse in charge of shift*, at the completion of the study to explore the enablers and barriers to collecting this data.

Total change in Code Grey activations will also be assessed in total and at the ward level. We will also record rates of data collection.

Participant Timeline

Figure 1 shows the study design flowchart, including participant recruitment and allocation, intervention components, and follow-up.

Figure 1. Study design. EMDABS: English Modified version of the De-escalating Aggressive Behaviours Scale; RN: registered nurse.



Sample Size

We plan to recruit 10 staff members to each arm of the study. This sample size, based on our experiences in an earlier study we conducted, is a good size for a pilot and feasibility study to assess recruitment, contamination, and data collection.

Recruitment

A study investigator will provide ward-based education about the study, providing clinical nursing staff with information about the study and an opportunity for questions during the double staff time in each ward two times in a 2-3-week period prior to commencement of the study. Hard copies of the study information will also be provided. Following face-to-face information sharing, study information and a request to participate in the study will be forwarded via email to each nurse in the ward by a study investigator. This email will describe the study and outline the participant requirements. It will include a participant information statement and consent form. Two reminder emails will be sent 1 week apart to potential participants to remind them to respond.

The first 10 nurses from each ward who agree to participate in the study and return the consent form will be accepted into the study. Following randomization, participants from each arm of the study will be sent an information email, specific to the group to which they have been randomized, with all the information they require to participate in the study. This email will include links to the relevant resources and surveys as well as links for securing a position into the simulation training and the focus group interviews. Then, 3 months posttraining, all participants will receive an email reminding them to complete the follow-up survey. This email will be resent two times as a reminder to participants. At the completion of the study, participants will receive a letter that provides a summary of the main study findings and thanks them for their participation in the study.

Assignment of Groups

Allocation

A researcher who is not associated with this study and is not based at the study site will use a coin toss to randomize the wards included in the study to either the training intervention or the comparison group. This will occur once recruitment is complete. The first coin toss will identify which ward is being considered (ie, heads for one ward and tails for the other). The second coin toss will decide whether the selected ward is assigned to the intervention arm or to the comparator arm. Once the wards have been allocated, the study investigator will be unblinded and will individually notify participants via email regarding the arm of the study to which they have been allocated.

Blinding

Blinding for the study investigators and participants will not be possible. To reduce bias, once data are exported to Microsoft

Excel, a researcher who is not involved with the study will code the intervention and comparator groups and remove data columns that relate to the intervention group only, so the person conducting the analysis will be blind to group allocation.

Data Collection, Management, and Analysis

Overview

The Kirkpatrick Four-Level Model

The Kirkpatrick Model will be used to measure the impact of the training. This four-level model evaluates training according to (1) reaction, (2) learning, (3) behavior, and (4) results [28-30].

1. Pre- and Posttraining Survey (Kirkpatrick Level 1)

A link to a short, electronic REDCap (Research Electronic Data Capture) survey will be administered to participants' before and after simulation training, incorporating the Confidence in Coping with Patient Aggression Instrument [25], short-answer questions, and free text. These will be used to assess self-perceived levels of confidence and competence in managing aggression as well as the acceptability of the simulation and web-based training.

2. Follow-Up Survey: 3 Months Posttraining (Kirkpatrick Level 1)

A link to a short, electronic REDCap survey will be emailed to participants 3 months after simulation training incorporating the Confidence in Coping with Patient Aggression Instrument [25], short-answer questions, and free text. These will assess self-perceived levels of confidence and competence in managing aggression as well as the acceptability of the simulation and web-based training.

3. Observer Evaluation of Use of De-escalation Skills Within the Simulation (Kirkpatrick Level 2)

The simulation exercises will be recorded using Sportstec software. Sportstec is video analysis software designed for use in medical simulation research that allows users to interpret and code the multifaceted elements of video while identifying patterns that form a comprehensive picture. The video recordings are securely held on RCH servers and the software license includes use for research purposes. Two clinicians with expertise in the management of clinical aggression will assess the participants' recorded performances for each scenario using the EMDABS [27,31]. The EMDABS is a one-dimensional, seven-item scale combined with a 5-point Likert scale ranging from 1 (*strongly disagree*) to 5 (*strongly agree*). Performance will be represented by the means of the seven items. The original German-language scale (De-escalating Aggressive Behaviour Scale, DABS) was enhanced and validated by Mavandadi et al [26] to create the EMDABS. This tool demonstrated good interrater reliability (intraclass correlation coefficient=.752) and strong internal consistency (Cronbach alpha=.901). Training materials have been provided by the authors of the EMDABS tool and will be used to train the clinicians in the use of the tool.

4. Ward Patient Aggression Record (Kirkpatrick Level 3)

Episodes of clinical aggression from patients with ASD will be recorded during each shift in participating wards 1 month prior to and 3 months after the training intervention. Numbers of successful de-escalation interactions will be recorded. A short, electronic REDCap survey will be emailed to ANUMs, and to any additional nurses who acted in the role of ANUM, at the completion of the study to explore the enablers and barriers to collecting this data.

5. Code Grey Activations (Kirkpatrick Level 4)

We will conduct a review of numbers and context of Code Grey activations in participating wards for 1 month prior to and 3 months after the training intervention. Strategies to be used by the study team to promote participant retention and completion of follow-up surveys are described in the Recruitment section.

Data Management

Participant confidentiality will be strictly held in trust by the study investigators and the sponsoring institutions. All surveys are anonymous so no personal details will be stored. The data from the EMDABS will be entered into a password-protected REDCap account by an administrative assistant. All survey data will be entered directly by participants into the secure REDCap web-based application. Sportstec recordings of the simulation-based education will be deleted once analysis is complete. All data for this study will be stored on a password-protected computer located in the Department of Neurodevelopment and Disability for 5 years. After 5 years, the data will be deleted.

Statistical Methods

Primary Outcomes

Percentages will be calculated to estimate recruitment, retention, outcomes, survey response rate, focus group participation, and the precision of those estimates. We will treat the Likert-scale scores as categories and dichotomize the 11- and 5-point scale responses. Changes in confidence and competence will be compared statistically with a chi-square test using before-and-after data to compare the proportion of those who have high confidence between the two arms at baseline and at follow-up.

Secondary Outcomes

The Code Grey data and daily aggression data will be analyzed using descriptive statistics, including descriptions of the clinical journey for children and young people who trigger more than one Code Grey response. We will report whether aggression de-escalation attempts were recorded during each shift on each ward as planned. The EMDABS data will be analyzed using mean values and SDs to understand the variation in performance of individuals who undertake the training.

Monitoring

A Data Monitoring Committee is not required, as this is a feasibility and pilot study of short duration and minimal risk. Due to the realism of simulation-based education, participants could potentially become distressed during, or at the completion of, a simulation scenario or the debrief for many reasons. If a member of the Simulation Faculty observes distress in a participant, they will offer them the option to leave the scenario or debrief and will support them both at the time they leave, as well as follow up with them through the following week. In addition, they will be offered the counsel of the RCH

Employees' Assistance Program. In a previous pilot study conducted prior to this work by the authors, distress following simulation-based education was minimal. Immediate support from the Simulation Faculty posttraining was sufficient to reassure a small number of participants who verbalized concern about their performance. No participants required referral to the RCH Employees' Assistance Program for continued support or follow-up.

It is not expected that the focus groups will cause participants any anxiety or distress. If participants do not feel comfortable answering any of the questions in the focus group, they do not need to answer them. Auditing of data is not required, as this is a feasibility and pilot study of short duration.

Ethics and Dissemination

Research Ethics Approval

The study received ethical approval from the RCH Melbourne Human Research Ethics Committee (HREC) on November 1, 2019 (HREC reference number: 56684).

Protocol Amendments

There are no anticipated amendments to the protocol for this pilot and feasibility study.

Consent

Participation will be voluntary and consistent with the National Statement on Ethical Conduct of Human Research Section 2.2.9: no coercion or pressure to participate will occur between the study investigators and potential participants [32].

A study investigator will email the participant information statement and consent form to all potential study participants. Nurses in the study wards will be asked within this email to return the consent form to the nominated study investigator if they would like to participate in the study.

All participants will be required to read the participant information statement and sign and return the consent form via email before participating in the study.

Participants in both arms of the study will be required to (1) complete the training intervention, (2) complete the pre- and posttraining surveys, (3) complete the follow-up survey, and (4) participate in a 1-hour focus group interview at the completion of the training.

Confidentiality

Overview

Participant confidentiality will be strictly held in trust by the study investigators and the sponsoring institutions. Participants in the simulation-based training will be asked to maintain and hold confidential all information regarding the performance of specific individuals and the details of the specific scenarios. Only study investigators will have access to the trial data.

Surveys

All surveys are anonymous and will be completed electronically using a web link to the REDCap survey sent to participants via email. While no personal details will be recorded, it is possible that years of clinical experience may potentially identify some participants. Participants will be asked to create their own unique identifier to be used for each survey, so that pretraining, posttraining, and follow-up survey results can be linked. Data stored in the secure REDCap database will be deleted following completion of data analysis.

Sportstec Recordings of the Simulation-Based Education

Confidentiality will be maintained by the assessors; no identifying participant information will be kept and the recordings will be deleted once analysis is complete.

Ward Patient Aggression Record

Completed daily ward patient aggression records will be stored in a locked filing cabinet in the ward nursing offices and collected daily on weekdays by a study investigator, who will then store the record sheets in a locked filing cabinet in the Department of Neurodevelopment and Disability. No patient names will be recorded on these records, which will only be identified by the patient Medical Record Number (MRN). This information is reidentifiable; however, only the study investigator (MJM) will have access to the data during the study period. The nurse in charge of the shift who completes the record will have access to the record sheets completed that day and will store them in a locked filing cabinet on the ward until they are collected by a study investigator (MJM). This investigator, who is an RCH clinician and works with this population, will access the medical records to locate the aggressive incident. No personal information will be recorded in REDCap; instead, what will be recorded is whether a de-escalation episode was found or not, to check the validity of the reported data as part of the pilot and feasibility study. Data, excluding the patient MRN, will be entered into the secure REDCap database and will be deleted following completion of data analysis. Written records will be shredded and disposed of securely once data has been entered into REDCap.

Dissemination Policy

The results of this study will be disseminated to study participants, staff of the study site, and health care professionals through the dissemination plan in Table 1.

Table 1. Dissemination plan.

Domain	Activities	Approach	Time frame	Responsibility	Budget
Dissemination objectives	Goal is to present main findings to participants, staff at study site, hospital executive, health care professionals, and consumers	Dissemination options are detailed below for each group	Within 6 months following completion of study	Study investigators	Nil
Identify target audience	Inform study participants	Letter summarizing the main findings	1 month following completion of study	Study investigators	Nil
	Inform staff at study site	Presentation at research forums, department meetings, and ward education session	Within 6 months following completion of study	Study investigators	Nil
	Inform hospital executive	Face-to-face meeting with Executive Director of Nursing and Allied Health and a written summary of findings	Within 2 months following completion of study	Study investigators	Nil
	Inform health care professionals	Publication in relevant journals, presentation at relevant local and international conferences, and webinar about the study and findings for the Department of Neurodevelopment and Disability	Within 1 year following completion of study	Study investigators	Funding will be sought from relevant scholarships and funding sources
	Inform consumers	Blog of main findings presented in plain English on department website	Within 2 months following completion of study	Study investigators	Nil
Key messages	Determine key messages for each target group following completion of study	Adapt content as appropriate	1 month following completion of study	Study investigators	Nil
Sensitivities	Determine sensitivities for each target group following completion of study	Adapt content as appropriate	1 month following completion of study	Study investigators	Nil
Evaluation plan	Evaluate the effect of the different strategies	Analyze *click* and *open* rates for web-based resources and note implementation strategies at the study site following dissemination of results	Within 1 year following completion of study	Study investigators	Nil

Results

This study gained ethical approval from the RCH Melbourne HREC on November 1, 2019 (HREC reference number: 56684). Data collection was completed in February 2020. Data analysis is due to commence with results anticipated by August 2020.

Discussion

Aggression demonstrated by children and young people with autism, with or without intellectual disability, is increasing in acute care pediatric hospitals. Nursing staff often feel underequipped to successfully de-escalate or prevent aggression or externalizing behaviors in this population. It is important that acute care nurses working with children with ASD are confident in managing aggression demonstrated by patients in their workplace. This study aims to develop and pilot test a simulation-based training program to upskill pediatric nursing staff who work with children and young people with autism who display aggression and externalizing behaviors.

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Authors' Contributions

MJM developed the training materials for this study with input from all authors. MJM wrote the draft of this manuscript. All authors have been involved in revising the manuscript and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
HREC Pre submission peer review.
[DOCX File , 136 KB - resprot_v9i6e18105_app1.docx]

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Abbreviations

ANUM: Associate Nurse Unit Manager
ASD: autism spectrum disorder
DABS: De-escalating Aggressive Behaviour Scale
EMDABS: English Modified version of the De-escalating Aggressive Behaviour Scale
HREC: Human Research Ethics Committee
MRN: Medical Record Number
NUM: Nurse Unit Manager
RCH: Royal Children’s Hospital
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture

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Protocol

Treatment of Childhood Obesity Based on Brazilian Dietary Guidelines Plus Energy Restriction (PAPPAS HUPE Study): Protocol for a Randomized Clinical Trial

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Abstract

Background: The Food Guide for the Brazilian Population relies on natural or minimally processed foods mainly of plant origin such as beans and rice with low oil, salt, and sugar content and limited consumption of ultraprocessed foods. Reduction of ultraprocessed foods improves diet quality and energy consumption.

Objective: The goal of this study is to evaluate the effectiveness of an intervention for the treatment of obesity in children, with counseling based on the Brazilian Food Guide plus control of total energy intake.

Methods: A parallel, randomized clinical trial will include children aged 7 to 12 years. Randomization will be performed in blocks of 10 individuals using computer-generated random sequence numbers. Both the control and intervention groups will participate in 6 standardized educational activities based on the 10 steps of the Brazilian Food Guide. These activities will be conducted at the University Hospital Toy Library, located in the pediatric outpatient clinic. For the intervention group, in addition to the educational activities, an individualized food plan based on the nutritional recommendations of the Brazilian Society of Pediatrics will be prescribed and discussed with the mothers and fathers. The primary outcome of the study will be variations in body mass index, and secondary outcomes will include analysis of insulin resistance, blood pressure, body fat percentage, and waist and neck circumference.

Results: This project was funded by the National Council for Scientific and Technological Development in December 2017 (grant no 408333/2017-0). Recruitment began in August 2018 and by September 2019, we had enrolled the 101 participants. In addition to the patients referred by the national system of regulation, recruitment was made by medical outpatient referral and external indication. This is an ongoing study. We expect the results to be published in November 2020.

Conclusions: At the end of the project, in case of a positive result, a protocol for the treatment of obesity based on the Brazilian Food Guide will be proposed to the Unified Health System. A successful method to reduce childhood obesity is expected.

Trial Registration: Brazilian Registry of Clinical Trials RBR-3st5sn; http://www.ensaiosclinicos.gov.br/rg/RBR-3st5sn

International Registered Report Identifier (IRRID): DERR1-10.2196/16170

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KEYWORDS

pediatric obesity; clinical trial; food guide

Introduction

The global prevalence of excessive weight among children aged 5 years and younger, which was 42 million in 2013, is expected to increase to 70 million in 2025 [1,2]. In Brazil, the increase in the prevalence of obesity over the past few decades has been higher among children aged 5 to 9 years compared with adolescents and adults, with an increase of approximately 6 times in the period from 1974 to 2009 [3]. During this period, Brazilian adolescents' diets were low in vegetables and fruits with a high intake of sodium-rich food, sweets, and soft drinks [4-6].

Obesity before the onset of puberty increases the risk of adult type 2 diabetes, particularly if it continues until puberty or even later [7], indicating a window of opportunity to reduce obesity and related diseases later in life.

The World Health Organization (WHO) recommends interventions to control obesity in childhood. Accordingly, in 2014, the World Health Assembly adopted the Global Action Plan for the Prevention and Control of Noncommunicable Disease 2013-2020, which includes reducing global obesity rates among children, adolescents, and adults [8].

The 2014 Food Guide for the Brazilian Population [9] is a strategy for the implementation of the Adequate and Healthy Food promotion guideline that integrates the National Food and Nutrition Policy. The guide is intended for the population aged 2 years and older and classifies foods based on the degree of industrial processing. This classification, called the NOVA food classification system, comprises four groups: (1) unprocessed or minimally processed foods, (2) culinary ingredients, (3) processed foods, and (4) ultraprocessed foods [10,11].

High consumption of ultraprocessed foods has been associated with obesity, diabetes, and cardiovascular disease in different age groups [12-16]. Ultraprocessed foods are more energy-dense and contain higher levels of total fat, saturated fat, sugar, and salt and lower levels of protein and dietary fiber in comparison with unprocessed or minimally processed foods. In addition, they stimulate excessive consumption because of hyperpalatability, large portion sizes, and easy consumption. Therefore, they can be consumed as snacks anytime, anywhere and are often marketed intensively and persuasively. In a randomized trial with individuals eating ad libitum, the poor quality of a diet rich in ultraprocessed foods was also associated with greater energy intake when compared with a diet very low in ultraprocessed foods [17].

Obesity prevention reviews based on the promotion of positive eating behaviors have not achieved the desired impact [18,19], and trials for the treatment of obesity in the primary care setting are effective only when they include caloric restriction and parental involvement, as shown in the available literature reviews [20]. Reduction of energy intake associated with consumption of ultraprocessed foods may be improved by combining the NOVA classification with a food plan. Accordingly, a review of interventions to increase fruit and vegetable consumption among school children found improved targeted dietary behaviors; however, there were no effects on adiposity [21], suggesting that for the treatment of obesity, the amount of food consumed is also an important aspect to be considered. Thus, the aim of this project is to compare a Food Guide for the Brazilian Population–based intervention incorporating the NOVA classification of food with and without energy intake counseling. If effective, this proposal could guide the development of clinical protocols for primary care aimed at the treatment of obesity in children, a challenge in the Brazilian public health agenda.

Methods

Design and Study Population

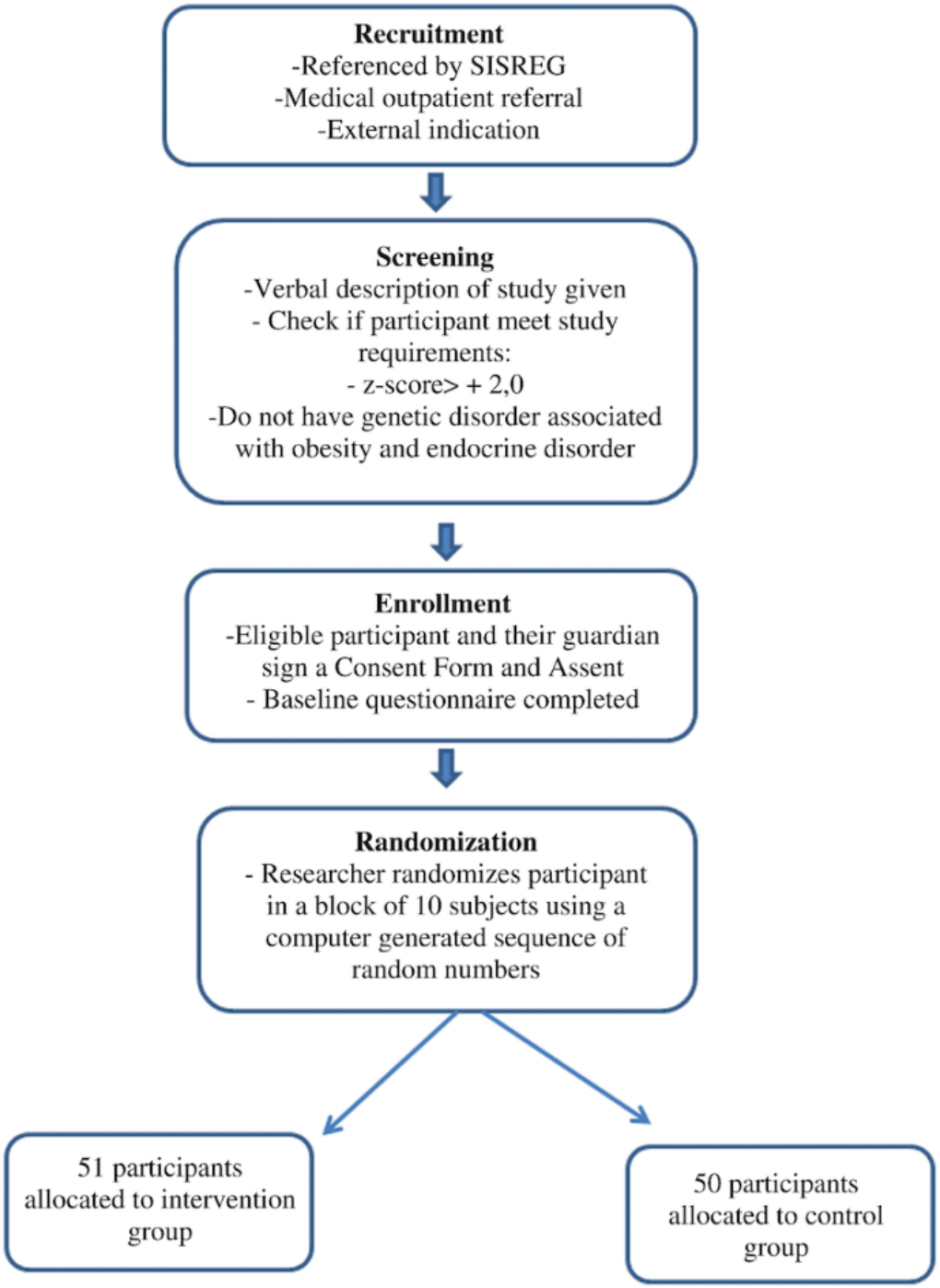
Parents and Professionals for Healthy Eating–Pedro Ernesto University Hospital (PAPPAS HUPE) is a nonblind randomized clinical trial for the treatment of obesity in children referred by the National Regulatory System to the pediatric nutrition clinic of a university hospital located in the metropolitan region of the city of Rio de Janeiro, Brazil. Obese children aged 7 to 12 years are eligible to participate in the study. The exclusion criteria will be children diagnosed with genetic disorders associated with obesity (congenital leptin deficiency, Down syndrome, Prader-Willi syndrome) or endocrine disorder (hypothyroidism, Cushing syndrome) and patients already under nutritional monitoring or using weight loss medications. These data will be obtained through medical records and/or a questionnaire completed by parents.

The study will employ a parallel design with 2 comparison groups (Figure 1):

- Control group that will receive monthly nutritional guidance based on the new Food Guide for the Brazilian Population [9];
- Intervention group that will receive monthly nutritional guidance based on the new Food Guide for the Brazilian Population and a home-based diet plan appropriate to the nutritional needs of the participants.

The protocol will follow the guidelines of the Consolidated Standards of Reporting Trials [22] and was registered prospectively with the Brazilian Registry of Clinical Trials [RBR-3st5sn].

Figure 1. Consolidated Standards of Reporting Trials diagram. SISREG: Sistema Nacional de Regulação (National Regulation System).



Ethics Approval and Consent to Participate

The project was approved by the Research Ethics Committee of the Pedro Ernesto University Hospital (CAAE: 87593118000005259). The parent or legal guardian of the child will be informed of the need to sign a consent form and assent according to Brazilian Resolution number 466/2012 on research involving human beings from the Health Council of the Ministry of Health to authorize the information provided by the population in a study, emphasizing privacy regarding identification of the content as well as the freedom to withdraw from the research at any time.

Sample Size Calculation and Randomization Procedure

The sample size of 48 individuals per group was calculated based on a standard deviation of body mass index (BMI) equal to 3.0 and an expected difference of 1.72 BMI [23] units between the groups, considering a statistical power of 80% and significance level of 5%. We estimate that 5% of participants are likely to drop out of the study during the study follow-up period. To account for this, we have enrolled 101 participants in total.

After the recruitment phase, eligible participants will be randomly assigned to the control or intervention groups. The randomization, which is performed by the dietitian responsible

for the trial, will be performed in a block of 10 subjects using a computer-generated sequence of random numbers. The allocation implementation mechanism will be numbered sequentially. Participants will be allocated to each group, and interventions will be promoted by trained nutritionists.

Intervention

Both groups will participate in 6 monthly standardized educational activities based on the 10 steps of the Food Guide for the Brazilian Population, which will be carried out in the Hospital Toy Library. Recreational materials, audiovisual resources, and pedagogical support necessary to carry out the proposed educational practice, already available, are based on the Activity Notebook–Promotion of Adequate and Healthy Food–Infant Education, developed by the Ministry of Health in partnership with the University of the State of Rio de Janeiro for teachers and health professionals (Table 1) [24]. Activities will be conducted in groups of 10 children. To avoid contamination, activities for the control and intervention groups will be conducted on alternate days.

Table 1. Description and objectives of the interventions.

Intervention	Description	Purpose of the activity

From food to meals	• Addresses the following Food Guide steps:
	  • Step 1: make food in natura or consume minimally processed food
	  • Step 3: limit consumption of processed foods
	  • Step 4: avoid consumption of ultraprocessed foods
		• Enable participants to recognize food groups by degree of processing
		• Facilitate reflection on the consumption of these food groups at home
		• Help participants understand that usual meals should integrate fresh or minimally processed foods, enabling them to limit/avoid the consumption of processed and ultraprocessed foods

Fat, salt, and sugar	• Addresses the following Food Guide step: • Step 2: use oils, fats, salt, and sugar in small amounts by seasoning and cooking food	• Make participants aware of the amount of fat, salt, and sugar present in food • Help participants reflect on the amount of these ingredients in meals and on the possible consequences of high consumption

What a happy time	• Addresses the following Food Guide steps:
	  • Step 5: eat with regularity and attention, in appropriate environments, and, whenever possible, with company
	  • Step 8: plan the use of time to give food the space it deserves
		• Help participants understand the concept and importance of commensality
		• Help stimulate reflection about this practice

Going shopping	• Addresses the following Food Guide step: • Step 6: make purchases in places that offer varieties of food in natura or minimally processed foods	• Help participants identify food sale locations close to where they live or study • Make participants aware of the importance of shopping in places that offer varieties of food in natura or minimally processed foods • Enable participants identify the characteristics that make places the most appropriate to buy their food
There is a child in the kitchen	• Addresses the following Food Guide step: • Step 7: develop, exercise, and share culinary skills	• Encourage participants to engage in healthy meal preparation and develop and/or exercise their culinary skills • Encourage participants to share the knowledge and recipes learned with family and friends

What do you have to eat and drink around here?	• Addresses the following Food Guide steps:
	  • Step 9: give preference, when away from home, to places that serve meals made at the time and with food in natura or minimally processed foods
	  • Step 10: be critical about information, directions, and messages in commercial advertisements
		• Enable participants to make healthy choices when eating out
		• Enable participants to critically analyze the advertisements and labels of food/products ready for consumption

Educational activities will also be held with parents addressing the same topics as those covered in the children's workshops. Advice will include changes in family behavior related to food choices and purchases.

After the group activities, individual family consultations for the control and intervention groups will be held. In the control group, the counseling will reinforce lessons learned in educational activities, focusing on food quality. In the intervention group, a food plan will be prescribed for each participant based on nutritional recommendations of the Federal

Council of Nutritionists and Brazilian Society of Pediatrics [25,26]. The plan will be reviewed monthly to match energy recommendations and weight change observed in the previous month.

In order to reduce follow-up losses and increase adherence to the study protocol, a telephone call in the week after the appointment will be made with those responsible for the children to evaluate potential difficulties in adhering to the guidelines provided. Those reporting difficulties in participating will be contacted weekly. This intervention description follows the template for the intervention description and replication checklist and guide [27].

Data Collection

Those responsible for data collection will be trained to ensure a high quality of assessment. This training will be conducted with the objective of standardizing the measurement of data and ensuring reliability.

Outcomes

The primary outcome of the study will be variations in BMI. The following secondary outcomes will be investigated: waist-to-height ratio (WHR), waist circumference (WC), neck circumference (NC), blood pressure, body fat percentage (BF%), and biochemical analysis of serum total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, glucose, and insulin resistance. Insulin resistance will be determined at the baseline and endpoint while the other biochemical analyses will be conducted at the baseline, midpoint, and endpoint. The remaining variables will be assessed at every consultation.

Body weight and BF% will be measured using a portable electronic scale (Tanita BC-558). Height will be checked in duplicate using an AlturaExata portable anthropometer (Belo Horizonte). Both measures will be collected with the children barefoot, wearing light clothes, with the arms extended from the side of the body, positioned by the Frankfurt horizontal plane [28,29]. To reduce potential BF% measurement errors, parents and children will be provided with guidelines regarding the intake of liquids, coffee, alcoholic beverages, laxatives, and diuretics prior to the anthropometric evaluation.

To measure WC and NC, a flexible and inelastic metric tape measuring 150 cm and a variation of 0.1 mm will be used. The WC will be measured with the tape placed horizontally at the midpoint between the lower edge of the last rib and the iliac crest [30]. The measurements will be performed with the tape firmly on the skin, without compression of the tissues. The evaluation will be made while standing with the abdomen relaxed and the arms extended out from the body. The WHR will be obtained by the quotient between WC and height, both in centimeters. The NC will be measured at the average neck height.

The classification of nutritional status will be based on BMI values for age, in z-scores, according to sex, based on the new curves proposed by WHO. BMI for age will be calculated using AnthroPlus 2007 software (WHO) [31], and the values obtained will be classified according to the recommended cutoff points for children aged 5 to 19 years: low weight (BMI for age <–2 z-scores), eutrophic (BMI for age ≥–2 and ≤+1 z-scores), overweight (BMI for age >+1 and ≤+2 z-scores), obese (BMI for age >+2 and <+3 z-scores), and severely obese (BMI for age >+3 z-scores). This classification will be performed at the baseline to confirm the inclusion criteria.

Blood pressure will be measured with the HEM-742 blood pressure monitor (Omron Healthcare Inc.), previously validated for use in adolescents [32]. Before taking the measure, it will be verified that the children do not have full bladders, have not taken medication and/or had coffee, and have not eaten up to 30 minutes before the procedure or engaged in physical exercise up to 1 hour before. The measurement will be performed on the right arm, at the level of the heart, supported on a table with a flat surface, with the palm facing up and the elbow slightly flexed. The individual should be seated with feet in contact with the floor or on a flat surface and remain at rest in that position for 5 minutes before the measurement [33]. Two measurements will be performed, with a minimum interval of 2 minutes, and the average of 2 measurements will be calculated. If the difference between the 2 measurements is equal to or greater than 5 mm Hg, a third measure will be taken.

Biochemical analysis of serum total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and glucose will be determined at the baseline, midpoint, and endpoint. The biochemical analysis will be performed at the hospital's central laboratory of clinical analyses. After 12 hours of fasting, 10 ml of blood from the left ventricle vein will be collected in vacutainer tubes. The samples will be divided into aliquots, placed in Eppendorf-type tubes, and stored at –80°C until use, when they will be processed and the serum analyzed in a biochemical analyzer (Cobas Integra 400 Plus/Cobas 6000, F Hoffman–La Roche Ltd) with a Roche cassette. Fasting glycemia will be determined by hexokinase, total cholesterol and triglycerides by the colorimetric method, and HDL cholesterol by the homogeneous method (F Hoffman–La Roche Ltd). LDL cholesterol will be calculated by the Friedewald et al [34] equation, recommended by the American Academy of Pediatrics: LDL cholesterol = total cholesterol – HDL cholesterol + triglyceride/5. Insulin will be measured in the hospital's endocrinology laboratory with the Elecsys 2010 and Modular Analytics E170/Cobas (F Hoffman–La Roche Ltd) by means of a kit that uses the immunoassay method of electrochemiluminescence. The cutoff points used for the evaluation of the serum levels of total cholesterol and fractions will follow the recommendation of the Brazilian Guideline for Dyslipidemias and Prevention of Atherosclerosis [35], and for fasting glycemia the parameter will be that recommended by the American Diabetes Association [36]. Undesirable levels of total cholesterol and LDL cholesterol values equal to or above 170 mg/dL and 110 mg/dL, respectively, and glucose above 100 mg/dL will be considered.

Insulin resistance will be assessed by means of the homeostatic model assessment–insulin resistance (HOMA-IR) index (HOMA-IR = fasting glycemia [mmol/L] × fasting insulinemia [μU/L]/22.5). Values >2.5 will be indicative of insulin resistance.

Adherence to Intervention

Data regarding food consumption will be collected at each consultation by means of a 24-hour food recall using netbooks equipped with a multiple-pass method–based computer program for monitoring adolescent food consumption [37].

Other Variables Investigated

At baseline, during the individual consultations, a questionnaire covering issues related to socioeconomic, demographic, and behavioral factors will be administered to the adults responsible for the children. Children will be asked about pubertal stage through the Tanner scale [38,39], sedentary activities (video games, television, and computer time), and physical activity using a validated questionnaire including 6 questions about frequency and duration of physical activities [40].

Family socioeconomic status will be evaluated using the Brazilian Economic Classification Criterion [41]. The number of sleeping hours will be ascertained from 3 questions based on 2 large epidemiological studies [42,43]: How many hours on average do you sleep on a normal night? Do you sleep fewer hours per night than you would like? How many hours would you like to sleep to feel like you have recovered? Sleep deprivation will be estimated from the difference between the usual hours of sleep and the hours of sleep the participant feels would facilitate recovery.

Statistical Analysis

The rate of change of primary and secondary outcomes over time will be tested by intention-to-treat analysis based on mixed-effects models, which allow for consideration of incomplete follow-up data and take into account the correlation of repeated measures. Adequacy of the models will be checked graphically through the diagnosis of the residues [44]. The models will be adjusted for sexual maturation. For the analyses, SAS software version 9.4 (SAS Institute Inc) will be used.

Results

This project was funded by the National Council for Scientific and Technological Development (CNPQ) in December 2017. The study protocol has undergone peer review by the funding body, which was not involved in the design of the study; collection, analysis, and interpretation of data; or in writing the manuscript.

Recruitment began in August 2018 and by September 2019, we had enrolled the 101 participants. In addition to the patients referred by the national system of regulation, recruitment was made by medical outpatient referral and external indication. This is an ongoing study. We expect the results to be published in November 2020.

Discussion

The PAPPAS HUPE randomized clinical trial will be the first to provide data on the effectiveness of the recommendations of the Food Guide for the Brazilian Population on the treatment of obesity in children.

The possibility of incorporating NOVA food classification based on the degree of food processing for the treatment of obesity is unprecedented and timely, since this approach has been pointed out as a promising vehicle of nutritional education and also due to the high consumption of these products by Brazilian children.

The inclusion of parents in the activities is a strong point of the study. This approach can contribute to increased adherence to the protocol by leading to changes in family eating habits [45].

A possible limitation of this study is the difficulty in obtaining accurate measurements of food consumption according to the NOVA classification since it requires details about the degree of food processing. There is also a lack of consensus regarding the best data collection method because this is a recent technique. However, we will use the 24-hour recall, which is the standard collection method in food consumption assessment.

An intervention program combining quantity and quality approaches could be more efficient in the fight against obesity, especially in late childhood, when they acquire autonomy in relation to their diet. Moreover, we expect that the proposed nutritional plan would be able to promote weight loss without compromising growth and development. If effective, this proposal could guide the development of clinical protocols for primary care aimed at the treatment of obesity in children, an emergency challenge in the Brazilian and global public health agenda.

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Authors' Contributions

DBC, RS, JMB, and SAR conceptualized the study. DBC acquired funding for the study. DBC, RS, JMB, SAR, IRRDC, BKH, and ASDDO developed of the intervention content. DBC, RS, JMB, SAR, IRRDC, BKH, and ASDDO wrote the original draft. RS, SAR, EVJ, RAP, IRRDC, BKH, ASDDO, ESM, and DBC reviewed and edited the manuscript. JMB was responsible for data collection. All authors read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Previous peer-review report (Portuguese): CNPQ (Conselho Nacional de Desenvolvimento Científico e Tecnológico).
[PDF File (Adobe PDF File), 164 KB - resprot_v9i6e16170_app1.pdf]

Multimedia Appendix 2
Previous peer-review report (English): CNPQ (National Council for Scientific and Technological Development).
[PDF File (Adobe PDF File), 146 KB - resprot_v9i6e16170_app2.pdf]

Multimedia Appendix 3
SPIRIT checklist.
[PDF File (Adobe PDF File), 126 KB - resprot_v9i6e16170_app3.pdf]

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Abbreviations

BF%: body fat percentage
BMI: body mass index
CNPQ: National Council for Scientific and Technological Development
HDL cholesterol: high-density lipoprotein cholesterol
HOMA-IR: homeostatic model assessment–insulin resistance
LDL cholesterol: low-density lipoprotein cholesterol
NC: neck circumference
PAPPAS HUPE: Parents and Professionals for Healthy Eating–Pedro Ernesto University Hospital
SISREG: Sistema Nacional de Regulação
WC: waist circumference
WHO: World Health Organization
WHR: waist-to-height ratio

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Protocol

An Internet-Based Intervention to Alleviate Stress During Social Isolation With Guided Relaxation and Meditation: Protocol for a Randomized Controlled Trial

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Abstract

Background: Psychophysiological stress and decreased well-being are relevant issues during prolonged social isolation periods. Relaxation practices may represent helpful exercises to cope with anxiety and stressful sensations.

Objective: The aim of this research protocol is to test whether remote relaxation practices such as natural sounds, deep respiration, and body scan meditation promote relaxation and improved emotional state and reduce psychomotor activation and the preoccupation related to the coronavirus disease (COVID-19) pandemic.

Methods: The study population will consist of 3 experimental groups that will randomly receive one of 3 internet-based audio clips containing a single session of guided breathing exercise, guided body scan exercise, or natural sounds. The participants will listen to the fully automated audio clip for 7 minutes and complete pre-post self-assessment scales on their perceived relaxation, psychomotor activation, level of worry associated with COVID-19, and emotional state. At the end of the session, the participants will also be asked to provide qualitative reports on their subjective experiences.

Results: Analyses will be performed to test the differences in the efficacy of the different audio clips in an internet-based intervention on 252 participants (84 per group), investigating whether natural sounds or remote guided practices such as deep respiration and body scan meditation positively enhance the participants' perceived psychological state.

Conclusions: The study will provide information on if and to what extent guided practices can help in reducing psychological side effects related to social isolation during the COVID-19 pandemic.

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KEYWORDS

relaxation; guided meditation; internet-based intervention; social isolation; stress; COVID-19; mental health; public health

Introduction

Background

The world is facing a new health emergency: coronavirus disease (COVID-19), an infectious disease caused by a newly discovered coronavirus [1].

The COVID-19 pandemic is the first pandemic to occur in the 21st century. Therefore, the majority of the world's population is living with an entirely new experience that has never happened in their lifetime. Since mid-March, Italy has faced a strict lockdown. For an extended period of time, people have been forced to live either alone or in "bubbles" with only a few

family members or a partner. In such conditions, it is not difficult to assume that people will feel lost and will experience loneliness and social isolation. These conditions may reduce health and mental well-being, thus affecting vital functions (eg, sleep quality), social connectedness, perceived support, and psychological status [2-4]. A recent rapid review on the effects of the quarantine [5] underlines that society is facing several negative cognitive and emotional problems, such as confusion, poor concentration, irritability, insomnia, distress, frustration, and anger. People are worried about the quarantine duration, insufficient information provision, economic problems, and stigma. These negative effects may impact individuals' bio-psycho-social functioning and lead to depressive or posttraumatic stress symptoms [5,6].

The lack of a vaccine for COVID-19, the high chance of contagion, and the severity of symptoms—which often lead to death—increase risk perception related to the pandemic. In all high-risk situations, cognitive and rational thinking interact with emotional appraisals, thus affecting people's state of mind; individuals feel vulnerable and may experience fear for themselves and for their loved ones [7,8]. Both physical and psychological dimensions are affected by the sense of uncertainty and the threat of contracting the virus. Under such conditions, it is not uncommon for people to also experience psychophysiological hyperarousal, which causes them to pay excessive attention to their bodily sensations and enhances their perceptions [9]. Overall, COVID-19 and social isolation have led to negative side effects, causing widespread concern and psychophysiological reactions [10].

Starting from these premises, it is necessary to develop an intervention to investigate people's psychosocial conditions and reduce possible psychophysiological activation; due to the current circumstances, such an intervention must be internet-based.

Previous studies demonstrated that interventions based on natural sounds, respiration, and meditation may help individuals to alleviate the effects of stress by reducing physiological arousal and restoring autonomic balance [11-14]. In fact, listening to natural sounds significantly reduces human stress processes [13,15]. On the other hand, guided relaxation techniques are widely used to produce a deep state of relaxation and enhance physical and emotional well-being. Deep breathing exercises and focusing attention on body perception are two of the main techniques used to reduce hyperarousal and achieve a more relaxed condition. Deep breathing can be also defined as "an efficient integrative body-mind training for dealing with stress, anxiety and psychosomatic conditions" [16]; it may help people to slow their breathing, take in more oxygen, and reduce the use of their shoulder, neck, and upper chest muscles, thus achieving better emotional balance and social adaptation [17]. On the other hand, body scan meditation aims to focus attention on different parts of the body and help people become aware of their bodily sensations, such as pain, tension, warmth, or relaxation [18,19]. We chose to employ these two techniques because they involve different cognitive and psychophysiological processes. In the present study protocol, we aim to test and compare the efficacy of natural sounds, breathing regulation, and body scan meditation to assess which intervention is the most effective for the target population. Applying these interventions to people forced into mandatory social isolation may help them become more aware of their mind-body condition and reduce negative effects. Moreover, scientific studies have shown that online relaxation techniques as well as in-person programs achieve significant results; these findings may support the implementation of remote interventions, which are currently a necessary feature of proposed programs [20,21]. However, a comparison of natural sounds, respiration, and body scan meditation techniques in internet-based interventions is still lacking in the literature.

Objective

The aim of this study is to test the difference in the efficacy of three audio clips related to three relaxation practices (deep breathing, body scan meditation, and natural sounds). We expect to find a decrease in the participants' levels of psychomotor activation/stress and of preoccupation with thoughts related to COVID-19 as well as enhanced relaxation levels and emotional state after exposure to all the audio clips; we also expect that the guided techniques (deep breathing and body scan) will have greater effects on the abovementioned dimensions than natural sounds.

Methods

Participants and Procedure

The invitation to take part in the study will be published on social media webpages (WhatsApp, Facebook, LinkedIn, and Instagram). The readers will be informed about the general aim of the study and that the study is conducted by researchers from the University of Milan. Potential participants will be encouraged both to take part in the study and to share the invitation with their acquaintances. The invitation will contain a link to the Qualtrics platform, where a more detailed description will be available.

The eligibility criteria to take part in the study will include being more than 18 years of age, being a proficient Italian speaker, not suffering from any impairment affecting auditive abilities, and having an appropriate level of computer literacy. Before taking part in the study, participants will be asked to read and complete an online consent form. The document will be shown and will be downloadable in .pdf format, and the participant will be asked to give their consent online. The document has already been redacted according to national legislation and by following the guidelines of the Ethical Committee of the first author's university.

The participation in the study will consist of 3 main parts: 1) completing a short questionnaire requesting background information and a preintervention evaluation, 2) listening to a 7-minute audio clip, and 3) completing the post-intervention evaluation. The estimated time for participating in the study (completing the three parts) will range from 12 to 17 minutes.

Participation in the study will be voluntary, and participants will be allowed to withdraw from the study at any moment. The research protocol follows the CONSORT-EHEALTH V1.6 Guidelines [22]. The study will be conducted according to the

principles stated in the Declaration of Helsinki (59th WMA General Assembly, Seoul, 2008).

Measures and Design

After completing the sociodemographic form, participants will be asked to report if they suffer from a chronic disease and how much the disease impacts their perceived vulnerability to COVID-19. Participants will also be asked to report their working situation, recent changes in occupational status due to COVID-19 restrictions, and if they have prior experience with relaxation techniques. Then, participants will be asked to complete 3 self-assessment questionnaires aimed at measuring their current level of anxiety, their tendency to worry about physical signals and sensations, and the degree of attention they pay to their bodily feelings.

To assess the abovementioned aspects, the following questionnaires will be used: the State-Trait Anxiety Inventory form-trait subscale (STAI-Y) (20 items on a 4-point Likert scale from 1=not at all to 4=very much) [23,24]), which assesses trait anxiety; the subscale physical concerns of the Anxiety Sensitivity Index-3 (ASI-3) [25,26], composed of 6 items that require them to rate how much they worry about physical sensations on a 5-point Likert scale from 1=very little to 4=very much; and finally, the Body Vigilance Scale (BVS) [27], a 4-item scale in which they will describe how much they usually pay attention to body sensations on a scale from 0=”not at all like me” to 10=“completely like me”. In the fourth item, participants will be required to rate their attention to 15 body sensations that are the core physical symptoms of panic attacks [28].

After completing the questionnaires, participants will be randomly assigned to one of the three experimental groups via the randomization procedure within Qualtrics. Specifically, in each experimental condition, participants will receive a 7-minute recorded audio clip aimed to promote a state of awareness and relaxation. In the first experimental condition (ie, square breathing), participants will hear a recorded voice that guides the regulation of breathing frequencies with the aim of making every breathing act (inhalation, holding breath, exhalation, and holding breath) last the same amount of time (4 seconds). In the second experimental condition (ie, body scan meditation), an audio clip with a voice that guides the participant’s attention through every part of the body will be presented, and the listener will be invited to feel tensions and unpleasant feelings and to let them go. Both tracks were recorded by a trained mindfulness and yoga expert in collaboration with a psychotherapist and were pretested on 4 participants to assess the ease and the perceived effectiveness of the exercise. In the third experimental condition (ie, natural sounds), participants will be stimulated by a prerecorded audio clip of natural sounds. All the audio clips will be preceded by instructions on the recommended place and body position for the exercises.

As pre-post measures, before and after the audio stimuli, the participants will be asked to self-rate their perceived relaxation level, perceived stress level, or psychomotor activation degree, to rate how concerned they feel about COVID-19, and to rate 3 specific features of their emotional state. Specifically, participants will be also asked to rate on a 3-item Visual Analogue Scale (VAS) (0=not at all to 10=completely) how relaxed they feel, how stressed/activated they feel, and how much their thoughts related to COVID-19 scare them; furthermore, they will complete the Self-Assessment Manikin (SAM) [29] for emotional states, which is a 3-item visual scale (valence, intensity/arousal, and dominance) commonly used to quantify properties of a person’s overall emotional state on a scale of 1 to 5 images. Immediately after listening to the audio, participants will also be asked if they heard the entire audio track, a part of it, or no part.

Finally, all the participants will have the opportunity to describe their personal experience and to provide suggestions for future changes. Specifically, participants will be asked to write a short paragraph answering 2 open-ended questions about their personal experience with the exercise (“Did you enjoy or dislike the experience with the audio clip?”) and any changes they would appreciate (“Would you change something in the audio clip?”).

Data Analysis

Group differences in demographic data and pretreatment measures will be analyzed with one-way analysis of variance (ANOVA) followed by *t* tests with Bonferroni corrected *P* values and chi-square tests. Differences in questionnaire scores (ie, STAI-Y, ASI-3, BVS) between groups will be examined using the same analysis. STAI scores will also be compared to clinical cutoffs. The internal consistency of the scales (Cronbach α) in our sample will also be assessed.

As the main aim of this study is to test the difference in efficacy between audio clips, our main analysis will be one-way ANOVA on gain relaxation scores [30], with 3 groups and fixed effects and with no interaction. According to our main objective, we performed a priori sample size calculation, considering a 0.25 effect size on the level of relaxation, with a high statistical power (0.95) and an alpha of .05. Considering the specified values, we will need a total sample size of 252 participants with complete surveys to reach the desired statistical power (84 per group). In view of the possibility of attrition of participants, which may occur in the present electronic health (eHealth) trial in the form of incomplete questionnaires or dropout before listening to the complete audio clips, we estimate that we will obtain incomplete data for 30% of the participants who will start the survey by clicking on the link and who will not continue with the questionnaires; thus, we should register a total of 328 participants.

Independent sample *t* tests of the relaxation level between paired groups will also be carried out on participants who will complete the entire survey (eg, without considering participants who dropped out before the randomized exposure to the audio clips).

The same analysis will be conducted for the participants’ perceived stress and fear related to COVID-19 thoughts, assessed with the VAS continuous scale, and for their emotional states, measured through the SAM. The between-group post-exercise Hedges g effect size (CI 95%) will be computed. As the randomization will be automatically performed by Qualtrics, the researchers who analyze the data will be blinded to which audio clip participants received.

Furthermore, we will perform other explorative analyses to test if and to what extent other covariates impact the efficacy of the proposed techniques. Specifically, we will test if having job issues or a chronic disease has an impact on the efficacy of the techniques.

All the aforementioned analyses will be performed in SPSS version 26.0 (SPSS, Inc., Chicago, IL).

Lastly, qualitative reports on subjective experiences and suggestions will be analyzed to understand the participants' subjective experiences, to evaluate the perceived efficacy of the audio, and to identify possible ameliorations of and issues with the proposed stimuli. Practical advice for future studies will be given accordingly.

Results

The expected results are that the audio clips will be effective in reducing the participants' perceived stress and degree of preoccupation with thoughts related to COVID-19; we also believe that the guided techniques will have a greater effect on relaxation and emotional state enhancement compared to the natural sounds.

The research protocol was approved by the Ethical Committee of the first author's university on April 30, 2020. Recruitment started in May 2020.

Discussion

People are confronting the COVID-19 pandemic worldwide. This alarming event and the unknown consequences it will trigger in citizens' lives have led to increases in stress levels and psychophysiological arousal. Moreover, lockdowns have forced people into social isolation and are preventing the implementation of in-person programs to target psychological issues.

The present randomized study will provide data on the effectiveness of remotely delivered interventions with natural sounds, deep breathing, and meditation practice in improving people's perceived relaxation, psychomotor activation, level of worries associated with COVID-19, and emotional state; we will also obtain data on people's experiences with these techniques.

The study will also shed light on whether one of these exercises provides increased benefits compared to the others and if so, to what extent. Indeed, a comparison among natural sounds, respiration, and body scan meditation techniques in internet-based interventions is lacking in the literature.

As a first assessment of the efficacy of these approaches, the present study will have the possible limitation of being a single-session guided intervention. Thus, we will not be able to assess differences in the efficacy of more prolonged exposure to the relaxation sessions. Furthermore, the length of the audio clips may need to be adjusted in future interventions in light of the participants' reports.

If effective, this study could guide the development of future low-cost remote interventions to reduce worries and anxiety in the general population. Future studies may also assess and compare the efficacy of these approaches in clinical protocols for patients struggling with anxiety and hyperarousal.

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Conflicts of Interest

None declared.

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Abbreviations

ASI-3: Anxiety Sensitivity Index-3
BVS: Body Vigilance Scale
COVID-19: coronavirus disease
eHealth: electronic health
SAM: Self-Assessment Manikin
STAI-Y: State-Trait Anxiety Inventory form-trait subscale
VAS: Visual Analogue Scale

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Protocol

Improving the Lifestyle of Adolescents Through Peer Education and Support in Vietnam: Protocol for a Pilot Cluster Randomized Controlled Trial

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Abstract

Background: In Ho Chi Minh City, Vietnam, recent studies found a rapid increase in overweight and obesity in adolescents. There is a need for effective health promotion interventions to support healthy diets and encourage a physically active lifestyle. This study will help fill an evidence gap on effective interventions to prevent excess weight gain in adolescents and generate new insights about peer-led education to promote healthy lifestyles.

Objective: We aim to assess the feasibility and acceptability of a combined peer-led and peer support intervention among junior high school students in Ho Chi Minh City. Additionally, the efficacy of the intervention on adolescents' dietary practices and time spent on physical activity will also be measured in this pilot study.

Methods: The Peer Education and Peer Support (PEPS) project is a pilot cluster randomized controlled trial with 2 intervention and 2 control schools. The intervention consists of 4 weekly education sessions of why and how to choose healthy food and drinks and how to be more physically active. Additionally, the intervention includes a school-based and online support system to help maintain student engagement during the intervention. We will use in-depth interviews with students, peer leaders, teachers, and parents; focus group discussions with peer educators; and direct observation of the school environment and peer leaders' interactions with the students. Acceptability and feasibility of the intervention will be assessed. We will also quantitatively assess limited efficacy by measuring changes in student' physical activity levels and dietary behaviors.

Results: We delivered the peer education intervention at the start of each school year over 3 months for all new grade 6 adolescents in the selected schools, followed by peer support and home engagement activities over 6 months until the end of the school year. There was a baseline assessment and 2 post-intervention assessments: the first immediately after the intervention to assess the short-term impact and the second at the end of the school year to assess the sustained impact on changes in adiposity, diet, and physical activity.

Conclusions: The findings of this study will be used to develop a larger-scale cluster randomized controlled trial to examine the impact of a multicomponent, school- and home-based health promotion intervention. The trial will use innovative peer education methods to reduce overweight and obesity and improve dietary choices and physical activity levels in Vietnamese adolescents.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12619000421134; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=376690&isReview=true

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KEYWORDS

peer education; peer support; peer leader; adolescents; dietary behaviors; physical activity; Vietnam

Introduction

Background

Child overweight and obesity is one of the major risk factors for health in later life, including cardiovascular diseases, some cancers, and lower quality of life in general [1-3]. Overweight and obesity are estimated to cause 3.4 million deaths and account for 4% of years of life lost and 4% of disability-adjusted life years (DALYs) worldwide [4,5]. Despite the paucity of data, child overweight and obesity seem to be rising rapidly in low- and middle-income countries (LMICs) [6] like Vietnam.

In Vietnam, the prevalence of overweight and obesity in children and adolescents is rapidly increasing in urban areas. Within the last decade, there has been a dramatic increase in the prevalence of overweight and obesity in junior high school students in Ho Chi Minh City, the main urban area of the country, from 5.0% and 0.8% in 2002 to 11.7% and 2.0% in 2004, respectively [7]. This upward trend has continued, with the prevalence of overweight and obesity in adolescents increasing from 14.2% to 21.8% over a 5-year period from 2005 to 2009 [8]. Multivariate analyses of survey data collected from 2684 junior high school students found that community and school environments, individual characteristics, and lifestyle behaviors were significantly associated with overweight and obesity in adolescents in Ho Chi Minh City [9].

Recently, a formative study revealed a willingness to increase physical activity to prevent the risk of obesity among junior high school students in Ho Chi Minh City [10]. However, the current physical education curriculum in junior high schools only consists of roughly 2 hours of both theory and practice of sports, which is well below the recommendations of the World Health Organization (WHO) [11].

Systematic reviews have provided evidence that multicomponent interventions have a stronger effect on childhood obesity than programs that focus only on physical activity or dietary behavior change [12,13]. However, there has been no intervention developed in Ho Chi Minh City to promote healthy lifestyles in adolescents. There is currently an urgent need for high-quality, evidence-based programs, which include both nutrition and physical education and a behavior change support system. To design an intervention that combines these components, a pilot study is essential to assess the feasibility and acceptability of the design and delivery strategy of the intervention. Teacher-led or health professional–led interventions can be costly and hard to sustain. In contrast, peer-led programs can be an achievable and effective alternative in economic-constricted settings.

The cost evaluation of the peer-led SALSA (Students As Lifestyle Activists) program in Australian high schools showed that the program was relatively economical to implement [14]. Moreover, the importance of peer relationships and influence intensify during secondary schooling [5,15], and in these settings, peers have a greater influence on the health behaviors of adolescents than parents, teachers, or health professionals [16,17].

The Peer Education and Peer Support (PEPS) project will generate evidence-based insight to design and implement a full-scale intervention to tackle the problem of low physical activity, increased time spent in sedentary activities, and high-energy dense food and imbalanced dietary intake among adolescent in Vietnam and other LMICs.

Objectives

This paper aims to describe the feasibility and acceptability of the PEPS pilot intervention that combines peer education and peer support delivered in the school setting to promote healthier lifestyle choices among adolescents. Additionally, the impact of the intervention on adolescents' dietary practices and time spent on physical activity will also be measured.

Methods

Study Design

This is a pilot cluster randomized controlled trial in which the intervention combines a peer education and peer support system for a total of 6 months.

Study Settings

We will select one intervention school in the city center area (District 5) and another intervention school in a suburban location (District 2). Similarly, one control school located in a city center area (District 11) and another control school located further away from the city center (Tan Binh District) will be selected.

Recruitment

Recruitment of participants for this pilot study include peer educators (undergraduate students at the Pham Ngoc Thach University of Medicine) (PNTUM), peer leaders (grade 8 students), and grade 6 students (the target group).

Peer Educators

Undergraduate students at PNTUM will be included as peer educators if (1) they can contribute the time required to work with peer leaders; and (2) they have some skills and experience in programs involving children.

Peer Leaders

Students will be recruited as peer leaders if they match the following criteria: (1) they are in grade 8 at the participating schools; (2) they are willing to participate as peer leaders (with parental consent); and (3) they do not have any major medical conditions that may interfere with training and peer-educating activities. All peer leaders are selected based on their willingness to volunteer and by the suggestion of teachers of grade 8 classes. All participating peer leaders will be required to sign a consent form, which is also signed by parents or guardians prior to the next steps.

Students

Students will be included in the target group of the intervention if they are: (1) grade 6 students at a participating school; (2) have no major medical issues that may interfere with communication with their peers and learning. Students will be excluded if they meet any of the following criteria: (1) they or their guardian refuse to participate in the intervention; and (2) the student has a medical condition(s) that physically prevents communication and learning. The age range for inclusion is between 10-12 years, and both male and female students will be included.

To increase the participation of schools, we will use a "delayed intervention" technique for the control schools; these schools will be given the opportunity to implement the intervention at the end of the study.

Intervention Plan

Intervention Group

The peer education part comprises 3 steps that involve training the peer educators (undergraduate students at PNTUM), peer leaders (grade 8 students), and target grade 6 students. Figure 1 illustrates the steps involved in implementing the intervention at a school. Preparations for the program will include explaining the intervention and seeking support with project partners, including the school principal, school staff, and parental groups.

In the first step, two 4-hour training workshops for peer educators will be organized at PNTUM using culturally tailored material for teaching and training (the PEPS Manual). The PEPS Manual will be adapted from the manual of the SALSA program implemented in Australia and other countries [18]. The Salsa program is based on the notions of modeling, self-efficacy, peer pressure, and environment from Bandura's social cognitive theory and Freire's empowerment education approach, and aligns with the WHO's Health Promoting Schools Framework [19,20,21, 22].

We will use the SALSA approach for peer-led education, but the contents will be tailored to the Vietnamese context. We will keep the structure of the education session unchanged (eg, the number of lessons will be three) and broader topics (Food Choices, Movement Matters, and Healthy Lifestyles) will remain unchanged from the SALSA manual. We will, however, change the content and specific examples of food, sport, etc, to make them appropriate to our research setting in Ho Chi Minh City. The module will be initially reviewed by a team of investigators that includes 3 Vietnamese researchers experienced in adolescent obesity research. They will identify content that could potentially require a modification. Then, the module will be shared with the peer educators in a training workshop. Feedback from the peer educators about content modification will be obtained. Finally, we will make suggested adjustments to the content. The SALSA program was successfully implemented in China, Jordan, and Australia. The program had a positive impact on secondary school students and peer leaders in Australia and improved energy balance–related behaviors and intentions to live a healthy lifestyle [14,21,22].

Apart from training on peer education theory and content, the peer educators will be given practical training through time spent with students as they work together as a team to learn about interactive peer education.

The second step is organized by the trained peer educators for peer leaders at the intervention schools and covers the content of the PEPS Manual and approaches to teaching and developing communication skills. The four 2-hour workshops, which take place over the course of 2 weeks, will cover crucial knowledge and updates on healthy, active lifestyles (through 4 lessons of the PEPS Manual) and communication skills for the peer leaders to gain trust and to build strong influence to lead their adolescent peers in this behavior-changing pilot intervention. Interactions between the participants will also be handled based on the principle of transparency, care, and benefits to the student during peer group work. The ratio between peer educators and peer leaders in the training sessions will be maintained as 1:5 to 1:6. During the training, the peer leaders are grouped in working teams of 5-6 peer leaders with 2 peer educators in each team as supervisors. One team is dedicated to a single grade 6 class. The total number of teams equals the total number of grade 6 classes. Prior to the second step, preparations for the program will be made, which include explaining the intervention and seeking support from project partners such as the school principals, school staff, school youth associations, and parental associations.

In the third step, grade 6 classes will participate in four 50-minute teaching sessions following the PEPS Manual, which are carried out by teams of peer leaders. The manual includes the following topics: Food Choices, Movement Matters, Healthy Lifestyles, and PEPS Actions (Figure 2). Each session comprises 2 main parts involving theory and practice skills. The theory part is based on specific facts and active learning that involves student participation and peer-to-peer interaction. Practice skills are designed with team and individual problem-solving games. Each session is delivered once a week by a team of 5 peer leaders and 2 peer educators (as supervisors) to the grade 6 class during the free learning hour every week in the school with consent from teachers and students. The 4 PEPS Manual sessions are delivered in 4 consecutive weeks. If any unforeseen obstacle were to arise and the session of the week is put on hold, the core team members of the PEPS project will discuss with the school principal and school board to find a solution. Preference will be given to reschedule the on-hold session for the next available free time. All sessions will be based on the PEPS Manual. The peer educators will help the peer leaders to practice and deliver the training material in a timely fashion. During any teaching week at any school, there will be one core team member of the PEPS project and one reserve peer educator to deal with logistic issues. During the last peer education session (PEPS Actions), each grade 6 class will produce several strategies and plans. The best plan nominated by the class will be put into practice within the class. The strategies and plans are based on adolescent health benefits, adolescent health objectives, school environment, and the willingness of adolescents to make behavioral changes. Subsequently, two of most suitable plans will be selected to apply to the whole school after the education sessions have finished.

The other part of the PEPS program is a peer-supporting system, which include a behavior reinforcement monitoring system and social network support run and led by peers (peer educators and peer leaders) and monitored by PEPS core team members. The personal reinforcement monitoring system consists of a predistributed personal health record diary, a monthly classroom merit board, and school awards every semester. The class reinforcement system includes organizing school events that stimulate the participation of the class to produce activities for class members. These school events are the plans for action for each school (ie, raising awareness of healthy lifestyles through funny health slogans; welcoming behavioral changes by adopting new action objectives). School events also include sports fairs for all grade 6 classes to take place 1 month after the PEPS teaching sessions end. Online peer support will be introduced to grade 6 students during the teaching sessions (Step 3) to encourage students to view, like, and share health posts on the PEPS Project Facebook public page. An IT (information technology) team working with one author will take responsibility for updating and coordinating the Facebook page. We will also support the schools with a student community/social platform (Facebook, Zalo, ZingVN, or other networks), which will be managed by PNTUM students; teachers will monitor the platform to share experiences, answer questions, and help solve challenges that may arise during school events. Peer educators and peer leaders take on an important role in this system as they serve as online helpers for students as they fulfil the health objectives they devised in session 4 (PEPS Actions). Three core team members will supervise all social networking platforms weekly to help the peer educators deal with students' queries.

Figure 1. Summary of the Peer Education and Peer Support (PEPS) program. PNTUM: Pham Ngoc Thach University of Medicine.

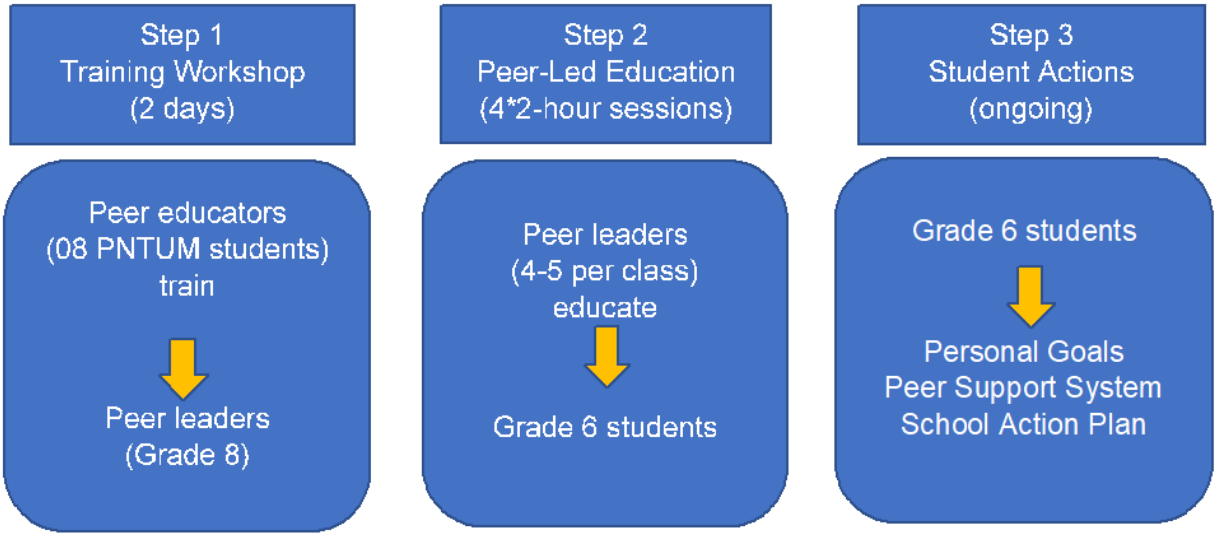

Figure 2. Content of the peer-led education program. SMART: Specific, Measurable, Attainable, Realistic, and Timely.

Control Group

The control group will receive the usual physical education curriculum of the school that comprises three 45-minute sessions (2 required and 1 voluntary) per week. One required session is theory-based and the other two are practical. All sessions are led by physical education teachers.

Outcome Assessment

Primary Outcomes

The primary outcomes include acceptability and feasibility of the intervention to the target population. We will use 3 indicators to measure acceptability: (i) satisfaction, (ii) intent to continue use, and (iii) perceived appropriateness. Feasibility will be assessed by measuring 2 indicators: (i) barriers and facilitators experienced during the implementation of the intervention, and (ii) perceived barriers and facilitators to intervention implementation on a larger scale [23].

Secondary Outcomes

Secondary outcomes consist of changes in dietary behaviors, including skipping breakfast, consuming soft drinks and fast food, and fruit and vegetable intake among targeted students (ie, grade 6 students). Dietary intake will be measured by a validated self-administered youth Food Frequency Questionnaire developed and validated in Ho Chi Minh City [24]. This questionnaire, which can be completed in 20 minutes, records the usual frequency of consumption over the past 6 months of 160 foods representing 8 groups: (i) processed foods; (ii) rice, breads, and cereals; (iii) meat, fish, and other seafood; (iv) fruits and vegetables; (v) sweets and snacks; (vi) milk and dairy; (vii) drinks; and (viii) miscellaneous. Information about breakfast and the frequency of out-of-home meals will also be collected.

Secondary outcomes also include time spent in moderate-to-vigorous physical activity as well as time spent performing sedentary behaviors among targeted students (ie, grade 6 students). Level of physical activity is assessed by the Adolescent Physical Activity Recall Questionnaire, which has

been validated in Vietnamese adolescents [25]. Activities are assigned a metabolic equivalent score according to the compendium of physical activities. The Adolescent Sedentary Activities Questionnaire, which has good-to-excellent reliability and good face validity in Vietnamese adolescents, is used to measure sedentary behaviors including time spent watching TV, playing games, on the computer, doing homework, and performing sedentary hobbies.

Sample Size

The sample size for the qualitative assessments (feasibility and acceptability) is based on the principle of reaching data saturation. We will stop data collection and analysis at the point when no significant new data is generated. The quantitative assessments consist of approximately 200 grade 6 students, because we expect small follow-up losses and a likely high correlation between baseline and follow-up outcome measures.

Intervention Allocation

The assignment of participants to the intervention or control group is based on the location and population size of the school. There are 2 intervention schools and 2 control schools. We allocated the interventions at the school level, but the outcome assessments will be at the individual level.

Consent

Written informed consent from each participant is obtained. Precautions were taken to ensure participants' privacy during data analysis.

Data Collection Methods

Qualitative Data Collection

We will assess acceptability by qualitatively measuring how the intended target populations (grade 6 students, peer educator, peer leaders, teachers, and parents) react to the intervention. Feasibility of the intervention will be assessed by qualitatively measuring the reported experience of implementing the intervention by the target populations involved in implementing the project, such as the peer educators, teachers, and project staff. Evaluation of acceptability and feasibility will be performed at the end of the intervention (6 months from the start of the intervention).

We will collect data from purposively selected multiple sources using in-depth interviews, focus group discussions, and direct observation. Qualitative tools, such as in-depth interviews with grade 6 students, peer leaders, teachers, and parents will be used. We will conduct focus group discussions to collect data from peer educators. We will also use direct observation of the school environment and peer leaders' interactions with the grade 6 students.

During the intervention, we will collect feedback from all participants and institutions after each class. Feedback content will be about the message quality, the instruction of the peer leaders, and the participation of students. Every step is closely monitored and audio or video recorded for analysis. A selection of students will also be invited to qualitative feedback sessions along with meetings with peer leaders weekly in the first month and each month afterwards.

Quantitative Data Collection

Dietary behaviors will be assessed using the validated Food Frequency Questionnaire developed for usage among junior high school students and used in previous studies. The secondary outcomes also include time spent on moderate-to-vigorous physical activity and time spent on sedentary behaviors among grade 6 students.

Time spent on moderate-to-vigorous activity will be assessed using the validated Physical Activity Questionnaire, and the time spent on sedentary behaviors will be assessed using the validated Sedentary Questionnaire that were used in previous studies among adolescents in Ho Chi Minh City [26,27].

Other Data Collected

Students' standing height will be measured with a portable direct-reading stadiometer to the nearest 0.5 cm using the standard stretch stature method [28]. Body weight will be measured with shoes and heavy clothes removed using a Tanita electronic scale (Tanita BF 571, Tanita Corporation) to the nearest 0.1 kg. Anthropometric standardization exercises will be conducted by 2 trained data collectors using standard methods to ensure all data will be collected with uniform techniques and standardized measurement procedures [28]. The adolescent's pubertal status will be self-assessed using a questionnaire with photographs illustrating 5 stages [29] of pubertal development for pubic hair, male genitalia, or female breasts; for female students, the date of their first menstruation is also recorded.

Data Management

All quantitative data will be collected and entered using tablets at each school.

Statistical Methods

Analyses will be conducted using Stata 15 (StataCorp). Descriptive statistics will be used to describe the baseline characteristics of the sample. Feasibility and acceptability will be assessed following the evaluation plan described above. BMI will be calculated as weight in kilograms divided by the square of height in meters (kg/m^2). The subjects were classified as overweight and obese by applying the age and sex-specific WHO BMI cutoff points [30]. Linear and logistic regression will be used to determine the effect of the intervention on the secondary outcomes, controlling for potential confounders (eg, sex, age, BMI).

Research Ethics Approval

This study was approved by the Committee of Medical Ethics of the Pham Ngoc Thach University of Medicine (3783/GXN-TĐHYKPNT) and registered with the Australian New Zealand Clinical Trials Registry (ACTRN12619000421134).

Results

The first participant was enrolled in early September 2018. Recruitment was completed by March 2019. We delivered the peer education intervention at the start of each school year over 3 months for all new grade 6 adolescents in the allocated schools, followed by peer support and home engagement

activities over 6 months until the end of the school year. However, the outcome assessments will be based on a cohort of adolescents only. There was a baseline assessment and 2 post-intervention assessments: the first immediately after the intervention to assess the short-term impact and the second at the end of the school year to assess the sustained impact on changes in adiposity, diet, and physical activity. In total, 326 grade 6 students were recruited. Data collection was completed in September 2019.

Discussion

This paper presents the protocol for a pilot trial to determine the feasibility and applicability of a peer education and peer support intervention to promote healthy lifestyles for the prevention of overweight and obesity in adolescents in Ho Chi Minh City. The intervention combines a peer education and peer support system for a 6-month period.

A recent systematic review of peer-led interventions to prevent child and adolescent obesity found that peer-led interventions significantly impacted both BMI and combined BMI outcomes of children and adolescents [31]. The review examined 25 peer-reviewed papers from 14 studies with 2506 participants and found a mean estimate of the effect on BMI to be a reduction of 0.15 kg/m^2 (95% CI –0.26 to –0.03). Subgroup analyses revealed an estimated effect twice as strong in adolescents aged 11 years or older than with younger children. The impact of the intervention was also found to be much stronger for longer-term interventions of 6 months and more. However, the studies in the review were conducted in high-income countries and many had small size samples. Findings from the review highlight the need for well-designed studies in LMICs with enough power to more precisely assess the impact of peer education and to evaluate the best approach to peer leading. Additionally, in many school-based obesity prevention trials, the initial positive impact was greatly reduced or eventually neutralized once the teachers or health workers were no longer onsite.

Hence, this study will generate evidence of feasible and acceptable approaches to interventions to prevent excess weight gain and methods of peer-led education to promote healthy lifestyles to prevent obesity in adolescents in LMICs. The findings of the study will be used to inform the development of a larger scale cluster randomized controlled trial to examine the impact of an intensive, multicomponent, school- and home-based lifestyle promotion intervention using innovative peer education methods to improve diet and physical activity and reduce obesity in urban Vietnamese adolescents.

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Authors' Contributions

HKT prepared the manuscript. NMN, MJD, THHDN, and AA contributed to the conceptualization and design of the study. All authors revised the manuscript critically and approved the version to be published.

Conflicts of Interest

None declared.

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Abbreviations

DALY: disability-adjusted life year
IT: information technology
LMIC: low- and middle-income country
PEPS: Peer Education and Peer Support
PNTUM: Pham Ngoc Thach University of Medicine
SALSA: Students As Lifestyle Activists
WHO: World Health Organization

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Original Paper

Achieving Optimal Gestational Weight Gain, Birth Weight, and Perinatal Outcomes Among Pregnant Women at Risk of Hypertension: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Hypertensive disorders, including preeclampsia, complicate 10% of all pregnancies, causing maternal and fetal morbidity and mortality. In Bangladesh, 24% of all maternal deaths are directly attributed to hypertensive disorders. Conventional antenatal care practices often delay or miss detecting hypertensive disorders in pregnancy, which may allow some women to become vulnerable to the adverse consequences of the hypertensive disorders. Regular self-monitoring of blood pressure and weight gain may improve maternal and fetal outcomes among pregnant women at risk of developing hypertensive disorders during pregnancy through early diagnosis, prompt referral, and timely clinical management; however, to undertake a randomized controlled trial of an intervention to reduce adverse consequences of hypertensive disorders in pregnancy, its feasibility must first be determined.

Objective: The objectives of this study are to evaluate the accuracy of a wearable blood pressure monitoring device (Health Gauge) in order to test the design and methods of a future definitive randomized controlled trial, and to examine the feasibility, acceptability, and fidelity of an intervention focusing on regular monitoring of weight gain and self-monitoring of blood pressure for pregnant women at risk of developing hypertensive disorders and their associated complications.

Methods: The study is located in Matlab, Bangladesh will be conducted in two phases. First, a wearable blood pressure device (Health Gauge) will be validated in accordance with the European Society of Hypertension International Protocol (revision 2010). Second, a prospective, two-arm, parallel, and nonblinded randomized controlled external pilot trial will be conducted. In the pilot trial, 70 eligible participants will be individually randomized to the intervention arm, in which pregnant women will self-monitor their blood pressure daily using a wearable device (Health Gauge) and be evaluated monthly by trained health workers for weight gain from 20 weeks of gestation until delivery, or the control arm, in which pregnant women will be assessed for weight gain every two months from 20 weeks of gestation until delivery (1:1 intervention to control allocation ratio using a permuted block randomization method with concealment). All women will receive standard antenatal care.

Results: A validation study of the wearable blood pressure device has successfully been conducted among the general adult population in Matlab, Bangladesh. As of September 2019, the pilot trial has completed enrollment of women who are pregnant (N=70; intervention: n=35; control: n=35) and follow-up of the participants is ongoing. Data analysis is expected to be completed by June 2020, and results are expected to be submitted for publication in August 2020.

Conclusions: The findings of this study will help us to design a comprehensive, full-scale randomized controlled trial to test the efficacy of regular self-monitoring of blood pressure and weight gain during pregnancy, a simple and inexpensive intervention to help to achieve optimal maternal and fetal outcomes in pregnant women at risk of developing hypertensive disorders and their associated complications during pregnancy.

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KEYWORDS

hypertensive disorder; hypertension; pregnancy; preeclampsia; gestational weight gain; continuous blood pressure monitor; wearable device; Health Gauge; birth weight; perinatal outcome

Introduction

Background

Hypertensive disorders complicate 10% of all pregnancies worldwide [1]. They include chronic hypertension (pre-existing or when detected prior to 20 weeks of gestation), white-coat hypertension (an elevated blood pressure at clinic but normal blood pressure at home), masked hypertension (normal blood pressure at clinic but elevated blood pressure at home), gestational hypertension (elevated blood pressure detected after 20 weeks but no other systemic manifestations), and preeclampsia (elevated blood pressure detected after 20 weeks with proteinuria or biochemical or hematological abnormalities) [2]. Hypertensive disorders during pregnancy lead to severe morbidity and long-term cardiovascular disability in pregnant women and their offspring and are responsible for 14% of all maternal deaths [3,4]. Hypertensive disorders during pregnancy also lead to fetal growth restriction, preterm birth, and increased perinatal mortality [3]. Preeclampsia, a particularly devastating form of hypertensive disorder, is responsible for approximately 70,000 maternal deaths and more than 500,000 perinatal deaths globally each year [2].

In Bangladesh, 24% of maternal deaths are attributable to hypertensive causes [5]. Although the maternal mortality ratio in Bangladesh declined by 40% between 2001 and 2010 [6], the maternal mortality ratio stalled thereafter. The ratio in 2016 of 196 maternal deaths per 100,000 live births was identical to the estimate in 2010. Furthermore, the cause-specific mortality ratio due to hypertensive disorders of pregnancy increased from 39 per 100,000 live births in 2010 to 46 per 100,000 live births in 2016 [5]. Additionally, the prevalence of fetal growth restriction in Bangladesh is manifested in 30.5% of births being small for gestational age which is among the highest in the world. The rate of preterm birth which is 14.1% [7] is also high. Reducing maternal mortality, small for gestational age births, and malnutrition in children under five years age in Bangladesh and other low- and middle-income countries are now the major concerns of many governments and international agencies [8]; however, the most tractable pathways for effective interventions to promote healthy pregnancy, gestational weight gain, and fetal growth remain uncertain.

In conventional practice, pregnant women are evaluated for hypertensive disorders or associated complications during routine antenatal care visits. Standard antenatal care practices often delay or miss detecting hypertensive disorders during pregnancy, which may allow the women to become vulnerable to the adverse consequences of hypertensive disorders. Although, over the last two decades in Bangladesh, there has been an increase in the occurrence of at least one antenatal care (78%) visit during pregnancy, only 31% of women attend the recommended 4 antenatal care visits [6]. Furthermore, the quality of health care, which is fundamental to translating use of antenatal care services into improved maternal and fetal health outcomes, is generally poor in Bangladesh [5]. Weight and blood pressure measurements are two essential components of antenatal care services and should be ensured for quality care. Monitoring weight gain is important because both inadequate and excessive weight gain during pregnancy have been associated with an increased risk of developing hypertensive disorders [9,10]. To achieve an optimal pregnancy outcome, the United States Institute of Medicine provided recommendations for gestational weight gain stratified according to prepregnancy body mass index (BMI). The 2009 US Institute of Medicine guidelines on total gestational weight gain suggest that women who are underweight (BMI less than 18.5 kg/m^2), normal weight (BMI from 18.5 to 24.9 kg/m^2), overweight (BMI from 25.0 to 29.9 kg/m^2) or obese (BMI greater than or equal to 30.0 kg/m^2) should gain from 12.5 to 18 kg, 11.5 to 16 kg, 7 to 11.5 kg, and 5 to 9 kg, respectively. The recommendations for rates of weight gain during the 2nd and 3rd trimester are 0.51 (range 0.44-0.58) kg/week, 0.42 (range 0.35-0.50) kg/week, 0.28 (range 0.23-0.33) kg/week and 0.22 (range 0.17-0.27) kg/week, respectively, for the same BMI stratification [11]. As blood pressure has a property of circadian and other temporal variations, the current blood pressure measurement practices, which are also subject to interclinician and terminal digit bias, result in misdiagnosis [12]. A better method of hypertension diagnosis in women makes use of multiple measurements taken over continuous monitoring of blood pressure. While 24-hour ambulatory blood pressure monitoring could be an option, it can cause discomfort, particularly during pregnancy and is limited to only 24 to 48 hours of continuous monitoring [13]. In contrast, physiological parameter–derived blood pressure measurement is novel, noninvasive, and convenient to regularly monitor blood pressure. Blood pressure is estimated through linear modeling of extracted physiological parameters and machine learning algorithms that use features such as electrocardiogram (ECG) and photoplethysmography (PPG) derived pulse width and pulse transit time. Health Gauge is an affordable, wrist-worn wearable device that uses pulse width and pulse transit time to provide blood pressure measurements and is convenient for obtaining a picture of blood pressure and heart rate variability over time (Figure 1). Other methods, such as uterine artery Doppler ultrasonography and maternal blood concentrations of angiogenic factors and metabolomics, are also available to predict and monitor hypertension in pregnancy [14]; however, these tools are more expensive and less convenient for use in resource-poor settings including Bangladesh.

Figure 1. Health Gauge blood pressure monitoring device.

As the optimal management of hypertensive disorders of pregnancy remains unclear, the International Society for the Study of Hypertension in Pregnancy recommends that "*every hypertensive pregnant woman be offered an opportunity to participate in research, clinical trials, and follow-up studies*" [2]. We believe a simple intervention such as regular self-monitoring of blood pressure and weight gain has the potential to improve gestational weight gain and perinatal outcomes in pregnant women at risk of developing hypertensive disorders and complications through early diagnosis, prompt referral, and timely management. To undertake a randomized controlled trial of an intervention to reduce adverse consequences of hypertensive disorders during pregnancy raises important practical concerns about the implementation of the study. This exploratory study will address the question of whether a randomized controlled trial is an appropriate design and if it is feasible.

Objectives

The aims of the pilot trial are to test the design and methods of a future definitive randomized controlled trial and to examine the feasibility, acceptability, and fidelity of an intervention focusing on regular monitoring of weight gain (once a month) during pregnancy using a digital weighing scale and regular self-monitoring of blood pressure (twice daily) using a wrist-worn blood pressure measuring device (ie, Health Gauge) in a sample of pregnant women who are at risk of developing hypertensive disorders and its associated complications. We will also evaluate the accuracy of Health Gauge in measuring blood pressure through validation studies. Acceptability and usability of Health Gauge for continuous self-monitoring of blood pressure in pregnancy will be assessed in the pilot trial.

Methods

Overview

The study will be conducted in two phases in Matlab, Bangladesh. Matlab is a low-lying riverine area which is situated 55 km southeast of the capital of Bangladesh. Since 1966, the icddr,b has been running an internationally recognized Health and Demographic Surveillance System involving a population of 230,000 in Matlab, Bangladesh [15]. Registration of vital events such as births, deaths, marriages, and migration are updated by community health research workers every two months. Information on reproductive health outcomes, contraceptive use, breastfeeding, and immunization is also collected.

Phase 1: Validation of Health Gauge

The Health Gauge device and an artificial intelligence and machine learning–based companion smartphone app will be provided by Salu Design Group Inc. Health Gauge is a compact, wrist-based, cuff-less blood pressure monitoring device that uses a combination of 2-contact ECG and PPG as well as a combination of pulse wave analysis algorithms, machine learning, and neural network computing techniques to calculate blood pressure instantly. The blood pressure data can be synchronized with and accessed from a smartphone through the secure-access app.

In internal quality control preliminary tests, Health Gauge provided precise and accurate blood pressure measurements in adults (personal communication, Randy Duguay, CEO, Salu Design Group Inc); however, further evaluation is required in our setting to determine whether the device functions effectively and records blood pressure measurements accurately. The validation study aims to assess the accuracy of the device in measuring blood pressure, according to the European Society of Hypertension International Protocol (ESH-IP revision 2010) [16].

A total of 33 participants who fulfill the age, sex, baseline blood pressure, and other requirements will be included in the validation study. For age criteria at least 10 men and 10 women who are 25 years or older, and for baseline blood pressure, 10 to 12 participants with systolic blood pressure in each of three ranges (90 mmHg to 129 mmHg, 130 mmHg to 160 mmHg, and 161 mmHg to 180 mmHg) and 10 to 12 participants with diastolic blood pressure in each of three ranges (40 mmHg to 79 mmHg, 80 mmHg to 100 mmHg, and 101 mmHg to 130 mmHg) will be included. Validation in specific groups such as adolescents or pregnant women may also be carried out with necessary modification of these requirements, and all such changes or additions will be clearly described during reporting. All the participants will be recruited from outpatients of Matlab hospital (icddr,b) or as volunteers residing in Matlab near the hospital.

The validation team will consist of three trained medical doctors (two observers and one supervisor). The gold standard reference blood pressure measurement will use two standard mercury sphygmomanometers and a good quality teaching stethoscope.

Simultaneous auscultations will be performed by two observers using the teaching stethoscope. These two observers will be blinded to each other's readings. The supervisor will verify the blood pressure readings of the other two observers to ensure that the difference between the two observations is less than or equal to 4 mmHg for either systolic or diastolic pressure values. If the difference is greater than 4 mmHg for either, the measurement will be repeated. The supervisor will also measure blood pressure using Health Gauge. The blood pressure measurements will be alternated between the mercury sphygmomanometer and Health Gauge device. In total, nine consecutive blood pressure measurements will be performed in each participant using the mercury sphygmomanometer (5 times) and Health Gauge (4 times).

Data will be analyzed and reported according to the ESH-IP revision 2010 requirements to conclude if Health Gauge passes the validation protocol; the differences between the measurements obtained from Health Gauge and the mercury sphygmomanometer will be classified according to whether the values are within 5 mmHg, 10 mmHg, or 15 mmHg. The differences will be classified separately for systolic and diastolic blood pressure. Details of the methods, procedures, and analysis have been described elsewhere [16,17]. Phase 2 will proceed when Health Gauge has been validated.

Phase 2: Pilot Randomized Controlled Trial

Study Design

This study is designed as a prospective, two-arm, parallel, and nonblinded randomized controlled external pilot trial. Eligible participants will be individually randomized in a 1:1 allocation ratio to the intervention arm, in which pregnant women will self-monitor their blood pressure daily using a wearable device (Health Gauge) and be evaluated for weight gain monthly from 20 weeks of gestation until delivery, or the control arm, in which pregnant women will be assessed for weight gain every two months from 20 weeks of gestation until delivery. All women will receive standard antenatal care.

Study Population Eligibility Criteria

Inclusion criteria are pregnant women in Matlab, Bangladesh with a high-risk pregnancy who are between 12 and 16 weeks of gestation and are between 15 and 50 years of age. Exclusion criteria are women who have a congenital malformation or anomaly, a chromosomal abnormality (such as Down syndrome), chronic debilitating illness, diagnosed psychosis, no electricity at home, and never used a smartphone. In this study, a high-risk pregnancy is defined to identify women at risk of developing hypertensive disorders of pregnancy or their complications [3], as a pregnant woman who meets any one or more of the following criteria: had preeclampsia or gestational hypertension in a previous pregnancy, has chronic hypertension, has chronic kidney disease, had pregestational diabetes, has systemic lupus erythematosus or antiphospholipid syndrome, pregnancy is her first pregnancy (nulliparity), is aged 40 years or older, interpregnancy interval is less than 2 years or greater than 10 years, has a BMI of 35 kg/m^2 or more, has polycystic ovary syndrome, has a family history of preeclampsia, pregnancy is a multiple pregnancy, has pre-existing thrombophilia, used of selective serotonin reuptake inhibitors beyond the first trimester, has donated a kidney, underwent in vitro fertilization, and has a family history of coronary heart disease.

Sample Size

Since this is an exploratory study, conventional sample size calculation may not be applicable; however, we will aim for 35 participants in each arm based on the recommendation by Whitehead et al [18] on the required sample size for pilot trials and by considering a conservative (small) effect size for the definitive trial designed with 90% power and two-sided 5% significance. Our sample size calculation takes into account a 20% attrition.

Randomization and Allocation Concealment

Participants will be assigned to the intervention or the control arm using a permuted block randomization method with concealment to ensure that the allocation is not made before the participant has given their consent and joined the study. A random allocation sequence will be generated using a computerized random allocation system (RALLOC module in Stata statistical software; version 14.1; StataCorp LLC) for permuted block randomization to ensure comparable allocation numbers at a certain equally spaced points in the sequence of patient assignment and randomization for parallel study design will be used. Reasonably large blocks with variable block size will be constructed to reduce predictability. The random allocation sequence will be prepared in advance by an independent researcher from icddr,b who has no involvement with the trial.

The randomization list will be transferred to health workers via the health research supervisor into sequentially numbered nontransparent sealed envelopes each containing the name of the group (intervention or control) on a card inside the envelope to ensure that the study personnel do not know the order of this list and are unable to predict the next assignment/allocation. Only one block will be supplied at a time from the independent researcher, and the next block will be provided just after completion of the previous block. The envelopes will be kept in a locker in a secured place, and the key of the locker will be available with the health research supervisor. The health research supervisor will not use the key to open the lock until the last envelope given to health worker has been used. The independent researcher will keep a duplicate set of sealed envelopes.

Blinding

Neither the participants nor the investigators and assessors of outcomes can be blinded to allocation because of the nature of service delivery that will be provided, and thus, we are obliged to make the randomized controlled trial nonblinded; however, it should be mentioned that the outcomes of the trial are objective in nature, therefore, the risk of bias is minimal. Furthermore, the randomization, as well as statistical analysis, will be carried out by someone unconnected to the enrollment process.

Intervention

Before 20 weeks of gestation, each woman in the intervention arm will be provided with a Health Gauge device and with a

smartphone, if she does not already have one. The app for Health Gauge will be installed on each participant's smartphone. The women will be asked to use the Health Gauge device and app to measure their blood pressure at least two times a day (morning and evening), starting from 20 weeks of gestation. The blood pressure measurement records will be automatically stored in the smartphone app. Participants will be trained to charge and operate the Health Gauge device. Most women in rural Matlab do not have internet access. Hence, trained health workers will visit the women weekly and synchronize the smartphones with tablet computers to collect the stored data and to upload the data to an online server. The health workers will also measure the weight of the participant using a digital weighing scale every month. If any woman is found to be hypertensive (blood pressure is greater than or equal to 140/90 mmHg on two consecutive measurements), is presenting signs and symptoms associated with hypertensive disorders or associated complications (described later), or is gaining weight outside of the applicable US Institute of Medicine recommended range [11], she will be advised to visit Matlab hospital (icddr,b) or a government health facility immediately for further evaluation and management. If the condition demands, our health worker will ensure that an appropriate referral is made to a tertiary health care facility. This intervention will be in addition to the conventional programs offered by icddr,b as well as government health facilities.

In conventional care, women without any major risk factors, danger signs, or health conditions should visit a health facility four times during the antenatal period (at 8 to 12 weeks, 24 to 26 weeks, 32 weeks, and 36 to 38 weeks, with an additional visit at 41 weeks if they have not yet given birth). Pregnant women are separated into two groups by their care requirements—those eligible to receive routine care and those who require special care based on their health conditions or risk factors. Women with risk factors or special conditions are referred to a specialized clinic or hospital for further evaluation, and care is continued according to a specialist's advice. Women who are initially referred to a specialist may be subsequently considered eligible for routine care and women who are initially enrolled in routine care may later need to be referred for specialized care [19].

Control

All women randomized to the control arm will receive standard antenatal care. In addition, health workers will visit the women every two months starting from 20 weeks of gestation to measure their weight using a digital weighing scale. If any woman is gaining weight outside of the applicable US Institute of Medicine recommended range, she will be advised to visit Matlab hospital (icddr,b) or a government health facility immediately for further evaluation and management. If the condition demands, our health workers will ensure that an appropriate referral is made to a tertiary health care facility.

Health workers will counsel all participants, both in the intervention and in the control group, to make at least four antenatal visits. All women will be provided with general education to maintain a balanced diet and to remain physically active during pregnancy.

Participant Enrollment and Follow-up

In Matlab, pregnancies are usually diagnosed by 12 weeks of gestation and recorded by Health and Demographic Surveillance System field staff. We will obtain this information from Health and Demographic Surveillance System and conduct baseline interviews to identify eligible participants for this study. Health worker will continue to conduct baseline interviews and enroll participants whenever newly pregnant women are identified, and to obtain information from the Health and Demographic Surveillance System until the desired sample size is met. Each potential participant will be provided with a consent form in the local language (Bengali). Health worker will also explain the study in detail and answer any questions. If a woman agrees to participate in the study, her signature or left thumb impression and that of a witness will be taken. A health worker will also sign the consent form in front of the woman and the witness on behalf of the principal investigator of the study. Then the health worker will conduct a short interview using a semistructured questionnaire and record the woman's height and weight. If eligibility criteria are satisfied, the health worker will open the sealed envelope (in sequence and in front of the participant and the witness) that assigns the participant to the allocated group (intervention or control). If the woman does not meet the eligibility criteria, she will be informed that she cannot take part in the study.

Once enrolled, the women will be followed from 20 weeks of pregnancy until delivery. Health worker will visit women in the intervention arm weekly and those in the control arm every two months. Furthermore, health workers will maintain mobile communication with all women to keep track of the progress of the pregnancy. Health worker will collect outcome data from the households and health facilities by follow-up visit or by phone.

Data Collection

Questionnaire Preparation

Questionnaires will be prepared in English, and then translated into Bengali with back-translation. The Bengali questionnaires will be used in the field. Pretesting will be done before finalizing the questionnaire. Field staff will be given training on administering the questionnaires.

Baseline Questionnaire

A brief questionnaire will be designed to collect baseline information on the participants. Questions on age, education level, occupation, and work status of the pregnant woman, her husband, and members in her household will be included. Information on household income, marital status, parity, whether pregnancy was intended, living conditions, tobacco use, health and nutrition, knowledge of nutrition and dietary practices, health-seeking behavior, and media exposure will also be collected.

Follow-up Questionnaire

Health worker will administer a follow-up questionnaire weekly to the women in the intervention group to collect information on signs and symptoms associated with hypertensive disorders and complications, including sense of awareness, headache,

blurring of vision, abdominal pain, nausea and vomiting, edema, and convulsions over the previous week.

Acceptability

The acceptability of using Health Gauge for continuous self-monitoring of blood pressure will be evaluated by women in the intervention group using a 5-point Likert scale. In addition, interviews will be conducted to assess the women's perception two times: during the third trimester and after delivery.

Perinatal Outcomes

Information including predelivery weight, perinatal outcomes, and infant length, weight, and head circumference at birth will be obtained from hospital records, discharge certificates given after institutional delivery or from the woman herself using a simple checklist.

Health and Demographic Surveillance System Records

Age and asset score (wealth quintile) of the study participants will be retrieved from the Health and Demographic Surveillance System database.

Anthropometry

Health worker will measure the height and weight of each pregnant women following standard anthropometric procedures. Height will be measured using locally made standardized stadiometer. Weight will be measured using a digital weighing scale.

Training of the Health Workers Delivering the Intervention

Four skilled and experienced health workers who each have at least 12 years of formal education will undergo a fifteen-day intensive training program, which will include lectures, mock interviews, role play, and field practice at the community level. A training manual will be developed to guide the health workers in the field.

Data Quality

To ensure the accuracy of the data, several quality control measures will be undertaken at different stages of the data collection procedure: (1) Since the participants are women, we will recruit experienced female health workers for data collection to minimize observer bias. (2) We will establish a multilayered monitoring system to maintain and standardize data quality. A health research supervisor will check data consistency daily by thoroughly checking the filled-out questionnaires at the end of the day. (3) We will perform spot-checking, re-interview, back-checking, and provide necessary feedback. (4) Regular meetings with the research team and refresher training sessions (if required) will be arranged for the health workers.

Outcome Measures

Primary

The feasibility outcomes (primary outcomes) will be recruitment rate, retention rate, adherence to the protocol, and acceptability. Recruitment rate will be defined as the mean number of participants recruited per month. Both eligibility and consent rate will be recorded. Recruitment rate is an important outcome because unforeseen enrolment challenges may arise and are crucial to identify in a pilot study. Retention rate will be defined as the proportion of participants who will participate in the full follow-up period of the study (from 20 weeks of gestation until delivery). Adherence will be defined as the proportion of participants following the intervention protocol. There may be several reasons why a participant does not follow the intervention protocol properly. Health workers will note the cause and the number of instances of nonadherence in a log sheet. Nonadherence will be classified into protocol deviations caused by circumstances beyond their control and those that are not (for example, the participant chose to remove Health Gauge). Participant will rate the acceptability of using Health Gauge for continuous self-monitoring of blood pressure two times during the follow-up period using a 5-point Likert scale. Acceptability will be evaluated once during the third trimester and again after delivery.

Secondary

Clinical outcomes will be rate of weight gain during pregnancy; infant weight, length, and head circumference at birth; hypertension status; adverse consequences of hypertensive disorders; blood pressure profile and heart rate; risk factors; and serious adverse events. Rate of weight gain during pregnancy will be measured in kilograms per week and be calculated by subtracting the baseline (enrollment) weight from the predelivery weight and dividing that value by the number of weeks between the two time points. Infant weight will be measured in grams, infant length will be measured in centimeters, and head circumference at birth will be measured in centimeters. The number of women with chronic hypertension and who develop hypertensive disorders will be recorded. Adverse consequences of hypertensive disorders of pregnancy will be defined as maternal or fetal complications or consequences that arise in a woman with chronic hypertension or in a previously normotensive woman who has developed some form of hypertensive disorder after at least 7 days of intervention. Maternal complications are abruptio placentae, disseminated coagulopathy or hemolysis, elevated liver enzymes and low platelets syndrome, pulmonary edema, acute kidney injury, eclampsia, liver failure or hemorrhage, stroke, or death. Fetal or neonatal complications are intrauterine death or stillbirth, preterm birth, small for gestational age, low birth weight, hypoxic brain injury, and complications associated with small for gestational age, low birth weight, or prematurity. Episodes, type, and timing of occurrence of adverse consequences will be reported. The blood pressure profile along with heart rate from 20 weeks of pregnancy until delivery will be recorded. The prevalence of specific risk factors along with the sociodemographic profile of the participants will be determined. We do not anticipate any serious adverse events in this trial; however, should any other adverse events arise they will be reported in detail.

Covariates

Covariates in this study are age (in years), height (in centimeters), weight (in kilograms), body mass index (in kg/m^2), parity, duration of pregnancy, maternal smoking (including

second-hand smoke) and use of chewing tobacco, and asset score (socioeconomic status).

Data Analysis

Data presentation, analysis, and reporting will be carried out according to CONSORT randomized pilot and feasibility trial guidelines [20]. The feasibility outcomes will be reported descriptively as well as narratively. Only descriptive statistics will be reported for the clinical outcomes. Mean and 95% confidence interval will be reported for continuous variables, median and interquartile range will be reported for ordinal variables, and raw count (number and percentage) will be reported for categorical variables. No conventional test of hypothesis will be performed since as a pilot trial, statistical power is lacking; however, the estimates of effect using clinical outcomes as they are likely to be measured in the definitive trial will be reported as estimates with 95% confidence interval. Analyses will be performed at the end of the study. No interim analyses or subgroup analyses are planned due to the short duration and small sample size of this pilot trial. Data will be analyzed using Stata software (version 14.1; StataCorp LLC).

Ethics Approval

The study was reviewed and approved by the Research Review Committee and the Ethical Review Committee of icddr,b (PR-18026). This study has been registered with ClinicalTrials.gov (NCT03858595).

Results

Phase 1, the validation of Health Gauge, was successfully conducted among general adult participants of both sexes in Matlab, Bangladesh. Validation among special groups is underway. As of September 2019, the pilot trial (phase 2) has completed enrollment of women who are pregnant (N=70; intervention: n=35; control: n=35). Follow-up of the participants is ongoing and is expected to be completed by the end of October 2019. Data analysis is expected to be completed by June 2020, and results are expected to be submitted for publication in August 2020.

Discussion

In this protocol, we present the design and procedures of a two-phase experimental study in which we validate an intervention tool (Health Gauge, a wrist-worn blood pressure measuring device) and evaluate the feasibility of an intervention (regular self-monitoring of blood pressure by Health Gauge and health worker–guided monitoring of weight gain during pregnancy using a digital weighing scale) through a pilot trial. To our knowledge, this is the first study of its kind in Bangladesh and worldwide. In this study, we focus on a well-defined at-risk population (pregnant women at risk of developing hypertensive disorders of pregnancy or their complications) with an urgent need for accessible, low-cost measures to mitigate the adverse consequences of hypertensive disorders of pregnancy. We conjecture that a simple intervention such as regular self-monitoring of both blood pressure and weight gain could be useful for improving maternal and fetal outcomes in this population through early diagnosis, prompt referral, and timely management. The proposed intervention will be tested for efficacy through a future randomized controlled trial, and this feasibility study will guide the definitive randomized controlled trial. This study provides a platform for both developing and testing a new technology for self-measurement of blood pressure among end-users. The findings will shed light on the acceptability of the device and appropriate measurement practices among the target population. The findings will also guide changes and improvements in the device, its companion app, and the monitoring protocol. That our research team consists of people from diverse background with expertise in maternal and child health and nutrition, clinical and public health research, trial design, and computer programming and machine learning algorithms will help us adopt a multidisciplinary and comprehensive approach to achieve a common goal—healthy pregnancy, healthy baby.

A major limitation of this study is that pregnant women without access to electricity at home or who are not familiar with smartphones must be excluded. Additionally, limited internet access to the internet among participants as a result of Matlab's rural setting makes live monitoring of blood pressure data difficult. Access to the blood pressure data will only be available at weekly intervals when the health workers visit the participants and synchronize the data with the online server. Nevertheless, pregnant women will be trained to take their own blood pressure measurements using Health Gauge. They will be informed to contact the health workers by phone and visit the nearest health facility if they find that their blood pressure is greater than or equal to 140/90 mmHg on two consecutive measurements. Another limitation is the lack of nonsubjective qualitative approach to ascertain acceptability and usefulness of the intervention. Finally, the small sample size limits the statistical power to detect any effect of the intervention on clinical outcomes; however, the sample size should be sufficient to accomplish the objectives of this pilot trial.

After successful completion of this study, the data will be accumulated, analyzed, and reported. The companion app for Health Gauge will be evaluated and improved using data generated in the study and machine learning for more accurate and precise blood pressure measurements; the design of Health Gauge may also be modified or adapted, if necessary. In the definitive trial, the intervention may include additional educational materials and focused counseling sessions. The implementation protocol may be revised to allow women to self-monitor weight gain akin to the protocol used for blood pressure measurements. Based on the results of and experience gained from this pilot trial, we will design a full-scale randomized controlled trial to test the efficacy of the intervention.

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Authors' Contributions

SMTH and SIA conceived and designed the study, composed the content and implementation procedures, contributed to development of the smartphone app, managed the implementation, and drafted the manuscript. AK and SAS contributed substantially to the study design and procedures. TA contributed to the development of methodology and intervention content. AK, SAS, and TA were involved in reviewing and revising the manuscript critically. All authors read and approved the final manuscript.

Conflicts of Interest

SMTH and SIA were involved in providing feedback and input to the current development of the smartphone app for Health Gauge, but neither SMTH nor SIA received any financial benefit from Salu Design Group Inc. There are no other conflicts of interest to declare.

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Abbreviations

ECG: electrocardiogram
ESH-IP: European Society of Hypertension International Protocol
icddr,b: International Centre for Diarrhoeal Disease Research, Bangladesh
PPG: photoplethysmography

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Protocol

Engaging Patients and Professionals to Evaluate the Seriousness of Maternal and Child Health Outcomes: Protocol for a Modified Delphi Study

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Abstract

Background: Maternal weight gain during pregnancy is one of the few potentially modifiable risk factors for many adverse maternal and child health outcomes. Defining the optimal pregnancy weight gain range is difficult because, while lower weight gain may prevent some outcomes, such as maternal and child obesity, it may increase the risk of others such as fetal growth restriction and infant death. These health outcomes vary in their seriousness to mothers and their health care providers, and these differences in seriousness should be taken into account when determining optimal weight gain ranges. However, the relative seriousness that women and their care providers place on different health outcomes is unknown.

Objective: We will determine the seriousness of 11 maternal and child health outcomes that have been consistently associated with pregnancy weight gain. We will achieve this by engaging patients and maternal and child health professionals using an online modified Delphi panel process.

Methods: We aim to recruit a racially/ethnically and geographically diverse group of 90 US maternal and child health professionals and 90 women who are pregnant or less than 2 years postpartum. We will conduct 3 concurrent panels using the ExpertLens system, a previously evaluated online modified Delphi system that combines 2 rounds of rating with 1 round of feedback and moderated online discussion. In Round 1, panelists are asked to rate the seriousness of each health outcome on a scale of 0-100 and to provide a rationale for their scores. In Round 2, panelists will review their responses relative to those of other panelists. They will discuss their seriousness ratings anonymously using a moderated online discussion board. In Round 3, participants will revise their Round 1 responses based on group feedback and discussion. Each round will be open for 1-2 weeks.

Results: The study protocol was reviewed by our ethics boards and did not require approval as human research. A pilot study of 6 professionals and 7 patients was completed in December 2019.

Conclusions: Our numeric estimates of the seriousness of maternal and child health outcomes will enable future studies to determine pregnancy weight gain ranges that balance the risks of low and high weight gain for mothers and children.

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KEYWORDS

children; Delphi method; ExpertLens; mothers; pregnancy; patient engagement; online stakeholder engagement panels

Introduction

Maternal and child health in the United States is far worse than expected from a high-income country. The US maternal mortality ratio (19 deaths per 100,000 live births) ranks 56th in the world, tied with Latvia, Romania, and Ukraine [1]. The infant mortality rate in the United States (6 deaths per 1000 live births) ranks 44th, behind Serbia, Poland, and Cuba [2]. These troubling statistics are driven in part by pregnancy complications (eg, preterm birth, gestational diabetes, preeclampsia, cesarean delivery, or a small-for-gestational-age infant) that occur in 1 of 3 US women [3]. Poor health at conception, including obesity and other chronic conditions, are also on the rise [3]. Despite decades of research, prevention of poor maternal and child health outcomes in the United States remains challenging.

Maternal weight gain during pregnancy is one of the few potentially modifiable risk factors for many maternal and child health outcomes [4]. Nevertheless, determining the range of pregnancy weight gain that optimizes maternal and child health is difficult. Although higher weight gain may reduce the likelihood of preterm birth, fetal growth restriction, and infant death, it may increase the risk of maternal obesity, gestational diabetes, preeclampsia, and childhood obesity [4-8]. Public health guidelines for pregnant women must identify the range of weight gain that minimizes the risks of both low and high weight gain for mothers and children.

In 2009, the Institute of Medicine (now the National Academy of Medicine) and National Research Council Committee to Reevaluate Gestational Weight Gain Guidelines sought to revise national weight gain recommendations such that they balanced maternal and infant risks associated with low and high pregnancy weight gain [4]. However, balancing risks is challenging because women and their care providers view some outcomes as more severe than other outcomes. For instance, a stillbirth is a more serious event than a cesarean delivery. Some complications, therefore, should carry more weight in the determination of optimal weight gain ranges.

The relative importance that women and their care providers place on different health outcomes is unknown. Although there are some tools for scoring adverse perinatal outcomes, they either do not consider outcomes for both the mother and child or do not include longer-term health outcomes [9-11]. Recognizing this limitation, the 2009 Institute of Medicine/National Research Council Committee commissioned a quantitative risk trade-off analysis [4]. Unfortunately, quantitative risk trade-off analysis requires estimates of health utility values, which quantify the preference, or value, that people place on a given health outcome, anchored in relation to death (a score of 0) and perfect health (a score of 1.0) [12]. However, health utility values have only been elicited for a limited number of adverse outcomes related to maternal-neonatal health [13]. As a result, the quantitative risk trade-off analysis was only able to account for the association between pregnancy weight gain and 3 health outcomes. With many other key outcomes left out, the relevance of the work was limited.

Our project was developed in response to the Institute of Medicine/National Research Council Committee's call for research to fill this critical knowledge gap [4]. We aim to determine the importance of 11 maternal and child health outcomes that have been consistently associated with pregnancy weight gain. We will achieve this by engaging patients and maternal and child health professionals using an online modified Delphi panel process. The Delphi technique is a well-established method for exploring the existence of agreement among diverse stakeholder groups on a specific topic [14]. In an iterative process, panelists score items, provide a rationale for their ratings, review other panelists' responses, and revise their initial scores. The process is anonymous, minimizing the negative effects of group decision making, such as groupthink.

Delphi panels have recently been used in perinatal research to achieve consensus on a list of core reporting outcomes for randomized trials of diet and lifestyle in pregnancy [15]. However, this study only sought to identify which components were important, and did not attempt to quantify their relative seriousness. A study by Oken et al [16] elicited weights on the seriousness of different health outcomes and incorporated these into a study associating pregnancy weight gain with adverse health outcomes; however, weights were only elicited for 5 health outcomes from a convenience sample of 12 Harvard researchers. Our project will build on this work by eliciting weights for a broad range of maternal and child health outcomes from a large, diverse, and multidisciplinary group of stakeholders, including both professionals and patients.

Methods

Participants

Although surveys aim to recruit a large, representative sample, the goal of an expert professional panel is to recruit the most knowledgeable individuals in the field to elicit their expertise.

Professionals

We will recruit 90 maternal and child health professionals in the United States who represent researchers, health care providers, public health experts, and policymakers from academic, government, or community sectors. Panel membership will therefore be chosen using content expertise as a primary selection criterion and ethnic/racial and geographic diversity as a secondary selection criterion.

We will recruit through our professional networks via email and social media. We will encourage respondents to nominate colleagues to participate. Interested participants will be asked to complete a study registration form, which will include questions about race/ethnicity, age, gender, state of residence, demographics, and professional background and experiences. We will use the responses to these questions to select participants. Participants must have access to the internet; they

will be able to use any internet-connected device, including mobile phones.

Patients

We will recruit 90 women who are pregnant or who carried a pregnancy to 20 weeks of gestation and are no more than 2 years postpartum. Women will not need to have had a poor outcome to be considered knowledgeable stakeholders. Our goal for participant recruitment is to ensure appropriate racial/ethnic and geographic variation. Purposeful sampling such as this is typical for stakeholder engagement panels [17].

We will recruit patients through social media. Interested patients will complete a screening form to determine eligibility. Participants must have access to the internet; they will be able to use any internet-connected device, including mobile phones. We will also inquire about age, race/ethnicity, state of residence, parity, whether they are currently pregnant or it has been less than 2 years since their last delivery, and how they heard about the study. We will use their responses to these questions to select participants.

Panel Design

We will collect data using ExpertLens, an innovative online panel approach with a modified Delphi structure, created by researchers at the RAND Corporation [18,19]. This approach facilitates data collection, replaces traditional face-to-face meetings with anonymous moderated online discussion boards, and automates data collection. The ExpertLens platform can be accessed from any internet-connected device, including mobile devices. ExpertLens will allow the engagement of a large number of geographically diverse panelists by providing them with an opportunity to anonymously share their perspectives and interact with other participants using their own computer at their convenience [20]. The ExpertLens platform will save on costs and minimize the burden for participants that is typically associated with typical large national consensus meetings [20]. It has been used in numerous studies to elicit opinions from diverse stakeholder groups including researchers, providers, policymakers, patients, and community members [21-28].

We will conduct 3 concurrent panels using an identical research protocol. One panel will include 60 maternal and child health professionals. A second panel will include 60 pregnant or postpartum women. The final panel will include 30 professionals and 30 pregnant or postpartum women. Conducting homogeneous panels and a mixed panel will help explore the existence of consensus within and between the stakeholder groups and to explore the extent to which exposing participants in a mixed panel to alternative views could change their perspectives. A panel size of about 20-40 participants has been shown to create an engaging environment for online discussion. Our inclusion of 60 individuals per panel recognizes that participation rates in such panels vary from 50%-60% across the 3 rounds [29].

Outcomes

We selected maternal and child health outcomes that will be rated on their importance by reviewing the 2009 Institute of Medicine/National Research Council scientific report [4], systematic reviews related to gestational weight gain, and other recent literature. We chose outcomes that have a consistent association with gestational weight gain in observational studies and can be clearly operationalized or measured in most research studies. We limited the health outcomes to no more than 12.

We developed background information for each outcome, including its definition and short- and long-term consequences [30-46]. We based this information primarily on UpToDate, a well-known evidence-based clinical resource. To make the information more accessible for patients, we relied on UpToDate's The Basics text, which are short overviews written with plain language principles.

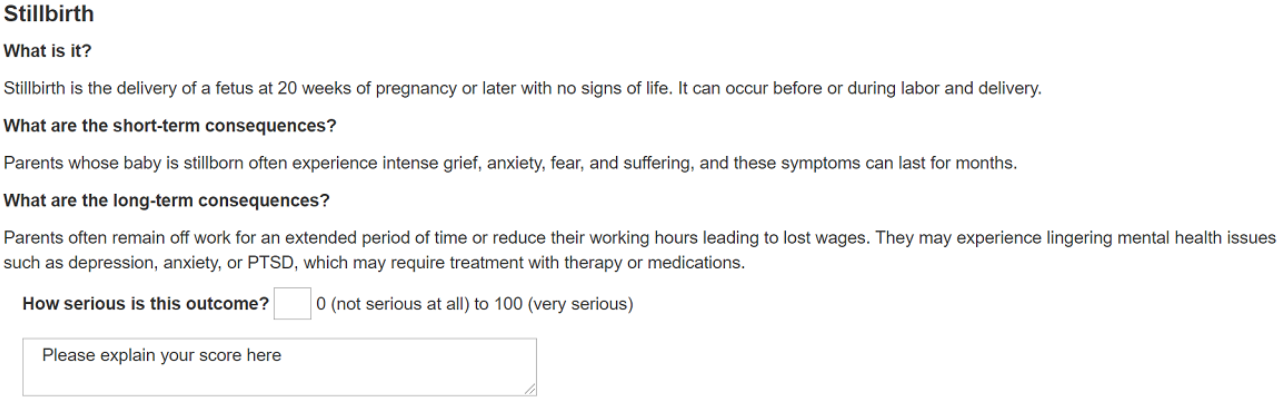
Data Collection

Each panel will complete a 3-round ExpertLens process lasting approximately 4-5 weeks.

Round 1

In Round 1, we will ask panelists to review the background information provided for each outcome and rate each outcome on its importance (Figure 1). They will use a rating scale of 0-100, where 0 corresponds to not important at all and 100 corresponds to the most important. We chose this scale to mirror existing perinatal morbidity scoring tools, where severity points are assigned to adverse outcomes, and a score of 0 indicates a lack of morbidity [9]. In addition to scoring each outcome, panelists will be asked to provide rationales for their answers using open-text boxes.

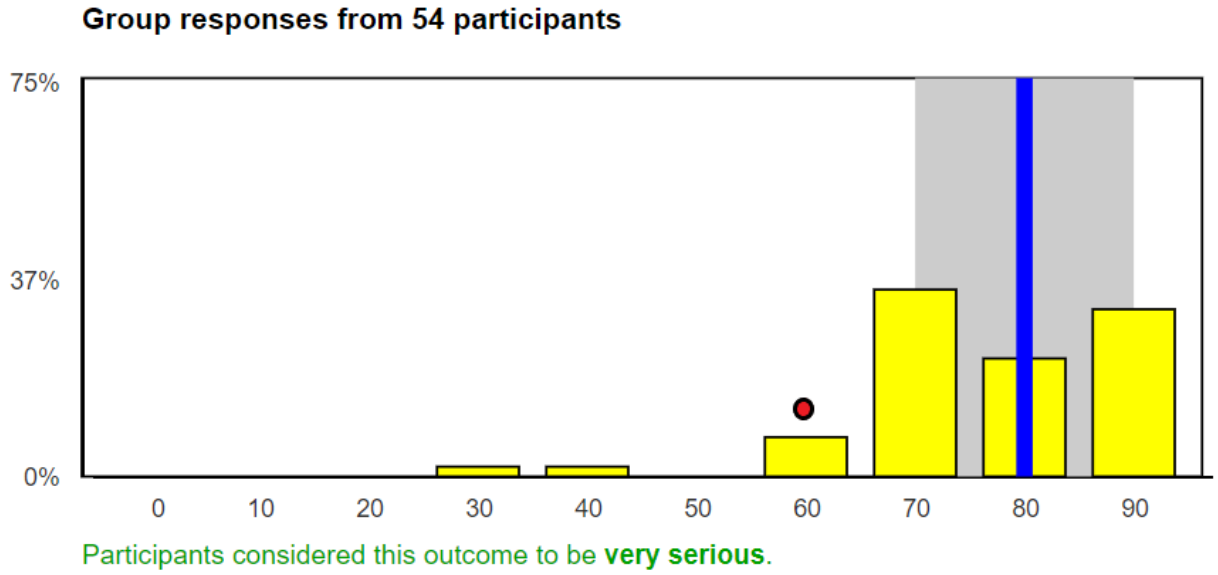
Figure 1. Mock-up of Round 1 graphic. PTSD: post-traumatic stress disorder.



Round 2

In Round 2, panelists will see how their Round 1 responses compare to those of other panelists and review the group results (Figure 2). Participants will see the distribution of the entire panel's ratings, their own ratings, and the ratings of each panelist who commented in Round 1 (listed with an anonymous identifier). For visual purposes, the panel's ratings will be collapsed into 10 intervals (scores 0-9, 10-19, 20-29, etc) that will be displayed in a histogram. As there are 101 possible ratings (0-100, inclusive), the last interval will have 11 points and the remaining 9 intervals will have 10 points. The frequency of the 10 intervals of the entire panel's ratings will be shown in yellow bars along with the group median (blue line), and the panelist's own response (red dot). This statistical feedback is an important component of the Delphi process [47]. When the participant hovers over the chart, text boxes will appear to further assist in interpretation of the data. Further, instructional videos will assist in the interpretation of statistical results. In addition, participants will be notified if the panel was able to reach consensus on the importance of each complication. We will summarize the themes from the Round 1 open-ended comments in groups according to the rating (those who rated the outcome low, medium, or high seriousness). All panelists' Round 1 comments will also be available for review.

Figure 2. Mock-up of Round 2 graphic. The frequency of the 10 intervals of the entire panel's ratings will be shown in yellow bars along with the group median (blue line), and the panelist's own response (red dot).



In addition to reviewing a summary of all comments, participants will be able to respond to any other participant's comment made in Round 1. Participants will discuss their ideas anonymously using an asynchronous moderated online discussion board [48]. The study team members, who are familiar with maternal and child health professionals and pregnant and postpartum women, have received training from RAND's ExpertLens team members on how to serve as neutral moderators and will follow a recommended discussion moderator protocol [49] that included a moderator discussion and best practices manual. Moderators will promote active discussion, encourage participants to elaborate on responses, ask clarification questions, and ensure that a single participant does not dominate the discussion.

Round 3

In Round 3, participants will answer all Round 1 questions again based on Round 2 feedback and discussion. We will also ask panelists to provide their rationale for changing or maintaining their ratings for each outcome. Finally, panelists will be asked to complete a survey about their experience. We will ask open-ended questions about their participation experiences, factors that influenced their final seriousness ratings, and ways to improve the online engagement process. In addition, they will be asked to rate their satisfaction with the online engagement process using 7-point Likert-type scales. They will express their agreement with such statements as, "participation in this study was interesting," "I was comfortable expressing my views in the discussion round," and "the discussions brought out views I hadn't considered." These questions are intended to improve the ExpertLens process in subsequent panels.

All panelists will receive US $150 for completing all 3 rounds.

Pilot

The ExpertLens platform was pilot tested by one panel of 7 patients and one panel of 6 professionals. They participated in all three rounds of the ExpertLens process as if they were real study participants. Rounds 1 and 3 were open 1 day, and Round 2 was open 2 days. Moderators practiced generating discussion comments during Round 2 by posting a series of neutral questions and comments. After Round 3, each participant shared feedback on system usability, question clarity and readability, and the use of the discussion boards via a phone interview. Pilot participants received a US $150 gift card after the completion of all 3 rounds.

Data Analysis

The primary analytic goal is to generate seriousness ratings for each maternal and child health outcome. Round 1 and 3 severity scores will be summarized for each panel by calculating the median, interquartile range (25th to 75th percentile), and maximum and minimum values. The severity scores that will

be used in primary regression analyses to establish optimal gestational weight gain ranges in the next phase of our research will be the Round 3 median score for each outcome summed across the 3 panels. To establish the robustness of findings, we will perform sensitivity analyses by replacing the median Round 3 scores with (1) upper and lower values of the range of scores and (2) the median from each of the 3 panels. These analyses will allow the impact of any differences in scores on the optimal ranges to be quantified and incorporated into policymaking decisions.

Secondary analyses will include quantifying the degree of within-panel consensus of severity ratings using a validated process, the RAND/UCLA Appropriateness Method (RAM) [50]. ExpertLens uses this method to automatically determine the group decision (eg, whether a particular outcome was deemed serious by the panel) for each outcome. RAM quantifies the dispersion of scores in relation to the interpercentile range (30th to 70th percentiles). We will also examine differences in distributions between panels.

Thematic analysis will be used to explore the types of rating justifications and the impact of group dynamics. Qualitative data will include text responses to the open-ended questions in the discussion forums and on the surveys.

Results

The ethics boards at University of Pittsburgh and The RAND Corporation determined the study protocol to be exempt from review. After completing the literature review to select the health outcomes of interest, we selected infant death, stillbirth, preterm birth, gestational diabetes, preeclampsia, small-for-gestational-age birth, large-for-gestational-age birth, unplanned cesarean delivery, obesity in women, childhood obesity, preterm birth, and metabolic syndrome in women.

We completed the pilot study and individual interviews with each of the 13 pilot testers. Based on their feedback, we made several key changes. First, we changed the wording of the panelists' task from "rate the *importance* of each maternal and child health outcome" to "rate the *seriousness* of each maternal and child health outcome." We operationalized seriousness as the severity of each condition based on the panelist's overall impression of the outcome's impact on a woman and child's health and quality of life. Second, we changed the Round 1 instructions to include a list of all health outcomes that will be rated and factors the panelists should consider in their ratings: the short- or long-term nature of the outcome; how the outcome impacts quality of life; and consequences for those individuals close to the woman and the child (such as family, friends, or caregivers). We also noted that the ratings should not consider whether the outcome can be prevented; how common it is in the United States; or whether more research is needed to understand the outcome.

Third, we clarified the definition of a health outcome for the patient panel and the mixed composition panel by stating, "A 'health outcome' is a health condition, medical complication, diagnosis or negative event related to your health or your baby's health." Fourth, we standardized the background information for each health outcome using headings (definition, short-term complications, and long-term complications) and bulleted text below each heading with the intention of making this text more accessible for panelists with lower health literacy. We added consequences to quality of life in this information. Financial costs of each complication were removed from the background information because the available literature is not consistent in estimates, and how these relate to an average woman is difficult to determine given variation in insurance coverage.

In the pilot study, we found that there was less discussion for the outcomes that appeared at the end of the list. We modified the ExpertLens system to randomize the outcomes for each panelist. The study was completed in December 2019.

Discussion

Our work will support the development of evidence-based pregnancy weight gain recommendations. The seriousness ratings for each individual outcome that our study generates will be used to develop a severity-weighted composite outcome that we will study in relation to gestational weight gain. This analysis will allow us to quantitatively account for expert and stakeholder opinion on the seriousness of these health outcomes. This will permit a determination of the range of pregnancy weight gain at which risks of adverse outcomes for mothers and children are balanced. Our incorporation of the perspectives of currently or recently pregnant women in this work is novel and important because it will help make the results of this work more patient-centered and will highlight any differences between the perspectives of experts and patients. As such, our project is consistent with the growing trend toward engaging patients in the development of evidence-based clinical practice guidelines. Our incorporation of the perspectives of current or recently pregnant women in this work is novel and important because it will help make the results of this work more patient-centered and will highlight any differences between the perspectives of experts and patients. As such, our project is consistent with the growing trend toward engaging patients in the development of evidence-based clinical practice guidelines [51,52].

We recognize that quantifying the perceived severity of different health outcomes is challenging, and panelists may not come to a consensus on the outcomes' relative seriousness. If there is no consensus, we believe that this represents the reality of the diverse experiences of women and care providers and should be reported in the literature. By reporting not only median scores, but also the range of scores for a given outcome and exploring the extent to which each panel was able to reach consensus, our work will enable researchers to explore the impact of different weights through sensitivity analyses that use the highest and lowest values elicited from each panel. These findings will also inform policymakers on the magnitude of variation in optimal ranges obtained from diverse opinions and account for the complex trade-off between low and high weight gain on maternal and child health.

Additionally, our project will illustrate a methodology for incorporating stakeholder perspectives on optimal treatment exposure beyond gestational weight gain. This may be especially important for treatments that are linked with multiple, competing

adverse health outcomes that differ in their seriousness to patients and providers. For example, such a methodology could be used to aid decision making for establishing optimal birth spacing (balancing risks of long spacing due to preeclampsia and infertility with risks of short spacing due to preterm birth) [53]. Other controversial areas where this methodology may be employed are decision making regarding antidepressant use during pregnancy [54] and vaginal birth after cesarean delivery [55]. Quantifying the seriousness of different health outcomes is a critical first step toward ensuring that optimal public health recommendations are both evidence-based and reflect the values of women and their care providers.

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All authors contributed to the design of the study. LMB had primary responsibility for drafting the manuscript and the remaining authors reviewed and approved the final version before submission.

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Conflicts of Interest

DK is the ExpertLens team leader.

Multimedia Appendix 1
Peer review of funded grant proposal.
[PDF File (Adobe PDF File), 163 KB - resprot_v9i6e16478_app1.pdf]

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Abbreviations

RAM: RAND/UCLA Appropriateness Method

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Protocol

Nurse-Led Education and Engagement for Diabetes Care in Sub-Saharan Africa: Protocol for a Mixed Methods Study

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Abstract

Background: As the impact of diabetes grows steeply in sub-Saharan Africa, improvement of the control and treatment of diabetes is a goal that health care systems in sub-Saharan Africa must achieve in the near future. Sub-Saharan Africa faces a number of challenges in addressing the increasing effects of diabetes. One important factor is the shortage of adequately trained health care workers. Diabetes management in sub-Saharan Africa would benefit from innovative approaches that are founded upon solid theoretical constructs, built upon existing human resources and infrastructure, and culturally tailored to the priorities and needs of the local population. Existing resources, such as mobile phones and task-shifting strategies, may be used to assist individuals with glycemic self-management and to facilitate management of additional day-to-day clinical responsibilities.

Objective: The objective of the Nurse-Led Education and Engagement Study for Diabetes Care (NEEDS) mixed-methods protocol is to develop a practical, collaborative, effective, and sustainable program for diabetes prevention and management specifically for patients with type 2 diabetes mellitus in sub-Saharan Africa. The protocol aims to improve access to care through task-shifting strategies and the use of mobile health technology.

Methods: This study was designed using a convergent parallel mixed-methods approach that consisted of surveys, key informant interviews, focus group discussions, and focused ethnography. Novel approaches, such as task-shifting strategies and the use of mobile technology, were implemented for type 2 diabetes mellitus health care in sub-Saharan Africa—currently an under-researched area.

Results: Data collection began in February 2018, after ethics approval, at the Kwame Nkrumah University of Science and Technology. As of May 2020, participant surveys have been completed (N=100), key informant interviews (n=7) have been completed, and focus groups (5 focus groups; patients, n=18; caregivers, n=6; community leaders, n=2; and faith leaders, n=3) as well as focused ethnographic field observations have been completed. All audio recordings have been transcribed and transcripts of sessions recorded in Twi have been translated to English. Data analysis is currently underway and anticipated completion is in the spring of 2020. Following data analysis, investigators plan to publish study findings.

Conclusions: Insights from this study will inform the preliminary development of a feasible and effective nurse-led education and engagement mobile health intervention that has the potential to reduce diabetes-related morbidity, mortality, and burden in sub-Saharan Africa.

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KEYWORDS

diabetes; mobile health; Ghana; sub-Saharan Africa; global health; nurses; task-shifting; mixed methods; focused ethnography

Introduction

Background

Diabetes is a global public health concern [1]. Africa, which is home to 49 diverse sub-Saharan African territories, had an estimated 15.5 million people living with diabetes in 2017 [2], and it is expected that number will increase to 40.7 million by 2045 [3]. Sub-Saharan Africa has the highest proportion of undiagnosed cases of diabetes (69.2%) and the highest complication rates compared to high-income countries [4]. Approximately 6% of mortality in Africa is attributed to diabetes and the highest all-cause mortality due to diabetes occurs among individuals aged 30 to 39 [4]. It has also been reported that over 90% of people in sub-Saharan Africa with diabetes have type 2 diabetes [4], and less than 40% of those living with the condition maintain optimal glycemic control [5].

The social, political, and economic constitution of sub-Saharan Africa is hugely diverse, as are its countries' health systems. Diabetes has a major economic impact at both the personal and national level [4,6]. Political instability, poor health literacy, limited health budgets, limited facilities, inadequate clinical expertise and personnel, poor drug supply, out-of-pocket health expenditures, minimal health insurance systems, and individual behavior factors are the most common challenges faced by health care systems in sub-Saharan Africa [4,6]. The rising prevalence of diabetes and its associated comorbidities also impose an increasing financial burden on health care systems. Many treatments for diabetes are too expensive for people in sub-Saharan Africa to afford [5]. Despite the high cost of managing diabetes, health care professionals in sub-Saharan Africa must often be more focused on acute medical treatment rather than on prevention; existing health care systems often lack adequate policies and guidelines to address the gap in needs [7]. Furthermore, poor diabetes management and self-care in the region have been associated with "healer shopping"—alternating between traditional providers and faith healers [8].

Major concerns within sub-Saharan Africa include a shortage in the number of health care workers and inadequate training of health care workers, both which have led to a crisis point which effectively prevents health care systems from being able to reduce diabetes-related morbidity and mortality [9]. In 2017, there were 2.7 physicians and 12.4 nurses (including midwifery personnel) per 10,000 people in sub-Saharan Africa compared to 21.5 physicians and 44.9 nurses per 10,000 people in North America [9]. Although task-shifting from physicians to nurses is increasingly advocated as a potential solution to shortfalls in the number of physicians in sub-Saharan Africa, there is a striking paucity of data to support this approach [10]. Many studies [9,11-14] demonstrate the effectiveness of task-shifting, but what makes task-shifting effective in terms of diabetes self-management and in improving health outcomes is not understood, particularly in low-resource settings.

Given the myriad of barriers to the management of diabetes within sub-Saharan Africa and evidence from high-income countries that chronic disease interventions are most successful when implemented from a multidimensional perspective [15,16], it is anticipated that an effective intervention to improve type 2 diabetes disease management in sub-Saharan Africa will benefit from a novel approach that is founded upon solid theoretical constructs, built upon existing human resources and infrastructure, and culturally tailored to the priorities and needs of the local population. A recognized challenge in the successful implementation of a multidimensional approach within sub-Saharan Africa is that theoretical frameworks do not take into consideration health behaviors within the social and environmental constructs within which people live [11,15,17]. Available resources, such as mobile phones, can be used to help patients maintain glycemic control through health messaging and clinical reminders that are delivered by nurses who have been trained to manage additional day-to-day clinical responsibilities [11,17].

Given the aforementioned challenges, diabetes prevention and treatment strategies in sub-Saharan Africa must be culturally relevant; use a multidisciplinary approach that incorporates clinically directed management; shift day-to-day management of chronic care tasks from overextended physicians to trained nurses; capitalize on existing, low-cost resources such as mobile devices for ongoing, intermittent disease management; and be theoretically derived. An urgent priority in sub-Saharan Africa is, therefore, the improvement of health outcomes, self-management, and access to care for individuals with diabetes through programs that are theoretically guided and culturally relevant and that make use of task-shifting and available technology.

Study Objectives

The objectives are to characterize the negative impacts of type 2 diabetes in sub-Saharan Africa and to prioritize the preferences of patients, caregivers, and health providers in the development of a theoretical, multilevel, culturally tailored nurse-led intervention that incorporates mobile health (mHealth) technology to increase treatment adherence, to improve outcomes, and to reduce the negative impact of diabetes in sub-Saharan Africa. Our mixed-methods protocol has the following goals:

1. Assess the characteristics (contextual factors, beliefs, practices, and self-management behaviors) of patients.

2. Assess the characteristics (beliefs, level of knowledge, access to, and familiarity with technology) of patients as well as technological barriers and facilitators, and their influence on outcomes at the various levels of the social-ecological model (individual, family/significant other/caregiver, health care organization, and community) using focused ethnography, a qualitative method.

3. To design a theory-based, multimodal nurse-led intervention that incorporates technology for diabetes management by converging quantitative and qualitative sets of data.

Our hypothesis is that a multilevel, culturally situated assessment of diabetes can be used to develop a nurse-led intervention and enhanced with mHealth technology for education and care management.

Methods

Study Setting and Population

The study will be conducted in Kumasi, Ghana which is among the largest metropolitan areas of Ghana and has a population of more than 2 million. The University Hospital, a district-level hospital located within the Kwame Nkrumah University of Science and Technology in Kumasi, will be the coordinating site for the study. The 100-bed hospital serves a population of over 200,000 people from more than 30 surrounding communities, treats approximately 86,000 outpatients each year, and has an active diabetes clinic that treats approximately 700 patients from diverse communities.

Study Design

The study will employ a convergent parallel mixed-method design [18] and will be guided by the social-ecological model and community-based participatory research [19,20]. Quantitative data and qualitative data will be simultaneously collected, analyzed separately, and then integrated. Investigators will conduct focused ethnography, which has been described in previous literature and is useful for situation or problem-directed inquiry that allows for context-specific exploration among a subgroup [21,22], to explore nuances that are specific to patients with diabetes in Ghana in order to best inform the development of a tailored intervention that meets the clinical needs of patients with diabetes in sub-Saharan Africa.

Social-ecological model [19] constructs are used to explore the individual, interpersonal, and population health factors that are related to diabetes. This includes individual factors (genetics, pathophysiology, knowledge, attitudes, beliefs, and behaviors), interpersonal factors (family, friends, colleagues, peers, and support networks), organizational factors (health care institutions, faith-based organizations, workplaces, and schools), community (neighborhoods), and policies to achieve broad change (government and health care) which provide the overall framework for organizing our research and a lens through which the quantitative and qualitative data can be interpreted. Focused ethnography, in-depth interviews with patients and their caregivers, home and clinic observation, and rapid appraisal during interpersonal interactions with family, friends, and clinicians will be conducted.

Study Procedures

Data will be collected from a convenience sample (N=100) of individuals with diabetes who are recruited from the hospital's clinic. Surveys (described in Table 1) will use an interview format in their native language. Survey items assess demographics, diabetes self-management practices, beliefs, access to technology, attitudes toward mobile phone monitoring, and attitudes toward expanded management of care by nurses. Participant treatment beliefs are assessed through questions about their perceptions of treatment and about their understanding of diabetes. Health behavior will be assessed through survey items related to dietary habits, smoking, physical activity, adherence to treatment, and self-measured blood glucose testing. Participant understanding of long-term sequelae will be assessed (levels of risk associated with prolonged elevated blood glucose such as micro and macrovascular changes). Participant perceptions of the use of mHealth technology for the management of care and the use of nurses to allow increased access to day-to-day care will also be assessed.

Table 1. Survey descriptions.

Characteristics assessed	Survey description
1. Socio-economic	Descriptive demographic data—education, employment, and time since diabetes diagnosis
2. Access and preferences to technology	10-item survey assessing access to mobile health technology, technology preferences, and receptivity to intervention delivery using technology. This survey has undergone prior pilot testing in Ghana with a different study population [12] and was modified slightly for this study by changing stroke terminology to diabetes terminology.
3. Access to care	Assesses factors related to health care service access
4. Knowledge and practices related to diabetes care and disease progression	Assesses understanding of long-term effects of elevated blood glucose and diabetes self-care practices
5. Health habits	Inventory assessing current health habits
6. Social context	Qualitative, open-ended questions assessing individual, interpersonal, community, organizational, and policy-related factors including knowledge, attitudes, beliefs, practices, and preferences on diabetes treatment, diabetes care, health behaviors, mobile technology, and task-shifting.

A purposive study design using focus group discussions will assess characteristics, knowledge, attitudes, beliefs, and practices of Ghanaian individuals with diabetes. We will conduct interviews and observations in locations convenient to participants. Data will consist of field notes and video or audio recordings. Methods developed by Tremblay [23] will guide the interview format. Approximately 5 focus group sessions will be conducted, each with approximately 6 to 10 participants who are either patients, caregivers, community leaders, or faith-based leaders. Patients will be recruited from the survey group participants. After the survey, participants will be asked if they or their caregivers would be willing to participate in focus group discussions. Community and faith leaders will be recruited through referrals from local community partner organizations and, subsequently, their referrals. Focus group sessions will be conducted in a semistructured interview format to ensure systematic and consistent data on the following: beliefs about diabetes risk factor control, existing self-management

practices and experiences, expectations and preferences, educational needs and preferences, impressions on nurse-led management of care and use of mHealth technology for remote monitoring, health reminders, or messaging. Separate focus groups will be held for community leaders in order to minimize inhibition in freely discussing ideas and thoughts. Patients and caregivers will be combined; these sessions are structured to maximize participant convenience with respect to transportation and scheduling. Focus group discussion prompts are tailored to general understanding of diabetes, current care practices and challenges, and preferences for future interventions. Since the individual roles and interpersonal relationships of patients and caregivers are not the focus, we hope to mitigate potential discomfort by openly sharing information across roles while maximizing convenience to participants. Focus group discussion prompt guides are detailed in Table 2.

Table 2. Focus group and interview discussion prompts.

Focus group composition	Discussion prompts
Patients and caregivers	1. What are some of the things you regularly do to help manage your (or your loved one's) diabetes? 2. What helps keep your blood glucose under control? What makes it difficult to control your blood glucose? 3. What are some of the things you are worried about when it comes to your diabetes? Do you have any difficulty getting the care you need? If so, why do you think this is? 4. What types of complications do you think you may have from your diabetes? 5. What would you like to change about taking care of your diabetes? 6. What types of things would you find more helpful to learn about? 7. Tell me your thoughts on having a nurse help you regularly manage your diabetes? What are your thoughts about if the nurse communicated with you through the mobile phone? 8. What else should we think about if we design a program to help people take better care of their diabetes?
Community and faith leaders	1. Do any of you have anyone in your community or home with diabetes? If so, what are some of the challenges people with diabetes face? 2. As you all are community leaders, do people with diabetes come to you for any reason? If so, what types of things do they come to you for? What types of support, care, or services are they looking for? 3. What do you think we can do to help people with diabetes in your community? 4. Tell me your thoughts on potentially having a nurse help people with diabetes regularly manage their disease. 5. What are your thoughts about using mobile phones to communicate with people with diabetes and help them manage their care? 6. What challenges do you foresee with using mobile phones or having nurses help educate patients and manage their care? 7. What recommendations do you have and what else should we consider that we haven't asked about?
Key informant interview	1. How do you currently provide treatment for patients with diabetes? What are some of the challenges you and your patients face? What are some of the things that are working well? 2. What do you perceive to be some of the main gaps in care and services for your patients with diabetes? 3. What challenges do you face in communicating with your patients? What barriers exist, if any? Are the any cultural or spiritual considerations you need to take into account when providing care? 4. What are your thoughts on the idea of task-shifting to a nurse-led model for day-to-day diabetes education and care management? What would you think is needed for education of the nursing personnel? What parameters should be considered in designing this type of care management system? 5. What are your thoughts on the use of mobile health technology to manage diabetes? 6. What are some considerations we should take into account in designing and planning for an intervention for diabetes care management in Ghana? 7. What else is important for us to consider that we may not have asked about?

Individual interviews with key informants (health care providers and hospital administrators) will be conducted using a semistructured guide. Participants will represent Kwame Nkrumah University of Science and Technology departments (endocrinology, social work, nursing, pharmacy, and information technology). Interviews will include discussions on the following areas: current approaches to diabetes management, perceived gaps in care, cultural competence and communication, knowledge of treatment guidelines, impressions on nurse task-shifting and mHealth technology, and considerations or recommendations for intervention development (Table 2).

Data Management and Analyses

Participants will be volunteers who have given written consent and will be free to withdraw at any time. All personal identifiers will be removed from any data and data will be analyzed and stored at the university on a secure network drive that is protected by password and used uniquely for this study. Access to the data will be limited to researchers involved in this study.

All data will be uploaded and stored on REDCap, a secure data storage system described in Harris et al [24]. Quantitative data will be analyzed using SPSS software (v24.0, IBM Corp). Focus group sessions and key informant interviews will be transcribed verbatim with any identifiers that might breach participant confidentiality redacted. For interviews conducted with non-English speaking individuals, transcriptions of audio recordings will be translated to English. De-identified transcripts of the audio recordings and field notes (including videos and photographs) will be used for qualitative data analysis. Transcripts will be verified using the recordings to confirm accuracy and authenticity. The transcripts will then be imported

into the qualitative text analysis software (NVivo 12.0, QSR International) for data management and analysis. Qualitative data will be analyzed according to the social-ecological model to include inductive and deductive coding; theme development; identification of barriers, facilitators, knowledge, attitudes, beliefs, and preferences; perceptions of and recommendations on diabetes care, its management, mHealth technology, and task-shifting to increase care access and delivery. To maintain rigor within the qualitative data analysis, investigators will conform to standards of credibility, confirmability, transferability, and dependability [25,26]. Credibility will be maintained through prolonged exposure with data [13]. An audit trail of data collection and analysis will be used to confirm dependability of analytical processes [13], and researchers will account for personal bias [26]. Transferability and confirmability will be addressed through thick descriptions provided when reporting results, enabling clinicians and researchers to determine whether findings are consistent and transferable to their own sites or populations, and to have confidence that the interpretation of findings is derived directly from data [13]. Mixed methods allow comparison of data convergence and divergence; a matrix display will be developed for each construct of the social-ecological model (individual, interpersonal, organizational, community, and policy) to compare findings and assess convergence appropriately.

Results

The study has been approved by the Committee on Human Research, Publications and Ethics at the Kwame Nkrumah University of Science and Technology (CHRPE/RC/241/17). The Medical University of South Carolina's Institutional Review Board determined that, because the team at the Medical University of South Carolina would not be engaged directly with participants since they would be working only with de-identified data, Institutional Review Board approval was not required. Quantitative and qualitative data collection began in February 2018. Data analysis and the final report are expected to be completed by Spring 2020. As of May 2020, participant surveys have been completed (N=100), key informant interviews (n=7) have been completed, and focus groups (5 focus groups; patients, n=18; caregivers, n=6; community leaders, n=2; and faith leaders, n=3) as well as focused ethnographic field observations have been completed. All audio recordings have been transcribed and transcripts of sessions recorded in Twi have been translated to English. Data analysis is currently in progress. After separate quantitative and qualitative analysis, data will be combined for mixed analysis. When complete, results will be reported through professional presentations, peer-reviewed publications, and directly to Community Advisory Board members in Ghana.

Discussion

The overall goals of this study are to develop a practical, collaborative, effective, and sustainable program for type 2 diabetes prevention and management in sub-Saharan Africa and to improve access to care through task-shifting and the use of technology. In addition, the proposed task-shifting strategy may mitigate the effects of the critical shortage in health care workers by allowing trained nurses to manage glycemic control in day-to-day care and by leveraging mobile phones that are already widely used in the region. To our knowledge, this would be the first study to establish a culturally sensitive, multilevel-systems effort to explore and document barriers and facilitators related to diabetes among Ghanaian patients; evaluate the knowledge, attitudes, and beliefs toward diabetes care management; identify access to technology and preferences related to mHealth technology as a mechanism for care delivery among Ghanaian patients with type 2 diabetes mellitus; develop a community-based intervention for patients with diabetes that will bridge the health system and community through a nurse-led model; and collect formative data from a diabetes intervention study in Ghana to use as a model for sub-Saharan Africa through focused ethnography. This study will inform the preliminary development of a feasible and effective mHealth intervention which may contribute to a definitive and more successful randomized control trial with the potential to reduce diabetes-related morbidity, mortality, and burden in sub-Saharan Africa.

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Conflicts of Interest

None declared.

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Abbreviations

mHealth: mobile health
NEEDS: Nurse-Led Education and Engagement Study for Diabetes Care

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Protocol

Closing the Psychological Treatment Gap During the COVID-19 Pandemic With a Supportive Text Messaging Program: Protocol for Implementation and Evaluation

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Abstract

Background: Coronavirus disease (COVID-19) has spread globally with far-reaching, significant, and unprecedented impacts on health and everyday life. Threats to mental health, psychological safety, and well-being are now emerging, increasing the impact of this virus on world health. Providing support for these challenges is difficult because of the high number of people requiring support in the context of a need to maintain physical distancing. This protocol describes the use of SMS text messaging (Text4Hope) as a convenient, cost-effective, and accessible population-level mental health intervention. This program is evidence-based, with prior research supporting good outcomes and high user satisfaction.

Objective: The project goal is to implement a program of daily supportive SMS text messaging (Text4Hope) to reduce distress related to the COVID-19 crisis, initially among Canadians. The prevalence of stress, anxiety, and depressive symptoms; the demographic correlates of the same; and the outcomes of the Text4Hope intervention in mitigating distress will be evaluated.

Methods: Self-administered anonymous online questionnaires will be used to assess stress (Perceived Stress Scale), anxiety (Generalized Anxiety Disorder-7 scale [GAD-7]), and depressive symptoms (Patient Health Questionnaire-9 [PHQ-9]). Data will be collected at baseline (onset of SMS text messaging), the program midpoint (6 weeks), and the program endpoint (12 weeks).

Results: Data analysis will include parametric and nonparametric techniques, focusing on primary outcomes (ie, stress, anxiety, and depressive symptoms) and metrics of use, including the number of subscribers and user satisfaction. Given the large size of the data set, machine learning and data mining methods will also be used.

Conclusions: This COVID-19 project will provide key information regarding prevalence rates of stress, anxiety, and depressive symptoms during the pandemic; demographic correlates of distress; and outcome data related to this scalable population-level intervention. Information from this study will be valuable for practitioners and useful for informing policy and decision making regarding psychological interventions during the pandemic.

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KEYWORDS

COVID-19; Text4Hope; mobile phones; text; anxiety; depression; stress; pandemic; e-mental health

Introduction

Background

Coronavirus disease (COVID-19), a severe acute respiratory syndrome caused by the SARS-CoV-2 virus (severe acute respiratory syndrome coronavirus 2; officially identified in January 2020 in Wuhan, China), is now a global pandemic with far-reaching, significant, and unprecedented impacts on human health and everyday life. The World Health Organization declared the COVID-19 outbreak a Public Health Emergency of International Concern [1] on January 30, 2020, with many countries globally struggling to adapt to its impact. The closing of schools and small and large businesses, extremely high unemployment rates, and the effects of quarantine are further stressors facing the global population due to COVID-19 [2].

Threats to mental health, psychological safety, and well-being are now emerging, increasing the impact of this virus on world health [3,4]. Over half of survey respondents in China rated the psychological impact of COVID-19 as moderate or severe, with 29% reporting significant anxiety symptoms and 17% reporting significant depressive symptoms [5]; these symptoms persisted after 4 weeks of the COVID-19 epidemic [6]. A number of factors may correlate with psychological impact, including female gender, student status, specific physical symptoms (eg, myalgia, dizziness, and coryza), and poor self-rated health status. A recent rapid review of 24 published studies on pandemics reported negative psychological effects, including posttraumatic stress symptoms, confusion, and anger [7]. Stressors included longer quarantine duration, infection fears, frustration, boredom, inadequate supplies, inadequate information, financial loss, and stigma.

In a study focused on health care workers (HCWs), over half had significant symptoms of depression, approximately 45% showed significant anxiety symptoms, and one-third experienced sleep disturbance and insomnia [8]. Correlates of symptomatology were related to exposure (eg, working in Wuhan, working on the front line) and demographic factors, including gender and occupation (eg, female, nurse). Although an important and inevitable public health measure during a highly infectious disease outbreak, quarantine is associated with a number of negative psychological and social effects (eg, posttraumatic stress, anger, fear, financial loss, and stigma) [7], and may serve as an additional risk factor. The literature describing the psychological impact of natural disasters suggests that a subset of people exposed to natural disasters struggle with clinically significant mental health conditions, including anxiety, depression, and substance use disorders [9-11]. Several risk factors were identified for the development of psychological conditions after disasters. In addition to the demographic factors described above, these include degree of exposure [12-16], gender [17-20], social stressors (eg, unemployment status [17] or low socioeconomic status [18]), as well as pre-existing mental health conditions [18,21,22].

Even at this early stage of the global pandemic, there is evidence of significant psychological effects among the general population, which may be more pronounced in certain groups (eg, female, socially stressed, frontline worker, pre-existing psychological disorder) [23,24]. Providing support for these challenges is difficult because of the high number of people requiring support in the context of a need to maintain physical distancing.

Mobile health technology offers a unique and innovative solution in this context. Specifically, this tool offers a convenient, cost-effective, and accessible means for implementing population-level interventions. Almost 90% of Canadians own a smartphone [25], and SMS text messaging is free to end users, does not require technical skill for use, and does not require expensive data plans. Text messages are also cost-effective to providers, costing cents per message to deliver.

Supportive text messages are associated with positive outcomes, including the reduction of depressive symptoms, increased abstinence duration in alcohol use disorder, and high user satisfaction, as reported in previous research. For example, in randomized controlled trials (RCT), patients with depression that received supportive text messages showed symptom reduction on a standardized self-report when compared to a similar patient group that did not receive text messages (with large effect sizes: Cohen d=0.85, Cohen d=0.67) [26,27]. In another RCT, to evaluate the effectiveness of an addiction-related supportive SMS text messaging mobile intervention in improving treatment outcomes for patients with alcohol use disorder, small to moderate effects were found for the cumulative abstinence duration. In addition, the intervention group's mean time to first day to drink was over twice the length of that of the control group (60 versus 26 days, respectively) [27]. In two user satisfaction surveys, over 80% of subscribers reported that a supportive SMS text messaging program improved their mental health [27,28]. Subscribers reported text messages made them feel more hopeful about managing issues (82%), in charge of managing depression and anxiety (77%,), and connected to a support system (75%); in addition, such messages improved their overall mental wellbeing (83%) [27].

Objective

This protocol describes the implementation of the Text4Hope program (a low-cost, evidence-based, supportive SMS text messaging service) in Canada. The objective of the project is to implement a self-subscribing daily supportive text message program (Text4Hope) to close the psychological treatment gap and reduce anxiety and stress related to the COVID-19 crisis among Canadians. Our research questions include the following: (1) What are the prevalence rates of stress, anxiety, obsessive

compulsive, and depressive symptoms in Canada related to the COVID-19 crisis? (2) What are the demographic correlates of stress, anxiety, obsessive compulsive, and depressive symptoms? (3) Will the Text4Hope program help reduce stress, anxiety, and depressive symptoms among Canadians experiencing psychological distress as a result of the COVID-19 crisis?

Methods

Evaluation Methodology and Measurement Plan

In the Text4Hope program, individuals self-subscribe to receive daily supportive text messages for 3 months by texting "COVID19HOPE" to 393939. The messages are aligned with a cognitive behavioral framework, with content written by mental health therapists as well as our research team members (authors MH and VIOA). The following is an example of the messages sent: "When bad things happen that we can't control, we often focus on the things we can't change. Focus on what you can control; what you can do to help yourself (or someone else) today" [29]. The messages are preprogrammed into an online software that delivers messages at 9 AM each morning. At the onset of the first message, respondents are welcomed to the service and are invited to complete an online baseline survey capturing demographic information; COVID-19–related self-isolation/quarantine information; and responses on the Generalized Anxiety Disorder-7 (GAD-7) scale [30], Perceived Stress Scale [31], and the Patient Health Questionnaire-9 (PHQ-9) [32]. Survey questions were programmed into SelectSurvey.net, an online survey tool operated by the Alberta Health Services Evaluation Services Team. No incentives are offered to respondents. Participation in the program is entirely voluntary, and completion of the survey was not a prerequisite requirement to receive supportive text messages. Subscribers may opt out at any time by texting "STOP" to 393939. Survey responses will be stored within our regional health system (Alberta Health Services) Select Survey account, and data will be exported, stored, and maintained by the Research and Evaluation team within our health region. The supportive SMS text messaging project subscriber recruitment plan was based on the success of a Text4Mood program in Alberta that was launched in response to the Fort McMurray wildfire disaster in 2016. Text4Hope has been the subject of a wide-exposure communications campaign (TV, radio, internet, and print media), including the local provincial mental health foundation, the single provincial government health care provider Alberta Health Services (AHS). Additionally, Text4Hope was the subject of a specific COVID-19 mental health support media release by the Provincial Chief Medical Officer [33]. Ethics approval has been granted by the University of Alberta Health Research Ethics Board (Pro00086163).

Sample Size Considerations

Based on previous experience using the technology, (ie, >10,000 recipients within 6 months), we expect about 300,000 Canadians to subscribe to the Text4Hope program over the next 6 months. Based on a response rate of 21.7% for our prior Text4Mood survey [27], we anticipate around 20,000 responses to the Text4Hope surveys per 100,000 subscribers.

Outcome Measures

The primary outcome is changed scores at 6 and 12 weeks from baseline on the Perceived Stress, GAD-7, and PHQ-9 scales. The secondary outcomes are the following: (1) changes in prevalence rates for perceived stress, anxiety, and depression from the early phase of the COVID-19 pandemic to a later phase, as measured with the Perceived Stress, GAD-7, and PHQ-9 scales, respectively; (2) the interaction between primary outcomes and the demographic characteristics of subscribers as well as the date of subscription to Text4Hope relative to the phase of the pandemic in Alberta; and (3) subscriber satisfaction/experience.

Proposed Timeline and Milestones

The first stage involved the creation and review of the supportive text messages (targeting stress and anxiety-related concerns to COVID-19), and the programming of the messages into the software. This stage was completed on March 20, 2020. The second stage involved the launch of the Text4Hope program, which occurred on March 23, 2020. The remainder of the project will be focused on data analysis and reporting.

Hypotheses

Our hypotheses, based on previous research, are as follows: (1) High rates of stress, anxiety, and depression will be reported, affecting one-third to half of the general population; the 1-week prevalence rates for these disorders will increase as the pandemic continues, compared to rates in the early phase. (2) Specific risk factors will be found for the experience of distress during the pandemic, such as female gender, risk of exposure, and social determinants of health (eg, employment, housing). (3) The intervention will result in a 25% or greater reduction in perceived stress, anxiety, and depressive symptoms (as measured by the Perceived Stress, GAD-7, and PHQ-9 scales) at 6 and 12 weeks from baseline. (4) At least 80% of subscribers will express satisfaction with the Text4Hope program and perceive the daily supportive text messages as contributing to their overall mental well-being.

Results

Project evaluation will proceed using the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) Framework [34] and the Alberta Quality Matrix for Health [35]. Specifically, dimensions considered will include the following: acceptability (subscriber satisfaction/experience), accessibility (ease of subscription to and utilization of the Text4Hope program), appropriateness (numbers of residents subscribing to the program), and effectiveness (6- and 12-week changes in the Perceived Stress, GAD-7, and PHQ-9 scales). It may also be possible to examine efficiency (cost avoidance and efficiencies through reduced need for face-to-face counselling) and safety (self-reports of decreased crisis and urgent service calls, and decreased emergency medical services utilization rates).

We will evaluate the efficacy of Text4Hope with the reductions of perceived stress, anxiety, and depression at 6 weeks and 12 weeks. Data analysis will include the standard use of parametric and nonparametric techniques (eg, within-subject general linear

models), including multiple comparison Type 1 error corrections. Power analysis with effect sizes based on Agyapong group research publications [26-28,36,37] indicates a sufficient effect size for the expected Text4Hope program subscriber sample size. As the sample size for the data set generated from this project will be large, in addition to the conventional statistics used in these projects, we plan to adopt a "big data" analysis approach to examine data-driven patterns. Using machine learning and data mining methods, we expect to capture the most powerful window on differences and high-order sets of potential interactions. With our program targeting 300,000 Canadians to self-subscribe, with an expected 60,000 completing the survey, we are confident that this project has adequate power for our basic cross-sectional approach. We will develop predictive models using baseline measurements (features) and machine learning algorithms (eg, the least absolute shrinkage and selection operator [LASSO], support vector regression [SVR], and random forest regression, etc [38-40]) to predict the efficacy of our intervention at 6 and 12 weeks, as measured by the change in assessment scores (eg, GAD-7, PHQ-9) compared to the baseline. We will perform a 10-fold cross-validation to evaluate the performance of the models. During cross-validation, the data will be randomly segmented into 10 folds, with each fold containing 10% of the data. For each iteration, 1 fold will be left out as the testing data and the remaining 9 will be the training data. Within each training session, another internal 10-fold cross-validation will be used to select the best features, algorithm, and corresponding hyperparameters as the model to be trained on this specific training session. The selected model in the training data will then be applied to the testing data. This procedure is crucial for predictive tools as the data being tested has never been seen in any way by the model. The performance of the models will be evaluated using the Pearson correlation between the predicted and actual reduction of the outcome measures.

Due to the ongoing shifts in infection rates and public health measures over time, together with a shifting and unpredictable pattern of economic impacts, it will be important to include data on infection and death rates as well as the overall economic measures (including unemployment rates) associated with the baseline, 6-week, and 12-week measures. Such variables will be included in the machine learning analysis of the project data [41]. Including these variables will enable the model to account for variables that may influence expected rates of anxiety- and depression-related symptoms.

Discussion

The impact of the COVID-19 global pandemic on health, way of life, and psychological safety and wellbeing is difficult to overstate. The psychological impact on the general population, both during and after the crisis, requires the use of innovative techniques that can serve the high number of people requiring support, while respecting the need to maintain physical distancing.

The current protocol describes the use of mobile health technology as a convenient, cost-effective, and accessible means for implementing a population-level psychological intervention during the pandemic. This program is empirically supported by previous research results, showing good outcomes as well as high user satisfaction [26,27]. This project will evaluate outcomes with standardized, empirically validated questionnaires, and will also provide key information regarding prevalence rates of stress, anxiety, and depression in the Canadian population during the COVID-19 pandemic; demographic correlates of this distress; and outcome data related to a scalable population-level intervention. Information from this study will thus be critical for practitioners, as well as useful for informing policy and decision-making regarding psychological interventions during the COVID-19 pandemic. If Text4Hope is effective for the Canadian population, we will explore scale-up and national implementation, and will disseminate this program for adaptation for potential global use through the APEC Digital Hub for Mental Health [42].

Limitations of this protocol include a lack of baseline data on stress, anxiety, and depression levels before self-isolation measures were implemented in Alberta; this was unavoidable as our study was initiated shortly after quarantine and self-isolation measures were introduced. Nonresponse bias may also affect the expected results, as program subscribers are a sample of the population, not the entire population of the province. Nonrespondents may differ in a systematic way compared to respondents. For example, they may differ in their baseline level of mental wellness, be more (or less) affected by the pandemic, or have limitations in literacy or English fluency. In view of the limitations noted above, any prevalence estimates must be interpreted with caution, and compared to the conventional baseline of subsequent conventional prevalence estimates. The authors also note that this protocol does not include a control group and this raises the question of specificity concerning hypothesis 3, which concerns reductions in perceived stress, anxiety, and depressive symptoms. Previous RCT work from this group has demonstrated the efficacy of supportive SMS text messaging in intervention groups, compared to control groups that did not receive supportive text messages; instead, the control group received the same survey requests as the intervention group in addition to a single text message every 2 weeks, thanking them for participating in the study [26,37]. Given the intention to provide support to the catchment population of this study and the prior evidence for efficacy, it would be unethical to include a control group in the current protocol. Nevertheless, prior studies did include subscriber satisfaction surveys, as does this protocol, and that measure will provide evidence for engagement of the subscribers with the program (simply put, if subscribers ignored the text messages, it is highly unlikely that there would be positive satisfaction survey results). In the current health implementation context of this protocol, the comparison of changes in outcome measures in relation to comparison with effect sizes from our prior work (together with an assessment of the degree of correspondence of subscriber satisfaction survey responses to changes in our outcome measures) will be a good indicator of subscriber engagement in the absence of a control condition. Despite these limitations and possible bias factors, our protocol will provide useful data about the mental health characteristics of individuals in the early stages of the COVID-19 pandemic. We expect that our results will represent an important initial source of

information for government and health care planners in determining the nature and quality of services required to address mental health challenges arising during this pandemic, as well as future pandemics that employ self-isolation or quarantine measures. Specifically, planning for and implementing virtual care programs, including supportive SMS text messages, may be a fruitful approach to supporting isolated or quarantined individuals. In addition, we expect the supportive SMS text messaging intervention to have a positive effect on mental well-being and we will be able to measure this well within the expected sample size.

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Conflicts of Interest

None declared.

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Abbreviations

COVID-19: coronavirus disease
GAD-7: Generalized Anxiety Disorder-7 scale
LASSO: least absolute shrinkage and selection operator
PHQ-9: Patient Health Questionnaire-9
RCT: randomized controlled trial
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
SVR: support vector regression

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Protocol

Intersectoral Cooperation in 12 European Case Studies Aiming for Better Health, Environmental Sustainability, and Health Equity: Protocol for a Qualitative Evaluation

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Abstract

Background: The INHERIT (INtersectoral Health and Environment Research for InnovaTion) project has evaluated intersectoral cooperation (IC) in 12 European case studies attempting to promote health, environmental sustainability, and equity through behavior and lifestyle changes. These factors are the concerns of multiple sectors of government and society. Cooperation of health and environmental sectors with other sectors is needed to enable effective action. IC is thus essential to promote a triple win of health, sustainability, and equity.

Objective: This paper describes the design of a qualitative study to gain insights into successful organization of IC, facilitators and barriers, and how future steps can be taken to improve IC in the evaluated case studies.

Methods: Each case study was assessed qualitatively through a focus group. A total of 12 focus groups in 10 different European countries with stakeholders, implementers, policymakers, and/or citizens were held between October 2018 and March 2019. Five to eight participants attended each focus group. The focus group method was based on appreciative inquiry, which is an asset-based approach focusing on what works well, why it is working well, and how to strengthen assets in the future. A stepped approach was used, with central coordination and analysis, and local implementation and reporting. Local teams were trained to apply a common protocol using a webinar and handbook on organizing, conducting, and reporting focus groups. Data were gathered in each country in the local language. Translated data were analyzed centrally using deductive thematic analysis, with consideration of further emerging themes. Analyses involved the capability, opportunity, motivation-behavior (COM-b) system to categorize facilitators and barriers into capability, motivation, or opportunity-related themes, as these factors influence the behaviors of individuals and groups. Web-based review sessions with representatives from all local research teams were held to check data analysis results and evaluate the stepped approach.

Results: Data collection has been completed. A total of 76 individuals participated in 12 focus groups. In December 2019, data analysis was nearly complete, and the results are expected to be published in fall 2020.

Conclusions: This study proposes a stepped approach that allows cross-country focus group research using a strict protocol while dealing with language and cultural differences. The study generates insights into IC processes and facilitators in different countries and case studies to filter out which facilitators are essential to include. Simultaneously, the approach can strengthen cooperation among stakeholders by looking at future cooperation possibilities. By providing knowledge on how to plan for, improve, and sustain IC successfully to deal with today's multisectoral challenges, this study can contribute to better intersectoral action for the triple win of better health, sustainability, and equity. This protocol can serve as a tool for other researchers who plan to conduct cross-country qualitative research.

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KEYWORDS

intersectoral cooperation; health; environmental sustainability; equity; focus groups; protocol

Introduction

Background

Many of today's behaviors and lifestyles and the drivers that shape them are unhealthy and damaging to the environment. For example, current diet trends involving high meat, fat, and sugar pose a risk to people's health in terms of overweight and noncommunicable diseases. Furthermore, our global food production system creates a huge pressure on the environment and damages ecosystems [1,2]. However, not all populations are affected equally by health and environmental problems. Changing our behaviors and lifestyles and the environments that shape these behaviors is being progressively acknowledged as vital for not only achieving better health but also creating a more sustainable environment for all [3]. Importantly, population health, environmental sustainability, and equitable health are influenced by factors located in multiple sectors of the government and society. Consequently, addressing current and future challenges of health, environmental sustainability, and equity requires a cross-sectoral approach involving multiple sectors, as not only the challenges themselves but also their solutions are interdependent. Intersectoral cooperation (IC), as an important condition for intersectoral action, allows for these "triple-win" solutions. For example, replacing car journeys with active transport (eg, walking and cycling) is better for both health (through physical exercise) and the environment (through reduced vehicle emissions). In this case, realizing these multisector benefits requires cooperation among the urban planning, environmental, and public health sectors, and between national and local government levels to allow for effective intersectoral action [4]. The importance of IC is recognized internationally [5]. It is believed to only be feasible to achieve the sustainable development goals (SDGs) that aim to achieve a better and more sustainable future for all by 2030, and many countries are committed to this by embracing intersectoral action and cooperation, as is proposed in SDG 17 [6].

We defined IC as cooperation between partners from different sectors, allowing for joint action that is more effective or efficient than actions taken separately by each individual sector. It entails cooperation among parties from different sectors (eg, health and environmental sectors), types of institutions (eg, nongovernmental and private organizations), different levels of government (eg, local and national), and professionals, policy makers, and citizens [7,8].

Previous research has documented the planning, implementation, and evaluation of IC, and the literature shows that working and cooperating intersectorally are not easy processes [8-14]. The barriers mentioned include failing to identify cobenefits, differences in interests, speaking different jargons, siloed ways of thinking, as well as a lack of political will or commitment [8,12,15]. Facilitators identified in the literature include having relationships based on trust and respect, open communication, investing in alliance building, and aiming to achieve consensus at the planning stage of cooperation [8,11,15]. Storm et al studied ways to improve cooperation between the health sector and other sectors in order to reduce health inequalities [16]. Their recommendations included focus on formal cooperation strategies and on working toward higher support for action at tactical and strategic levels.

A wide variety of methods have been applied to study IC. For example, Wagemakers et al developed a coordinated action checklist for community health promotion based on literature and an existing framework, and piloted it sequentially among partnerships in multiple settings [11]. Storm et al used document analysis, questionnaires, and interviews in their study [16]. James et al examined intersectoral policy and action regarding consumer adoption of healthy and sustainable food behaviors by conducting 29 semistructured interviews with key Australian stakeholders [17].

Aims and Contributions to the Field

Intersectoral Cooperation

This protocol paper describes and discusses the design of a qualitative study to gain insights into how IC can be organized successfully, what are the facilitators and barriers to IC, and how future steps could be taken to improve IC in evaluated case studies. Previous evaluation literature on IC mostly focused on health and wellbeing or was nationally oriented. This study can potentially generate new insights as compared with the existing literature, because the cooperation processes of our case studies do not only deal with improving health and wellbeing, but simultaneously aim to promote environmental sustainability and equity. Moreover, in this study, we looked at case studies that cover a diverse range of topics (eg, food consumption, green space, active travel, and energy efficient housing) and are spread out over 10 different European countries. This variety of case studies allows for the generation of insights and perspectives from many different sectors, stakeholders, and countries. The first aim of this study was to gain more insights into processes, facilitators, and barriers of IC and find ways to improve intersectoral action. The results can be used to make generic recommendations and more context, culture, or topic-specific recommendations on what steps to take to effectively organize IC to not only achieve better health and wellbeing for all, but also promote environmental sustainability. In addition, we adopted a qualitative study design using focus groups, as this approach was deemed to be the most suitable for our study; focus groups enable obtaining rich and detailed information about the experiences of the key persons involved in collaborations regarding facilitators and barriers. By using focus groups to study IC in such a wide variety of case studies and countries, we believe that the findings will add to existing

literature in which other methods were used or in which focus groups were used to assess national or topic-specific case studies. This can potentially lead to new or additional insights into IC.

Stepped Approach

This study aimed to assess IC in 10 different European countries with different cultural backgrounds. Performing such cross-country research poses a methodological challenge, as it requires researchers to know and understand cultural subtleties, language, and behavior in different countries' contexts. Therefore, the second aim of this study was to pilot a stepped approach that allowed conducting cross-country qualitative research while taking cultural contexts and language barriers into account.

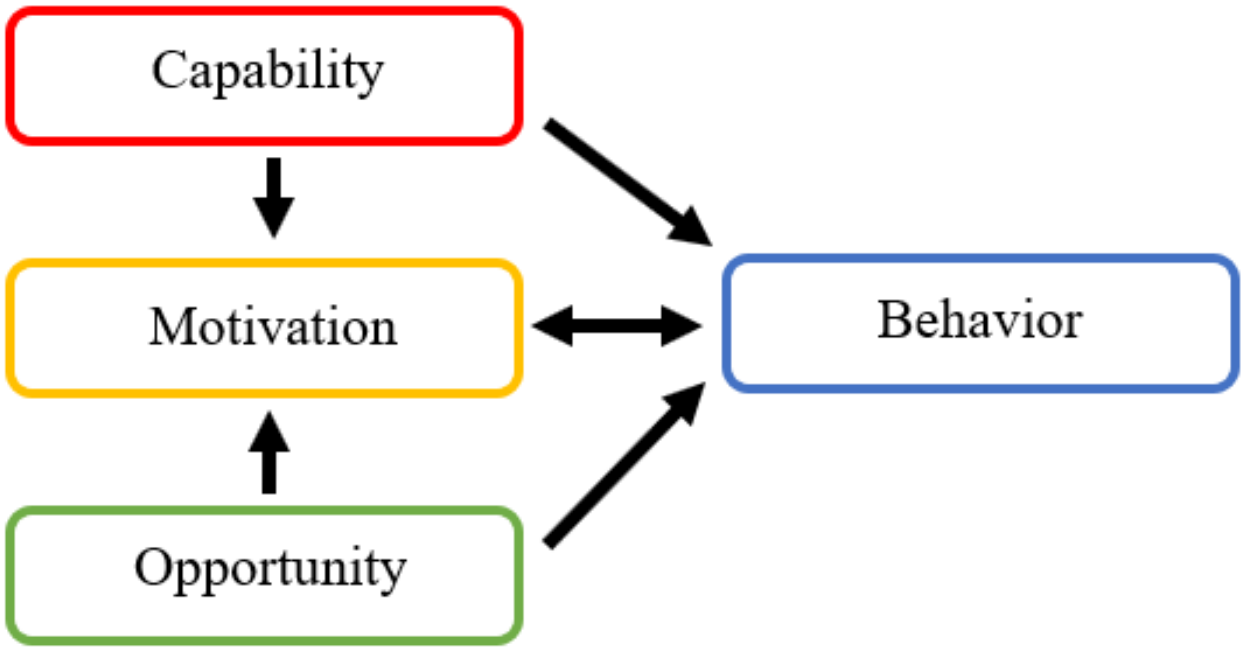
Appreciative Inquiry

We applied appreciative inquiry (AI) in our approach, which is an asset-based approach that focuses on what works well, why it is working well, and how to strengthen assets in the future [18,19]. AI has been used successfully in interviews and for the development of a coordinated action checklist to facilitate and evaluate community health promotion partnerships [11,19], and it was found to stimulate participants to appreciate those aspects of cooperation that already exist and inspire them to envision and plan desired future steps in cooperation. Our four core questions were based on AI principles, and we asked participants to discuss (1) how the cooperation began and developed? (2) what and how factors facilitated the cooperation? (3) what were the core barriers and challenges? and (4) how to satisfy future needs and wishes for cooperation?

Capability, Opportunity, Motivation-Behavior

Understanding what works, with whom, and under what circumstances when cooperating intersectorally requires understanding people and their behaviors [20]. The capability, opportunity, motivation-behavior (COM-b) system can be used to understand the behaviors of individuals and groups and was therefore deemed suitable to understand a group of cooperating partners [21]. Capability, opportunity, and motivation are factors that together influence and interact with behavior (Figure 1) [21]. Capability is about being able to perform a certain behavior by having the necessary knowledge and skills. Regarding IC, having good network skills and being able to speak the language or jargon of another sector can be categorized as an aspect of capability [11]. Motivation is about all the brain processes that energize and direct behavior, including more automatic (habits and emotions) and more reflective processes (conscious decision-making). Regarding IC, being motivated to find and work toward a common goal can be categorized as an aspect of motivation, as would be having a positive attitude toward another organization [12]. Opportunity is about having an environment or context that facilitates a certain behavior. Regarding IC, having a work environment that facilitates cooperation can be categorized as an aspect of opportunity. This can include both a social environment (having a boss who stimulates cooperating with other organizations) and a physical environment (in terms of having the necessary resources and time to develop external relationships) [22]. Cooperation involves a group of people and their interactions and behaviors, which are influenced by these behavioral factors, such as their willingness to cooperate and their ability to cooperate, as well as the contexts in which their cooperation takes place and the means available to cooperate (eg, resources [time, budget, etc] and organizational position). The COM-b system has been commonly applied in health promotion (eg, in categorizing healthy food consumption behavior) [23]. Moreover, it has previously been applied in the context of IC by Hendriks et al, who used it to analyze interviews exploring the views of local policy officials on IC [24]. In addition, van Rinsum et al used the COM-b system to identify the types of behaviors of health brokers, who support health promotion in complex public health challenges by facilitating IC [25]. The COM-b system is also part of the conceptual and analytical INtersectoral Health and Environment Research for InnovaTion (INHERIT) model, which was developed to understand health, environmental sustainability, and equity while taking behaviors into account [26]. We applied the COM-b system to analyze focus group data. Applying the COM-b system to study IC using focus groups may provide new insights, as it can highlight factors that influence cooperation (behaviors), which are the most important to develop, improve, and maintain for successful IC in order to allow for triple-win solutions.

Figure 1. The capability, opportunity, motivation-behavior system. This system is part of the behavioral change wheel and consists of the three behavioral determinants capability, motivation, and opportunity that influence each other and behavior. These determinants can be used to categorize and understand aspects of intersectoral cooperation.



The INHERIT Project

This study is part of the 4-year (2016-2019) European Union-funded INHERIT project. INHERIT is a research project that aims to understand how lifestyles and behaviors can be changed in order to achieve a triple win, which involves promoting health, environmental sustainability, and equity simultaneously. From the INHERIT project's promising practices database with over 100 promising practices throughout Europe, INHERIT has identified 15 case studies in the areas of "living" (eg, green areas), "moving" (eg, active transport), and "consuming" (eg, food consumption) that were considered to potentially contribute to the triple win. These were evaluated quantitatively and/or qualitatively, and/or the cost benefit was assessed. IC was studied qualitatively in 12 of these case studies, adding to the quantitative approaches used in the other evaluations. The case studies all involved stakeholders from different sectors that had been cooperating to promote health, environmental sustainability, and equity.

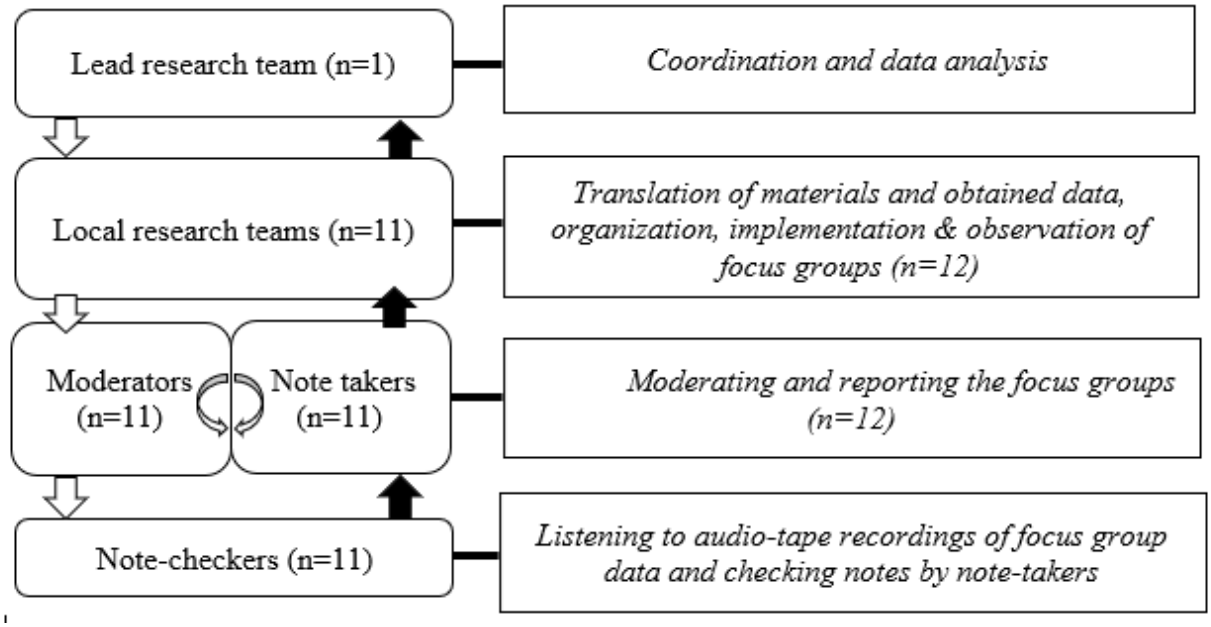
Methods

Procedures

Central Coordination

Multiple focus groups were conducted from 2018 to 2019 in 10 European countries (Multimedia Appendix 1). This qualitative study involved a stepped design. Figure 2 provides an overview of the procedure and roles of the research teams in each country. One lead research team coordinated the data collection, mostly through group and bilateral teleconferences and emails. In addition, the lead research team also functioned as a local research team for two focus groups conducted in the Netherlands. This resulted in 11 local research teams who conducted the 12 focus groups in their local language. The lead research team provided detailed instructions to standardize procedures and realize similar focus groups while taking into account that these took place in different contexts and were led by heterogenous teams. This was established by providing (1) a webinar to train local research teams on AI and the COM-b model, and to provide practical advice regarding planning, conducting, note taking, and reporting with regard to the focus groups, (2) a detailed handbook with different checklists for local coordinators, moderators, and note takers and information about the COM-b system and AI, (3) a standardized reporting form used by all research teams to report the data from the focus groups, and (4) telephone and email support by the lead team for each local team when needed. At the start, dates were set out for the focus group of each case study. The lead research team ensured that local research teams had received the necessary documents and guidance before starting the planning, conducting, and reporting of the focus groups. For further information on how the local teams were trained and instructed to conduct the focus groups in a similar fashion, the webinar and handbook can be accessed over the internet and in Multimedia Appendix 2 and Multimedia Appendix 3 [27,28].

Figure 2. Procedures and roles regarding the focus group process.



Local Data Collection

One way to investigate IC is through focus groups. O Nyumba et al concluded that a focus group is particularly useful when one's goal is to generate and evaluate a discussion about a topic that requires collective views and meanings (experiences and beliefs) that lie behind those views [29]. Since we were interested in qualitatively evaluating collective views by cooperation partners on IC, focus groups appeared to be a suitable approach. Thus, each local research team organized one focus group in the respective region of their case study. The moderator was supported by a note taker, who took notes of the focus group discussions using a standardized form provided by the lead research team. Focus group participants were invited to write their views on sticky notes, which were also included in the note-taking form. In addition, all focus group discussions were recorded using an audio recorder (after obtaining permission from the participants). The note-taking form was checked by a second person (who was preferably present as an observer at the focus group), using the audio recordings for reference. Notes could be expanded and corrected by this "note checker." Any corrected notes were discussed with the note taker to reach an agreement. We focused on IC within the 12 case studies and did not study IC between the different involved countries and case studies.

Central Analysis and Checking

Since the focus groups were conducted in native languages, local research teams translated the focus group reports into English before sending it out to the lead research team for analysis. Translated data were anonymized and sent to the lead research team using a secure file sender. Data were stored on a secure server by the lead research team. After the data were analyzed by the lead research team, the local research teams checked the analyses to make sure that the results still reflected focus group outcomes correctly. For this purpose, online review sessions were held with all local research teams to provide feedback on the results and reflect back on the focus groups and to evaluate the used method. This allowed the lead research team to make adjustments if necessary.

Conducting the Focus Groups

For each focus group, a member of the local research team acted as the focus group moderator. In eight focus groups, a member from the project consortium adopted this role. Only in two cases, the moderator came from an external agency, and this moderator followed the webinar and received the handbook. In addition, a note taker attended the focus group and took notes using a reporting form. Each focus group followed the same time schedule and question structure, with a similar time allocation to each question, allowing for some flexibility (Table 1). Focus groups lasted between 90 and 120 minutes. Participants were given the opportunity to provide informed consent before starting the focus groups. First, participants were asked to introduce themselves. Following AI procedures, these introductions included a warm-up question on what was the most positive experience of the day for each participant attending the focus group. Subsequently, the core questions regarding IC were discussed. Table 1 presents an overview of these questions and time allocation during the focus groups. The core questions regarding success factors and the future of cooperation involved the use of sticky notes to ensure that all participants could provide input. All questions were based on the AI approach [18]. Discussions followed the question structure shown in Table 1 to allow for open discussions that were not guided by already known facilitators and barriers of IC. We believed this could increase the potential to generate new insights. Local research teams were given the option to expand the focus group by a maximum of 30 minutes for additional research questions pertinent to the specific interests of the local research team, which were not related to IC (these data were not analyzed by the lead research team). Immediately after the focus group finished, the moderator and note taker met to discuss outcomes, clarify confusions, and check interpretations.

Table 1. Overview of focus group topics and questions.

Topic (time allocation)	Questions
Start and development of the cooperation (an approximately 10-minute discussion)	"How did the cooperation/project start?" "How did it develop to where it is now?" "What contributed to the cooperation process?"
Core (success) factors of the cooperation (an approximately 15-minute discussion)	"What are the core factors that made this cooperation happen and that energized and inspired cooperation?" "Describe a peak experience in (intersectoral) cooperation in [case study X], when you felt really engaged and motivated"
Core barriers, challenges, and missing factors in the cooperation (an approximately 15-minute discussion)	"How could the cooperation have been?" "What would you change if you could change anything in this cooperation? What could it still become?"
Future of the cooperation (an approximately 15-minute discussion)	"Where do you want to be between now and a certain period and what does this future look like? If your dream is X, what would you want to have accomplished in Y years?" "What are possible options (actions and projects) to reach this and enhance cooperation in the future?"
Wrap up and summary by moderator (approximately 5 minutes)	"Of all things discussed, what was the most important to you regarding intersectoral cooperation?"

Participants

The number of focus groups was set in advance (n=12) owing to strict planning requirements to achieve data collection in 10 different countries. The 12 focus groups consisted of five to eight participants, as this is the ideal size of focus groups for noncommercial topics [30]. In the focus group, at least one policy maker, one implementer of the case study, and a target population representative needed to be present to make sure perspectives from these different groups were represented in the focus group. Together with local case study contact persons, local research teams determined which essential case study stakeholders had to be included in the focus group. All focus group participants should have been involved in the cooperation process.

Theoretical Framework for Analysis

We used thematic analysis to search for themes and patterns across the data set of the focus groups [31]. Within the thematic analysis, we used a semantic approach to identify themes within explicitly mentioned data and an essentialist or realist approach in which we assumed that language reflects and enables participants to express their experiences. This entails that we assume that the language we use reflects how we give meaning and what we experience [31,32]. Top down (deductive) coding is used; we developed an analytical code tree containing predetermined codes that incorporate our research questions and previously identified elements from existing frameworks in the literature [33]. The code tree is based on the following six conditions for effective IC, as described by Harris et al: necessity, opportunity, capacity, relationships, planned action, and sustained outcomes [9]. Moreover, the codes were developed from other existing literature on success factors and barriers of IC, such as the WHO report on Multisectoral and Intersectoral Action and the Coordinated Action Checklist by Wagemakers et al [8,11]. These factors from previous frameworks were incorporated in our analytical framework, which builds on the INHERIT model and, more specifically, on the COM-b system that is embedded in it [21,26]. The COM-b system (with capability, opportunity, and motivation as interacting determinants of behavior) served as the main structure of our framework, and previously identified IC factors were categorized in one of the COM elements. An explanation of how the COM-b system can help categorize data into codes is provided in the Introduction. In addition, the code tree was structured in accordance with the focus group questions that were inspired by AI [18]. However, further emerging themes that do not fit the analytical framework themes were considered, allowing for new insights.

Results

Data collection has been completed, and a total of 76 individuals participated in 12 focus groups. In November 2019, data analysis was nearly complete, and the final results are expected to be published in fall 2020. All participants were asked for informed consent beforehand. The study was classified as "exempted from ethical approval" by the Clinical Expertise Centre of the National Institute of Public Health and the Environment.

Discussion

Principal Findings

IC is important when looking for triple-win solutions to simultaneously improve health and environmental sustainability and tackle inequity by changing behaviors and lifestyles. In order to develop and implement effective multisector policies and interventions to tackle these challenges, it is important to know which factors contribute to successful cooperation and which factors present barriers. Moreover, it is important to know whether there are similar factors for different settings (eg cultural and national), topics, and types of cooperation, necessitating cross-country research. The approach proposed in this study protocol provides a guideline to conduct

cross-country research, allowing the retainment and utilization of local knowledge, while at the same time, striving toward comparable outcomes to combine knowledge on an international cross-cultural level.

This protocol paper proposes centrally organizing coordination and analysis but local organization of 12 focus groups. The use of this approach may allow for better knowledge of local cultural contexts, with local research teams who understand and speak the local language. This may enable local teams to collect more meaningful data, facilitate discussions, and allow capturing concepts and sayings that are culture specific. These advantages were mentioned by local research teams during the web-based review sessions. In addition, local teams are in more direct and close contact with local case study implementers and therefore may know better which cooperation partners should be present at the focus group. In addition, the stepped approach minimizes travelling between the widely spread case studies and allows for a relatively resource-efficient way of conducting international focus group research, while incorporating predefined data-checking steps to ensure data quality.

We use an approach inspired by AI, which is an asset-based approach that focuses on what works well and how to do more of it in the future [18]. A common criticism on AI is that it ignores issues and problems. However, there is room for negative experiences, and practice has shown that these do emerge when using AI, but they are dealt with from a reframed perspective. Participants are asked to think about what they are missing, what created the gap between what they see and what they want to see, and how to close that gap instead of dwelling on these negative experiences [34,35]. AI fits our combined aims of generating knowledge and further improving IC processes well. Moreover, although the case studies are evaluated in different contexts and languages and by different moderators, AI principles are relatively easy to implement, which could partly address the limitation of having many different local research teams conducting the focus groups. AI facilitated similarity in local approaches as executing it is quite straightforward. This was confirmed by the review sessions with local teams, who mentioned the ease of working with AI principles when conducting the focus groups. Moreover, from these review sessions, there were indications that the AI approach is particularly useful in more hierarchical situations to have open and equal conversations between partners.

Limitations

A limitation of this approach may be that the researcher conducting data analysis was not the note taker and was not present at all the focus groups, as this was not feasible owing to language barriers. Original focus group notes had to be translated into English by local research teams, which might have caused some richness of data to be lost. If the focus groups had been conducted in English by the lead research team to gain more compatible data, it would have resulted in exclusion of the possibility of evaluation in some countries with case studies owing to the lack of mastery of the English language. Moreover, it could have resulted in an overrepresentation of participants with higher education and misrepresentation of different socioeconomic status backgrounds. In addition, this would have led to a loss in data richness and misunderstandings, as participants were nonnative English speakers in 11 focus groups. To partly overcome misrepresentation of data that could arise by translation and central analysis, the analysis results were checked by those who were present at the focus group (either an observer or the note taker).

The number of focus groups was set in advance owing to project requirements. This restricted theoretical sampling opportunities to achieve data saturation, where new information from data collection and analysis produces little to no change in the codebook [36]. However, a recent study found that 80% of themes among 40 focus groups were already discovered in two to three focus groups, confirming earlier literature on the relatively small number of focus groups or interviews needed to achieve data saturation [37].

An additional limitation of this study may be that although the notes taken during focus groups were checked and expanded afterwards with the audiotape recordings, no verbatim transcripts and translations were available owing to limited budgets. To allow for this cross-country stepped approach, it was decided to use budgets for translation and note taking with checking of audio recordings. More importantly, although transcription has been considered the “gold standard” in qualitative research, this combination of note taking and using audio recordings allows for the comparison of notes to actual responses and helps fill in blank spaces in field notes [38]. Moreover, as Halbcomb indicated, in the case of thematic analysis in which common themes are sought, verbatim transcription is not always necessary [38]. This author refers to several other authors who state that verbatim transcription is just one of the methods to capture verbal data [39]. Note taking with a check using audio recordings of the focus groups was therefore deemed sufficient in the context of this cross-country study, allowing data collection in local languages.

Comparison With Prior Work

IC has been studied by previous researchers [8-14]. However, a great part of the resulting literature centers around promotion of health and well-being, while some literature looks at IC or action to improve both health and environmental sustainability and other literature looks at health inequalities. Our study focuses on the combination of simultaneously promoting health and environmental sustainability and addressing inequities, which may lead to new insights as a wider variety of sectors are involved. In addition, while previous research often focused on a specific topic, our case studies center around a diverse range of topics from healthy and sustainable food consumption to active travel by cycling and from energy efficiency to green space. Previous methods to study IC mainly included interviews and literature reviews. We decided to study IC by means of focus groups, as this approach allows us to evaluate collective views in groups of cooperation partners and generate discussion and future plans among the cooperation partners [29]. In addition, we used the COM-b system to categorize and structure data analysis. The COM-b system is a relatively simple behavioral model consisting of three factors that influence and interact with behavior. To our knowledge, the COM-b system has not been applied previously to analyze focus group data on

IC, and this can lead to new insights and recommendations regarding what is needed for individuals and groups to practice effective IC in terms of capability, opportunity, and motivation. The results of this study will contribute to evidence on whether COM-b is a useful model to apply for group behaviors, such as IC.

Conclusions

To our knowledge, no other qualitative study has been conducted in a similar manner to evaluate IC in a diverse range of European interventions in order to achieve the aforementioned triple-win solutions. Performing this type of cross-country research requires a strict approach, and our protocol can serve as a tool for other researchers who plan to conduct this type of research. The results of our study will demonstrate how the COM-b system can contribute to understanding the conditions for behavior that are necessary to develop and maintain successful IC. In addition, the applied stepped approach can be used by other researchers who wish to conduct focus groups in cross-country research. Insights from this qualitative evaluation will be used as one of INHERIT's input sources for the development of a policy toolkit that will help and inform policy makers on actions that can lead to a healthier, more environmentally sustainable, and more equitable future. Often, approaches that work in one country or context do not necessarily work in another country or context. This study will provide an overview of key elements of successful cooperation according to stakeholders who cooperate in the context of a wide variety of European case studies. In addition, this study will generate rich data as it allows for comparison among a broad variety of interventions that enhance health, environmental sustainability, and equity by means of behavioral or lifestyle change, but differ strongly in terms of topic, cultures, and contexts. Therefore, the study can provide valuable lessons about what works when engaging in IC, and whether and how it differs among contexts (political, social, and cultural) for a broad set of topics.

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Authors' Contributions

Funding acquisition: CC; investigation: NvdV and LdB; methodology: NvdV, LdB, and MRV; project administration: CC; supervision: JS; writing-original draft: NvdV; writing-review and editing: NvdV, LdB, MRV, HK, BS, and JS.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Overview of the 12 case studies, with name, country, and a short description.
[DOCX File , 22 KB - resprot_v9i6e17323_app1.docx]

Multimedia Appendix 2
Webinar for qualitative evaluation (INHERIT).
[PPTX File , 42162 KB - resprot_v9i6e17323_app2.pptx]

Multimedia Appendix 3
Handbook for qualitative evaluation (INHERIT).
[PDF File (Adobe PDF File), 812 KB - resprot_v9i6e17323_app3.pdf]

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Abbreviations

AI: appreciative inquiry
COM-b: capability, opportunity, motivation-behavior
IC: intersectoral cooperation
INHERIT: INtersectoral Health and Environment Research for InnovaTion
SDG: sustainable development goal

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Protocol

A Telerehabilitation Intervention for Youths With Arthrogryposis Multiplex Congenita: Protocol for a Pilot Study

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Abstract

Background: Arthrogryposis multiplex congenita (AMC) is characterized by joint contractures present in at least two body areas. In addition to these contractures, individuals with AMC can have decreased muscle mass, leading to limitations in activities of daily living. Exercise has the potential to maintain or improve the range of motion and muscle strength. However, this type of intervention necessitates frequent follow ups that are currently difficult to provide for youths with AMC because they often live far from a specialized hospital. To overcome this distance challenge, telecommunication technologies can be used to deliver rehabilitation remotely, which is called telerehabilitation. The study protocol for one such type of rehabilitation will be presented in this paper.

Objective: This pilot study aims to (1) evaluate the feasibility of using telerehabilitation to provide a home exercise program for youths with AMC, and (2) assess the effectiveness of a home exercise program.

Methods: A total of 10 youths aged 8-21 years with AMC will be recruited. The intervention consists of a 12-week individualized home-based exercise program delivered remotely using telerehabilitation. At baseline, youths will complete the Physical Activity Questionnaire for Adolescents and the Pediatrics Outcomes Data Collection Instrument to assess pain, function, and level of physical activity. During the first telerehabilitation meeting, the rehabilitation therapists will measure range of motion using a virtual goniometer and assess the youth's functional level. The therapists will then use the Goal Attainment Scale to set objectives and develop the individualized intervention. Follow ups will occur every 3 weeks to make sure exercises are performed safely and to progress the exercises when needed. At the end of the 12-week intervention, rehabilitation therapists will re-evaluate the youth using the same outcome measures as the initial evaluation. The youths will be asked to complete the same questionnaires, with the addition of questions about their satisfaction regarding the intervention. Nonparametric and descriptive statistics will be used to evaluate the feasibility and effectiveness.

Results: Ethics approval was obtained in October 2018. Recruitment and data collection started in January 2019 and was completed in May 2020.

Conclusions: This pilot study will help us learn how a large-scale project may work in practice to improve outcomes in physical activity, pain, and function, and goal attainment among youths with AMC, thus informing a future clinical trial.

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KEYWORDS

telerehabilitation; arthrogryposis multiplex congenita; physical therapy; occupational therapy

Introduction

Arthrogryposis multiplex congenita (AMC) or arthrogryposis is a term representing a heterogeneous group of over 400 disorders characterized by congenital contractures present in at least two different body joints [1]. AMC is rare and affects 1 in 3000 to 1 in 4300 live births [2]. Amyoplasia and distal arthrogryposis are the most common types and combined together, they represent about 50%-65% of all AMC diagnoses [3,4]. Contractures, which are defined as the limitation of passive movement of a specific joint, can affect the joints of the upper and/or lower limbs, as well as the spine and jaw [1]. Contractures can be caused by an increase of connective tissue around the joints, joint fibrosis replacement of muscle, muscle atrophy, or articular deformities [1]. AMC is typically nonprogressive, as no new contractures appear during an individual's life. However, contractures can recur after intervention or worsen over time [5]. In addition to these contractures, individuals with AMC may present with decreased muscle mass and bone density, bone deformities, and pain, leading to activity limitations and participation restrictions in activities of daily living such as feeding, dressing, mobility, and sports [3,6-9]. Early interventions such as stretching, splinting, bracing, casting, rehabilitation, and surgical procedures have been shown to augment and maintain range of motion and strength, and therefore, to promote independence in daily activities [10].

Rehabilitation can improve physical function and maintain gains after surgery [5]. Structural changes of the joint surface in AMC further limit range of motion when the joint is not used [10]. Besides, a positive association has been reported between knee and hip muscle strength and motor function [11], suggesting that rehabilitation exercises can maintain or increase range of motion and preserve muscle strength for optimal motor function. Currently, most interventions in AMC, specifically rehabilitation, occur in early childhood and their frequency decreases during school-age and adolescent years, despite new challenges arising during these transition periods [5,12]. Rehabilitation for school-aged children focuses mostly on body functions and structure, which does not always correspond to the youth's specific needs, such as participating in activities [12].

As AMC is rare, youths are mainly treated in subspecialized health care centers, which may be geographically distant from where they live. Therefore, clinicians face an important challenge in implementing regular exercise interventions. Novel intervention approaches and technologies are needed to increase access to subspecialized care for youths with AMC across geographical boundaries. Telerehabilitation, defined as "an innovative way to deliver rehabilitation services remotely using information and telecommunication technologies" [13], can be used to overcome this challenge. Some aspects can limit the usability of telerehabilitation, such as the lack of direct contact with participants, difficulties with manipulation of technology for individuals with physical limitations, or having a poor internet connection [14,15]. Nevertheless, telerehabilitation has been studied with different clinical populations (eg, total knee arthroplasty or vascular surgery patients) and was found to be as effective as face-to-face interventions [13], save travel time [16], and reduce cost for people living at a distance of 30 km or more from the health care center [17]. In the pediatric population, telerehabilitation has been used to provide various interventions (physical therapy, psychology, and speech language therapy) for different populations (patients with acquired brain injury, autism spectrum disorder, or cerebral palsy) [18]. Despite the potential benefits of telerehabilitation, there is a lack of research on its use for youths with physical impairments [18]. Therefore, the purpose of this study is to pilot the delivery of a home-based exercise program (HEP) for youths with AMC using telerehabilitation. Specifically, this pilot study aims to (1) evaluate the feasibility of using telerehabilitation to provide a physical assessment and to deliver an HEP for youths with AMC; and (2) explore the potential effectiveness of the HEP on goal attainment, physical activity, pain, and function. The provision of an HEP through telerehabilitation will provide an unprecedented opportunity for service equity to this vulnerable population, regardless of geographical location. The methodology of this study is reported in this paper.

Methods

Study Design

This is a pilot study to evaluate the feasibility and effectiveness of a telerehabilitation intervention for youths with AMC.

Participants Eligibility

Youths aged between 8 and 21 years with a confirmed clinical diagnosis of multiple congenital contractures, or AMC, will be invited to participate. Inclusion criteria include the ability to communicate in English or French and residence in Canada. Youths living in another country will be excluded as rehabilitation therapists participating in this study hold only a Canadian professional license. To align with postintervention precautions, those having undergone a recent surgery (ie, 3 months for soft tissue and 6 months for bony surgery) will be excluded. Youths with cognitive deficits or unstable health will also be excluded, to ensure participants can take part in the HEP. To assess the level of cognition, medical records will be reviewed for the presence of central nervous involvement or intellectual impairment. In addition, the treating physician, therapists, and parents will be consulted to determine eligibility based on type of schooling and ability to follow instructions. No restriction will be made about the degree of severity of contractures or physical impairment.

Recruitment

Youths with AMC followed at Shriners Hospital for Children - Canada (SHC-C) will be recruited during their clinic visit. Potential youths with the appropriate clinical diagnosis who do not have an upcoming visit to SHC-C will be contacted by postal mail and phone. For youths with AMC who are not followed

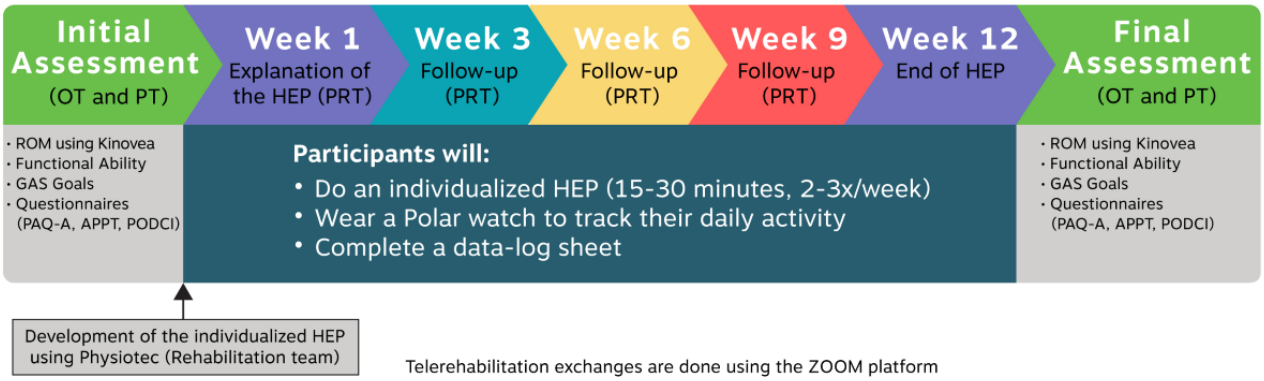
at SHC-C, an advertisement describing the study will be posted on social media of a Canadian AMC support group (ie, Facebook). Those interested in participating will be asked to contact the clinical research coordinator for more information. Prior to participating in the study, informed consent will be sought from parents as well as from youths aged 14 years and older, as per provincial regulations. Youths between the ages of 8 and 13 years will be asked to provide assent. For these younger participants, the research team will encourage parents to be available during the telerehabilitation sessions to provide support during the sessions and throughout the HEP. As we expect to complete this study on 10 youths, 13 youths will be recruited to account for a 30% dropout rate [19].

Intervention

A rehabilitation team including a physical therapist, an occupational therapist, and a physical rehabilitation therapist will collaborate to provide the intervention. A physical rehabilitation therapist is defined as a professional among the interdisciplinary team whose role is to obtain necessary prerequisite information from a leading physical therapist in order to develop treatment plans and provide appropriate interventions to reduce activity limitations and participation restrictions.

The intervention will consist of a 12-week HEP. Prior to the assessment with the therapists, youths will complete an online questionnaire consisting of the Physical Activity Questionnaire for Adolescents (PAQ-A), the Pediatrics Outcomes Data Collection Instrument (PODCI), and demographic questions. The occupational therapist and physical therapist will conduct the initial assessment of each youth using ZOOM Pro (Zoom Video Communications, Inc), a videoconferencing platform allowing an encrypted connection. During this assessment, the therapists will perform an active joint range-of-motion (AROM) assessment of the upper and lower limbs, evaluate overall function, assess pain using the Adolescent and Pediatric Pain Tool (APPT), and establish individualized goals with each youth using the Goal Attainment Scale (GAS). The information gathered through this initial assessment will be used by the rehabilitation team to develop an individualized 12-week HEP. A week after the initial assessment, the physical rehabilitation therapist will exchange with the youth using ZOOM to explain and deliver the HEP as well as ensure comprehension and safe execution of the exercises. Youths will be asked to perform their HEP three times a week for approximately 15-30 minutes each time. They will be sent a physical activity monitor (POLAR watch A370) by postal mail and will be instructed to wear it on their wrist during HEP sessions, as it will be used to capture heart rate and the duration of the exercise sessions. Youths will have the possibility to wear the physical activity monitor at all times if they desire. If needed for the HEP, exercise materials such as resistant elastic bands or TheraPutty will also be sent to them by postal mail. A follow up with the physical rehabilitation therapist will be provided through ZOOM every 3 weeks (ie, at weeks 3, 6, and 9) to address any questions and to adjust the HEP as needed. At the end of the 12-week intervention, the occupational therapist and physical therapist will re-evaluate the youth using the same outcome measures as the initial evaluation. Youths will be asked to complete the same questionnaire, with the addition of questions about their satisfaction regarding the intervention. Figure 1 provides a summary of the intervention. The outcome measures used in this study are described in the following sections. In addition, parents will be asked to complete a cost questionnaire (direct and indirect costs incurred in relation to their child's condition), which will be described elsewhere as it extends beyond the scope of this study.

Figure 1. A summary of the 12-week telerehabilitation intervention. APPT: Adolescent and Pediatric Pain Tool; GAS: Goal Attainment Scale; HEP: home-based exercise program; OT: occupational therapist; PAQ-A: Physical Activity Questionnaire for Adolescents; PODCI: Pediatrics Outcomes Data Collection Instrument; PRT: physical rehabilitation therapist; PT: physical therapist.



Measurement

Feasibility

Operationalization

The source of recruitment (eg, in clinic, postal mail, phone, or social media), recruitment and withdrawal rates, compliance to the HEP and to the telerehabilitation meetings, and missing data will be calculated to determine feasibility of the intervention for youths with AMC. The compliance to the HEP will be measured using the data from the activity monitor as well as from a data-log sheet on which youths will have to record when they perform their exercise program. Refer to Table 1 for the operationalization of the feasibility criteria.

Table 1. Operationalization of the criteria to evaluate feasibility.

Parameters	Definition	Criteria/examples
Source of recruitment	The method used to recruit each youth.	In clinic, postal mail, phone, social media
Recruitment rates	From a list of patients with AMC[a] followed, the number of eligible youths will be determined. Those that are reachable will be accounted.	≥50% of eligible and reachable youths
Withdrawal rates (before the intervention)	Youths who will consent to participate but will withdraw before the start of the intervention will be accounted.	≤20% of the youths who consent
Withdrawal rates (during the course of the intervention)	Youths who will complete at least one telerehabilitation meeting and will decide to withdraw afterward will be counted. The time points when they decide to withdraw will be collected as well as the reason, if applicable.	≤30% of the youths who start the intervention
Completion rates	The number of youths who will complete all 6 telerehabilitation meetings out of those who have consented.	≥50% of the youths who consent
Compliance to the HEP[b]	The amount of time youths performed their HEP will be collected using a participant-completed log sheet and data from the physical activity monitor.	≥50% of compliance to the HEP
Compliance to the telerehabilitation meetings	The number of meetings cancelled the same day among the meetings that occurred, as well as lateness to the meetings. Lateness is defined as joining the meeting 15 minutes or more after the scheduled time.	≤15% of the meetings
Missing data	The number of questionnaires not completed and the number of unusable range-of-motion data.	≤10% for each outcome
Technical issues	Problems that will arise and disrupt or delay the meeting or possibly prevent the telerehabilitation meeting from taking place.	Echo voices, connection, image quality

[a]AMC: arthrogryposis multiplex congenita.

[b]HEP: home-based exercise program.

Cost

The total amount of time spent during the telerehabilitation intervention by the physical therapist, occupational therapist, and the physical rehabilitation therapist providing the assessment and the HEP as well as their time outside the direct intervention with the youth (planning the HEP and writing the report) will be recorded. The cost of the ZOOM plan and of the federal professional licenses for the occupational therapist and physical therapist will be reported.

Satisfaction

Satisfaction regarding the telerehabilitation intervention, the assessment with the therapists, and the HEP will be evaluated in the final online questionnaire with open-ended questions and using a 5-point Likert scale.

Effectiveness

GAS

The GAS will be administered by the occupational therapist with the youth during the initial online assessment to set individualized goals with the youths and to calculate the extent to which their goals are met at the end of the 12-week HEP [20].

AROM

AROM will be measured to provide an overview of the youths' ability to build the HEP. Screenshots of each youth performing specific movements during the initial and final assessment will be taken and then AROM will be measured using a virtual goniometer (Kinovea). This method has been shown to be feasible on 10 healthy adult participants [21]. AROM of the following joints will be measured as degrees of movement: shoulder (abduction, flexion, and extension), elbow (flexion and extension), forearm (pronation and supination), wrist (flexion and extension), hip (flexion, extension, internal rotation, and external rotation), knee (flexion and extension), and ankle (dorsiflexion and plantar flexion). Some movements are expected to be difficult to measure with a virtual goniometer because of the wrong plane of movement, so we will report the following AROM as full, limited, or absent: finger and thumb (flexion, extension, abduction, and adduction), shoulder (internal and external rotation), and hip (abduction). When possible, AROM will be measured in positions that allow being with and without the effect of gravity to estimate muscle strength. Although passive range of motion is usually taken clinically, it will not be measured in this context of telerehabilitation.

PODCI

This questionnaire was developed by the American Academy of Orthopaedic Surgeons and the Pediatric Orthopaedic Society of North America to measure functions in the following dimensions among children aged 2-18 years with musculoskeletal conditions: upper extremity functioning, transfers and basic mobility, sports and physical function, and comfort/pain [9]. The four dimensions are computed together to give a global functioning score, and in addition, a separate

scale evaluating happiness with physical condition is provided. The PODCI response scales use a 3- to 6-point format. The internal consistency is high and the test–retest reliability is excellent for all subscale scores [22]. The PODCI was shown to be sensitive to change in function over time in 74 children with amyoplasia [9].

PAQ-A

This questionnaire measures the general levels of physical activity in the last 7 days. The PAQ-A is a self-administered questionnaire developed for typically developing high-school-age youths. This questionnaire has shown a moderately high concurrent validity when compared with an activity monitor and a good internal consistency [23]. The PAQ-A provides a summary physical activity score derived from 8 items, each scored on a 5-point scale. The final mean of the 8 items is reported to classify the level of physical activity [24].

Adolescent Pediatric Pain Tool

This tool assesses current pain for children and adolescents between ages 8 and 17 years with different conditions such as cancer and orthopedic and traumatic injuries. The APPT shows good validity, test–retest reliability, and sensitivity. The questionnaire uses a visual analog scale, a list of 42 qualitative words describing pain, and 2 body diagrams on which the child has to circle the location of the pain [25]. A summary of the outcomes to assess the effectiveness is presented in Table 2.

Table 2. Summary of outcomes used to determine effectiveness.

Tools/outcome measures	What does it assess?
Adolescent Pediatric Pain Tool (APPT)	• Pain
Goal Attainment Scale (GAS)	• Progress of the individualized goals
Physical Activity Questionnaire for Adolescents	• Level of physical activity
Pediatrics Outcomes Data Collection Instrument	• Upper extremity function • Transfers and basic mobility • Sports and physical function • Comfort and pain • Global function • Happiness
Range of motion	• Shoulder: abduction, adduction, flexion, and extension • Elbow: flexion and extension • Forearm: pronation and supination • Wrist: flexion and extension • Hip: flexion, extension, internal rotation, and external rotation • Knee: flexion and extension • Ankle: dorsiflexion and plantar flexion

Statistical Analyses

Given this is a pilot study with a small sample size and a heterogeneous population, nonparametric and descriptive statistics will be used. To assess feasibility, the compliance to the HEP and to the telerehabilitation meetings, recruitment and completion rates, missing data, and closed-ended questions on satisfaction will be analyzed using descriptive statistics and compared with the established feasibility criteria. Table 1 describes the feasibility criteria for operationalization that will be used in the study. Youths' experience about use of technology and overall satisfaction with the program will be reported as collected in the open-ended questions. The cost of the telerehabilitation intervention (ie, therapists' time, federal professional license, and teleconferencing cost), recruitment source, and technical issues experienced during the program will be described. For the effectiveness of the HEP, raw GAS scores will be converted to GAS T-scores for each youth and for the global HEP. Preintervention and postintervention data of the range of motion, APPT, PAQ-A, and PODCI will be compared using the Wilcoxon signed-rank test to measure change among the same youth.

Results

Administrative site approval was obtained from the Department of Medical Research at Shriners Hospital for Children (CAN1806) in July 2018. Ethics approval was provided by the McGill University Faculty of Medicine Institutional Review Board (#A08-B38-18B) in October 2018. Recruitment and data collection started in January 2019 and was completed in May 2020.

Discussion

Overview

The proposed telerehabilitation pilot study is designed to provide an HEP to youths with AMC. Establishing the feasibility of this study has the potential to inform service delivery models using technology, thereby overcoming geographical barriers, to provide an individualized HEP to youths living with a rare condition.

To date, little is known about the potential effectiveness of exercises in adolescents with AMC [5]. Using this type of

technology in a study that includes frequent follow ups as proposed in this protocol has the potential to reach more participants because it transcends geographical barriers, improving the sample size needed for research with heterogeneous populations such as AMC. Telerehabilitation allows inclusion of youths from across Canada, regardless of proximity to a specialized health care center. Although telerehabilitation has previously been used in studies on children with asthma and autism spectrum disorders [26,27], the only musculoskeletal disorder in which a telerehabilitation intervention was used is with children with cerebral palsy [18]. However, the results were variable among those studies which justify studies with other populations such as AMC [28,29]. In addition, little is known about the cost efficiency of this type of intervention [26,30].

Limitations

This pilot study has some limitations. Because of the remoteness of the assessment, even if passive range of motion is normally measured in the clinic, it will not be assessed in this study. Despite passive range of motion being important to measure, it is expected that therapists will have sufficient information to develop the individualized HEP from the initial telerehabilitation assessment. Another consideration is that youths will be instructed to wear the activity monitor on their wrists, even in the presence of upper extremity contractures that may interfere with the movement capture, therefore with the accuracy of step count. As the purpose of the activity monitor in this study is to measure heart rate and duration of the exercise sessions, and not to record steps, all youths will wear the watch at the wrist. Importantly, the goal of using telerehabilitation is not to replace face-to-face clinic visits or in-person therapy, but rather to propose a complementary intervention therapists can offer youths and their families during adolescence, at which time rehabilitation has been shown to decrease [12]. The aim to provide an individualized HEP is to help youths maintain their physical gains and assist them in reaching new goals that may arise as they grow. This telerehabilitation pilot study will also inform the possible pitfalls, beneficial effects, and cost associated with this new method of care, thus informing its use in other populations with musculoskeletal conditions.

Conclusion

Establishing the feasibility of using telerehabilitation for children with AMC will inform us for a future clinical trial. Information about the potential effectiveness of using telerehabilitation to deliver an HEP for children with AMC will be provided, thus leading to the development of a novel approach in this population. If proven successful, this service delivery model can be tailored to other pediatric musculoskeletal conditions, such as osteogenesis imperfecta and juvenile rheumatoid arthritis.

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Authors' Contributions

NDO initiated, planned, and received funding for this study. NDO wrote the study protocol. MG wrote the paper. JC, CE, GMM, JM, BS, RY, RH, LNV, and NDO revised the manuscript. MG, JC, CE, GMM, and RY are involved in the data collection.

Conflicts of Interest

None declared.

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Abbreviations

AMC: arthrogryposis multiplex congenita
APPT: Adolescent and Pediatric Pain Tool
AROM: Active range of motion
GAS: Goal Attainment Scale
HEP: Home-based exercise program
PAQ-A: Physical Activity Questionnaire for Adolescents
PODCI: Pediatrics Outcomes Data Collection Instrument
SHC-C: Shriners Hospital for Children - Canada

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Protocol

The Safety, Efficacy, and Tolerability of Microbial Ecosystem Therapeutic-2 in People With Major Depression and/or Generalized Anxiety Disorder: Protocol for a Phase 1, Open-Label Study

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Abstract

Background: The bidirectional signaling between the gut microbiota and the brain, known as the gut-brain axis, is being heavily explored in current neuropsychiatric research. Analyses of the human gut microbiota have shown considerable individual variability in bacterial content, which is hypothesized to influence brain function, and potentially mood and anxiety symptoms, through gut-brain axis communication. Preclinical and clinical research examining these effects suggests that fecal microbiota transplant (FMT) may aid in improving the severity of depression and anxiety symptoms by recolonizing the gastrointestinal (GI) tract with healthy bacteria. The microbial ecosystem therapeutic (ie, microbial ecosystem therapeutic-2 [MET-2]) used in this study is an alternative treatment to FMT, which comprises 40 different strains of gut bacteria from a healthy donor.

Objective: The primary objective of this study is to assess subjective changes in mood and anxiety symptoms before, during, and after administration of MET-2. The secondary objectives of this study are to assess the changes in metabolic functioning and the level of repopulation of healthy gut bacteria, the safety and tolerability of MET-2, and the effects of early stress on biomarkers of depression/anxiety and the response to treatment.

Methods: Adults experiencing depressive or anxiety symptoms will be recruited from the Kingston area. These participants will orally consume an encapsulated MET-2 once daily—containing 40 strains of purified and laboratory-grown bacteria from a single healthy donor—for 8 weeks, followed by a 2-week treatment-free follow-up period. Participants will undergo a series of clinical assessments measuring mood, anxiety, and GI symptoms using validated clinical scales and questionnaires. Molecular data will be collected from blood and fecal samples to assess metabolic changes, neurotransmitter levels, inflammatory markers, and the level of engraftment of the fecal samples that may predict outcomes in depression or anxiety.

Results: Given the association between the gut bacteria and the risk factors of depression, we expect to observe an improvement in the severity of depressive and anxiety symptoms following treatment, and we expect that this improvement is mediated by the recolonization of the GI tract with healthy bacteria. The recruitment for this study has been completed, and the data obtained are currently being analyzed.

Conclusions: This is the first time MET-2 is being tested in psychiatric indications, specifically depression and anxiety. As such, this may be the first study to show the potential effects of microbial therapy in alleviating psychiatric symptoms as well as its safety and tolerability.

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KEYWORDS

depression; anxiety; microbial ecosystem therapy; gut-brain axis; microbiome; clinical trial; protocol

Introduction

Depression and Anxiety

Major depressive disorder (MDD) is the leading cause of disability worldwide and is a major contributor to the overall global burden of diseases [1]. Globally, over 300 million people of all ages are affected by MDD over their lifetime, and the mortality risk of suicide for these individuals is 20-fold greater than that of the general population [2]. MDD is characterized by either a persistent depressed mood or loss of interest or pleasure in surroundings accompanied by a variety of symptoms that cause clinically significant distress or impairments [3]. MDD may have a severe and chronic course, with the majority of affected individuals subjected to multiple recurrent episodes throughout their lifetime as well as academic, occupational, and interpersonal functioning impairments and high levels of medical and psychiatric comorbidities [4].

A common comorbidity in individuals with MDD is generalized anxiety disorder (GAD). GAD is characterized by excessive anxiety and worry, particularly due to life circumstances, such as work, school, and relationships [5]. GAD is one of the most common and the broadest anxiety disorder affecting 3% of the general population in 1 year, with a lifetime prevalence of 5% [6,7]. The psychological symptoms of GAD can also be accompanied by physical symptoms, such as abdominal pain, muscle tension, restlessness, or sleeping problems. The association between generalized anxiety and gastrointestinal (GI) symptoms may be explained by the close connection between the gut and the brain.

Gut Brain Axis

In the last several years, there has been a growing appreciation for research in the field of the *gut-brain axis*, which consists of bidirectional signaling between the GI tract and the brain. Over 100 trillion commensal bacteria are estimated to exist symbiotically in the human gut and are critical in the normal development of the immune system, central nervous system (CNS) circuitry, GI functioning, and autonomic nervous system functioning [8]. Detailed analyses of human gut microbiota have shown considerable individual variability in bacterial content, as this dynamic system is influenced by a variety of factors, such as genetics, diet, metabolism, age, geography, antibiotic treatment, and stress [8]. Studies have also shown that human gut bacteria play a vital role in regulating important aspects of brain development and function, along with other host physiology [9,10].

By being able to shape brain physiology and, therefore, behavior through gut-brain axis communication, gut bacteria may be a vital trigger in the development of neuropsychiatric conditions [11]. Given the adaptable nature of the gut microbiome, it may be a good representation of the individual's history and could explain the differences in risk of illness, disease course, and response to treatment. The interaction of the gut with the environmental risk factors of depression and anxiety, such as diet and early life stress, also suggests that interventions that target the gut microbiome could prevent and treat depression and anxiety symptoms [12]. In past studies, depressed patients have been shown to have a dissimilar microbiota composition compared with healthy individuals due to the decreased diversity and abundance of their gut microbiota [13-15].

Gut Microbiome and Psychiatric Symptoms

MDD pathophysiology involves three different physiological systems: (1) neurotransmitter dysfunction between the prefrontal cortex regions in the CNS and the hypothalamic-pituitary-adrenal (HPA) axis, (2) chronic inflammation of the immune system, and (3) an imbalance in the microbiota-gut-brain axis [16-20]. The prefrontal cortex, hippocampus, and amygdala play a vital role in the regulation of emotion, anxiety, stress responses, self-control, motivation, and cognitive reactions. However, in depressed patients, the function of the prefrontal cortex and hippocampus is impaired, whereas the activity of the amygdala is increased [21]. These arguments are supported by the monoaminergic neurotransmitter deficiency hypothesis, which postulates that monoamine neurotransmitters serotonin (5-HT), norepinephrine (NE), and dopamine (DA) are at insufficient levels and ultimately result in depressive symptoms. The immune system plays an important role in depression; the cytokine and neuroinflammation hypotheses suggest an increase in pro-inflammatory cytokines (interleukin 6 [IL-6] and tumor necrosis factor alpha [TNF-α]), and a decrease in anti-inflammatory cytokines (interleukin 10 [IL-10] and transforming growth factor beta [TGF-β]), contribute to a pro-inflammatory state in depressed patients. These cytokines inhibit the negative feedback of the HPA axis, increase the permeability of the blood-brain barrier, reduce the synthesis of 5-HT, disturb the glutamatergic systems, and influence neuroglial cells. These actions play a vital role in the regulation of neuro-immunity and neuroplasticity and are hypothesized to result in depressive behavior [22-27]. In 2012, Maes et al [28] showed that bacterial translocation from the gut, or *leaky gut*, which may be due to systemic inflammation in depression or may be a primary trigger that is associated with the onset of depression, can activate immune cells to elicit selective immunoglobulin A (IgA) and immunoglobulin M (IgM) response—both antibodies that fight and protect against infections. The results of this study suggest that this phenomenon may be involved in the pathophysiology of depression by causing progressive amplifications of immune pathways [28].

Microbial Ecosystem Therapeutics

Despite increasing research, a complete understanding of gut microbial changes is still lacking. Interestingly, depressive symptoms have been shown to be transmissible via fecal microbiota transplantation (FMT) in animal models [29]. Zheng et al [30] demonstrated that FMT material from depressed but not neurotypical human patients resulted in depressive-like symptoms upon transfer to germ-free recipient mice. Given that disturbances to the gut microbiome can increase susceptibility

to depression, repopulating the gut microbiome may allow for improvement in mood and anxiety symptoms. Microbial ecosystem therapeutic-2 (MET-2) is a new treatment approach for repopulating the gut with healthy bacteria that has been developed as an alternative to FMT. This is a biological compound comprising live microbes that normally reside in the gut of a healthy individual. Given that stool contains a highly complex and dense community of microbes, including bacteria, fungi, and viruses, many of which have not been fully characterized, the product focus of MET-2 is on defined mixtures of isolated strains of intestinal bacteria as the treatment [31]. MET-2 capsules contain 40 strains of purified lyophilized bacteria from a healthy 25-year-old donor, chosen for their favorable safety profile. MET-2 capsules are produced under conditions compatible with good manufacturing practice, at the University of Guelph, sealed under anaerobic conditions, and shipped at room temperature. The vials of MET-2 capsules are transferred at room temperature from the University of Guelph to the Providence Care Hospital pharmacy. The investigator ensures that the product is stored at room temperature ready for use in appropriate conditions and in a secure, locked storage with controlled access until use. Capsules are used to improve MET-2's appeal to participants to allow for easier administration over consecutive days, in contrast to FMT, which involved of rectal administration. Moreover, capsules allow for oral administration of controlled fecal colonies, which confers an increased level of safety over the use of raw fecal material administered via rectal suspension. This protocol will outline a phase 1, open-label clinical trial that will assess the safety, efficacy, and tolerability of MET-2 on depression and anxiety symptoms.

Objectives

Primary Objective

The primary objective of this study is to assess subjective changes in mood and anxiety symptoms before, during, and after MET-2 treatment in participants with major depression and/or generalized anxiety, using the Montgomery-Asberg depression rating scale (MADRS), GAD 7-item scale (GAD-7), and other mood/anxiety scales. Those with a 50% reduction in the GAD-7 and/or MADRS scores will be considered successful responders to treatment.

Secondary Objectives

The secondary objectives are to assess changes in metabolic functioning/levels before, during, and after treatment; to assess safety and tolerability, including adverse events (AEs) with a severity of grade 2 or above; and to assess potential correlation between early life stress (childhood emotional/physical/sexual abuse history, etc) and changes in MDD biomarkers as well as response to treatment.

Methods

Study Design

This is an 8-week, open-label, phase 1 clinical trial assessing the safety, tolerability, and efficacy of MET-2 on depression and anxiety symptoms. All participants will consume the investigational product, MET-2, in *a* capsule form, daily for 8 weeks. MET-2 is administered orally at 0.5 g of MET-2 per capsule, containing 3.2×10^5-3.2×10^{11} colony-forming units (CFUs). At each in-hospital visit, participants take home the appropriate number of MET-2 capsules needed for a 2-week period, packaged in bottles. Loading/booster doses are provided in separate vials from maintenance daily doses. Each vial is stored by the participant at room temperature. MET-2 is meant to be taken after a light meal, preferably in the morning and at the same time every day.

Participants will consume an initial loading dose of 5 g MET-2. An initial MET-2 dose in the range of 10^8 to 10^{12} CFUs was selected with the aim of ensuring delivery of a sufficient quantity of the MET-2 bacterial community that is expected to colonize the gut. The first loading dose, at baseline, is to be consumed under the supervision of the study staff to ensure immediate safety, and further compliance is assessed using the returned investigational product and by reviewing participants' personal logs at each in-hospital visit. For the remainder of the 2-week period, the participants will consume 1.5 g of MET-2 per day. The loading dose is repeated for the first 2 days at the week 2 time point, and participants return to the maintenance dose for the remainder of the treatment period. At week 4, participants are assessed for treatment response. Responders remain on the maintenance dose until the end of treatment. Nonresponders are given an additional loading dose (booster dose; Table 1).

Table 1. Dosing schedule.

Dose	Baseline to week 2	Weeks 2-4	Weeks 4-6	Weeks 6-8
Loading/booster dose (5 g of MET-2[a]: 10 capsules per day for 2 days)	Days 1 and 2 only	Days 1 and 2 only	Days 1 and 2 (only NR[b])	N/A[c]
Maintenance dose (1.5 g of MET-2: 3 capsules per day)	Days 3-14	Days 3-14	R[d]: Days 1-14; NR: Days 3-14	Days 1-14

[a]MET-2: microbial ecosystem therapeutic-2.

[b]NR: nonresponders.

[c]N/A: not applicable.

[d]R: responders.

Definitions

Depression/Presence of Depressive Symptoms

The diagnosis of MDD is based on the mini-international neuropsychiatric interview (MINI). A score of ≥15 on the MADRS is also used to diagnose MDD.

Anxiety/Presence of Anxiety Symptoms

The diagnosis of GAD is based on MINI. A score of ≥8 on the GAD-7 is also used to diagnose GAD.

Treatment Success

Treatment success is defined as a reduction in the MADRS/GAD-7 scores by 50% from the baseline. Those who do not meet the 50% threshold are considered nonresponders. Nonresponders at the week 4 visit will be given a booster dose.

Treatment Failure

Treatment failure is defined as same or increased MADRS/GAD-7 scores from pre- to post-treatment.

Study Setting

This study is being carried out at the Providence Care Hospital, a tertiary care mental health and continuing care hospital in Kingston, Ontario There will be a total of 7 visits, of which 6 will be in-person and 1 will be over the phone.

Participants

A total of 10 to 15 eligible participants aged between 18 and 65 years will be recruited from the Kingston area. At the first visit, consent will be obtained from potential trial participants by a study team member and overseen by the principal investigator. Following informed consent, the participants will be screened to ensure that they fit the inclusion criteria (Textbox 1). In this study, we define depression as a confirmed diagnosis of MDD based on the MINI and a score of ≥15 on MADRS; anxiety is defined as a confirmed diagnosis of GAD based on the MINI and a score of ≥8 on the GAD-7. These participants are not to be in a current episode of MDD or GAD and should not have been taking any antidepressant medication. Textboxes 1 and 2 provide the full study criteria.

Textbox 1. Inclusion criteria.

- Able to provide informed consent
- Not pregnant
- Willing to participate in follow-up as part of the study
- Diagnosis of major depressive disorder and/or generalized anxiety disorder (GAD) by the mini-international neuropsychiatric interview
- Current depressive episode with a Montgomery-Asberg depression rating scale score of ≥15 or current GAD episode with a GAD 7-item scale score of ≥8
- Able to understand and comply with the requirements of the study
- Able to provide stool and blood samples

Textbox 2. Exclusion criteria.

- History of chronic diarrhea
- Need for regular use of agents that affect gastrointestinal motility (narcotics such as codeine or morphine and agents such as loperamide or metoclopramide)
- Colostomy
- Elective surgery that will require preoperative antibiotics planned within 6 months of enrollment
- Pregnant, breastfeeding, or planning to get pregnant in the next 6 months
- Any condition for which, in the opinion of the investigator, the participant should be excluded from the study
- Current use of any antidepressant/antianxiety drug (eligible to participate after a 4-week washout period)
- Use of any antibiotic drug in the past 4 weeks (may be eligible to participate after a 4-week washout period)
- History of alcohol or substance dependence in the past 6 months
- Daily use of probiotic products in the past 2 weeks (may be eligible to participate after a 2-week washout period)
- Use of any type of laxative in the last 2 weeks
- Consumption of products fortified in probiotics

Recruitment

Participants were recruited from the Kingston community using web-based and paper advertisements. Web-based advertisements were posted on the internet to social media platforms such as Facebook and Twitter. Posters were posted around Kingston—on university and college campuses, community bulletin boards, clinics, and counsellor centers. Recruitment was completed in December 2019.

Treatment Compliance

Treatment compliance was assessed by recording unused clinical trial material and reviewing participants' personal logs.

Discontinuation Criteria

A participant may be discontinued from treatment or withdrawn from the study at any time if the participant, the principal investigator, or the investigational product sponsor does not feel that it is not in the participant's best interest to continue. The following is a list of possible reasons for treatment discontinuation:

- Participant's withdrawal of consent
- An AE that in the opinion of the investigator would be in the best interest of the participant to discontinue the study treatment
- Protocol violation requiring discontinuation of the study treatment
- Lost to follow-up
- Request by NuBiyota LLC for early termination of the study
- Newly pregnant participants.

If a participant is withdrawn from treatment due to an AE, the participant will be followed up and treated by the investigator until the abnormal parameter or symptom has resolved or stabilized. All participants are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice. Reasonable attempts will be made by the investigator to provide a reason for the withdrawal of participants. No further data will be collected once a participant has been withdrawn.

Outcome Measures

Clinical Measures

Mood, anxiety, and GI symptoms and sleep quality will be assessed at all treatment visits. At week 10, only the MADRS and GAD-7 will be administered. The primary outcome measure will be mood and anxiety symptoms measured biweekly by changes in the MADRS and GAD-7 scores, respectively. The clinical measures include self-rated and clinician-rated measures. The self-rated questionnaires that will be used are the GAD-7 to assess anxiety symptoms and severity, the Snaith-Hamilton pleasure scale to assess anhedonia, quick inventory of depressive symptomatology to assess depressive symptoms, the gastrointestinal symptom rating Scale (GSRS) to assess GI symptoms, the Toronto side effects scale (TSES) to assess tolerability of the therapeutic product, and the Pittsburgh sleep quality index to assess subjective sleep quality. The clinician-rated questionnaires and interviews are the MADRS to assess depressive symptoms and severity, the clinical global impressions scale to assess illness severity and improvement, and the childhood experience of care and abuse questionnaire to assess early life stress and environmental risk factors associated with upbringing. Table 2 gives more details on the scales used in assessing outcome measures.

Table 2. Study visit schedule.

Procedure	Screening	Week 0	Week 2	Week 4	Week 6	Week 8	Week 10
Clinical							
ICF[a] review and signing	X[b]	—[c]	—	—	—	—	—
Study criteria review	X	—	—	—	—	—	—
Mini-international neuropsychiatric interview	X	—	—	—	—	—	—
Demographics	X	—	—	—	—	—	—
Medical and antidepressant history	X	—	—	—	—	—	—
Physical examination	—	X	—	—	—	—	—
Pregnancy test (females)	—	X	—	—	—	—	—
Montgomery-Asberg depression rating scale	X	X	X	X	X	X	X
Generalized anxiety disorder 7-item scale	X	X	X	X	X	X	X
Clinical global impressions scale	—	X	X	X	X	X	—
Snaith-Hamilton pleasure scale	—	X	X	X	X	X	—
Quick inventory of depressive symptomatology	—	X	X	X	X	X	—
Pittsburgh sleep quality index	—	X	X	X	X	X	—
Toronto side effects scale	—	X	X	X	X	X	—
Gastrointestinal symptom rating scale	—	X	X	X	X	X	—
Childhood experience of care and abuse	—	—	—	—	X	—	—
Adverse events	—	X	X	X	X	X	X
Molecular							
Blood samples	X	—	—	X	—	X	—
Fecal samples	—	X	X	X	—	X	X

[a]ICF: Informed Consent Form.

[b]X: will be completed.

[c]Will not be completed.

Safety and Tolerability

Participants will use a personal mood and symptom log to track any symptoms that they have been newly experiencing since the beginning of treatment, assess the tolerability of treatment, and keep track of their mood and sleep. AEs will be assessed and recorded at all in-hospital visits and on phone calls; they will be categorized by frequency, severity, and causality. The frequencies and severity of AEs will be collected on a questionnaire from the first day of the assigned study treatment through 14 days following the last assigned study treatment. Investigational product safety will be assessed via recorded symptoms and AEs. Investigational product tolerability will also be assessed using the TSES and GSRS during all visits except screening.

Molecular Analysis

Blood samples will be taken at screening, *w*eek 4, and *w*eek 8 and sent to Core Laboratories at Kingston Health Sciences Centre, Kingston General Hospital to analyze changes in cortisol levels, liver function, lipids, inflammatory markers (cytokines IL-10 and IL-6, TNF-α, TGF-β, and C-reactive protein), neurotransmitters (5-HT, *DA*, and *NE*), and immunoglobulins (IgA, IgG, and IgM). Baseline levels of creatinine, electrolytes, thyroid-stimulating hormone, complete blood count, and glucose will be taken only at screening to ensure that it is safe for participants to consume the investigational product at baseline. Fecal samples will be collected at all in-hospital visits. The participants will be provided with a stool kit and a Styrofoam case, with instructions at each visit. Upon collecting the sample from the participants, it will be stored at –62°C. Throughout the study, the samples will be sent to the University of Guelph for 16s RNA gene sequencing to determine the gut microbiome composition before, during, and after treatment.

Data Management

Data will be collected on case report forms and source documents pertaining to the questionnaires mentioned earlier in this paper and stored at the Providence Care Hospital. It will then be entered into a secure web-based database at the Providence Care Hospital and will only be accessible by the study team. To ensure confidentiality during the study, subject data will be analyzed under a randomized assigned study number. Participants' study files will be kept in a designated locked room, only accessible by the study co-coordinator and study investigators for 25 years, as per the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines.

Blood and fecal samples will be stored at the Providence Care Hospital until the time of transfer, which will occur intermittently throughout the study. A material transfer agreement will be in place as per the Health Sciences and Affiliated Teaching Hospitals research ethics board (HSREB) protocol for all biological specimen transfers.

Statistical Analyses

Treatment success and failure will be measured individually. Those who have an improvement of at least 50% in MADRS or GAD-7 scores will be considered responders. The SPSS will be used to analyze all data from clinical measures obtained throughout the study. Repeated measures analysis of variance (ANOVA) will be used to analyze changes in clinical measures from baseline to week 10. Paired *t* tests will be used to compare clinical measure means at each time point with the baseline. If a participant returns after the first course of treatment and is later withdrawn, their final scores for primary outcomes will be projected to week 10. In the event of missing data, the data from the last time point will be projected forward. Similarly, stool samples will be analyzed to provide diversity scores, which will then be compared using paired *t* tests and repeated measures ANOVA. Changes in diversity scores will be compared with clinical scores to assess for correlations.

Data Monitoring

Monitoring visits will be conducted by representatives of NuBiyota LLC according to the ICH guidelines for good clinical practice (GCP; E6). All information obtained during the course of this study is strictly confidential, and each subject's anonymity will be protected at all times. The investigator grants permission to NuBiyota LLC (or designee) and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation. Subjects will be identified by a study number and will not be identified in any publication or reports. The information collected for the study will be kept in a locked and secure area by the study doctor for 25 years. Only the study team, the representatives of the Research Ethics Board, and the representatives of Health Canada will have access to the data.

In addition, the study data may be transferred to the people or groups listed above to be processed for the purposes of the study, for product registration purposes and scientific purposes in general, ensuring compliance with laws and regulations. Any study data transferred outside of this study site will not include the name, address, or health insurance number of the subject. Instead, the study data will be coded to ensure that each subject's identity is kept confidential.

Adverse Events

The frequencies and severity of AEs will be collected on a questionnaire from the first day of the assigned study treatment through 14 days following the last assigned study treatment. AEs will be assessed and recorded at all in-hospital visits and phone calls; they will be categorized by frequency, severity, and causality.

Severity

To rate the severity of AEs, the following 4-point rating scale will be used:

1. Life-threatening (4 points): The subject is at risk of death due to adverse experiences as it occurred. This does not refer to an experience that hypothetically might have caused death if it was more severe.
2. Severe (3 points): Signs or symptoms result in a complete inability to pursue regular activities.
3. Moderate (2 points): Signs or symptoms disrupt regular activities.
4. Mild (1 point): Signs or symptoms present but do not disrupt regular activities.

Causality

To gauge the causal relationship of the AEs to the treatment, the following 4-point scale will be used:

1. Probable (4 points): A clear-cut temporal association with improvement on cessation of investigational medicinal products or reduction in dose. Reappears upon rechallenge.
2. Possible (3 points): Follows a reasonable temporal sequence from administration. May have been produced by the subject's clinical state, environmental factors, or other therapies administered.
3. Unlikely (2 points): Does not follow a reasonable temporal sequence from administration. May have been produced by environmental factors or other therapies administered.
4. Unrelated (1 point): Due only to extraneous causes and does not meet the criteria listed under unlikely, possible, or probable.

The investigator will probe, via discussion with the participant, for the occurrence of AEs during each patient visit and record the information in the site's source documents. AEs will be recorded in the participant case report form. AEs will be described by duration (start and stop dates and times), severity, outcome, treatment, and relation to the study drug or, if unrelated, the cause.

AEs will be collected in the following ways: (1)any symptoms or events self-reported spontaneously by the patient,

(2) the patient will be asked open-ended questions to answer about their health (eg, "How are you feeling since we saw you last in clinic?"), and (3) any clinically relevant abnormalities noted by the investigator during follow-up interviews.

In the event of a reported AE, if the principal investigator decides that it would be in the best interest of the participant to discontinue treatment, the participant will be removed from the study. If a participant is withdrawn from treatment due to an AE, the participant will be followed and treated by the investigator until the abnormal parameter or symptom has resolved or stabilized.

Once withdrawn, if participants choose to withdraw the biological samples they provided before the AE, they are able to do so, and we will ensure that the samples are destroyed. If tests have already been performed on the sample(s), it will not be possible to withdraw those results. However, no further

testing will be performed. The samples that have already been tested will continue to the analysis portion of the study.

Serious Adverse Events

Serious adverse events (SAEs) will also be reported to the HSREB and given immediate care. SAEs are any untoward medical occurrence that at any does results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

Requirement to Report

AEs that are considered serious, unexpected, and possibly or probably related to the study drug are subject to expedited reporting to the REB and Health Canada in accordance with C.05.014 of the Canadian Food and Drug Regulations. It is the responsibility of the investigator to report serious, unexpected, and possibly or probably related AEs to the REB. It is the responsibility of NuBiyota LLC to report serious, unexpected, and possibly or probably related AEs to Health Canada.

Reporting Procedures

After learning that a participant has experienced an SAE, the investigator or designee is responsible for reporting the SAE to the medical monitor, regardless of relationship or expectedness, within 24 hours of becoming aware of the event.

This report may be accomplished by completing an SAE form, which will include the following:

- Subject's study number
- Subject's gender
- Date of first dose of investigational drug(s)
- Date of last dose of investigational drug(s), if applicable
- AE term
- Time and date of occurrence of the event
- A brief description of the event, outcome to date, and any actions taken
- The seriousness criteria (on) that were met
- Concomitant medication at the onset of the event
- Relevant medical history information
- Relevant laboratory test findings
- Investigator's opinion of the relationship to investigational drug(s) ("Is there a reasonable possibility that the investigational drug caused the SAE? Yes or No?").

Approvals and Registration

This trial will be conducted in compliance with the protocol, GCP, and the applicable local regulatory requirements and laws. Ethics approval was obtained from Queen's University HSREB (protocol number 6025187) on March 28, 2019. A no-objection letter from Health Canada was obtained for the use of MET-2, in accordance with part C, division 5 of the Food and Drug Regulations. The trial was registered on ClinicalTrials.gov on August 9, 2019 (NCT04052451), and is being funded by NuBiyota LLC and MITACS.

If any changes are made to the study protocol by the investigator, such as changes to eligibility criteria, informed consent, outcomes, and/or analyses, they will be communicated to the sponsor, the HSREB, Health Canada, and trial registry. If required, all participants will be informed and consented once again.

Access to Data

The investigator and team will have access to the final trial dataset. This has been outlined in a clinical trial agreement and has been agreed upon by both the investigator and the sponsor. Upon completion of trial and data analysis, the study results will be published for participants, health care professionals, the public, and all other relevant groups to access. The publications will be written and authored by the principal investigator and team.

Results

The study received approval from the Queen's University Health Sciences and Affiliated Teaching Hospital Research Ethics Board on March 28, 2019. Participant recruitment began in May 2019. As of March 2020, we have enrolled 21 participants, of which 12 participants completed the study with at least one visit postbaseline. We have completed recruitment for this study and are currently in the process of analyzing data. We expect to see improvement in depressive and anxiety symptom scores from baseline to week 10, to be mediated by a decrease in pro-inflammatory markers and an increase in anti-inflammatory markers. Furthermore, we hope to see lasting changes in the microbiome composition reflecting a similar composition to that of the donor by the end of the study.

Discussion

Currently, there are many different psychological and pharmacological treatments that target symptoms of depression and anxiety as well as other emerging novel treatment methods. However, progress in research on MDD and GAD has been challenging due to high individual variability in symptoms and course, high levels of comorbidity with other psychopathology, and genetic *and* environmental influences. Given these challenges, identifying novel and personalized methods is crucial for advancements in research on depression and anxiety. The therapeutic link between MDD/GAD and gut microbiota is advantageous because of the greater accessibility and modifiability of the microbiome compared with the human genome [32]. Given the adaptable nature of the microbiome, it may be a good representation of the individual's history and could explain the differences in risk of illness, disease course, and response to treatment. If MET-2 alleviates symptoms of neuropsychiatric disorders, they could be offered to patients as personalized, alternative, and/or adjunctive treatments to combat specific symptoms that tie together specific gut bacteria strains or the gut as a whole to the brain.

However, possible limitations of this trial include difficulty recruiting individuals with depression or anxiety that are not currently on any antidepressant medication or due to stigma associated with fecal and/or natural products. Compliance with the treatment schedule can also be more difficult for individuals with mental illness [33]. These issues will be minimized by widespread advertising and a detailed explanation of study

requirements before signing the informed consent form. Participants will also be asked to keep a mood and symptom chart where they will also track their investigational product use. A researcher from the study team will discuss the details of the chart at each in-hospital visit to assess potential adverse symptoms and maintain a record of investigational product compliance. Given that this is an open-label trial, other limitations include small sample size, lack of a placebo arm, and a short follow-up period.

In summary, to our knowledge, this will be the first study to show evidence for the role of microbial therapy in treating depression and anxiety. Furthermore, the results of the trial will contribute to a growing body of research on assessing gut repopulation as a potential treatment method for MDD and GAD and could further explain the relationship between the gut and the brain and the underlying mechanisms.

Acknowledgments

This trial was funded by NuBiyota LLC and MITACS Canada. The funders did not have any role in the design of the study and did not have a role in interpreting the results. The study protocol was approved by Queen's University HSREB.

Authors' Contributions

ACM and RM developed the protocol for this study. Both authors provided their individual expertise and read and approved the final manuscript.

Conflicts of Interest

RM has received consulting and speaking honoraria from Allergan, Janssen, KYE, Lundbeck, Otsuka, Pfizer, and Sunovion and research grants from Canadian Biomarker Integration Network for Depression, Canadian Institutes of Health Research, Janssen, Lallemand, Lundbeck, NuBiyota, Ontario Brain Institute, Ontario Mental Health Foundation, and Pfizer. ACM declares no conflict of interest.

Multimedia Appendix 1
Peer-reviewer report from MITACS.
[PDF File (Adobe PDF File), 236 KB - resprot_v9i6e17223_app1.pdf]

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Abbreviations

5-HT: serotonin
AEs: adverse events
ANOVA: analysis of variance
CFU: colony-forming unit
CNS: central nervous system

DA: dopamine
FMT: fecal microbiota transplantation
GAD: generalized anxiety disorder
GCP: good clinical practice
GI: gastrointestinal
GSRS: gastrointestinal symptom rating scale
HPA: hypothalamic-pituitary-adrenal
HSREB: Health Sciences and Affiliated Teaching Hospitals research ethics board
ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgA: immunoglobulin A
IgM: immunoglobulin M
IL-10: interleukin 10
IL-6: interleukin 6
MADRS: Montgomery-Asberg Depression Rating Scale
MDD: major depressive disorder
MET-2: microbial ecosystem therapeutic-2
MINI: mini-international neuropsychiatric interview
NE: norepinephrine
SAEs: serious adverse events
TGF-β: transforming growth factor beta
TNF-α: tumor necrosis factor alpha
TSES: Toronto side effects scale

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Protocol

Diagnosing Preclinical Cardiac Dysfunction in Swiss Childhood Cancer Survivors: Protocol for a Single-Center Cohort Study

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Abstract

Background: Cardiovascular disease is the leading nonmalignant cause of late deaths in childhood cancer survivors. Cardiovascular disease and cardiac dysfunction can remain asymptomatic for many years, but eventually lead to progressive disease with high morbidity and mortality. Early detection and intervention are therefore crucial to improve outcomes.

Objective: In our study, we aim to assess the prevalence of preclinical cardiac dysfunction in adult childhood cancer survivors using conventional and speckle tracking echocardiography; determine the association between cardiac dysfunction and treatment-related risk factors (anthracyclines, alkylating agents, steroids, cardiac radiation) and modifiable cardiovascular risk factors (abdominal obesity, hypertension); investigate the development of cardiac dysfunction longitudinally in a defined cohort; study the association between cardiac dysfunction and other health outcomes like pulmonary disease, endocrine disease, renal disease, quality of life, fatigue, strength and endurance, and physical activity; and gain experience conducting a clinical study of childhood cancer survivors that will be extended to a national, multicenter study of cardiac complications.

Methods: For this retrospective cohort study, we will invite ≥5-year childhood cancer survivors who were treated at the University Children's Hospital Bern, Switzerland with any chemotherapy or cardiac radiation since 1976 and who are ≥18 years of age at the time of the study for a cardiac assessment at the University Hospital Bern. This includes 544 childhood cancer survivors, of whom about half were treated with anthracyclines and/or cardiac radiation and half with any other chemotherapy. The standardized cardiac assessment includes a medical history focusing on signs of cardiovascular disease and its risk factors, a physical examination, anthropometry, vital parameters, the 1-minute sit-to-stand test, and echocardiography including 2-dimensional speckle tracking.

Results: We will invite 544 eligible childhood cancer survivors (median age at the time of the study, 32.5 years; median length of time since diagnosis, 25.0 years) for a cardiac assessment. Of these survivors, 300 (55%) are at high risk, and 244 (45%) are at standard risk of cardiac dysfunction.

Conclusions: This study will determine the prevalence of preclinical cardiac dysfunction in Swiss childhood cancer survivors, inform whether speckle tracking echocardiography is more sensitive to cardiac dysfunction than conventional echocardiography, and give a detailed picture of risk factors for cardiac dysfunction. The results will help improve primary treatment and follow-up care of children with cancer.

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KEYWORDS

cardiotoxicity; Switzerland; echocardiography; speckle tracking; strain; anthracyclines; alkylating agents; steroids; cardiac radiation

Introduction

Survival of childhood cancer has improved, and the number of childhood cancer survivors (CCS) has greatly increased during recent decades [1,2]. Consequently, more survivors face increased long-term morbidity and mortality due to chronic health conditions such as cardiovascular disease, pulmonary disease, and secondary neoplasms [3-5]. Among these, cardiovascular disease is the leading nonmalignant cause of death among CCS [3] with a cumulative incidence that increases up to 30 years after cancer diagnosis [6]. Heart failure, myocardial infarction, pericardial and valvular disease, and arrhythmias are all associated with treatments used in childhood cancer patients.

Studies from North America, Germany, and The Netherlands have assessed survivors exposed to cardiotoxic cancer therapy, in whom a prevalence of subclinical cardiac dysfunction ranging from 6% to 27% was identified via conventional echocardiography [7-10]. This suggests that many CCS have impaired cardiac function that might progress to clinical heart failure later in life. The North American study also found that a further 32% of survivors with otherwise normal conventional echocardiography showed evidence of cardiac dysfunction with abnormal strain measurements by speckle tracking echocardiography, a novel echocardiographic technique [7]. Additional studies have also suggested that speckle tracking echocardiography might be more sensitive to preclinical cardiac dysfunction than conventional echocardiography in CCS [11,12].

Most studies have assessed survivors exposed to anthracyclines and cardiac radiation, which are the most important treatment-related risk factors [13]. Yet, other treatments may also increase the risk of cardiac dysfunction in CCS. Survivors who were not exposed to anthracyclines or cardiac radiation have demonstrated decreased left ventricular (LV) mass and increased cardiac biomarkers compared to siblings [14].

The North American Childhood Cancer Survivor Study analyzed self-reported data on cardiovascular risk factors in more than 10,000 adult CCS and showed that hypertension alone and in combination with other modifiable cardiovascular risk factors significantly increased the risk for heart failure, coronary artery disease, valvular disease, and arrhythmia in adult CCS [15]. The likelihood that modifiable cardiovascular risk factors might potentiate the increased risk of treatment-related cardiovascular disease in CCS thus motivates this study of cardiac dysfunction in adult CCS.

Methods

Study Objectives

The first and primary objective of this study is to assess the prevalence of preclinical cardiac dysfunction in adult CCS using 2-dimensional (2D) and 3-dimensional (3D) conventional and 2D speckle tracking echocardiography. Second, we will determine the association between cardiac dysfunction and the risk related with treatment (anthracyclines, alkylating agents, steroids, and cardiac radiation) as well as the modifiable cardiovascular risk factors abdominal obesity and hypertension. Our third objective is to investigate the development of cardiac dysfunction longitudinally in a defined cohort. Fourth, we will study the association between cardiac dysfunction and other health outcomes like pulmonary, endocrine, and renal diseases; quality of life; fatigue; strength and endurance; and physical activity. Finally, pursuing these objectives will provide experience conducting a clinical study of CCS that could be used for a national, multicenter study of cardiac complications.

Primary Outcome

The primary outcomes of this study are abnormal 2D and 3D LV ejection fraction (LVEF) measured using conventional echocardiography and abnormal global longitudinal strain (GLS) measured using 2D speckle tracking echocardiography (Textbox 1).

Textbox 1. Components of cardiac assessment collected for childhood cancer survivors.

Conventional echocardiography

- Left ventricular (LV) systolic function
  - 2-dimensional (2D) and 3-dimensional (3D) LV ejection fraction (LVEF)
- LV diastolic function
  - Early diastolic LV filling velocity (E)
  - Late diastolic LV filling velocity (A)
  - Early to late LV filling velocity (E/A ratio)
  - Mitral annular early diastolic velocity (e') (septal and lateral)
  - Peak mitral flow velocity (E/e' ratio)
  - Peak tricuspid regurgitation (TR) velocity
  - Left atrial (LA) maximum volume index
- Right atrium (RA), right ventricle (RV), RV/RA ratio
- Valvular dysfunction, respiratory variation, size of the vena cava

2D speckle tracking echocardiography

- LV systolic function
  - Global longitudinal strain (GLS)
  - Global circumferential strain (GCS)
  - Global radial strain (GRS)

Personal history

- Demographic and socioeconomic characteristics
- Clinical characteristics
  - Cardiac symptoms
  - History of cardiovascular disease
  - Modifiable cardiovascular risk factors
  - Chronic conditions
  - Sleeping habits
  - Medications
  - Thoracic surgeries
  - Family history of cardiovascular disease and risk factors
- Pictorial images for perception of weight status
- Qualitative questions

Anthropometry and blood pressure

- Weight and height
- Waist and hip circumference
- Blood pressure

Physical examination

- Auscultation of the heart and lungs
- Palpation of pulses
  - Carotid
  - Radial

- Tibial
- Dorsal feet

- Signs of heart failure
  - Jugular vein pressure
  - Hepato-jugular reflux
  - Edema of the lower extremities
  - Size of the liver and spleen
  - Documentation of thoracic scars

1-minute sit-to-stand test

Counselling of survivors and medical letter

Online questionnaires

Secondary Outcomes

Secondary outcomes are other conventional echocardiographic parameters of abnormal LV diastolic function (early diastolic LV filling velocity [E], late diastolic LV filling velocity [A], early to late LV filling velocity [E/A ratio], mitral annular early diastolic velocity [e'], peak mitral flow velocity [E/e' ratio], peak tricuspid regurgitation [TR] velocity, left atrial [LA] maximum volume index), right atrium [RA], right ventricle [RV], RV/RA ratio, valvular dysfunction, respiratory variation, and size of the vena cava, and speckle tracking echocardiography–derived parameters of abnormal LV systolic function (global circumferential strain [GCS], global radial strain [GRS]). Other secondary outcomes include impaired quality of life and fatigue.

Intermediate Outcomes and Exposures

We also collect information about treatment with anthracyclines, alkylating agents, steroids, and cardiac radiation; modifiable cardiovascular risk factors (abdominal obesity and hypertension); and other health outcomes including pulmonary, endocrine, and renal diseases; strength and endurance; and physical activity.

Study Design, Study Population, and Inclusion Criteria

This retrospective cohort study is part of routine clinical follow-up care and a collaborative and interdisciplinary effort of the Childhood Cancer Registry, Swiss Childhood Cancer Survivor Study, and departments of Pediatric Hematology and Oncology and Pediatric and Adult Cardiology at the University Hospital Bern, Switzerland (Textbox 2, Figure 1). The study includes all ≥5 year CCS diagnosed with childhood cancer starting in 1976, treated at the University Children's Hospital Bern in Switzerland with any chemotherapy and/or cardiac radiation, aged ≥18 years at the time of the study, and registered in the Childhood Cancer Registry. The registry includes all patients in Switzerland diagnosed at age 0-20 years with leukemia, lymphoma, central nervous system tumors, malignant solid tumors, or Langerhans cell histiocytosis [16]. We classify cancer diagnoses according to the International Classification of Childhood Cancer, third edition into 12 main groups [17] and Langerhans cell histiocytosis. Recent estimates indicate that the registry includes >95% of children diagnosed at <16 years since 1995 in Switzerland [18]. We exclude survivors who were treated with surgery only and/or radiation other than cardiac radiation because these survivors have a low risk of developing cardiac dysfunction. Ethics approval of this study was granted by the Ethics Committee of the Canton of Bern, Switzerland (KEK-BE: 2017-01612), and the study is registered at ClinicalTrials.gov (identifier: NCT03790943). Informed consent, as documented with a signature, is obtained from each survivor prior to participation in the study.

Textbox 2. Teams and staff members involved in the workflow of the study of preclinical diagnosis of cardiac dysfunction.

Childhood Cancer Registry

- Administrative staff

Swiss Childhood Cancer Survivor Study

- PhD student
- Study nurse
- Master students

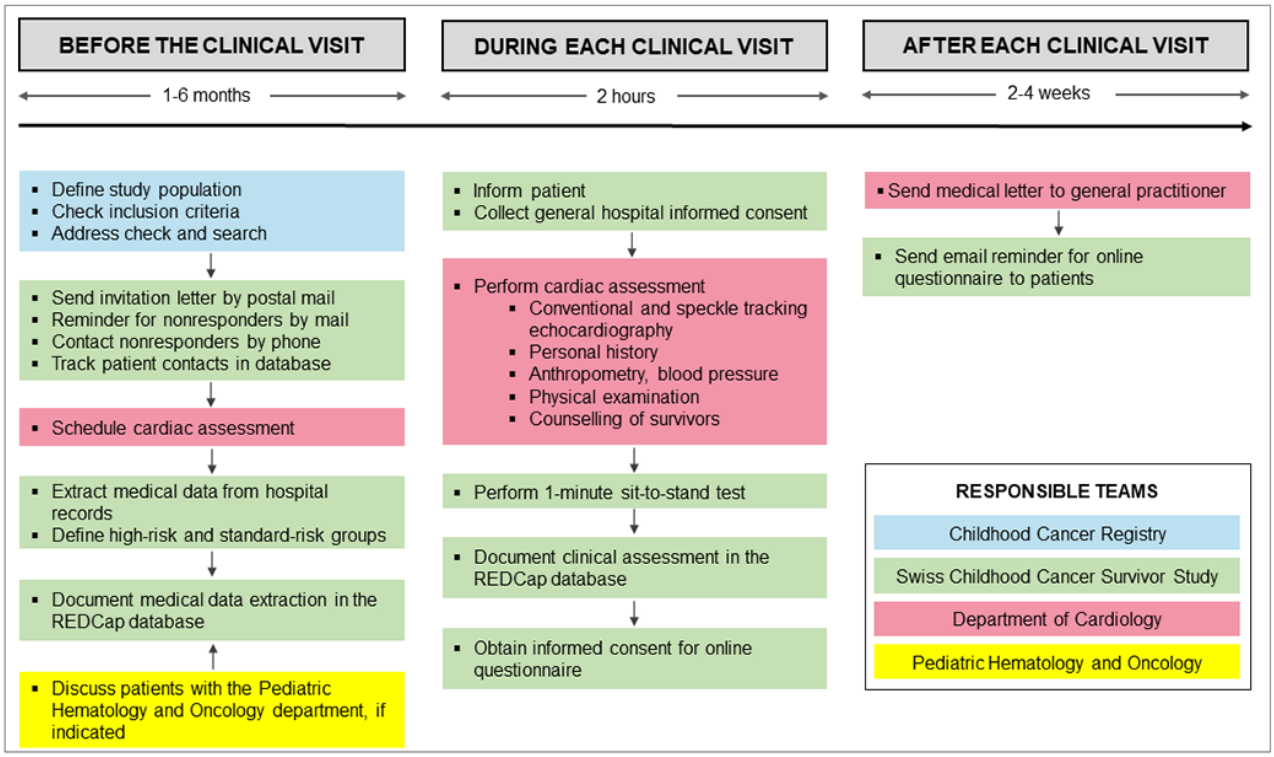
Pediatric Hematology and Oncology

- Head of pediatric hematology and oncology

Department of Cardiology

- Cardiologists specialized in echocardiography
- Cardiologist specialized in cardio-oncology
- Nurse practitioner specialized in cardio-oncology
- Administrative staff

Figure 1. Responsible teams in the study of preclinical diagnosis of cardiac dysfunction in childhood cancer survivors.



Study Logistics

Current addresses of eligible survivors are obtained from the Childhood Cancer Registry and updated via the Swiss postal service where necessary (Figure 1). We send an invitation letter to survivors explaining why a cardiac assessment is useful, and it also describes the planned examinations and visit location in the Department of Cardiology at the University Hospital Bern. Survivors are asked to return a response form indicating their interest in participation in the study and the date and place of previous cardiac assessment(s). Nonresponders receive up to two reminders by mail before we try to contact them by phone. The administrative personnel of the Department of Cardiology schedules an appointment for a cardiac assessment via mail with survivors who agree to participate. The study is part of the routine follow-up care offered to CCS and is paid for by health insurance. All patient contacts are documented in a patient-tracking database.

Medical Data Extraction

We extract the following data on each survivor from the cancer registry: cancer diagnose(s), relapse(s), age at cancer diagnosis,

year of cancer diagnosis, and whether the person had chemotherapy, radiation (if so, the location of radiation), surgery, or hematopoietic stem cell transplantation (Figure 1).

We collect cumulative doses of anthracyclines, steroids, and alkylating agents from medical records (Textbox 3). We record patient weight, patient height, and the doses in each chemotherapy cycle. We calculate the cumulative doses per unit body surface area, expressed in milligrams or grams per square meter (Textbox 3).

Cardiac radiation includes different radiation fields [19] and is collected from medical records (Textbox 3). We use the maximum documented dose of the field involving the heart and add the dose of total body irradiation.

Textbox 3. Cumulative doses of chemotherapy and cardiac radiation extracted from medical records.

Cumulative doses of chemotherapy

- Anthracyclines with doxorubicin-equivalent doses (mg/m^2) [19]
  - Doxorubicin x 1.0
  - Daunorubicin x 0.5
  - Epirubicin x 0.67
  - Idarubicin x 5.0
  - Mitoxantrone x 4.0
- Alkylating agents with cyclophosphamide-equivalent doses (mg/m^2) [20]
  - Cyclophosphamide x 1.0
  - Ifosfamide x 4.09
- Steroids with prednisone-equivalent doses (g/m^2) [21]
  - Prednisone x 1.0
  - Dexamethasone x 6.67

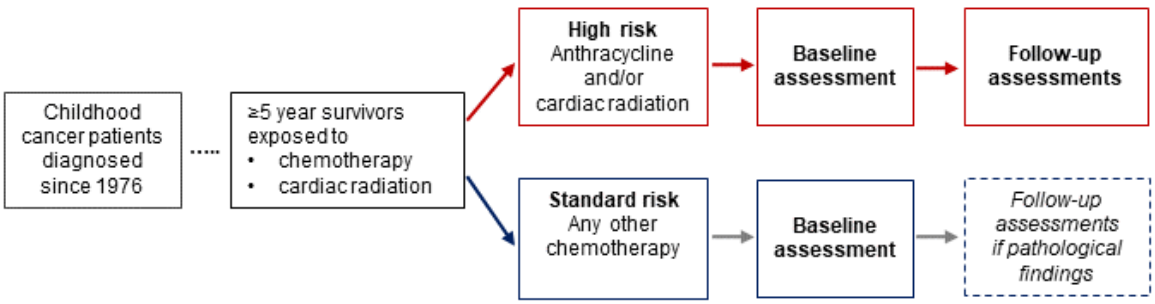
Cumulative doses of cardiac radiation [19]

- Cardiac radiation (gray)
  - Chest
  - Abdomen
  - Whole or thoracic spine
  - Total body irradiation

Definition of High-Risk and Standard-Risk Groups

Patients with exposure to any cumulative dose of anthracyclines and/or cardiac radiation (chest, abdomen, whole or thoracic spine, total body irradiation) are placed in the high-risk group (Figure 2). High-risk patients are assessed longitudinally with baseline and follow-up cardiac assessments according to the Children's Oncology Group Long-Term Follow-Up Guidelines, Version 5.0, October 2018 [19]. Survivors with exposure to any chemotherapy other than anthracyclines are assigned to a standard-risk group and evaluated cross-sectionally unless a cardiac follow-up assessment is clinically indicated. All survivors with surgery only or radiation other than cardiac are excluded from this study and are seen only within the routine follow-up care without echocardiography.

Figure 2. Study design and risk group stratification of childhood cancer survivors.



Patient Information and Informed Consent

At the cardiac assessment, we give survivors oral and written information about the clinical study (Figure 1). The general hospital informed consent form that participants sign is a standard consent form widely used in Swiss inpatient and outpatient settings to enable research with clinical data.

Echocardiography and Definition of Cardiac Dysfunction

Echocardiography is performed by experienced cardiologists from the Department of Cardiology who are blinded with respect to the patient's cancer treatment and risk group (Textbox 2). Conventional echocardiography includes assessment of LV systolic function (2D and 3D LVEF), LV diastolic function (E, A, E/A ratio, septal and lateral e', E/e' ratio, peak TR velocity, LA maximum volume index), RA, RV, RV/RA ratio, valvular dysfunction, respiratory variation, and size of the vena cava (Textbox 1, Figure 1) using a GE Vivid E9 or E95 (GE Vingmed, Horten, Norway). 2D speckle tracking echocardiography includes GLS, GCS, and GRS and is performed using vendor-independent software (Tomtec Imaging Systems, Unterschleissheim, Germany).

We define cardiac dysfunction according to the American Society of Echocardiography and European Association of Cardiovascular Imaging recommendations [22,23].

LV systolic dysfunction is defined as 2D/3D LVEF <52% for men and <54% for women [22].

The LV diastolic dysfunction definition depends on whether a patient has normal or impaired LVEF [23]. In patients with normal LVEF, four parameters and cutoff levels are used: (1) E/e´ ratio >14, (2) septal e´ velocity <7 cm/s or lateral e´ velocity <10 cm/s, (3) TR velocity >2.8 m/s, and (4) LA volume index >34 mL/m². Diastolic function is defined as abnormal if more than half of available parameters meet the cutoff levels, as normal if more than half of available parameters do not meet cutoff levels, and as inconclusive if half of the parameters do not meet the cutoff levels. In patients with impaired LVEF, the E/A ratio is used for stratification into three grades of diastolic dysfunction. An E/A ratio ≤0.8 and a peak mitral flow velocity E ≤50 cm/sec are defined as grade I diastolic dysfunction. An E/A ratio ≥2.0 is defined as grade III diastolic dysfunction. If the E/A ratio is ≤0.8 and peak mitral flow velocity E is >50 cm/sec, or E/A >0.8 but <2, three additional parameters and cutoff values are used: (1) peak TR velocity >2.8 m/sec, (2) E/e´ ratio >14, and (3) LA maximum volume index >34 mL/m². Grade II diastolic dysfunction is present if more than half of parameters meet the cutoff values, grade I diastolic dysfunction is present if only one available parameter meets the cutoff levels, and the study is inconclusive if only one parameter is available or in case of 50% discordance [23].

Abnormal strain (GLS, GCS, GRS) is defined as >2 SD below the mean using sex-specific, age-specific, vendor-specific, and software-specific strain values [24].

Personal History

We take a comprehensive personal history of survivors' demographic and socioeconomic characteristics: current occupation, employment status, work hours per week, marital status, offspring, and housing situation (Textbox 1, Figure 1). We also obtain clinical characteristics including cardiac symptoms (New York Heart Association class I-IV), history of cardiovascular disease, modifiable cardiovascular risk factors (hypertension, diabetes, dyslipidemia, smoking, physical inactivity, drug consumption), chronic conditions (pulmonary, endocrine, and renal diseases), sleeping habits, medications, thoracic surgeries, and family history of cardiovascular diseases and risk factors. To determine perception of weight status, we use pictorial images of women and men similar to Harris et al [25] and ask the patient to indicate the picture that best matches the weight status of his or her parents, siblings, and the patient's own weight. We also ask patients: "Was it a big effort for you to come to the hospital for today's appointment, does your history of childhood cancer play a role in your daily life, and are you afraid that your treatment for cancer during childhood caused any medical problems in adulthood?" We also ask patients if they have any questions, requests, or wishes to direct to us.

Anthropometry and Blood Pressure

Weight and standing height are measured using standard procedures, while the patient is barefoot and in light clothes (Textbox 1, Figure 1). Weight is determined to the nearest 0.1 kg and height to the nearest 0.5 cm. BMI is expressed as kg/m^2 [26]. Waist and hip circumferences are measured using a measuring tape to the nearest 0.1 cm. Waist circumference is measured at the midpoint between the lower margin of the lowest rib and the top of the iliac crest, and hip circumference is measured at the widest circumference over the buttocks [26]. The waist-hip ratio is calculated as waist circumference divided by hip circumference. Blood pressure is measured comfortably in a quiet environment with three measurements repeated in a sitting position, and the average of the last two readings is recorded. Additional measurements are taken if the first two readings of systolic or diastolic blood pressure differ by >10 mm Hg [27].

Physical Examination

We perform a thorough physical examination with special emphasis on signs of cardiovascular disease (Textbox 1, Figure 1). This includes auscultation of the heart and lungs; palpation of the carotid, radial, tibial, and dorsal foot artery pulses; and examination of the jugular vein pressure, hepato-jugular reflux, edema of the lower extremities, size of the liver and spleen, and documentation of thoracic scars.

1-Minute Sit-to-Stand Test

We have the patient perform the 1-minute sit-to-stand test (STS), which captures the number of times a person can stand up and sit down on a regular chair in 1 minute (Textbox 1, Figure 1) [28]. The STS is an estimate of lower body muscular strength and endurance. We compare our population with population-based, age-adjusted, and sex-adjusted Swiss reference values [28].

Counselling of Survivors and the Medical Letter

At the end of the cardiac assessment, a cardiologist specialized in cardio-oncology and who did not perform the echocardiography explains the results of the echocardiography to survivors and counsels them on their cardiac function and the presence (or absence) of modifiable cardiovascular risk factors (Textbox 1, Figure 1). Recommendations on follow-up assessments are based on the Children's Oncology Group Long-Term Follow-Up Guidelines, Version 5.0, October 2018 [19]. A medical letter summing up the results of the cardiac assessment is sent to the survivor's general practitioner.

Online Questionnaire

We ask survivors to complete 4 questionnaires after returning home. The Short Form 36 Health Survey assesses health-related quality of life [29] and has been used before in CCS [30]. The Seven-Day Physical Activity Recall questionnaire measures moderate physical activity, vigorous physical activity, and sleep during the last 7 days [31]. Fatigue is assessed using the Checklist Individual Strength questionnaire, a validated 20-item questionnaire that identifies different aspects of fatigue within the previous 2 weeks [32]. Diet and alcohol consumption are obtained using questions from the Swiss Childhood Cancer Survivor Study questionnaire [33]. We ask survivors to provide separate informed consent for the online questionnaires. Survivors not completing the online questionnaires within 2 weeks after the clinical visit are reminded by email.

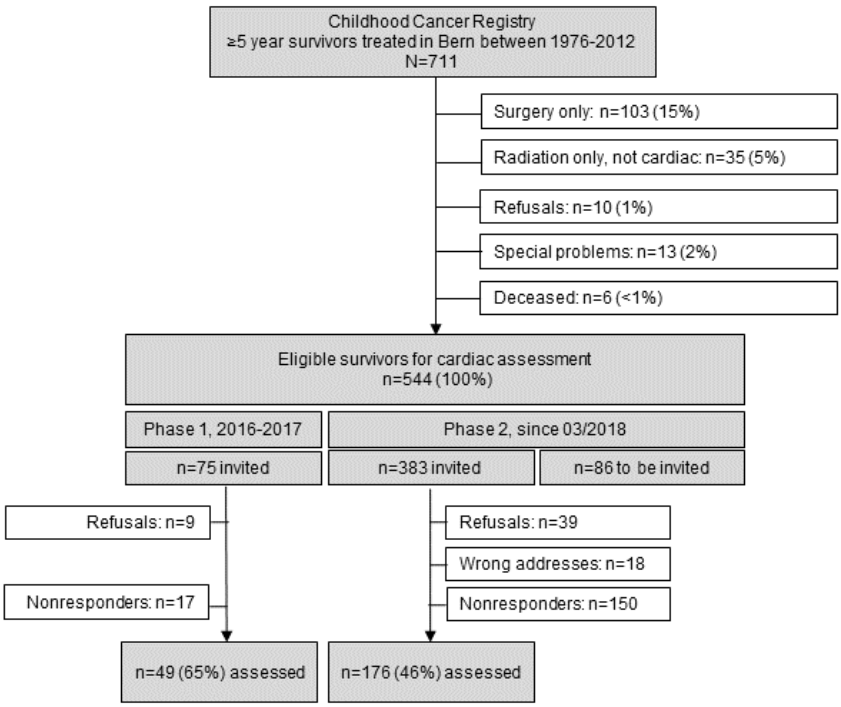
Documentation

All parts of the cardiac assessment are directly entered into a dedicated REDCap (version 8.5.19, Vanderbilt University, Nashville, TN) database to minimize risk of disclosure. Within the database, each survivor has a unique ID. No personal information can be obtained with this number. Data containing survivors' unique IDs are stored on encrypted devices or secured servers at the University of Bern.

Cardiac Assessment, Phase 1

In 2016-2017, we started using standardized echocardiography for cardiac assessment, as already described (Figure 3). At that time, personal history, blood pressure, physical examination, and the STS were not yet assessed in a standardized way. The personal history and online questionnaires were retrospectively completed by phone interviews between May 2017 and June 2017.

Figure 3. Recruitment of childhood cancer survivors eligible for the study, current as of October 1, 2019.



Cardiac Assessment, Phase 2

Since March 2018, we have been collecting all data in a standardized way. Data collection is performed by the study team from the Childhood Cancer Registry, Swiss Childhood Cancer Survivor Study, Department of Pediatric Hematology and Oncology at the University Hospital Bern, and Department of Cardiology at the University Hospital Bern (Textbox 2, Figure 3).

Statistical Analyses and Power Calculations

We will compare characteristics of responders and nonresponders using chi-square tests and perform univariable and multivariable logistic regression analyses to investigate the association between cardiotoxic treatment exposures (anthracyclines, alkylating agents, steroids, cardiac radiation) and modifiable cardiovascular risk factors (abdominal obesity, hypertension) and cardiac dysfunction adjusting for sex, age at study, and follow-up time.

From our eligible study population of 544 CSS and based on an expected response rate of 65%, we estimate that

approximately 354 survivors will attend the cardiac assessment (Figure 3). Among these participants, about 55% (195/354) are at high risk, and 45% (159/354) are at standard risk for cardiac dysfunction. These numbers will provide a power of 80% and α of .05 to detect a significant difference in cardiac dysfunction in high-risk survivors, assuming 6% cardiac dysfunction for LVEF and 32% for GLS [7]. In standard-risk survivors, the prevalences of abnormal LVEF and GLS will be lower; therefore, the sample size might be borderline sufficient. Considering that we plan to extend this single-center cohort study to a multicenter study, numbers will substantially increase.

We will use STATA software (Version 15.1, Stata Corporation, Austin, TX) for statistical analyses.

Results

On January 1, 2018, the Childhood Cancer Registry included 711 survivors aged ≥18 years who had been diagnosed and treated at the University Children's Hospital Bern since 1976 and had survived ≥5 years (Figure 3). Among those, 103 were excluded because of surgery as the only treatment, 35 survivors because of radiation only other than cardiac, and 29 survivors because they did not want to be contacted, had specific problems (eg, did not want to be invited for clinical studies because of emotional stress), or had died. Among the remaining survivors, 544 met the inclusion criteria for an invitation to a clinical visit (Table 1, Figure 3). This number includes 300 survivors (300/544, 55%) at high risk for cardiac dysfunction and 244 survivors (244/544, 45%) at standard risk for cardiac dysfunction, with a median age at the time of the study of 32.5 years and a median time since diagnosis of 25.0 years (Table 1). In Phase 1 (2016-2017), 75 survivors were invited, and 49 survivors attended the cardiac assessment, for a response rate of 65%; phase 2 is ongoing (Figure 3). We plan to recruit new 5-year survivors continuously into the study, so the size of the cohort will increase and numbers will change.

Table 1. Demographic and clinical characteristics of survivors eligible for participation in the cohort study (n=544), as of January 1, 2018.

Demographic and clinical characteristics	n (%)
Male sex	297 (55)
Age at the time of the study (years)[a]	32.5 (25.4-38.5, 18.3-56.0)
Age category at the time of the study (years)	
<20	30 (6)
20-29	197 (36)
30-39	207 (38)
>39	110 (20)
Age at diagnosis (years)[a]	6.7 (3.1-12.5, 0.1-17.5)
Age category at diagnosis (years)	
<5	207 (38)
5-9	134 (25)
10-14	149 (27)
15-19	54 (10)
Time since diagnosis (years)[a]	25.0 (17.9-32.0, 6.2-42.0)
Time since diagnosis (years)	
5-10	31 (6)
11-20	130 (24)
21-30	220 (40)
31-40	147 (27)
>40	16 (3)
ICCC-3[b] cancer diagnoses	
I Leukemia	218 (40)
II Lymphoma	118 (22)
III CNS[c]	35 (6)
IV Neuroblastoma	17 (3)
V Retinoblastoma	11 (2)
VI Renal tumor	38 (7)
VII Hepatic tumor	6 (1)
VIII Bone tumor	40 (7)
IX Soft tissue sarcoma	33 (6)
X Germ cell tumor	8 (2)
XI&XII Other rare tumors[d]	20 (4)
Era of treatment	
1976-1985	136 (25)
1986-1995	199 (36)
1996-2005	156 (29)
2006-2012	53 (10)
Risk group	
High-risk[e]	300 (55)
Standard-risk[f]	244 (45)

Demographic and clinical characteristics	n (%)
Any radiation therapy	213 (39)
Any surgery	329 (61)
Any chemotherapy	531 (98)
Hematopoietic stem cell transplantation	28 (5)

[a]median (IQR, range).

[b]ICCC-3, International Classification of Childhood Cancer third edition.

[c]CNS, central nervous system.

[d]including Langerhans cell histiocytosis, other malignant epithelial neoplasms, malignant melanomas, and other or unspecified malignant neoplasms.

[e]anthracyclines and/or cardiac radiation.

[f]any chemotherapy other than anthracyclines.

Discussion

This retrospective, single-center cohort study is investigating the prevalence of cardiac dysfunction and its risk factors in adult CCS and comparing conventional and speckle tracking echocardiography.

Few studies are comparable to ours. A single-center study in The Netherlands included 525 adult CCS who had been treated during 1966-1997 with anthracyclines, high-dose cyclophosphamide, high-dose ifosfamide, and/or cardiac radiation [8]. Conventional echocardiography was performed during 1996-2004 to measure LV shortening fraction, and subclinical cardiac dysfunction was observed in 27% of survivors during a median follow-up time of 15 years. Another hospital-based, single-center study at St. Jude Children's Research Hospital in the United States assessed 1820 adult CCS exposed to anthracyclines and/or cardiac radiation during a median follow-up time of 23 years using conventional and speckle tracking echocardiography [7]. One-third of survivors with normal LVEF had abnormal longitudinal strain seen on speckle tracking echocardiography. Risk factors for pathological findings in conventional and speckle tracking echocardiography were treatment with anthracyclines and cardiac radiation. The modifiable cardiovascular risk factors of hypertension, abdominal obesity, dyslipidemia, and high fasting glucose were associated with abnormal longitudinal strain but not with LVEF, suggesting that speckle tracking might be more sensitive for detecting cardiac dysfunction.

Conventional and speckle tracking echocardiography have some strengths and weaknesses that need to be addressed. Until now, conventional echocardiography has been the most commonly used noninvasive imaging modality to quantify cardiac function [22]; therefore, most studies of cancer patients and survivors are based on LVEF. Impaired LVEF is a late sign of cardiac damage, and the chance of recovery is already small. Speckle tracking echocardiography might overcome this limitation as it has been shown to be superior to LVEF in diagnosing cardiac dysfunction and predicting cardiac mortality in patients with underlying cardiac disease [34,35] and in adults undergoing cancer therapy [36]. Also, there are studies that have investigated the evidence of strain measurements for the surveillance of chemotherapy-related cardiac dysfunction in adult cancer patients (SUCCOUR trial) [37]. However, for CCS, we do not know the prognostic value of speckle tracking echocardiography yet. Another limitation is that strain analysis depends on image quality, and is age-, sex-, vendor-, and software-dependent [38]. We try to overcome this by strictly adhering to our standard operating procedures and using reference values stratified by age and sex using the same vendor (GE Vivid E9) and software (Tomtec Imaging Systems) [24]. By using only one type of vendor equipment and software, we also avoid intervendor variability.

First among this study's limitations is that it is currently confined to a single center. However, the 9 centers treating children and adolescents with cancer in Switzerland collaborate closely and use uniform treatment protocols; we therefore expect that results from the University Hospital Bern are representative of all 9 centers in the country. We are also concerned that our study includes a heterogeneous group of CCS with relatively small numbers of patients in each subgroup defined by treatment exposure or type of cancer. We plan to overcome this limitation by expanding this study to a nationwide study that includes all 9 Swiss Pediatric Oncology Group clinics. Also, our study might be affected by survival bias, as the most severely affected childhood cancer patients and survivors have already died. This could underestimate the cardiotoxic effect of anticancer management. We will collect the number of cardiac deaths from the Swiss Mortality Statistics, and this information will be considered in the analysis and interpretation of the results.

Among this study's several strengths is our attempt to include the complete cohort of survivors treated at the University Children's Hospital Bern since 1976 based on the database of the Childhood Cancer Registry. We repeat our invitation to nonresponders several times and ask about reasons for not participating. This reduces the potential for selection bias. Also, we link the Childhood Cancer Registry with the Swiss Federal Statistical Office to collect cardiac causes of death in ≥5-year survivors. Second, we have access to all treatment exposures based on actual chemotherapy road maps and are able to look into dose-response relationships. Third, we will continuously include new 5-year survivors and therefore gain knowledge about the risk of cardiac dysfunction in younger patients treated more recently. Finally, our study has been set up within routine survivorship follow-up care using the experience of a multidisciplinary and interdisciplinary team with close collaboration between pediatric and adult cardiology, pediatric hematology and oncology, and clinical epidemiology.

The preliminary results from this retrospective, single-center study suggest that a standardized cardiac assessment that is part of routine follow-up care done in collaboration between pediatric and adult specialists is feasible in Switzerland and widely accepted by survivors and health care providers. In the next step, we will include more Swiss centers in the study to provide standardized clinical follow-up care longitudinally to all CCS on a nationwide scale.

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Authors' Contributions

NXvdW, MP, TS, CEK, and CS designed the study and developed the study material. MP, TS, CEK, NXvdW, CS, ESHL, DR, and JR participated in study management and coordination. CS, CEK, and NXvdW drafted the manuscript. All authors commented on and approved the final version.

Conflicts of Interest

JR reports personal fees from SOBI, Roche, and Pierre Fabre for advisory board membership, which is independent of the submitted work.

Multimedia Appendix 1
Peer review reports, Swiss Cancer League.
[PDF File (Adobe PDF File), 282 KB - resprot_v9i6e17724_app1.pdf]

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Abbreviations

2D: 2-dimensional
3D: 3-dimensional
A: late diastolic left ventricular filling velocity
CCS: childhood cancer survivors
E: early diastolic left ventricular filling velocity
E/A: early to late left ventricle filling velocity
E': mitral annular early diastolic velocity
E/e': peak mitral flow velocity
GCS: global circumferential strain
GLS: global longitudinal strain
GRS: global radial strain
ICCC3: International Classification of Childhood Cancer third edition
LA: left atrial
LV: left ventricular
LVEF: left ventricular ejection fraction
RA: right atrium
RV: right ventricle
STS: 1-minute sit-to-stand test
TR: tricuspid regurgitation

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Protocol

Prospective Associations Between Working Time Arrangements and Psychiatric Treatment in Denmark: Protocol for a Cohort Study

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Abstract

Background: The burden of mental ill health in working-age populations has prompted research on possible links between work-related factors and mental ill health. Long working hours and night shift work are some of the factors that have been studied in relation to the risk of developing mental ill health. Yet, previous studies have not generated conclusive evidence, and further studies of high quality are needed.

Objective: This study aims to investigate the prospective association between working time arrangements and mental health in terms of psychotropic drug usage or psychiatric hospital treatment in the general working population of Denmark.

Methods: Data on total weekly working hours in any job and night shift work from the Danish Labor Force Survey 2000–2013 will be linked to data from the Psychiatric Central Research Register (expected 2400 cases during 700,000 person years at risk) and National Prescription Registry (expected 17,400 cases during 600,000 person years at risk). Participants will be followed for up to 5 years. We will use Poisson regression to separately analyze incidence rates of redeemed prescriptions for psychotropic medicine and incidence rates of psychiatric hospital treatment due to mood disorders, anxiety disorders, or stress-related disorders as a function of weekly working hours and night shift work. The analyses will be controlled for sex, age, calendar time of the interview, and socioeconomic status.

Results: This is a study protocol. Power calculations indicate that the study has sufficient statistical power to detect relatively small differences in risks and minor interactions (eg, ~90% power to detect a rate ratio of 1.1 for psychoactive medication use). We expect the analyses to be completed by the end of 2020 and the results to be published in 2021.

Conclusions: In this study protocol, all hypotheses and statistical models of the project have been completely defined before we link the exposure data to the outcome data. The results of the project will indicate to what extent and in what direction the national burden of mental ill health in Denmark has been influenced by long working hours and night shift work.

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KEYWORDS

occupational health; long working hours; night shift work; mood disorders; anxiety; stress-related disorders; psychiatric hospital treatment; prescription drugs; psychotropic medicine

Introduction

Background

The average prevalence of mental ill health in the working-age population of Organization for Economic Co-operation and Development (OECD) countries has been estimated at 20% [1]. It has, moreover, been estimated that approximately 30% to 50% of all new disability benefit claims in OECD countries can be attributed to mental ill health [1]. The massive burden of mental ill health in working-age populations has prompted research on possible links between work-related factors and mental ill health [2,3]. Long working hours and shift or night work are some of the factors that have been studied in relation to the risk of developing mental ill health.

A theoretic argument for an adverse effect of long working hours on mental health is their association with short sleep [4-6] and fatigue due to insufficient recovery between work shifts [4,6-9], which are known risk factors for mental ill health [10-16]. The same argument may be applied to shift work, which, especially if it includes night shifts, disrupts the circadian chronobiologic rhythm and increases the risk of sleeping problems and fatigue [17-19]. Prolonged working hours as well as shift work may, however, generate extra income compared with equivalent daytime work without overtime, and a higher income has been associated with a decreased risk of developing psychological distress [20], depressive symptoms [21], and depression [22]. There are, in other words, theoretical arguments for beneficiary as well as detrimental mental health effects of long working hours and shift work.

Most of the published prospective studies on the relationships between long working hours and mental ill health have, however, been underpowered to such a degree that they do not impart any meaningful information [23]. The few studies in which the statistical power has been acceptable have reported rate ratios (RRs; for long vs normal working hours) that are close to unity in study populations from Europe, North America, and Australia and slightly elevated in study populations from Asia [3,24]. The meta-analysis by Virtanen et al [24] included 28 cohort studies with a total of 189,729 participants from 35 countries and estimated the RR for development of depressive symptoms between workers with long vs standard working hours at 1.50 (95% CI 1.13-2.01) in Asia, 1.11 (95% CI 1.00-1.22) in Europe, 0.97 (95% CI 0.70-1.34) in North America, and 0.95 (95% CI 0.70-1.29) in Australia. Recent literature reviews on shift work and mental health [3,18,25-27] do not yield any clear evidence of a prospective association between shift or night work and mental disorders.

Aims and Objectives

In a previous study of prospective associations between long working hours or shift work and redeemed prescriptions for psychotropic medicine among employees in the general population of Denmark [23,28,29], we did not find any statistically significant effects after adjustment for multiple comparisons. However, our previous study could not reject the possibility that excessive overtime work (>48 vs 32-40 working hours a week) is associated with a clinically important effect (RR 1.15, 95% CI 1.02-1.30). Thus, although not statistically significant, our primary analyses suggested that the average risk among employees with excessive overtime work might be slightly higher than it is among employees with normal working hours. Our secondary (hypothesis-generating) analyses suggested that excessive overtime work may be an important risk factor among shift workers (RR 1.51, 95% CI 1.15-1.98) [23]. Our secondary analyses suggested, moreover, that the RR among shift vs non-shift workers was markedly higher for redeemed prescriptions of antidepressants (RR 1.23, 95% CI 1.08-1.40) than it was for redeemed prescriptions of anxiolytics (RR 0.86, 95% CI 0.72-1.02) [29].

In the present project, we will test/retest some of the hypotheses that were generated or tested in our previous study, in a data set that is independent of and larger than those previously used. The target population (employees in the general population of Denmark) is the same, and the working hours of the participants will be categorized in the same way as in our previous study (32-40 hours/week, 41-48 hours/week, and 49-100 hours/week). We will, however, not be able to reproduce the shift work categories, which in our previous study were defined as “fixed night shifts or rotational shift work schedules” vs “fixed day, morning, or evening shifts.” Instead, we will look at the contrast “schedules that include night shift work” vs “other work schedules (including non-night shift work and evening work)”.

Methods

Ethics Approval

The study will comply with The Act on Processing of Personal Data, Denmark (Act No. 429 of May 31, 2000), which implements the European Union Directive 95/46/EC on the protection of individuals. The data usage is approved by the Danish Data Protection Agency, file number 2001-54-0180. The ethical aspect of the project was approved by Statistics Denmark, account number 704291.

Clinical Endpoints

The following endpoints will be regarded: redeemed prescriptions for any type of psychotropic medicine (ie, drugs in the ATC-code category N05 [psycholeptica] or N06 [psychoanaleptica]); redeemed prescriptions for antidepressants (ATC-code: N06A); redeemed prescriptions for anxiolytics (ATC-code: N05B); redeemed prescriptions for hypnotics and sedatives (ATC-code: N05C); psychiatric hospital treatment with a mood disorder, anxiety disorder, or stress-related disorder (ICD-10: F30-F41 or F43) as the principal diagnosis; psychiatric hospital treatment with a mood disorder (ICD-10: F30-F39) as the principal diagnosis; and psychiatric hospital treatment with an anxiety-related or stress-related disorder (ICD-10: F40, F41, or F43) as the principal diagnosis.

The following mental disorders are included in the case definitions: F30 Manic episode, F31 Bipolar affective disorder, F32 Depressive episode, F33 Recurrent depressive disorder, F34 Persistent mood [affective] disorders, F38 Other mood [affective] disorders , F39 Unspecified mood [affective] disorder, F40 Phobic anxiety disorders, F41 Other anxiety disorders, and F43 Reaction to severe stress, and adjustment disorders.

Hypotheses Tests

In this section, we list the statistical significance tests of the study. All of the tests will be adjusted for age, sex, socioeconomic status (SES), and calendar year of interview. Moreover, the tests for effects of weekly working hours will be adjusted for night shift work, and the tests for effects of night shift work will be adjusted for weekly working hours.

Incident Use of Psychotropic Medicine

With regard to prospective associations between long working hours or night shift work and redeemed prescriptions for any type of psychotropic medicine, we will test the following effects for statistical significance at an α of .01: main effect of weekly working hours, effect of interaction between age and weekly working hours, effect of interaction between sex and weekly working hours, effect of interaction between SES and weekly working hours, effect of interaction between night shift work and weekly working hours, main effect of night shift work, effect of interaction between age and night shift work, effect of interaction between sex and night shift work, and effect of interaction between SES and night shift work.

The familywise error rate denotes the probability of at least one false positive result among a family of related hypothesis tests, under the overall null hypothesis of no association. Since each of the hypotheses are tested at the significance level of .01 and 5 hypotheses are tested for each of the factors "long working hours" and "night shift work," the familywise error rates for effects on incident use of psychotropic medicine will be ≤0.05 for each of these factors.

Psychiatric Hospital Treatment

Hazard ratios for incident use of psychotropic medicine are often used in occupational health research as a proxy measure for hazard ratios of mental ill health [30]. A large proportion of people who use psychotropic medicine do so to cope with sleeping problems [31]. Sleeping problems may be consequences (symptoms) of mental health problems, such as depression, anxiety disorders, and stress-related disorders [32]. They may, however, also be caused by factors that are unrelated to mental health, which may be especially true among shift or night workers, where sleeping problems often occur as a natural consequence of a disrupted circadian rhythm [17]. Sleeping problems may be treated not only with hypnotics and sedatives but also with anxiolytics and antidepressants [31]. Increased rates of incident use of psychotropic medicine are therefore not necessarily the same as increased rates of mental ill health. We will therefore supplement our analyses of psychotropic medicine usage with an examination of hazard ratios for psychiatric hospital treatment, although the threshold for this type of treatment is much higher. Unfortunately, valid data for diagnoses and treatment of mental disorders by general practitioners or private psychiatrists or psychologists in Denmark are not available.

With regard to prospective associations between long working hours or night shift work and psychiatric hospital treatment due to a mood disorder, anxiety disorder, or stress-related disorders, we will test the following effects for statistical significance at an α of .05: main effect of weekly working hours and main effect of night shift work.

Psychiatric hospital treatment is a relatively rare event, which makes the statistical power too low to allow testing for interaction effects.

Odds of Antidepressants vs Anxiolytics

Antidepressants are primarily designed to treat depressive mood disorders but can also be used for the treatment of anxiety and sleeping disorders [31]. In our previous study of employees in Denmark [29], we did not find any significant effect of shift work on incident use of psychotropic drugs when all types of psychotropic drugs were combined into a single outcome. We observed, however, a difference between shift workers and non-shift workers in the distribution of prescriptions for antidepressants and anxiolytics. The odds that a prescription was for antidepressants rather than for anxiolytics were markedly higher among shift workers than they were among non-shift workers.

The observed difference may have been due to chance, different practices for prescription of psychotropic drugs to shift workers compared with non-shift workers to avoid side effects of anxiolytics that may impede wakefulness during night shifts, or an increased risk of mood disorders combined with a decreased risk of anxiety and stress-related disorders among shift workers compared with non-shift workers.

In the present study, we will try to shed some light on this issue.

Among the employees who redeem a prescription for either antidepressants or anxiolytics, we will test if the odds for antidepressants vs anxiolytics differ between employees with and without night shift work.

Among the employees who receive hospital treatment for a mood disorder, anxiety disorder, or stress-related disorder, we will test if the odds that the treatment concerns a mood disorder vs an anxiety disorder or stress-related disorder differ between employees with and without night shift work.

Both tests will be performed at the significance level .05.

If the odds for antidepressants vs anxiolytics are significantly higher among the night shift workers, then it is unlikely that our previous observation was due to chance (hypothesis A).

If the odds for antidepressants vs anxiolytics are significantly higher while the odds for mood disorders vs anxiety disorders and stress-related disorders are lower among the night shift workers than they are among the non-night shift workers, then we have generated support for the hypothesis of prescription bias (hypothesis B).

If the odds for mood disorders vs anxiety disorders and stress-related disorders are significantly higher among the night shift workers than they are among the non-night shift workers, then we have generated support for hypothesis C.

Data Material

Our project will be based on interview data from the Danish Labor Force Survey (DLFS) 2000-2013, which, by use of the participants' personal identification numbers, will be linked to

data from a series of Danish national registers. The following registers will be used: Central Person Registry [33], Employment Classification Module [34], Psychiatric Central Research Register [35], and National Prescription Registry [36]. The Danish Labor Force Survey has been conducted all year long since 1994. Each quarter of a calendar year, a random sample of people 15-74 years old is drawn from the Population Statistics Register. An extra sample of unemployed people is drawn from the register-based unemployment statistics (RAM). The samples are divided into 13 equal portions, one for each week of the given quarter, and the persons are invited to be interviewed about circumstances that relate to the reference weeks in question. The participants are also invited to participate in interviews three more times during a period of approximately 15 months after the first interview. Each sample is drawn independently of previous samples, which means that the same person may be sampled in several different quarters. In 2007, the quarterly sample sizes were increased from approximately 20,000 to 40,532 persons. The interviews were conducted by telephone during the time period of the present study and covered various aspects of, inter alia, labor market attachment and working time arrangements [37]. The response rate has decreased with time, from 70% in 2002 to 53% in 2013. The Central Person Registry contains information on gender, addresses, and dates of birth, death, and migrations for every person who is or has been an inhabitant of Denmark sometime between 1968 and the present time. Since 1995, the Psychiatric Central Research Register has covered inpatient, outpatient, and emergency ward visits of all psychiatric hospital departments in Denmark, while the National Prescription Registry covers all redeemed prescriptions at pharmacies in Denmark. A person's SES, occupation, and industry have been registered annually in the Employment Classification Module since 1975. Persons are classified on the basis of their main income source during a calendar year.

Exposure Variables

The exposure variables of the present project will be based on responses to the DLFS. The variables will be defined in the same way as in a previous DLFS-based study that examined the association between working time arrangements and ischemic heart disease [38]. The exposure data and exposure variables are described in the previous study [38], as follows: "The labor force surveys gather person-based information on weekly working hours, calculated by adding the hours worked in secondary jobs to the ones worked in a primary job. The participants are asked first how many hours they usually work and then how many hours they worked during the reference week (a predetermined work week, which occurred 1-4 weeks prior to the interview). They are also asked whether and to what extent they work at night. The questions used to gather this information have changed slightly with time. Before 2001, there was no mention of whether meal breaks should be counted as working hours. During 2001-2006, all participants were instructed to exclude meal breaks when they counted their work hours. As of 2007, the time used for meal breaks is to be counted if the person was paid while eating and is to be excluded otherwise. Another peculiarity that was introduced in 2007 is that the participants are asked whether the weekly working hours vary a lot or there are other reasons that make it difficult to provide a meaningful estimate of usual weekly working hours. If they answer 'yes' to any of these questions, then 'average working hours' is to be used as a proxy for 'usual working hours'."

Before 2001, the participants were simply asked whether they worked at night, but from 2001 onward, the question has been whether they worked at night during the last 4 weeks. Until 2006, the response categories were "yes, regularly," "yes, occasionally," and "no, never." From 2007 onward, the response categories were expanded to "yes, regularly" (ie, more than half of the working days in the last 4 weeks), "yes, occasionally" (ie, at least once within the last 4 weeks, but less than half of the working days), and "no, not within the last 4 weeks."

We will disregard the changes in the data collection routines in the primary analyses of this project. We will define the exposure variables as follows.

Weekly Working Hours

In keeping with Kleppa et al [39] and Hannerz and Albertsen [28], we will treat working hours as a categorical variable, with 32-40 hours representing normal weekly working hours, 41-48 hours representing overtime work that lies within the limits of the European working time directive, and 49-100 hours representing overtime work beyond the threshold of the directive. We will base the categorization on the person's usual working hours.

Nighttime Work

Participants who responded either "yes, regularly" or "yes, occasionally" to the question about nighttime work will be defined as being exposed, and those who responded with "no..." will be defined as being unexposed to nighttime work.

Follow-up and Inclusion Criteria

The study will include people who responded to DLFS sometime during the calendar years 2000-2013. The participants will be followed from the end of the calendar year of their baseline interview. The follow-up will end after 5 years or at the time the participant reaches the clinical endpoint of the analysis, emigrates, or dies, or the study period ends (December 31, 2014 for psychotropic medicine; December 31, 2018 for psychiatric hospital treatment), whichever comes first. To be eligible for inclusion, participants should be between 20 and 59 years old at the start of the follow-up period and employed with ≥32 weekly working hours at the time of the interview. People who received psychiatric hospital treatment or redeemed a prescription for psychotropic drugs during the calendar year preceding the start of the follow-up period will be excluded from the analyses. We will moreover exclude all participants who were registered in the Employment Classification Module as unemployed or otherwise not economically active during the main part of the calendar year preceding the start of the follow-up.

Statistical Analysis

Incidence Rates of Redeemed Prescriptions for Psychotropic Medicine and Psychiatric Hospital Treatment

We will use Poisson regression to separately analyze incidence rates of redeemed prescriptions for psychotropic medicine and incidence rates of psychiatric hospital treatment, due to mood disorders, anxiety disorders, or stress-related disorders as a function of weekly working hours (32-40 hours/week, 41-48 hours/week, >48 hours/week), night shift work (Yes vs No), sex, age (10-year categories), calendar time of the interview (2000-2004, 2005-2009, 2010-2013), and SES (legislators, senior officials, and managers; professionals; technicians and associate professionals; workers in occupations that require skills at a basic level; workers in elementary occupations; and gainfully occupied people with an unknown occupation). SES is based on job category, according to the Employment Classification Module, during the calendar year of the baseline interview. The logarithm of person years at risk will be used as offset. Likelihood ratio tests will be used to test the effects that are listed in the section entitled “Hypothesis Tests”. Each of the effects on incidence rates of redeemed prescriptions for psychotropic medicine will be tested at the significance level .01. The effects on incidence rates of psychiatric hospital treatment will be tested at the significance level .05.

RRs for redeemed prescriptions of psychotropic drugs as a function of weekly working hours will, thereafter, be estimated by sex, age, night shift work, and SES, and the results will be presented as shown in Figures 1 and 2. As shown in the table, we intend to pool the results of the present study with results from our previous study [23]. The pooled results will be obtained through inverse-variance weighting. The pooled results will provide estimates that are based on the present as well as our previous project. These estimates will afford a higher confidence with regard to the concerned RRs than the present study alone. The statistical significance tests of the present study will, however, only be based on the results of the present project. Since the present study has the same target population as our previous study and the study periods are overlapping, it is likely that some of the participants in our previous study also have participated in the DLFS. Based on the number of participants in our previous study in relation to the number of people in the target population, we expect that approximately 1% of the participants of the present study also participated in our previous study. This overlap will be taken into account in the pooling of the results by use of the following strategy: Before the results are pooled, the standard error of the present study will be multiplied by the square root of $(1/(1-x))$, where $x = 0.01$ is the proportion of the participants in the present study that are likely to have participated in our previous study.

RRs for redeemed prescriptions of psychotropic drugs as a function of night work will be estimated by sex, weekly working hours, age, and SES, with results presented as shown in Figure 3.

Figure 1. Dummy table: rate ratios (RRs) with 99% CIs for incident use of psychotropic drugs as a function of weekly working hours among employees in Denmark, with reference to the study by Hannerz and Albertsen [23]. PY: person years at risk.

Type of population	Weekly working hours	This study				Hannerz and Albertsen study		Pooled results	
		PY	Cases	RR	99% CI	RR	99% CI	RR	99% CI
All workers									
	>48					1.15	0.98-1.35		
	41-48					1.04	0.92-1.19		
	32-40			1.00	-	1.00	-	1.00	-
Male workers									
	>48					1.13	0.92-1.38		
	41-48					0.97	0.80-1.18		
	32-40			1.00	-	1.00	-	1.00	-
Female workers									
	>48					1.16	0.87-1.53		
	41-48					1.11	0.93-1.33		
	32-40			1.00	-	1.00	-	1.00	-
Workers with night shift work									
	>48					1.51	1.06-2.16		
	41-48					1.18	0.81-1.71		
	32-40			1.00	-	1.00	-	1.00	-
Workers without night shift work									
	>48					1.08	0.90-1.30		
	41-48					1.03	0.89-1.18		
	32-40			1.00	-	1.00	-	1.00	-
Legislators, senior officials, and managers									
	>48					1.31	0.61-2.83		
	41-48					0.76	0.34-1.72		
	32-40			1.00	-	1.00	-	1.00	-
Professionals									
	>48					1.27	0.88-1.85		
	41-48					1.05	0.78-1.42		
	32-40			1.00	-	1.00	-	1.00	-
Technicians and associate professionals									
	>48					1.20	0.81-1.76		
	41-48					1.13	0.85-1.50		
	32-40			1.00	-	1.00	-	1.00	-
Workers in occupations that require skills at a basic level									
	>48					1.09	0.82-1.45		
	41-48					1.05	0.86-1.29		
	32-40			1.00	-	1.00	-	1.00	-
Workers in elementary occupations									
	>48					1.16	0.66-2.06		
	41-48					1.02	0.59-1.76		
	32-40			1.00	-	1.00	-	1.00	-
Gainfully occupied people with an unknown occupation									
	>48					0.95	0.63-1.44		
	41-48					0.91	0.60-1.38		
	32-40			1.00	-	1.00	-	1.00	-

Figure 2. Dummy table: age group–specific rate ratios (RRs) with 99% CIs for incident use of psychotropic drugs as a function of weekly working hours among employees in Denmark in the calendar years 2000-2013.

Age at baseline (years)	Weekly working hours	Person years	Cases	RR	99% CI
20-29					
	>48				
	41-48				
	32-40			1.00	-
30-39					
	>48				
	41-48				
	32-40			1.00	-
40-49					
	>48				
	41-48				
	32-40			1.00	-
50-59					
	>48				
	41-48				
	32-40			1.00	-

Figure 3. Dummy table: rate ratios (RRs) with 99% CIs for incident use of psychotropic drugs as a function of night work among employees in Denmark 2000-2013.

Categories	Night shift work	Person years	Cases	RR	99% CI
All workers					
	Yes				
	No			1.00	-
Male workers					
	Yes				
	No			1.00	-
Female workers					
	Yes				
	No			1.00	-
Work >48 hours a week					
	Yes				
	No			1.00	-
Work 41-48 hours a week					
	Yes				
	No			1.00	-
Work 32-40 hours a week					
	Yes				
	No			1.00	-
20-29 years old					
	Yes				
	No			1.00	-
30-39 years old					
	Yes				
	No			1.00	-
40-49 years old					
	Yes				
	No			1.00	-
50-59 years old					
	Yes				
	No			1.00	-
Legislators, senior officials, and managers					
	Yes				
	No			1.00	-
Professionals					
	Yes				
	No			1.00	-
Technicians and associate professionals					
	Yes				
	No			1.00	-
Workers in occupations that require skills at a basic level					
	Yes				
	No			1.00	-
Workers in elementary occupations					
	Yes				
	No			1.00	-
Gainfully occupied people with an unknown occupation					
	Yes				
	No			1.00	-

Odds Ratio for Antidepressants vs Anxiolytics

This analysis will include all participants who, during the follow-up for psychotropic drugs, redeemed a prescription for either antidepressants or anxiolytics. Logistic regression analysis will be used to estimate the odds that their first redeemed prescription was for antidepressants rather than anxiolytics as a function of night shift work (Yes vs No). The analysis will be controlled for weekly working hours, sex, age, calendar time, and SES. The control variables will be defined as described earlier in the manuscript. A likelihood ratio test will be used to test for a main effect of night shift work. The significance level is set at .05. The estimated odds ratio will be presented with the 95% CI.

Odds Ratio for Mood Disorders vs Anxiety Disorders and Stress-Related Disorders

This analysis will include all participants who, during the follow-up, underwent psychiatric hospital treatment for a mood disorder, anxiety disorder, or stress-related disorder. Logistic regression analysis will be used to estimate the odds that their first psychiatric hospital contact during the follow-up was for a mood disorder vs anxiety disorders and stress-related disorders, as a function of night shift work (Yes vs No). The analysis will be controlled for weekly working hours, sex, age, calendar time, and SES. The control variables will be defined as described earlier in the manuscript. A likelihood ratio test will be used to test for a main effect of night shift work. The significance level is set at .05. The estimated odds ratio will be presented with the 95% CI.

Power Calculations

Based on the National Prescription Registry and Psychiatric Central Research Register, we expect to find approximately 29 new cases of psychotropic drug use and 3.4 new cases of psychiatric hospital treatment per 1000 person years at risk. Based on the number of participants in the DLFS included in previous research [40] and these rates, we expect the follow-up for redeemed prescriptions of psychotropic drugs to encompass 600,000 person years at risk and 17,400 cases, and we expect the follow-up for psychiatric hospital treatments to encompass 700,000 person years at risk and 2400 cases. We expect that 84% of the included participants are working 32-40 hours a week, that 10% are working 41-48 hours a week, and that the remaining 6% are working more than 48 hours a week [41]. We expect that 12.6% of the participants will be categorized as exposed to night shift work [42].

Power to Detect Main Effects

The statistical power for the main effects of night shift work and weekly working hours on the rates of new cases of psychotropic drug use and psychiatric hospital treatment for mood disorders, anxiety disorders, or stress-related disorders, as a function of the underlying RR, is given in Figures 4 and 5. The calculations are based on the expected number of cases, the Poisson distribution, Gauss' propagation of error formulas, and the central limit theorem.

Figure 4. Power to detect main effects of night shifts and long working hours on the rates of new cases of psychotropic drug use, as a function of underlying rate ratios (α=.01).

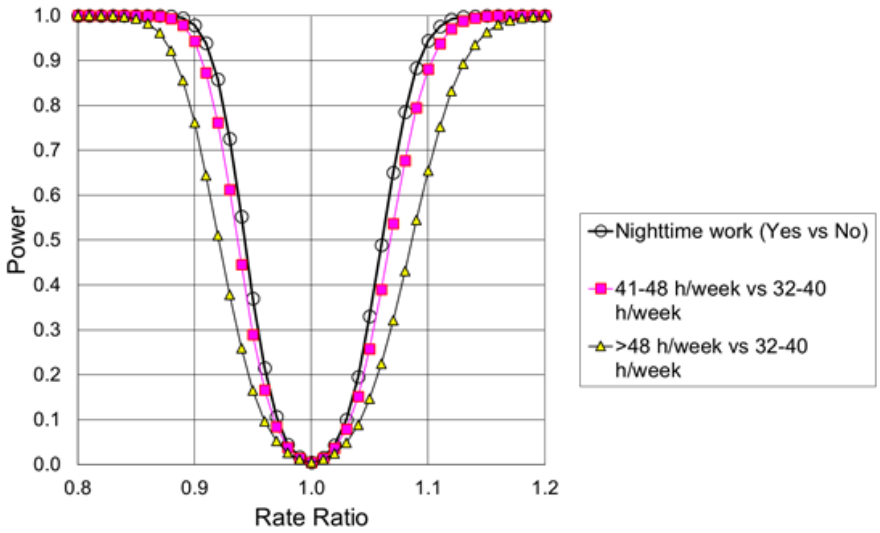
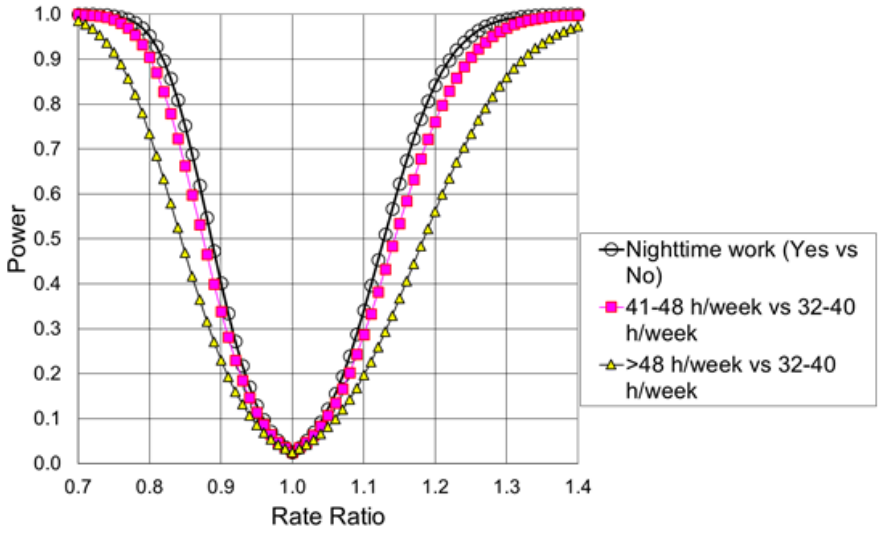


Figure 5. Power to detect main effects of night shift work and long working hours on the rates of new cases of psychiatric hospital treatment for mood disorders, anxiety disorders, or stress-related disorders, as a function of underlying rate ratios (α=.05).



Power to Detect Interaction Effects

In the present project, we calculated the statistical power to detect interaction effects in relation to Cohen w, defined as

where p_{0ij} and p_{1ij} are the expected proportions of cases that fall into exposure category I, j under the null hypothesis and alternative hypothesis, respectively. According to Cohen, w=0.1 is a small effect, w=0.3 is a medium effect, and w=0.5 is a large effect [43].

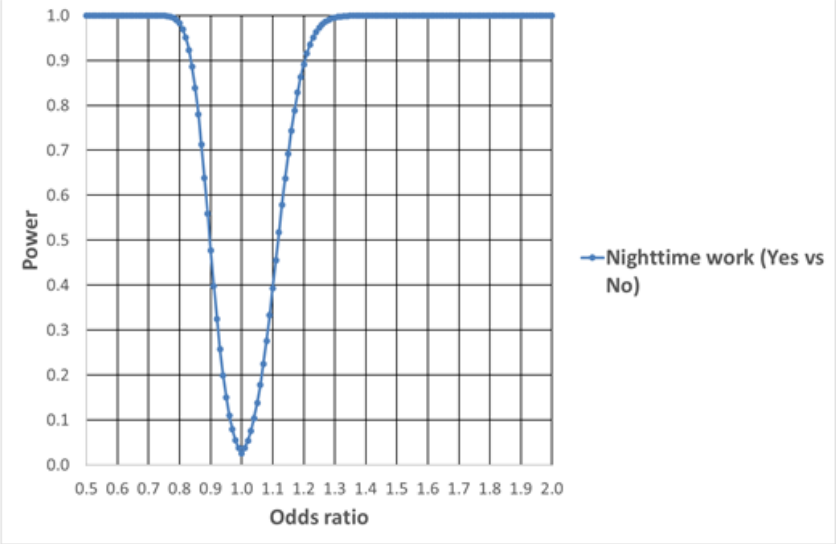
The estimated statistical power to detect a small interaction effect (w=0.1) was greater than 99% for each of the interaction tests listed in the section entitled "Hypothesis Tests." The power calculations were based on the total number of expected cases, the non-central chi-square distribution, and a two-tailed significance level of .01.

These analyses indicate that the power to detect effects of the concerned working time arrangements is sufficient.

Power for the Analysis of the Odds for Antidepressants vs Anxiolytics

We expect to find 7900 cases of redeemed prescriptions for antidepressants and 4600 cases of redeemed prescriptions for anxiolytics. The power to detect an effect of night shift work on the odds for antidepressants vs anxiolytics is given in Figure 6. The calculations are based on the expected number of cases, the binomial distribution, Gauss' propagation of error formulas, and the central limit theorem.

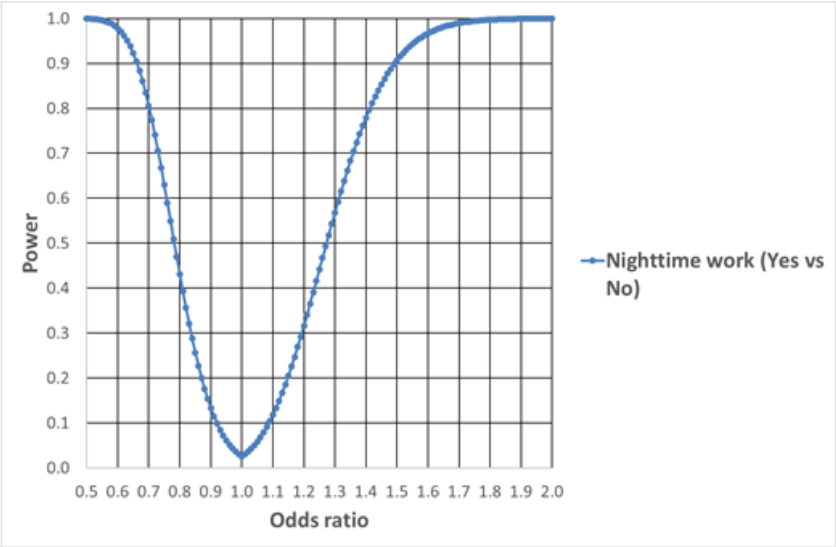
Figure 6. Power to detect an effect of night shift work on the odds of redeemed prescriptions for antidepressants vs anxiolytics, as a function of underlying odds ratios (α=.05).



Power for the Analysis of the Odds for Mood Disorders vs Anxiety Disorders and Stress-Related Disorders

We expect to find 1090 cases of psychiatric hospital treatment for mood disorders and 1310 cases of psychiatric hospital treatment for anxiety disorders and stress-related disorders. The power to detect an effect of night shift work on the odds for mood disorders vs anxiety disorders and stress-related disorders is given in Figure 7. The calculations are based on the expected number of cases, the binomial distribution, Gauss' propagation of error formulas, and the central limit theorem.

Figure 7. Power to detect an effect of night shift work on the odds of psychiatric hospital treatment for mood disorders vs anxiety disorders and stress-related disorders, as a function of underlying odds ratios (α= .05).



Sensitivity Analyses

We will conduct a series of sensitivity analyses that will include all of the covariates listed in the statistical analysis section, and all the analyses will have redeemed prescriptions for psychotropic drugs as the endpoint. Only main effects will be considered. The sensitivity analyses will not be tested for statistical significance. Their results may, however, strengthen, weaken, or invalidate statistical conclusions of the primary analyses.

Sensitivity Analysis 1: Stable Exposure to Night Shift Work

To determine if the estimated strength of the association between night shift work and redeemed prescriptions for psychotropic drugs increases when the supposedly harmful exposure to night shift work is more stable over time (dose-response association), we will conduct a sensitivity analysis that will only include people who (1) participated in more than one interview, (2) were between 20 and 59 years old during their last interview, (3) were employed 32 or more working hours a week according to their first as well as their last interview, and (4) belonged to the same category in relation to night shift work (yes vs no) during their last interview as they did during their first interview. The follow-up of the included participants will commence at the very end of the calendar year of their last interview. The statistical model will otherwise be the same as in the primary analysis.

Sensitivity Analysis 2: Stable Exposure to Weekly Working Hours

Similarly, to determine if the estimated strength of the association between working hours and redeemed prescriptions for psychotropic drugs increases when exposure is more stable over time, we will conduct a sensitivity analysis that will only include people who (1) participated in more than one interview, (2) were between 20 and 59 years old during their last interview, (3) were employed 32 or more working hours a week according to their first as well as their last interview, and (4) did not move more than one step among the ordered working time categories between the first and last interview. The included participants will then be categorized by weekly working hours into 32-40 hours/week, 41-48 hours/week, and ≥49 hours/week, according to the mean of the reported usual working hours during their first and last interview. The follow-up of the included participants will commence at the very end of the calendar year of their last interview. The statistical model will otherwise be the same as in the primary analysis.

Sensitivity Analysis 3: Occasional vs Regular Night Shift Work

We want to know if the estimated strength of association between night shift work and redeemed prescriptions for psychotropic drugs is greater among participants with regular night shift work than it is among participants with occasional night shift work. We will therefore conduct a sensitivity analysis where we divide night shift work into three categories (no; yes, occasionally; yes, regularly) and then estimate the RRs for the contrasts of "yes, occasionally" vs "no" and "yes, regularly" vs "no". The statistical model and inclusion criteria will otherwise be the same as in the primary analysis.

Sensitivity Analysis 4: Inclusion of Workers with 28-31 Working Hours a Week

In the primary analysis, we will only include employees who usually worked ≥32 hours a week. There are, however, relatively large groups of night shift workers in nursing homes and home care whose standard full-time work schedules (eg, 7 night shifts,

7 days off-duty) imply an average of only 28 working hours a week. We want to know if the estimated effect of night shift work on the rates of new cases of psychotropic drug use would change if our reference group was changed from 32-40 hours/week to 28-40 hours/week. We will therefore conduct a sensitivity analysis with a redefined inclusion criterion at ≥28 hours/week and a redefined reference group at 28-40 hours/week. The statistical model will otherwise be the same as in the primary analysis.

Sensitivity Analysis 5: Controlling for Possible Bias due to Preexisting Mental Health Problems

In the primary analysis, we will exclude participants who received psychiatric hospital treatment or redeemed a prescription for psychotropic drugs during the calendar year preceding the start of the follow-up period. It is, however, possible that the results of the primary analysis will be influenced by cases that occurred earlier than one year prior to baseline. To explore this possibility, we will conduct a sensitivity analysis in which the sample is stratified into two cohorts. The first cohort will exclude all participants who underwent psychiatric hospital treatment or redeemed a prescription for psychotropic drugs some time during the 5-year period prior to the start of follow-up. The second cohort will consist of the participants who were excluded from the first cohort due to psychiatric hospital treatment or redeemed prescription for psychotropic drugs within 2-5 years prior to the start of the follow-up. Participants who underwent psychiatric hospital treatment or redeemed a prescription for psychotropic drugs some time during the 1-year period prior to the start of follow-up will still be excluded. As a genetic or social disposition might increase the development of mental illness in response to an exposure such as night shift work, the second cohort will supplement the primary analyses with information on the effect in people who have previously been treated for mental health problems. This particular analysis will only include participants who lived in Denmark throughout the 5-year period of concern. Moreover, it will only include people who participated in DLFS sometime during the calendar period 2004-2013. The statistical methods and inclusion criteria of the analysis will otherwise be the same as in the primary analysis. The results will be presented as shown in Figures 8 and 9. The results of the first cohort will be interpreted as incidence RRs, while the results of the second cohort will be interpreted as relapse RRs.

Figure 8. Dummy table: rate ratios (RRs) with 99% CIs for incident or recurrent use of psychotropic drugs, as a function of night work among employees in Denmark 2004-2013. Populations 2 and 3 are disjointed and exhaustive subsets of population 1. *The term occurrences refers to “occurrences of redeemed prescriptions for psychotropic medicine or psychiatric hospital treatment.”.

Type of population	Night work at baseline	Person years	Cases	RR	99% CI
1. Workers with no occurrences* in the year prior to baseline					
	Yes				
	No			1.00	-
2. Workers with no occurrences* 1-5 years prior to baseline					
	Yes				
	No			1.00	-
3. Workers with no occurrences* in the year prior to baseline, but at least one occurrence 2-5 years prior to baseline					
	Yes				
	No			1.00	-

Figure 9. Dummy table: rate ratios (RRs) with 99% CIs for incident or recurrent use of psychotropic drugs, as a function of weekly working hours among employees in Denmark 2004-2013. Populations 2 and 3 are disjointed and exhaustive subsets of population 1. *The term occurrences refers to “occurrences of redeemed prescriptions for psychotropic medicine or psychiatric hospital treatment.”.

Type of population	Weekly working hours	Person years	Cases	RR	99% CI
1. Workers with no occurrences* in the year prior to baseline					
	>48				
	41-48				
	32-40			1.00	-
2. Workers with no occurrences* 1-5 years prior to baseline					
	>48				
	41-48				
	32-40			1.00	-
3. Workers with no occurrences* in the year prior to baseline, but at least one occurrence 2-5 years prior to baseline					
	>48				
	41-48				
	32-40			1.00	-

Sensitivity Analysis 6: Controlling for the Industrial Sector

In order to pool results of the present study with results obtained in our previous study (see Figure 1) we will use the same covariates in the primary analysis of the present study as we did in our previous study [23]. The primary analysis therefore controls for an occupational-based SES, but it does not control for the industrial sector, which has been shown to be a predictor for mood disorders in the general working population of Denmark [44]. We want to know if the results of the present study will change if we add the industrial sector to the model and will therefore conduct a sensitivity analysis where we first control for and thereafter stratify by industrial sector. The statistical methods and inclusion criteria of the analysis will otherwise be the same as in the primary analysis. The industrial groups will be classified as shown in Table 1. The coding of the industries is based on the industrial classification DB93 [45] in the calendar years 1999-2002, DB03 [46] in 2002-2007, and DB07 [47] in 2008-2013.

Table 1. Industrial groups coded according to the subclassifications within the main classifications of DB93, DB03, and DB07.

Industrial group	Classification		
	DB93[a]	DB03[b]	DB07[c]
Agriculture, forestry, hunting, and fishing	A+B	A+B	A
Manufacturing, mining, and quarrying	C+D	C+D	B+C
Construction	F	F	F
Wholesale and retail trade; repair of motor vehicles and motorcycles	G	G	G
Transporting and storage	I	I	H
Accommodation and food service activities	H	H	I
Human health and social work activities	N	N	Q
Other			
Missing	-	-	-

[a]for years 1999-2002.

[b]for years 2002-2007.

[c]for years 2008-2013.

Sensitivity Analysis 7: Estimated RRs Without Exclusion of Prevalent Cases

In this sensitivity analysis, we will estimate the RRs for redeemed prescriptions for psychotropic drugs as a function of night shift work and weekly working hours without exclusion of prevalent cases. The statistical methods and inclusion criteria of the analysis will otherwise be the same as in the primary analysis.

Results

We expect the analyses to be completed by the end of 2020 and the results to be published in 2021.

Discussion

In the present study protocol, we give a complete description of the hypotheses and statistical methods of a project aimed at investigating night shift work and long working hours as predictors for mental ill health in the general population of Denmark. To reduce the risk of hindsight bias and within-study selection bias, the protocol will be peer reviewed and published before we link the exposure data to the outcome data of the project. The statistical analyses are thereby blinded in the sense that all hypotheses, inclusion criteria, significance levels, and statistical models will be completely defined before we look at any relation between working time arrangements and psychotropic drugs or psychiatric hospital treatment in the datasets at hand. It should, however, be noted that the exposure data of the project have previously been analyzed in relation to circulatory disease [38,40,48,49], injuries [50], and all-cause mortality [41,42].

The clinical endpoints of the study as well as the censoring events (deaths and emigrations) will be ascertained through data in national registers, which cover all residents of Denmark. Since the outcome data are based on registers rather than follow-up interviews, we have minimized the risk of bias from missing follow-up data.

Our power calculations indicate that the power of the study is sufficiently large to test overall effects of weekly working hours and night shift work on the overall incidence rates of psychotropic drug usage and psychiatric hospital treatment for mood disorders, anxiety disorders, or stress-related disorders. It is, moreover, sufficiently large to test for interaction effects between working time arrangements on one hand and sex, age, and SES on the other on the incidence rates of psychotropic drug usage. The power to detect a difference in the distribution of mood disorder vs anxiety disorder and stress-related disorder diagnoses between participants with and without night shift work is, however, quite low. Hence, for this particular analysis, the absence of a statistically significant effect cannot be interpreted as the absence of a clinically important effect. It is, however, of interest to see if the estimated odds ratio for mood disorder vs anxiety disorder and stress-related disorder diagnoses

points in the same or opposite direction of the odds ratio for antidepressants vs anxiolytics. If it points in the same direction, it will weaken the hypothesis of "different practices for prescription of psychotropic drugs to people working in shifts compared to non-shift workers to avoid side effects that may impede wakefulness during night shifts."

An advantage of the study is that the questionnaires asked not only for the hours worked in the participants' primary jobs but also for the hours worked in secondary jobs, which enabled us to categorize the participants' working hours on the basis of the sum of the hours worked in their primary and secondary jobs. "If we had disregarded hours worked in secondary jobs, then 25.0% of the workers working 49-100 hours a week would have been misclassified as working less than 49 hours and 24.6% of the workers working 41-48 hours a week would have been misclassified as working less than 41 hours" [41].

A drawback of the questionnaires is that they did not ask for the duration of the exposure. We only know the participants' usual working hours around the time of the interview and whether they had worked at night during a 4-week period preceding the interview. It has, however, been shown that working time arrangements tend to be quite stable over time [28]. Moreover, it has been judged that the exposure to shift work as well as to long working hours are stable enough in the Danish labor force to make 5-year follow-up studies worthwhile, even if the exposure is only measured at a single timepoint [28].

Since this is an observational study, we cannot ignore the possibility of bias due to self-selection into the various working time categories. It is possible that a worker's decision and ability to work at night or to work long hours depend on his or her working environment, lifestyle, and mental health. This may be especially true when it comes to the decision and ability to work long hours. It is possible that employees with poor mental health tend to be more reluctant to work long hours than employees with good mental health, which would bias the results towards decreased rates of mental ill health among employees with long working hours. It is, however, also possible that employees with poor mental health tend to be less reluctant to work long hours. It has, for example, been shown that workaholics are highly overrepresented among people with long working hours [51]. It has, moreover, been shown that workaholism is associated with obsessive-compulsive disorders, attention deficit hyperactivity disorder, anxiety, and depression [52]. To mitigate potential healthy worker effects, we will exclude employees who redeemed a prescription for psychiatric drugs in the year preceding baseline. A residual healthy worker effect is possible since mental health problems may exist also among employees who do not use prescription drugs. In our previous studies, sensitivity analyses, in which participants with poor self-rated health at baseline were excluded, suggested that any such bias is small [23,28].

It should also be noted that participation in the Danish labor force surveys is voluntary, which provides an additional potential for self-selection bias (non-response bias). We know that response rates to questionnaires on work environmental issues and health in Denmark depend on calendar year [28], age, sex, marital status, SES, and ethnic background [53-55]. It is possible that the response rates also depend on the persons' working time arrangements as well as their mental health. If the response rates among people with poor mental health depend on their working time arrangements, the results of our analysis will be biased. Any such bias will, however, be mitigated by our decision to exclude prevalent cases, and it will be further mitigated by our decision to control for calendar year of the interview, age, sex, and SES.

Another reason to control for calendar year of the interview, age, sex, and SES is that each of these factors has been associated with indicators of mental ill health [56-60].

It has been suggested that smoking [61,62] and overweight [63] are risk factors for depression. Unfortunately, the labor force surveys do not contain any data on BMI or smoking. We can therefore not control for these factors in the analyses. We have, however, previously examined the relationship between night shift work, long working hours, and prevalences of smoking, overweight, and BMI in our target population [38]. The study indicated that weekly working hours are independent of smoking and BMI. However, among employees with vs without night shift work, we found that the prevalences were higher among night shift workers for smoking (25.8% vs 21.6%), overweight (38.4% vs 34.5%), and obesity (15.4% vs 12.7%). The risk ratio of depression has been estimated at 1.46 (95% CI 1.03-2.07) for smokers vs non-smokers [61], 1.08 (95% CI 1.02-1.14) for overweight vs normal weight, and 1.57 (95% CI 1.23-2.01) for obesity vs normal weight [63]. Based on these numbers and some high school algebra, we estimate that the effect of not controlling for smoking and BMI will bias an estimated RR of depression among employees with vs without night shift work upwards by a factor of 1.03, and this needs to be taken into account when the results of the present study are evaluated.

Another drawback of the labor force surveys is that they do not contain any data on work-environment factors. A sensitivity analysis in a previous study showed, however, that after adjustment for age, sex, and SES, the RR for incident use of psychotropic drugs as a function of working time arrangements did not change when the analyses were further controlled for job satisfaction and job insecurity [23,28].

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Authors' Contributions

KA obtained the funding. KA, MLN, and HH designed the statistical analyses and prepared the first draft of the manuscript. All authors participated in the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

DLFS: Danish Labor Force Survey.
OECD: Organization for Economic Co-operation and Development.
RR: rate ratio.
SES: socioeconomic status.

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Protocol

Morbidity Prevalence Estimate at 6 Months Following a Stroke: Protocol for a Cohort Study

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Abstract

Background: Knowledge of the prevalence of morbidity secondary to stroke is important for health care professionals, health care commissioners, third sector organizations, and stroke survivors to understand the likely progress of poststroke sequelae and to aid in commissioning decisions, planning care, and adjusting to life after stroke.

Objective: The primary aim of the Morbidity PRevalence Estimate In StrokE (MORe PREcISE) study is to determine the prevalence of morbidity secondary to a stroke, predictors of morbidity, and trends in quality of life and functional status using patient-reported outcomes, cognitive and functional assessments.

Methods: A total of 500 participants will be recruited across Wales and England within 14 days following an admission to a stroke unit for either an ischemic or hemorrhagic stroke as part of a multicenter cohort study. Participants are assessed at baseline ≤14 days poststroke and subsequently at 90 (± 14) days and 180 (± 14) days poststroke. At each time point, data will be collected relating to the following domains: participant demographics, routine clinical, patient reported, cognitive status, emotional well-being, and functional ability.

Results: Recruitment commenced in October 2018 with 20 sites opened as of September 2019 and was closed on October 31, 2019.

Conclusions: The primary outcome is the prevalence of morbidity at 6 months secondary to a stroke. Further analysis will consider temporal changes in the health-related domains to describe trends among baseline, 3-, and 6-month time points.

Trial Registration: ClinicalTrials.gov NCT03605381; https://clinicaltrials.gov/ct2/show/NCT03605381

International Registered Report Identifier (IRRID): DERR1-10.2196/15851

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KEYWORDS

stroke; prevalence estimate; morbidity; disability; PROMs; outcomes; quality of life (QoL)

Introduction

Stroke Morbidity

There are 1.2 million stroke survivors currently living in the United Kingdom [1]. Although mortality as a consequence of stroke is decreasing [1,2], over two-thirds of stroke survivors have a form of disability on discharge from hospital [3]. During a stroke, hypoxic injury leads to neuronal death [4,5], which can occur in potentially any part of the brain. Thus, due to the diverse functions of the brain, stroke can lead to significant impairments to diverse functions and structures of the body, resulting in a significant prevalence of morbidity secondary to stroke [6].

The prevalence of morbidity secondary to stroke is of central importance to health professionals to understand the prognosis of the disease in patients under their care. Further, providing an accurate estimation of the prevalence of morbidity secondary to stroke will allow commissioners of care, planners, and third sector organizations to adapt to and answer the needs of a poststroke population. Additionally, information regarding the likely progression of impairments secondary to stroke is important to stroke survivors, allowing them to plan for the future and to adjust to life after stroke.

Measures of Morbidity

Expanding data collection beyond current routinely collected data in stroke relates to the work undertaken by the International Consortium for Health Outcomes Measurement (ICHOM) [7] and their minimum outcome dataset for stroke [8]. In the ICHOM Standard Set for Stroke, a number of, what ICHOM terms, “variables” (demographic, clinical, and treatment) and “outcomes” (survival, disease control, and patient reported) are included. The ICHOM Standard Set for Stroke takes important steps to collect data outside of the process of care data in areas such as patient-reported outcome data, which includes domains such as toileting, walking, and assistance with feeding. However, the ICHOM group does not advocate the specific collection of data related to cognitive impairment or emotional problems secondary to stroke. This study will address this by the inclusion of measures of emotional problems and mild cognitive impairment. Therefore, the scope of this study is to build on routinely collected health care and poststroke data not currently collected by the ICHOM Standard Set for Stroke for the purpose of estimating morbidity prevalence.

Aims and Objectives

This paper describes the protocol for the Morbidity Prevalence Estimate at 6 Months Following a Stroke (MORe PREcISE) study (ClinicalTrials.gov NCT03605381—Registered: 30/07/19). The primary objective is to determine the prevalence of morbidity at 6 months secondary to a stroke, predictors of morbidity, trends in health-related quality of life (HRQoL), and function. The definition of morbidity secondary to stroke includes the following: aphasia, anxiety, depression, dysarthria, dysphagia, hemianopia, hemiparesis, hemiplegia, hemi-inattention, cognitive impairment, and functional impairment including activities of daily living and social interaction or roles.

Therefore, this study will collect a wide range of data related to the most common morbidity secondary to stroke, from stroke onset to 6 months poststroke across England and Wales. The secondary objectives include describing trends in domains such as HRQoL from acute onset to 6 months poststroke. It will also explore trends in pre- and poststroke functional levels, as assessed by the Modified Rankin Scale (mRS) [9] from the prestroke period to 6 months poststroke. Lastly, trends in outcomes (patient reported, functional, treatment, and process of care) by geographical distribution, such as country, health board/trust, local authority, and hospital (research site) coverage, will be explored.

Methods

Study Design

This study uses a 6-month prospective cohort study of stroke survivors and aims to recruit 500 participants between August 2018 and October 2019. Data measuring morbidity will be collected at three distinct periods: baseline (≤14 days poststroke), 3 months, and 6 months poststroke. This takes place in 20 centers across England and Wales which routinely admit acute or hyperacute stroke patients (Textbox 1). All sites were selected after expressing an interest via the National Health Service (NHS) research networks, and the geographic spread was considered during site selection.

Textbox 1. Participating research sites.

Participants:

- Aneurin Bevan University Health Board, South East Wales, United Kingdom
- Bronglais General Hospital, Aberystwyth, Wales, United Kingdom
- Glangwili General Hospital, Carmarthen, Wales, United Kingdom
- Gloucestershire Royal Hospital, Gloucester, England, United Kingdom
- Kingston Hospital, London, England, United Kingdom
- University Hospital of Wales, Cardiff, Wales, United Kingdom
- Morriston Hospital, Swansea, Wales, United Kingdom
- New Cross Hospital, Wolverhampton, England, United Kingdom
- Oxford University Hospitals, Oxford, England, United Kingdom
- Peterborough City Hospital, Peterborough, England, United Kingdom
- Prince Charles Hospital, Merthyr Tydfil, Wales, United Kingdom
- Princess of Wales Hospital, Bridgend, Wales, United Kingdom
- Somerset Partnership (SOMPAR), Somerset, England, United Kingdom
- Southmead Hospital, Bristol, England, United Kingdom
- University Hospital Lewisham, London, England, United Kingdom
- West Middlesex University Hospital, London, England, United Kingdom
- Withybush General Hospital, Haverfordwest, Wales, United Kingdom
- Wrexham Maelor Hospital, Wrexham, United Kingdom
- Yeovil District Hospital, Yeovil, England, United Kingdom
- Ysbyty Glan Clwyd, Bodelwyddan, Wales, United Kingdom

Participants and Eligibility Criteria

Participants eligible to be recruited for this study include those aged 18 years or over with a clinical diagnosis of stroke, within the previous 14 days; cerebral infarct (ICD I63) [10]; intracerebral hemorrhage (ICD I61) [10]; or stroke not specified as hemorrhagic or infarction (ICD I64) [10]. Exclusion criteria include a diagnosis of transient ischemic attack (ICD G45) [10], subarachnoid hemorrhage (ICD I60) [10], or any condition defined under ICD G93 (eg, anoxic brain damage) [10]. Patients receiving palliative care or are eligible for palliative care are also excluded from this study.

Sample Size

In order to estimate the prevalence of stroke morbidity at 6 months, assuming a 35% morbidity rate, with a 95% CI width of ±5%, will require 350 stroke survivors. Assuming that there is a 30% dropout [11] at the 6-month visit, the aim is to recruit a minimum of 500 stroke survivors. This will be achieved by aiming to approach all appropriate inpatients fulfilling the eligibility criteria across the 20 sites. Stata Statistical software will be used for the analyses.

Outcomes

The primary outcome is to quantify the prevalence of poststroke morbidity, at three time points, using a range of assessments and outcome measures, which are as follows:

- Patient-reported outcomes:
  - Patient-Reported Outcomes Measurement Information System Global Health Short Form-10 (PROMIS-10) [12].
  - Three Questions from the Riksstroke [13].
  - Two Questions from the ICHOM Standard Stroke Set for Stroke [8].
- Cognitive status:
  - Short-Form Montreal Cognitive Assessment (SF-MoCA) [14] (domains, clock drawing, abstraction, five-word recall).
  - Telephone Montreal Cognitive Assessment Short (T-MoCA-Short) [15] (domains, verbal fluency, orientation, five-word recall).
- Emotional well-being:
  - Patient Health Questionnaire-4 (PHQ-4) [16].
  - PHQ-9 [17].
  - Generalized Anxiety Disorder-7 (GAD-7) [18].
- Functional ability:
  - Modified Rankin Scale [9].
  - Rankin Focused Assessment (RFA) [19].
- Treatment:
  - Recurring stroke (cerebral infarct [ICD I63]), intracerebral hemorrhage [ICD I61], and stroke not specified as hemorrhage or infarction [ICD I64] [10].
- Process:

- Length of stay following primary admission for stroke.
- Readmission to hospital within 30 days of discharge.

Data Collection

Following enrolment into the study, data collection is divided into three distinct periods: Period A (within 14 days from the onset of stroke), Period B (90 days poststroke ± 14 days), and Period C (180 days poststroke ± 14 days) as per the participant flow diagram (Figure 1). A standardized SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) [20] schedule of assessments is presented in Figure 2.

Figure 1. Participant flow diagram. Electronic Case Report Form/Case Report Form (eCRF/CRF).

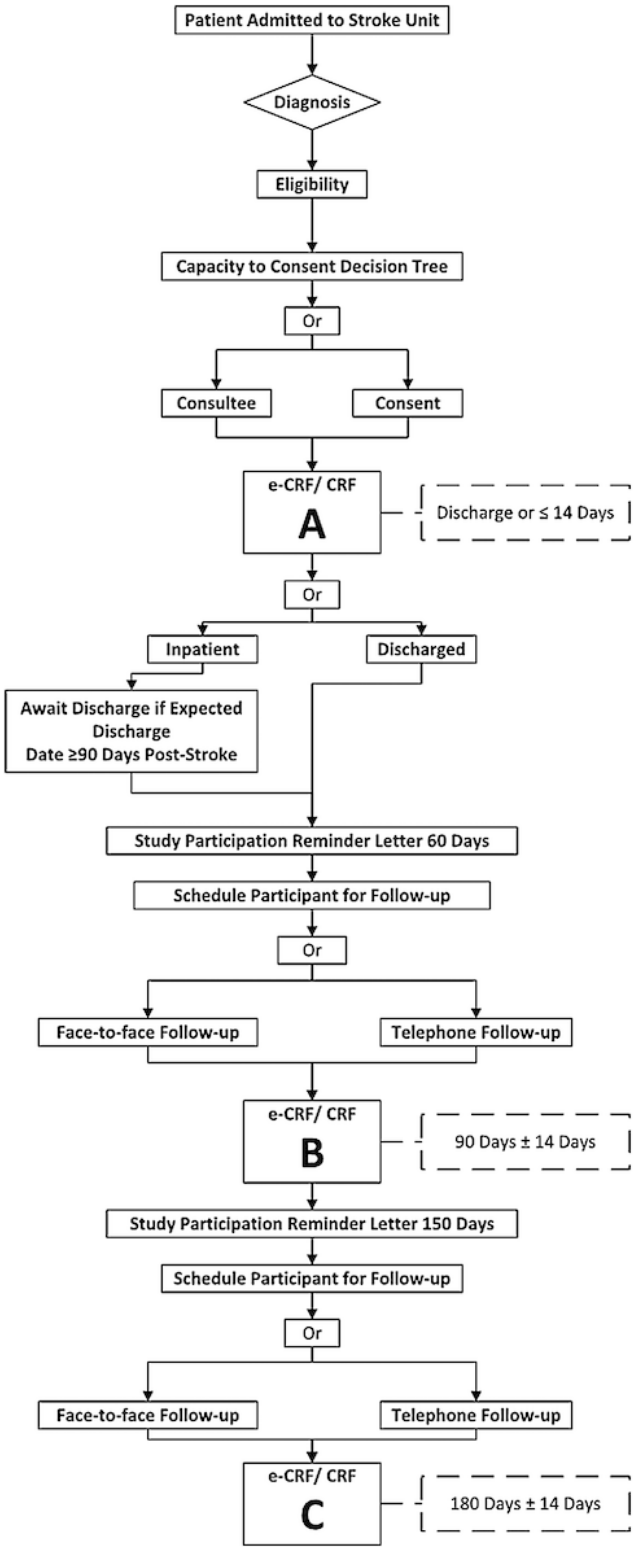

Figure 2. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist. SF MoCA: Short-Form Montreal Cognitive Assessment; T-MoCA-Short: Telephone Montreal Cognitive Assessment Short; PROMIS-10: Patient-Reported Outcomes Measurement Information System Global Health Short Form-10; ICHOM: International Consortium Health Outcomes Measurement; PHQ-4: Patient Health Questionnaire-4; GAD-7: Generalized Anxiety Disorder-7; PHQ-9: Patient Health Questionnaire-9; mRS: Modified Rankin Scale; RFA: Rankin Focused Assessment.

	STUDY PERIOD			
	Enrolment	Post Recruitment		
TIMEPOINT POST-STROKE	0-14d	0-14d	90 d	180d
ENROLMENT:				
Eligibility Screen	X			
Informed Consent	X			
Consultee Advice	X			
ASSESSMENTS:				
Demographics – [DOB MM/YYYY, Sex, District Level Postcode, Type of Education, Primary Language]		X		
Pre-Stroke Lifestyle – [Smoker, Alcohol Consumption, Lives Alone, Type of Care Received]		X		
Post-Stroke Lifestyle – [Discharge, Smoker, Alcohol Consumption, Lives Alone, Type of Care Received]			X	X
Pre-Stroke Clinical – [Previous TIA, Previous Stroke, Type II Diabetes Mellitus, Atrial Fibrillation, Hypertension, Blindness]		X		
Post-Stroke Clinical – [Date of Index Event, Stroke Type, NIHSS on Arrival, Thrombolytic Therapy, Intra-arterial intervention (thrombectomy)]		X		
Post-Stroke Sequelae – [Aphasia, Dysphagia, Dysarthria, Hemiplegia, Hemiparesis, Hemi-inattention, Hemianopia]		X		
Short Form Montreal Cognitive Assessment (SF MoCA)		X		
Telephone Montreal Cognitive Assessment Short (T-MoCA Short)			X	X
PROMIS-10		X	X	X
2 ICHOM Questions		X	X	X
3 RiksStroke Questions		X	X	X
PHQ-4		X	X	X
If PHQ-4 Positive GAD-7		X	X	X
If PHQ-4 Positive PHQ-9		X	X	X
Pre-Stroke Modified Rankin Scale (mRS)		X		
Post-Stroke Rankin Focused Assessment (RFA)		X	X	X
[Death, Recurring Stroke, Re-hospitalisation]		◆———		———◆

Period A—Within 14 Days of Stroke Onset

Period A begins following consent or following consultee declaration with data collection attempted as soon as possible during the participant's admission. Baseline data collection will occur at 14 days or less poststroke and before discharge from hospital. All data will be collected using Case Report Form A (CRF A). There is a further window of 24 hours available for data collection if necessary. Baseline data will not be recorded outside these time points. Additionally, provided consent was received before discharge, data collection from the participant may occur after discharge to the community if no opportunity arose prior to discharge.

The baseline data collected comprise participant demographic and routine clinical data including their prestroke lifestyle data, cognitive assessment, Patient Reported Outcome Measure (PROM), and anxiety and depression screen. Demographic data are collected via medical notes or a care team and then confirmed by the participant or participant's family or friends. An equivalent process will be undertaken to gather prestroke lifestyle data.

During baseline data collection, a cognitive screen will be administrated in the form of a SF-MoCA [14]. Alongside this assessment, the participants are required to self-complete a PROM using the PROMIS-10 [12], Riksstroke questions [13], and ICHOM questions [8]. Participants will also self-complete a PHQ-4 [16]. If the PHQ-4 is positive, as indicated by a score ≥3 for the sum of questions 1 and 2 or 3 and 4, for anxiety or depression, the patient will then self-complete the PHQ-9 [17] and GAD-7 [18]. If the participants are unable to self-complete, the study allows for assessments or outcomes to be administered verbally.

To gain a representation of any prestroke disability in participants, a prestroke mRS [9] will be completed. This must be carried out by a suitably trained health care professional. RFA [19] will be carried out by a suitably trained health care professional for an estimate of the level of poststroke disability.

60 Days Poststroke (± 7 Days)

Between Periods A and B at 60 days poststroke, it should be established whether the participant remains as an inpatient or is discharged. It should be ascertained whether the participant has deceased, had another stroke, or is eligible for or already receiving palliative care. In the case of further stroke or palliative status, a serious adverse event (SAE) form should be completed and the participant should be withdrawn from the study. In the event of an unscheduled admission, an adverse event or SAE form should be completed and the principal investigator (PI) should be informed. The PI makes the decision regarding whether the participant should continue to participate or be withdrawn from the study. Participants themselves or their consultees have the right to withdraw from the study at any time, without providing a reason.

The research site team will ensure the accuracy of participant's address and contact details on file, which may be confirmed using primary and secondary care–linked health records to ensure accuracy. To ensure participant retention, following these checks, a study involvement reminder letter should be sent to the participant's home address, provided they have been discharged.

Period B—90 Days Poststroke (± 14 Days)

At this point, within the study, it is expected that a large proportion of participants will reside in the community. Therefore, participants are to receive study follow-up via either telephone or face-to-face appointment [21]. Telephone appointments should be scheduled with the participant to complete the patient-reported aspect of CRF B via the telephone. Follow-up appointments should be arranged to fall within the 90 days (± 14 days) poststoke window of opportunity, and a maximum of three attempts should be made to contact the participant. In circumstances where three unsuccessful attempts have been made to contact the participant or if the window of opportunity has elapsed, then the participant is to be considered lost to follow-up.

Face-to-face appointments can be used by research sites as a first preference. Participants with either or both communication difficulties and prestroke or poststroke cognitive impairment should be offered the option of either face-to-face or telephone appointments. The face-to-face follow-up appointments should be conducted in accordance with procedures outlined in Period A (≤14 days poststroke) data collection.

If participants are yet to be discharged from the hospital by 90 days (± 14 days) poststroke or have been rehospitalized, for reasons other than further stroke, then participants can also be followed up with CRF B but in line with procedures outlined in Period A (≤14 days poststroke) data collection.

150 Days Poststroke (± 7 Days)

This occurs between Periods B and C at 150 days poststroke (± 7 days). The procedure is identical to that outlined in the 60-day poststroke section of this protocol paper, which should be repeated at the 150-day poststroke (± 7 days) time point.

Period C—180 Days Poststroke (± 14 Days)

Data collection at this point is identical to Period B (90 days poststroke). The procedure for this period should be repeated exactly as outlined in the Period B section of this protocol paper using CRF C at the 180-day poststroke (± 14 days) window of opportunity.

Long-Term Data Collection

Further funding may be sought to obtain repeat data measurement at future time points, in keeping with the recommendation of the ICHOM Standard Set for Stroke. Currently, there are no defined plans for these types of data collection, but all data will be collected using assessments and outcome measures as outlined in the protocol presented in Figure 2.

Completion of Assessments, Screens, and Patient-Reported Outcomes

Response options for these data are either complete or incomplete and whether the participant is able or unable to self-complete the relevant PROMs, cognitive screen, and anxiety and depression screen. If the participant is unable to self-complete, then the reason for non–self-completion is to be recorded. Where participants cannot self-complete but are able to give verbal responses, then baseline data collection of PROMs, assessments, and screens are to be administered verbally to ensure that all questions are completed. If the participant is unable to give responses when verbal administration is attempted, the reason for this noncompletion should be recorded on the CRF. Reasons for both non–self-completion and noncompletion of verbal administration should be identified as either potentially cognitive or physical impairment.

Cognitive Causes of Noncompletion

Cognitive causes of noncompletion should be recorded on the CRF, and no further attempt at patient-reported data collection should be made at this time. Cognitive causes of noncompletion include, but are not limited to, the following: confusion,drowsiness, history of dementia, aphasia—expressive or receptive, and anosognosia.

Physical or Visual Causes of Noncompletion

If the suspected reason for non–self-completion is physical or visual impairment, then the participant is to be provided assistance to complete the PROMs, cognitive screen, and anxiety and depression screen. The administrator should read the question and note down the response. However, there should be no deviation from the wording of the questions or response options. Potential physical or visual deficits that could be expected are as follows: hemiparesis, hemiplegia, hemi-inattention, and hemianopia.

During Periods B and C, if the participant is unable to complete the PROM, cognitive screen, or anxiety and depression screening questions via telephone, a decision about whether a suitable alternative follow-up method is appropriate should be made. This is to be based on clinical judgment, provided the participant still wishes to continue in the study.

During collection of data, the use of secondary sources to aid data collection is permitted for the following; demographic, clinical, lifestyle, poststroke sequelae and functional assessments. The participant's family, friends, care team, or medical notes are permissible sources of consultation. However, secondary sources are not permitted to aid the completion of the patient-reported data such as cognitive screen, PROM, or anxiety and depression screen.

Data Analysis

The objective of this study is to estimate the prevalence of morbidity at 6 months with a 95% CI width of ±5%.

The study will be deemed to have ended following the collection of data for Period C from the last participant registered in the study. All participants recruited in the study will be included in the analysis population. All clinical characteristics will be presented in a descriptive narrative.

Morbidity Prediction

Baseline clinical and patient demographic variables will be used to predict the mediating effects of a patient exhibiting poststroke morbidity.

Continuous outcomes are analyzed using a mixed-effects linear model, and binary outcomes are analyzed using logistic regression. All estimates will be presented with 95% CI. Sites will be fitted by a random intercept model. For outcomes that analyze at a single time point, we will fit a single random intercept of patients nested within the site using a random intercept model. Moreover, we will be fitting a three-tier multilevel model, including two random intercepts. Multiple patient time points will be fitted within a patient, and the patient will be fitted within a site. Statistical analysis will be performed using Stata Statistical software (StataCorp LLC).

Psychometric Analysis

The patient-reported outcomes will be assessed for the following psychometric properties: validity (content validity and convergent validity) and reliability (internal consistency).

Missing Outcome Data

Due to the nature of our data collection methods, and evidence from previous studies of this nature, we anticipate negligible missing instrument levels, and in this case, a complete case analysis will be carried out. If the level of missing outcome data is not considered negligible (>5%), missing data will be explored for patterns of missingness and may be imputed using appropriate methods. Imputation methods will depend on the proportion of missingness and reason for the missing data.

Ethical and Regulatory Considerations

Ethical approval has been granted by an NHS Research Ethics Committee (REC; 18/WA/0299) before recruitment for the study began. The NHS REC has reviewed the study protocol and all relevant trial materials. Where necessary, the REC will review any amendments or alterations to the study design or conduct.

The protocol was developed using the SPIRIT guidelines [20] and a completed SPIRIT checklist is included Multimedia Appendix 1.

Amendments

Amendments will be internally reviewed at the coordinating center, and no study amendments will proceed without prior approval of the study sponsor. Amendments that require review by NHS REC will not be implemented until full REC approval has been obtained for the amendment under review and the local participating NHS organization approvals are in place to implement the amendment at the research site. The coordinating center will work with the participating research site to ensure that the necessary arrangements are in place to implement the amendment. The full amendment history of the study protocol will be tracked in the appropriate section of the protocol.

Data Management

Data will be collected by appropriate health care staff appointed by the PI, and training will be provided by the study team for the delivery and use of assessments required to complete the data collection. A secure online data input and management system is used for all study data. Regular data inspection and quality control will be performed throughout the lifetime of the study. Research sites will retain identifiable study data securely for a minimum of 5 years. Anonymous study data at the study office level will be held for 10 years in line with the sponsor's requirements. The data custodians will work together to establish a suitable trial data repository for the anonymized study dataset following the conclusion of primary and secondary data analyses.

Data Monitoring and Oversight Committee

The Data Monitoring and Oversight Committee (DMC) will convene to oversee the study by providing independent scrutiny of the progress and conduct of the study. The committee consists of a funder's representative, sponsor's representative, patient

representative/s, and an independent member. The patient's representative/s will be stroke survivor/s or relative/s or carer/s of a stroke survivor with an interest in stroke care or research. The independent member will be an academic (clinical academic or academic involved in the design and conduct of clinical research) or a suitably qualified health care professional with experience, knowledge, and understanding of the design and conduct of clinical research. Moreover, the independent member will have no institutional affiliation with the chief investigator, coinvestigators, research team at the coordinating center, sponsor, or funder nor will the independent member be involved in the design or conduct of the study. All independent members of the DMC listed previously will have full voting rights.

Study Sponsor and Funder

The sponsor, Aneurin Bevan University Health Board, will provide institutional level support for this study. They will ensure safe and proper conduct of the study in line with the International Conference on Harmonization Guideline for Good Clinical Practice and the Declaration of Helsinki [22] and reserve the right to audit all study documents and standard operating procedures at the coordinating center and research sites. The sponsor and the funder (Stroke Implementation Group of the Welsh Government) are entirely independent of the study and have no influence or involvement in the trial design or decision to publish results.

Protocol Compliance

Compliance with the protocol and study procedures must be monitored at the research site by the PI, whereas compliance of all study sites will be monitored by the coordinating center, study sponsor, and DMC. Deviations will be monitored by the supplied deviation log, and all deviations must be reported to the study coordinating center within 24 hours of the discovery of the deviation.

All deviations should be reported to the PI at the research site, and all deviation logs are to be ratified by the PI at the research site before they are reported to the coordinating center. The coordinating center will classify the nature of the deviation and will either request the completion of the corrective and preventive action (CAPA) form or, depending on the severity of the deviation, may escalate the deviation to the study sponsor, DMC, local NHS organization research and development department, and national research authority. Adherence to the CAPA outlined in the CAPA form is ultimately the responsibility of the PI. Where deviations from the protocol are found to reoccur, immediate action will be required and such instances could potentially be classified as a serious breach of the protocol or Good Clinical Practice (GCP). Moreover, where deviations are previously the subject of a CAPA, they will be reviewed by the coordinating center, study sponsor, and potentially the DMC. Continued deviations, especially those deviations previously resulting in a CAPA, may be escalated to the local NHS organization's Research and Development department, which is the national research authority and may result in the suspension of recruitment at the research site.

Serious breaches of GCP or protocol should also be self-referred by the PI at the research site to the appropriate research governance authority, in line with the applicable local and national guidelines.

Access to the Final Study Dataset

Access to the final deidentified study dataset will be restricted to the chief investigator, coinvestigators, data manager, and study sponsor. Granting access to the final deidentified study dataset to third parties must be unanimously agreed by the chief investigator and study sponsor. Thus, the chief investigator and the study sponsor will jointly hold the role of data custodians for the study. All requests to access the final study dataset are to be made formally in writing to all those acting as data custodians, whereby all intended analyses are outlined clearly. Acting as a PI this does not grant the individual named as PI at the research site the right to utilize any data arising from the trial. Those PIs wishing to utilize any data resulting from the trial must formally request, in writing, permission to analyze any part of the data arising from the study. Access to the final data will only be granted with the unanimous agreement of the data custodians. Those given access to the final study dataset are only permitted to undertake analyses as outlined in the formal request. A further formal request must be made to the data custodians to adapt, change, or run new analyses not outlined in previous formal requests. The data custodians will work together to establish a suitable trial data repository for the anonymized study dataset following the conclusion of all primary and secondary data analyses

Consent

Informed Consent

All potentially eligible participants will have the capacity to offer valid and informed consent assessed. Potentially eligible participants who do not have the capacity to offer informed consent can also take part in the study through the use of a consultee, thereby ensuring that the study cohort is representative of the poststroke population.

In line with the Mental Capacity Act (2005) England and Wales [23], the potentially eligible participant's capacity to consent will be presumed unless it is established otherwise. Informed consent will be sought from those potentially eligible participants, where a lack of capacity to consent could not be established as outlined under the Mental Capacity Act (2005) [23].

All potentially eligible participants with the capacity to consent are to be presented with the most current version of the participant information sheet and given a minimum of 24 hours to consider their participation in the study and ask questions or request clarifications. Following this period, written informed consent will be sought from all potential participants with the capacity to consent from the PI or a registered health care professional delegated by the PI.

Aphasia or Communication Difficulties

Participants who present with or have a known diagnosis of aphasia or communication difficulties and have the capacity to provide informed consent should be approached using the latest version of the aphasia or communication difficulty–specific participant information sheet.

Limb Weakness or Paralysis

If a patient is unable to sign the consent form due to limb weakness or paralysis but has the capacity to provide informed consent, then oral consent will be taken in the presence of a witness, who must not be involved in the study in any capacity. The witness must sign the designated witness consent area on the consent form on behalf of the participant.

Consultee

A consultee must be sought when a potential participant who, under the provisions of the Mental Capacity Act (2005) [23], cannot provide informed consent. The consultee is to be provided with the most current version of the consultee information sheet and should be given a minimum of 24 hours to consider the wishes of the potential participant. Following this period of reflection, a written declaration must be obtained from the consultee if he/she believes the potential participant would have no objections to taking part in the study. Those participants who do not regain the capacity to consent are to remain under the consultee declaration for the duration of the study. The consultee has the right to advise the withdrawal of the participant from the study at any time without giving a reason. Moreover, participants have the right to withdraw their participation at any time if they indicate signs of unwillingness to participate.

Regaining Capacity to Offer Informed Consent

The loss of capacity to offer informed consent should not be considered as a fixed state, and the assessment of capacity to offer informed consent should not be considered as a final decision to be applied across the whole of the study period. Consultees should be informed that they are to make the study team aware if they believe the participant has regained the capacity to offer informed consent. Participants suspected of regaining capacity to offer informed consent are to be given the most recent version of the regained capacity participant information sheet and 24 hours to consider their continued participation in the study and to ask any questions or clarifications. Subsequently, the participant should be asked to provide informed consent. Alternatively, if a participant wishes to decline continued participation, he/she should be withdrawn from the study. Anonymized data collected prior to withdrawal will be used in the study analysis.

Loss of Capacity to Offer Informed Consent

Where it is determined that a participant has lost his/her capacity to offer informed consent, help should be sought from the appointed consultee. Nominated consultees will be made aware of their status as a nominated consultee when the participant initially consents to the study. Therefore, the nominated consultee is to be provided with the appropriate information sheet and given 24 hours to consider if he/she believes that the participant has no objections to continuing to participate in the study. Following the period of reflection, where the consultee believes that the participant would have no objections to continuing in the study, he/she will complete a consultee deceleration form. If the consultee believes that the participant would not want to continue to participate in the study, then the participant should be withdrawn. All anonymized data collection prior to withdrawal will be utilized in the study analysis.

Further Contact

All consent and consultee declaration forms include an optional section, which asks participants or consultees to consent to or declare to being contacted at future time points poststroke to seek further consent or consultee declaration to participate in answering longer-term follow-up questions for the study.

Confidentiality

Data will be collected and stored in line with the General Data Protection Regulations [24]. Following the receipt of informed consent, each participant will be anonymized and assigned a unique 6-digit Participant Research Number (PRN). Data collected for each participant will be stored alongside their PRN. These tables will not contain any identifiable information from participants. A separate database linking the PRN to the participant's NHS number will be stored at the research site. This database will be encrypted and restricted to named researchers only under the direct supervision of the PI. Information shared by the research team to the lead researchers outside of the individual research site will be completely anonymized, and lead researchers will only have access to data stored against the PRN. Following the conclusion of the study, the anonymized data will be archived for a period of 10 years in line with the sponsor's requirements.

Results

Recruitment opened in October 2018, with 536 participants recruited and 20 sites opened in England and Wales as of September 2019. Patient recruitment was closed on October 2019, with follow-up occurring until April 2020. Data analysis is scheduled to start after all data have been collected, with an aim to publish a peer-reviewed article in late 2020.

Discussion

This study aims to assess morbidity poststroke using patient-relevant outcome measures. Assessment of morbidity in stroke survivors will indicate the prevalence and type of morbidity to allow for the concentration of support needed for stroke survivors in these areas.

The research team will plan a longer term follow-up of participants of the MORe PREcISE study to explore further changes in morbidity, outcomes, and quality of life.

Acknowledgments

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The funder (the Stroke Implementation Group of the Welsh Government) had no part in the design of the study and will not be involved in the analysis or interpretation of the study results or writing of the report. The study design was reviewed by independent expert reviewers on behalf of the research funder. Moreover, the study design, protocol, and all research documents were expert reviewed by the study sponsor.

Authors' Contributions

JH, AS, and BC designed the study. AS developed the protocol. AS, BC, and JH contributed to the refinement of the study protocol. All authors have read and commented on the drafts of the study protocol and gave approval to the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 308 KB - resprot_v9i6e15851_app1.pdf]

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Abbreviations

CAPA: corrective and preventative action
CRF: case report form
DMC: Data Monitoring and Oversight Committee
GAD-7: Generalized Anxiety Disorder-7
GCP: Good Clinical Practice
HRQoL: health-related quality of life
ICD: International Classification of Diseases
ICHOM: International Consortium Health Outcomes Measurement
MoCA: Montreal Cognitive Assessment
mRS: Modified Rankin Scale
NHS: National Health Service
PHQ-4: Patient Health Questionnaire-4
PHQ-9: Patient Health Questionnaire-9
PI: principal investigator
PRN: Participant Research Number
PROM: Patient-Reported Outcome Measure
PROMIS-10: Patient-Reported Outcomes Measurement Information System Global Health Short Form-10
REC: Research Ethics Committee
RFA: Rankin Focused Assessment
SF MoCA: Short-Form Montreal Cognitive Assessment
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
T-MoCA-Short: Telephone Montreal Cognitive Assessment Short

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Protocol

Prediction Model for Timing of Death in Potential Donors After Circulatory Death (DCD III): Protocol for a Multicenter Prospective Observational Cohort Study

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Abstract

Background: Controlled donation after circulatory death (cDCD) is a major source of organs for transplantation. A potential cDCD donor poses considerable challenges in terms of identification of those dying within the predefined time frame of warm ischemia after withdrawal of life-sustaining treatment (WLST) to circulatory arrest. Several attempts have been made to develop models predicting the time between treatment withdrawal and circulatory arrest. This time window determines whether organ donation can occur and influences the quality of the donated organs. However, the selected patients used for these models were not always restricted to potential cDCD donors (eg, patients with cancer or severe infections were also included). This severely limits the generalizability of those data.

Objective: The objectives of this study are the following: (1) to develop a model predicting time to death within 60 minutes in potential cDCD patients; (2) to validate and update previous prediction models on time to death after WLST; (3) to determine timing and patient characteristics that are associated with prognostication and the decision-making process that leads to initiating end-of-life care; (4) to evaluate the impact of timing of family approach on organ donation approval; and (5) to assess the influence of variation in WLST processes on postmortem organ donor potential and actual postmortem organ donors.

Methods: In this multicenter observational prospective cohort study, all patients admitted to the intensive care unit of 3 university hospitals and 3 teaching hospitals who met the criteria of the cDCD protocol as defined by the Dutch Transplant Foundation were included. The target of enrolment was set to 400 patients. Previously developed models will be refitted in our data set. To further update previous prediction models, we will apply least absolute shrinkage and selection operator (LASSO) as a tool for efficient variable selection to develop the multivariable logistic regression model.

Results: This protocol was funded in August 2014 by the Dutch Transplant Foundation. We expect to have the results of this study in July 2020. Patient enrolment was completed in July 2018 and data collection was completed in April 2020.

Conclusions: This study will provide a robust multimodal prediction model, based on clinical and physiological parameters, that can predict time to circulatory arrest in cDCD donors. In addition, it will add valuable insight in the process of WLST in cDCD donors and will fill an important knowledge gap in this essential field of health care.

Trial Registration: ClinicalTrials.gov NCT04123275; https://clinicaltrials.gov/ct2/show/NCT04123275

International Registered Report Identifier (IRRID): DERR1-10.2196/16733

(JMIR Res Protoc 2020;9(6):e16733) doi:10.2196/16733

KEYWORDS

organ donation; tissue and organ procurement; clinical prediction rule; donation after circulatory death; clinical protocols; withdrawal of life-sustaining treatment; end-of-life care; organ transplant; circulatory death; cohort study; intensive care unit; organ donor

Introduction

Background

There is a worldwide shortage of deceased organ donors. Controlled donation after circulatory death (cDCD) is an increasing source of organs for transplantation. In the Netherlands, 59% of the effectuated postmortem organs were from cDCD donors. An increasing number of countries worldwide are establishing a cDCD program. The proportion of organ donations from cDCD donors compared to brain death donors is projected to increase in the upcoming years [1].

However, there are major challenges specific to the cDCD program. First, these patients are not brain-dead and organ donation can only occur after circulatory death (cardiac arrest). As such, withdrawal of life-sustaining treatment (WLST), including stopping mechanical ventilation, should occur to allow circulatory arrest. The time between WLST and circulatory arrest determines whether organs can be donated or not. In most countries, this time is set at a maximum of 1 or 2 hours to preserve organ quality for transplantation purposes. If patients do not arrest within this time frame, organ donation cannot occur. One of the hurdles of cDCD donations is to predict which patients will arrest within the specific time frame. This directly affects family guidance as the treating team and families have to manage family expectations, especially when failure to donate occurs because patients do not arrest within the specified time frame after WLST. Finally, inaccurate prediction of time to circulatory death also influences efficient utilization of the organ procurement and transplantation teams; after WLST is started, these teams need to be fully prepared and present in the operating room to manage recovery and transplantation of organs if the potential donor dies within the given time frame [2].

Factors associated with early circulatory arrest after treatment withdrawal include a younger age, being on artificial ventilation without spontaneous triggering by the patient, needing a high percentage of oxygen, the use of vasopressors, the absence of brain stem reflexes, and a low arterial pH [3]. Interestingly, there are studies that suggest that the use of analgesics or sedatives does not significantly influence the timing of death [4-6].

Several attempts have been made to develop models that predict the time between treatment withdrawal and circulatory arrest [3,7-10]. Two predictive models, the University of Wisconsin Donation After Cardiac Death Evaluation tool and the United Network for Organ Sharing (UNOS) scoring system, were developed in the United States, but neither have been fully validated for practice in European countries [11,12]. The usability of these predictive models is limited as there is a 50% failure of predicting time to death within 1 hour of WLST [13]. The 1-hour time frame is used in many countries as a cutoff to exclude the harvesting of organs from cDCD donors. The DCD-N model, developed from a patient population dying from a neurologic condition, reached 72% accuracy [14-16]. This still means that nearly 30% of patients would not be correctly identified using the DCD-N model. In addition to the limited accuracy, patients with known contraindications to organ donation were included in most previous prediction studies (eg, patients with end-stage cancer and severe infections). This greatly hampers the generalizability of such models [14].

Another important factor that could affect donor potential is end-of-life treatment. The practice of WLST is highly variable between intensive care units (ICUs) and countries [13,17,18]. This influences the dying process and possibly the timing of circulatory arrest. To our knowledge, none of the previously published prediction modelling studies thoroughly assessed the process of WLST. As such, it is unknown if WLST practices could have a major influence on the timing of death in cDCD donors.

Necessary steps to be taken before the initiation of a cDCD procedure are as follows: prognostication, making the decision to withdraw life-sustaining treatment, and approaching family and obtaining their consent for organ donation. Initiation of end-of-life care in acute settings and inexperience in organ donation practices outside ICUs have a negative impact on the number of potential donors [19,20]. Postponing the discontinuation of medical treatment gives professionals more time to guide families adequately and inform them about the dying process and organ donation [21]. Data collected about end-of-life decision-making can provide more insight into whether a patient may be eligible for a cDCD procedure based on time to circulatory death. Such insight can be useful when giving grieving families estimations of time to death and the likelihood that a donation procedure could be performed. However, studies on this important topic are lacking.

Objectives

The primary objective of this large multicenter study is to develop a model predicting time to circulatory death within 60 minutes in potential cDCD patients. A second important aim is to validate and update previous predicting models on time to death after WLST. Other objectives are to assess the process of end-of-life decision-making, to evaluate the effect of the timing of family approach on consent to organ donation, and to determine the influence of variations of WLST on the timing of death and the corresponding effect on the number of donated organs.

Methods

Study Design

This protocol describes a multicenter observational prospective cohort study of all potential cDCD donors of 3 university hospitals and 3 teaching hospitals in the Netherlands. The teaching hospitals were selected based on their diverse focus

(including one hospital with cardiologic facilities, one with cardiologic and cardiothoracic facilities, and one with neurosurgical and traumatology facilities), which will result in a highly generalizable cDCD cohort due to the varied patient population admitted to these hospitals.

This study has an observational design and will analyze, without intervention, the characteristics of deceased potential cDCD donors and end-of-life care as provided by the participating hospitals. Therefore, informed consent is not required.

Participants

The participants of this study are all patients that are admitted at the ICU of one of the hospitals included in this study and are eligible for a cDCD procedure as defined by the Dutch Transplant Foundation [22]. In addition to these organ donation–specific criteria, the following general inclusion and exclusion criteria will be used.

Inclusion and Exclusion Criteria

Inclusion criteria are the following: (1) patients aged between 18 and 75 years; (2) patients that are mechanically ventilated; and (3) patients in whom medical intervention is not of benefit, resulting in an end-of-life decision. Exclusion criteria are the following: (1) nonintubated patients; (2) patients who are clinically brain-dead but in whom relatives nevertheless specifically requested a cDCD procedure; and (3) patients with contraindications as defined by the Dutch Transplant Foundation, including the following: unknown cause of death, unknown identity, untreated sepsis, malignancy, or active viral infection with herpes zoster, rubella, rabies, HIV, or tuberculosis.

Data Collection and Management

Data will be prospectively collected by the local investigators, supported by a research manager (International Organization for Standardization certified), and recorded using a web-based electronic case report form (eCRF). The variables will be obtained from the electronic medical records of the following hospitals: Radboudumc Nijmegen, Erasmus University Medical Center Rotterdam, University Medical Center Groningen, Isala Hospital Zwolle, Jeroen Bosch Hospital 's-Hertogenbosch, and Elisabeth-Tweesteden Hospital Tilburg. Before inclusion, all local investigators received detailed written instructions and on-site training regarding the completion of the eCRF. In addition, the lead investigator team will have regular site visits to perform random sample checks on patient files and data entry. The primary investigator has access to the encrypted data. The primary investigator reviews all incoming data for accuracy and completeness. The research manager can generate data queries and provide trailing records on adjustments of data entered. After completion, the data will be exported in SPSS files (IBM Inc) for further analysis.

A preceding pilot analysis with retrospectively collected data was performed. Two different retrospective data sets were created. One included data from a single hospital (Elisabeth-Tweesteden Hospital, Tilburg, the Netherlands) with a neurosurgical and traumatology focus [23]. The second data set included nationwide demographic data from 2014 to 2016 of all cDCD donors that did not arrest within the set time frame of circulatory arrest of 120 minutes. Anonymized data were provided by the databases of the Dutch Transplant Foundation [24]. Apart from discussion within our own research group, previously published prediction models and analysis of these two data sets contributed to the assessment of key variables to be collected, refinement of the eCRF, defining the appropriate prediction models on time to death for external validation, and providing insight in the donor potential pool after 2, 3, and 4 hours.

Variables to be collected are summarized in Multimedia Appendices 1 and 2. Diagnosis on admission will be classified according to the International Statistical Classification of Diseases and Related Health Problems by the World Health Organization (WHO), tenth revision (ICD-10). Variables related to end-of-life care are shown in Textbox 1.

Textbox 1. Parameters to be collected during and after withdrawal of life-sustaining treatment (WLST).

- Withdrawal of mechanical ventilation
- Removal of endotracheal or tracheostomy tube
- After endotracheal or tracheostomy tube removal: insertion of an oropharyngeal airway, suction of secretions, lateral decubitus positioning, oxygen administration
- Type and dose of medication administered for palliative care purposes

Variables on neurologic examination; physiological variables; and dose of sedation, analgesia, and vasopressors will be evaluated at 3 time points (1) at time of end-of-life decision-making of the medical team, (2) 30 minutes before WLST, and (3) at 1 time point after WLST until circulatory arrest (Multimedia Appendix 3).

Additionally, the computed tomography (CT) images of the brain of all included patients at admission and the last brain CT prior to WLST will be evaluated using a standardized blinded approach by a neurologist and neuroradiologist. The location and size of brain disorders, magnitude of brain shift, and presence of hydrocephalus will be assessed.

Statistical Analysis and Sample Size Calculation

First, the patient population will be randomly split in two groups: the first group will consist of 80% of the sample population and will be used for developing the model, while the second group (20% of the sample population) will be used to estimate the performance of the model developed. For the development of a new prediction model, we will apply least absolute shrinkage and selection operator (LASSO) as a tool for efficient variable selection to develop the multivariable logistic regression model.

For this, we will use the glmnet library (Version 3.0-2). To find the regulation parameter λ, 20-fold cross-validation is applied. To gain some robustness in the choice for the optimal model, we will use the λ.1se option. As quantification of the model fit, the area under the curve (AUC) from the 20% testing portion of the sample population will be presented.

Previous studies on time to circulatory death in cDCD patients found that approximately 50% to 70% will die within 60 minutes after WLST [3,7,15,23,25]. We estimated that approximately 50% of our cohort will have circulatory death within this time frame, which is balanced to patients that will die after this time frame. The sample size determination for our study was based on including enough patients to reach a sufficient level of precision for the AUC for the 20% testing group. Our goal is to have a 95% confidence interval for the AUC with a width of 0.16. This translates into a standard error of 0.04 for the AUC. With an expected AUC of approximately 0.84 and a population with balanced outcomes (50% mortality within 60 minutes of WLST), this requires a sample of N=100. As we will split our patient population into an 80% development portion and a 20% portion for assessing predictive performance, this study requires the inclusion of 400 patients overall.

Second, previously published prediction models will be externally validated using our data set of 400 patients [7,15,25]. We will use logistic regression models with death within 60 minutes (yes/no) as the outcome. These models will be applied to the validation data and performance of the models will be assessed in terms of discrimination and calibration. The calibration process will consist of three steps. First, a calibration plot will be made for the original predictor. Second, the coefficients of the original predictor will be shrunk by multiplying them by the slope of the calibration curve. For this shrunken predictor, a new calibration curve is fitted. Third, calibration will be completed by adjusting the original intercept with the intercept from the calibration curve with the shrunken coefficients. The models will be refitted in the new data set.

Ethical Consideration

The Medical Research Ethics Committee Brabant in the Netherlands has approved the study protocol (NW2014-36). The Medical Ethics Committees of all participating hospitals assessed and consented the study protocol. This study is registered at ClinicalTrials.gov with the unique identification number NCT04123275.

Results

The results of this study are expected to be presented at international scientific meetings and published in 2020 or 2021. The study findings will be reported according to the guidelines outlined by the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) and TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) statements [26,27].

Discussion

An accurate and generalizable model that can be used in clinical practice to predict time to death in cDCD donors is currently lacking. This large prospective multicenter study aims to provide a robust multimodal prediction model based on clinical, physiological, and neuroimaging parameters. In addition, it will provide valuable insights into the process of WLST in cDCD donors and its effect on timing of death (and thus donor potential). As such, this study will fill important knowledge gaps in this essential field of health care.

Accurate estimation of time to circulatory death will help clinicians and nursing staff guide grieving family members and improve the ability of medical teams to predict the chances of organ donation. This helps to manage expectations and prevent disappointment in families that are grieving but motivated to donate. In addition, it could aid in the management of organ donation procurement and transplantation team resources.

Many studies that aim to develop a new prediction tool neglect previously published models. Use of earlier data with refinement of existing models leads to more generalizable models that could be used in daily practice. In our study, we will address external validation using a large cohort with the intention to update previously published prediction tools.

Importantly, this will be the first study that extensively describes donor management in combination with end-of-life care and its impact on the timing of circulatory death in potential cDCD donors. We will provide data on the trajectory of such care during the WLST process. Valuable information on the use of sedatives and analgesics and their influence on the dying process will be obtained. Apart from the timing of death, we will also be able to analyze whether differences in end-of-life care affect family consent rates. We will demonstrate the extent of the variability in cDCD donor care.

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The DCD III study includes the authors of this manuscript and the following local investigators: M Witjes, researcher, Department of Intensive Care, Radboudumc, Nijmegen; M Volbeda, intensivist, Department of Intensive Care, University Medical Center, Groningen; JL Epker, intensivist, Department of Intensive Care, Erasmus University Medical Center, Rotterdam; JPC Sonneveld, intensivist, Department of Intensive Care, Isala Hospital, Zwolle; KS Simons, intensivist, Department of Intensive Care, Jeroen Bosch Hospital, ‘s-Hertogenbosch. All hospitals are located in the Netherlands.

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Authors' Contributions

AMMK is the lead clinical researcher and contributed to developing the study and writing the study protocol; AMMK is also the local clinical investigator at Elisabeth-TweeSteden Hospital, Tilburg. PV developed the electronic case report form (eCRF) and was responsible for the initiation and implementation of the study at the participating hospitals. NEJ contributed to the development, correction, and approval of the study protocol. EMB was responsible for biostatistics analysis planning. JGvdH revised the final version of the study protocol. WFA contributed to the study development and corrections of the study protocol. The lead clinical researcher (AMMK) has full access to all study data, takes responsibility for the integrity of the data, and is accountable for the accuracy of the analysis. All authors will interpret the results of the analysis.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Overview of demographic, clinical, and neurological parameters to be collected from potential cDCD donors. cDCD: controlled donation after circulatory death.
[PDF File (Adobe PDF File), 420 KB - resprot_v9i6e16733_app1.pdf]

Multimedia Appendix 2
Overview of ventilatory, hemodynamic, and pharmacological parameters to be collected from potential cDCD donors. cDCD: controlled donation after circulatory death.
[PDF File (Adobe PDF File), 412 KB - resprot_v9i6e16733_app2.pdf]

Multimedia Appendix 3
Axis showing the corresponding parameters to be collected per time point.
[PDF File (Adobe PDF File), 323 KB - resprot_v9i6e16733_app3.pdf]

Multimedia Appendix 4
Peer reviewer report from the Dutch Transplant Foundation.
[PDF File (Adobe PDF File), 223 KB - resprot_v9i6e16733_app4.pdf]

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Abbreviations

AUC: area under the curve
cDCD: controlled donation after circulatory death
CT: computed tomography
eCRF: electronic case report form
ICD-10: International Statistical Classification of Diseases and Related Health Problems by the World Health Organization (WHO), tenth revision
ICU: intensive care unit
LASSO: least absolute shrinkage and selection operator
STROBE: STrengthening the Reporting of OBservational studies in Epidemiology
TRIPOD: Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis

WLST: withdrawal of life-sustaining treatment

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Corrigenda and Addenda

Authorship Correction: Understanding and Addressing Variation in Health Care–Associated Infections After Durable Ventricular Assist Device Therapy: Protocol for a Mixed Methods Study

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The authors of "Understanding and Addressing Variation in Health Care–Associated Infections After Durable Ventricular Assist Device Therapy: Protocol for a Mixed Methods Study" (JMIR Res Protoc 2020;9(1):e14701) noticed errors in the author list after publication.

Author Donald Likosky's name was missing the middle initial. Their name has been revised to "Donald S Likosky". Additionally, there were errors in some of the author degrees. Preeti N Malani's degrees have been revised from "MSCJ, MD" to "MSJ, MD", Tessa M F Watt's degrees have been revised from "MD" to "MSc, MD", and Keith D Aaronson's degrees have been revised from "MSc, MD" to "MS, MD".

The correction will appear in the online version of the paper on the JMIR website on June 11, 2020, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Correction: Youth Experiences With Referrals to Mental Health Services in Canada: Protocol for a Web-Based Cross-Sectional Survey Study

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In "Youth Experiences With Referrals to Mental Health Services in Canada: Protocol for a Web-Based Cross-Sectional Survey Study" (JMIR Res Protoc 2020;9(3):e16945) the authors noted a footnote was erroneously omitted from the text of Multimedia Appendix 2. The footnote has been added to Multimedia Appendix 2, and is positioned under the question "What are the ethnic or cultural origins of your ancestors? [Please check all that apply]". The footnote reads:

> *Ethnicity question and responses were adapted using information from the following documents: 1) Statistics Canada Census of Population 2016, Appendix 5.1 Ethnic Origins disseminated from 2016, 2011, and 2006. Retrieved from: https://www12.statcan.gc.ca/census-recensement/2016/ref/dict/app-ann/a5_1-eng.cfm, 2) Archived Census 2A-L - 2016. Retrieved from: http://www23.statcan.gc.ca/imdb/p3Instr.pl?Function=getInstrumentList&Item_Id=295122&UL=1V&, 3) Ethnic Origin Reference Guide, Census of Population, 2016. Retrieved from: https://www12.statcan.gc.ca/census-recensement/2016/ref/guides/008/98-500-x2016008-eng.cfm & 4) Data Tables 2016 Census: Ethnic Origins. Retrieved from: https://www12.statcan.gc.ca/census-recensement/2016/dp-pd/dt-td/Av-eng.cfm?LANG=E&APATH=3&DETAIL=0&DIM=1&FL=A&FREE=0&GC=0&GID=0&GK=0&GRP=1&PID=112450&PRID=10&PTYPE=109445&S=0&SHOWALL=0&SUB=0&Temporal=2017&THEME=120&VID=29591&VNAMEE=&VNAMEF=*

The corrected Multimedia Appendix 2 file will be uploaded to the online version of the original paper on the JMIR website on June 12, 2020, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

Multimedia Appendix 2
Questionnaire.
[DOCX File , 80 KB - resprot_v9i6e19019_app2.docx]

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Corrigenda and Addenda

Correction: Unibody Endograft Using AFX 2 for Less Invasive and Faster Endovascular Aortic Repair: Protocol for a Multicenter Nonrandomized Study

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Related Article:

Correction of: https://www.researchprotocols.org/2020/4/e16959/

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In "Unibody Endograft Using AFX 2 for Less Invasive and Faster Endovascular Aortic Repair: Protocol for a Multicenter Nonrandomized Study" (JMIR Res Protoc 2020;9(4):e16959) there were two errors in the Collaborators List.

The collaborator Sonia Ronchey was inadvertently not included in the collaborator list. Additionally, the collaborator name Pietro Volpet should have been listed as Pietro Volpe.

The Collaborator List was initially published as follows:

> *The LIVE Study Collaborators are as follows: Giancarlo Accarino; Dimitri Apostolou; Guido Bajardi; Stefano Bartoli; Filippo Benedetto; Franco Briolini; Stefano Camparini; Emidio Costantini; Giovanni Credi; Ruggiero Curci; Raffaello Dallatana; Gianmarco de Donato; Carlo Dionisi; Vittorio Dorrucci; Leonardo Ercolini; Gianfranco Fadda; Mauro Ferrari; Loris Flora; Andrea Gaggiano; Roberto Gattuso; Franco Grego; Sabrina Grimaldi; Giovanni Impedovo; Arnaldo Ippoliti; Antonio Jannello; Sergio Losa; Nicola Mangialardi; Isaac Martinez; Javier Martinez; Stefano Michelagnoli; Giancarlo Palasciano; Vincenzo Palazzo; Domenico Palombo; Raffaele Pulli; Giovanni Rossi; Antonino Scolaro; Gianantonio Simoni; Francesco Spinelli; Francesco Talarico; Maurizio Taurino; Marco Trogolo; Nicola Tusini; Gianfranco Veraldi; Pier Francesco Veroux; Gennaro Vigliotti; and Pietro Volpet.*

The Collaborator List has now been updated to the following:

> *The LIVE Study Collaborators are as follows: Giancarlo Accarino; Dimitri Apostolou; Guido Bajardi; Stefano Bartoli; Filippo Benedetto; Franco Briolini; Stefano Camparini; Emidio Costantini; Giovanni Credi; Ruggiero Curci; Raffaello Dallatana; Gianmarco de Donato; Carlo Dionisi; Vittorio Dorrucci; Leonardo Ercolini; Gianfranco Fadda; Mauro Ferrari; Loris Flora; Andrea Gaggiano; Roberto Gattuso; Franco Grego; Sabrina Grimaldi; Giovanni Impedovo; Arnaldo Ippoliti; Antonio Jannello; Sergio Losa; Nicola Mangialardi; Isaac Martinez; Javier Martinez; Stefano Michelagnoli; Giancarlo Palasciano; Vincenzo Palazzo; Domenico Palombo; Raffaele Pulli; Sonia Ronchey; Giovanni Rossi; Antonino Scolaro; Gianantonio Simoni; Francesco Spinelli; Francesco Talarico; Maurizio Taurino; Marco Trogolo; Nicola Tusini; Gianfranco Veraldi; Pier Francesco Veroux; Gennaro Vigliotti; and Pietro Volpe.*

The correction will appear in the online version of the paper on the JMIR website on June 24, 2020, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Original Paper

Tackling Research Inefficiency in Degenerative Cervical Myelopathy: Illustrative Review

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Abstract

Background: Degenerative cervical myelopathy (DCM) is widely accepted as the most common cause of adult myelopathy worldwide. Despite this, there is no specific term or diagnostic criteria in the International Classification of Diseases 11th Revision and no Medical Subject Headings (MeSH) or an equivalent in common literature databases. This makes searching the literature and thus conducting systematic reviews or meta-analyses imprecise and inefficient. Efficient research synthesis is integral to delivering evidence-based medicine and improving research efficiency.

Objective: This study aimed to illustrate the difficulties encountered when attempting to carry out a comprehensive and accurate evidence search in the field of DCM by identifying the key sources of imprecision and quantifying their impact.

Methods: To identify the key sources of imprecision and quantify their impact, an illustrative search strategy was developed using a validated DCM hedge combined with contemporary strategies used by authors in previous systematic reviews and meta-analyses. This strategy was applied to Medical Literature Analysis and Retrieval System Online (MEDLINE) and Excerpta Medica dataBASE (EMBASE) databases looking for relevant DCM systematic reviews and meta-analyses published within the last 5 years.

Results: The MEDLINE via PubMed search strategy returned 24,166 results, refined to 534 papers after the application of inclusion and exclusion criteria. Of these, 32.96% (176/534) results were about DCM, and 18.16% (97/534) of these were DCM systematic reviews or meta-analyses. Non-DCM results were organized into imprecision categories (spinal: 268/534, 50.2%; nonspinal: 84/534, 15.5%; and nonhuman: 8/534, 1.5%). The largest categories were spinal cord injury (75/534, 13.67%), spinal neoplasms (44/534, 8.24%), infectious diseases of the spine and central nervous system (18/534, 3.37%), and other spinal levels (ie, thoracic, lumbar, and sacral; 18/534, 3.37%). Counterintuitively, the use of human and adult PubMed filters was found to exclude a large number of relevant articles. Searching a second database (EMBASE) added an extra 12 DCM systematic reviews or meta-analyses.

Conclusions: DCM search strategies face significant imprecision, principally because of overlapping and heterogenous search terms, and inaccurate article indexing. Notably, commonly employed MEDLINE filters, human and adult, reduced search sensitivity, whereas the related articles function and the use of a second database (EMBASE) improved it. Development of a MeSH labeling and a standardized DCM definition would allow comprehensive and specific indexing of DCM literature. This is required to support a more efficient research synthesis.

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KEYWORDS

cervical; myelopathy; spondylosis; spondylotic; stenosis; disc herniation; ossification posterior longitudinal ligament; systematic review; research inefficiency; imprecision

Introduction

Background

Degenerative cervical myelopathy (DCM) arises when degenerative changes of spinal structures cause myelopathy of the cervical spinal cord [1]. These degenerative changes include spondylosis, disc prolapse, hypertrophy, calcification, and ossification of the posterior longitudinal ligament and ligamentum flavum [1]. Ultimately, this results in stenosis of the spinal canal leading to cord compression, mechanical stretch, repetitive microtrauma, and chronic reduction in cord blood flow [1,2]. A complex pathological cascade follows with neuroinflammation, demyelination, neurodegeneration, and gliosis, resulting in the clinical entity we know as myelopathy [1,3,4].

The prevalence of DCM has proven difficult to ascertain owing to the novel umbrella term, difficulty in diagnosis, and the relative paucity of data [1]. Nevertheless, it is widely accepted as the most common cause of adult myelopathy worldwide [5]. DCM is not only very prevalent but also quite disabling, with the quality of life scores (36-Item Short Form Health Survey) in patients with DCM being lower than those in patients with most other common conditions, with heart failure and sciatica being identified as the only 2 conditions with lower scores [6].

Despite this, there remains no specific term or diagnostic criteria in the International Classification of Diseases 11th Revision (ICD-11), which encompasses the related and often coexisting conditions covered under the DCM umbrella [7]. Similarly, there exists no Medical Subject Headings (MeSH) term for PubMed (or an equivalent grouping index term for other databases) for DCM or its constituent terms (Textbox 1) [7]. MeSH terms improve the precision and efficiency of literature searches [8]. The hierarchical structure arrangement of MeSH *trees* allows for narrower terms to fall under the MeSH term heading and for search engines to consider other terms as MeSH synonyms [9]. This has proven particularly useful in medical terms that follow umbrella structures [9], for example, the MeSH *Spinal Cord Injuries* encompasses terms such as *spinal cord transection*, *traumatic myelopathy*, and *spinal cord contusions* and includes useful subheadings such as *etiology*, *diagnosis*, and *surgery*. This structure is likely to be useful in DCM terminology, which encompasses terms such as *cervical spondylotic myelopathy* and *ossification of the posterior longitudinal ligament* [1]. The relative novelty of the term DCM does not entirely explain its lack of MeSH terms. In 2019, 421 new MeSH terms were added to the Medical Literature Analysis and Retrieval System Online (MEDLINE)/PubMed database, some of which are in reference to other equally novel terms, such as emerging monoclonal antibody-based therapies and small molecule inhibitors [10]. Indeed, the use of free-text searches alone of DCM returns imprecision in the form of overlapping terms, including the subjects of noncervical myelopathy, noncervical spine degenerative changes, and gynecological cervix [7].

The lack of a consistent index term and MeSH term for DCM makes searching the literature imprecise and inefficient. This is particularly crucial when considering the importance of thorough systematic reviews and meta-analyses in reducing research wastage [11]. Indeed, in 2010, an estimated US $240 billion was spent on biomedical research, with an estimated 85% of this research wasted, resulting in no clinical translation or benefit [11,12]. Reviews of the literature increase research efficiency by preventing research duplication and directing future primary research [11]. However, previous surveys have indicated that over half of the clinical trial designers may be unaware of all the existing major reviews relevant to their study design [13]. The omission of this crucial step in informing trials has led to countless numbers of trials with inappropriate design, with one series highlighting that up to 75% of trials without the mention of systematic reviews or meta-analyses informing their protocols had trial designs that were considered inadequate [14,15]. In addition, systematic reviews and meta-analyses are important in preventing duplication of existing knowledge and in putting the results of trials into the context of existing literature so that the clinical relevance of findings is more interpretable [15].

Textbox 1. PubMed/Medical Literature Analysis and Retrieval System Online Medical Subject Headings (MeSH) terms contained within the Spinal Diseases and Spinal Cord Diseases categories. Of note, the Ossification of the Posterior Longitudinal Ligament (OPLL) MeSH that currently exists does not specify OPLL with radiculomyelopathy or OPLL without radiculomyelopathy.

Spinal diseases

- Intervertebral disc degeneration
- Intervertebral disc displacement
- Ossification of the posterior longitudinal
- Platybasia
- Posterior cervical sympathetic syndrome
- Spinal curvatures
- Spinal neoplasms
- Spinal osteochondrosis
- Spinal osteophytosis
- Spinal stenosis
- Spondylitis
- Spondylosis
- Spondylolysis

Spinal cord diseases

- Pneumorrhachis
- Spinal cord compression
- Spinal cord injuries
    - Central cord syndrome
- Spinal cord neoplasms
- Spinal cord vascular diseases
- Spinocerebellar degeneration
- Stiff-Person syndrome
- Subacute combined degeneration
- Syringomyelia
- Tabes dorsalis
- Amyotrophic lateral sclerosis
- Epidural abscess
- Spinal muscular atrophy
- Myelitis

Objectives

Currently, the process of conducting systematic reviews and meta-analyses in many fields is laborious and inefficient [15,16]. This study aimed to illustrate the difficulties encountered when attempting to carry out a comprehensive and accurate evidence search in the field of DCM by identifying the key sources of imprecision and quantifying their impact.

Methods

Developing an Illustrative Search Strategy

Studies concerning DCM within the last 5 years were initially identified using a search filter/hedge, which has been previously validated for DCM and has returned a 100% sensitivity in DCM datasets [7]. Search strategies used in these systematic reviews and meta-analyses were compared with the search strategies of the validated hedge. The validated strategy was combined with the strategies that have been actively used by authors, forming our example search strategy (Textbox 2). Effectively, this resulted in the addition of the terms *Degenerative Cervical*

Myelopathy and *Ossification of Posterior Longitudinal Ligament* to the strategy. This approach, rather than the exclusive use of the search filter, was chosen because it most closely aligned with the current search practices in DCM.

Inclusion and Exclusion Criteria

A search filter (Textbox 3) encompassing the inclusion and exclusion criteria was applied to our search terms. Relevant studies were identified through hand searching all articles returned after the application of the search filter.

Textbox 2. Search terms used to identify relevant studies.

OR

- DCM/Degenerative Cervical Myelopathy
- OPLL/Ossification of Posterior Longitudinal Ligament
- CSM/Cervical Spondylotic Myelopathy
- JOA/Japanese Orthopaedic Association
- Cervical Vertebrae OR Cervical Cord

AND

- Myelopathy OR Myeloradiculopathy OR Spondylomyelopathy OR Spinal Cord Diseases OR Spinal Cord Disorder OR Spinal Cord Compression

Textbox 3. Search filters (Phase 1 and Phase 2) applied to the search terms.

Inclusion criteria

- English
- Full text available
- Last 5 years range
- Meta-analyses
- Systematic reviews
- Adult (Phase 1 only)
- Human (Phase 1 only)

Exclusion criteria [7,17]

- Nonspinal disease
- Thoracic and lumbar disease
- Radiculopathy without myelopathy
- Other nondegenerative myelopathy
- Traumatic spinal cord injury
- Tumor/neoplasm/hemangioma/metastases
- Infection
- Arteriovenous fistula
- Radiation injuries
- Motor neuron disease/amyotrophic lateral sclerosis
- Multiple sclerosis
- Autoimmune diseases of the nervous system
- Inflammatory arthritis
- Congenital, hereditary, and neonatal diseases and abnormalities

For this illustrative search, only meta-analyses and systematic reviews were searched. This aimed to emulate the crucial initial step in performing any systematic review or meta-analysis, that is, avoiding duplication and/or identifying previous systematic reviews or meta-analyses to update. This style of search also is frequently used by clinicians to provide an efficient evidence update [18,19]. Moreover, it allowed the use of meta-analysis, systematic review, or review filters, which pragmatically

reduced the labor-intensive process of hand searching. The performance of these filters is validated for identifying systematic reviews and meta-analyses, with sensitivities of up to 19.1% for meta-analyses, 22.1% for systematic reviews, and 77.5% for reviews and with specificities of up to 99.7% for meta-analyses, 99.8% for systematic reviews, and 92% for reviews [19,20].

Each search strategy phase was tested against 2 index articles identified a priori [1,21]. Of note, during the first search (*Phase 1*, searched on January 6, 2019), additional search filters (Textbox 3) were applied and trialed. However, as this *Phase 1* search strategy failed to identify assorted reference articles [1,21] prospectively collected to test the strategy, adjustments were made (Textbox 3). This refined search was termed *Phase 2* (searched on January 17, 2019).

Evaluate Performance of the Illustrative Search Strategy

Databases Searched

Searching multiple databases is often required in thorough literature searches [11]. Thus, searches (Phase 2) were first carried out on the MEDLINE database via PubMed and repeated using Excerpta Medica dataBASE (EMBASE).

Filters (Medical Literature Analysis and Retrieval System Online)

The function of the selected common PubMed filters was also tested. Filters in Textbox 3 served as the baseline for search results. Additional filters were then added and removed, and their effects were studied. The adult, human, and English filters, common filters employed in DCM systematic reviews and meta-analyses, were examined.

Related Articles Function (PubMed/Medical Literature Analysis and Retrieval System Online)

The related articles feature is commonly used in research synthesis. The utility of this filter within the DCM literature base was tested on the DCM systematic review or meta-analysis results of Phase 1 (low sensitivity) and Phase 2 (high sensitivity). All of the DCM systematic review or meta-analysis articles in Phase 1 were examined. In Phase 2, a pragmatic 10% a priori of the total relevant systematic reviews or meta-analyses were hand searched. Random number table selection was used to identify these articles from our identified cohort. Our search filters (Textbox 3) were applied to each article's related articles results, looking for additional studies not yet identified with our search strategies.

Analysis

The outcomes measured during Phase 1 and Phase 2 searches were as follows:

1. Total number of articles returned.
2. Number of relevant articles (DCM systematic reviews or meta-analyses) meeting the inclusion criteria.
3. Categorization of irrelevant studies—using ICD-11 categories as a guide to creating themes of imprecision [22].
4. The number of additional relevant articles using the Related Articles function (MEDLINE database via PubMed).
5. The number of additional articles found using a second literature database, stratified into relevant and irrelevant articles.

Results

Phase 1

This search strategy returned 3439 results, refined to 175 results using the above filters and with 1 duplicate being subsequently removed. The categorization of the remaining 174 results is summarized in Multimedia Appendix 1. Of note, 18.4% (32/116) results fitted the inclusion criteria, totaled in the *DCM* category of Multimedia Appendix 1. Of these, 9.8% (17/116) DCM studies were systematic reviews or meta-analyses, with the 15 other studies consisting of case reports and narrative reviews.

With regard to the overlapping terms when considering non-DCM search results relating to the spine (116/174, 66.6% of results), the most common categories involved were spinal neoplasms (25/174, 14.4%), spinal cord injury (15/174, 8.6%), and infectious diseases of the spine and central nervous system (CNS; 15/174, 8.6%). When considering nonspinal categories (26/174, 14.9% of results), diseases of the nervous system—cerebral diseases (9/174, 5.7%)—and disorders of the urological tract and male genital tract (3/174, 1.7%) were the most commonly encountered.

As stated above, this *Phase 1* search strategy failed to identify our chosen index articles [1,21]. Resultantly, this search was refined via removal of the *adults* (>19 years old) and *human* filters and thereafter termed the *Phase 2* strategy (Textbox 3), searched on January 17, 2019.

Phase 2

This search strategy returned 24,166 results, refined to 537 results using filters. Of these, 2 duplicates and 1 letter to editor publication were subsequently removed (Figure 1). The remaining 534 studies are categorized in Table 1. We found that 32.9% (176/534) of results fitted into the *DCM* category of Table 1. Of these, 18.2% (97/534) DCM studies were systematic reviews or meta-analyses, with the 79 other studies consisting predominantly of case reports and narrative reviews.

Figure 1. MEDLINE search strategy with the most common imprecision categories. CNS: cerebral nervous system; DCM: degenerative cervical myelopathy; MA: meta-analysis; SR: systematic review.

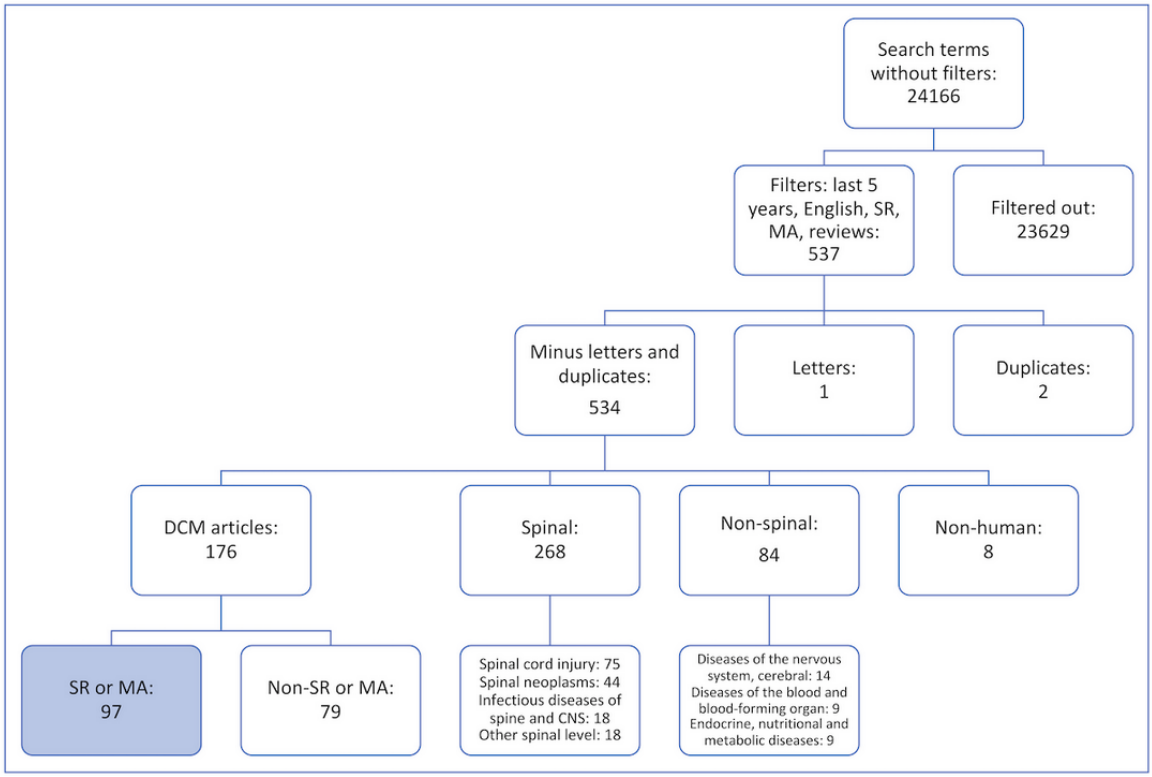


Table 1. Phase 2 search results categorization guided by the International Classification of Diseases 11th Revision.

Category and subcategory	Values, n (%)
DCM[a]	
Systematic review or meta-analysis	97 (18.16)
Nonsystematic review or non–meta-analysis	79 (14.79)
Subtotal	176 (32.96)
Non-DCM, spinal	
Spinal cord injury	75 (14.04)
Spinal neoplasms	44 (8.24)
Infectious diseases of the spine and CNS[b]	18 (3.37)
Other spinal level (thoracic, lumbar, or sacral)	18 (3.37)
Miscellaneous[c]	17 (3.18)
Vascular pathologies	14 (2.62)
Surgical techniques and complications (non-DCM)	13 (2.43)
Traumatic spondylopathy	9 (1.69)
Congenital spinal diseases	8 (1.50)
Inflammatory and demyelinating diseases of the CNS	8 (1.50)
Cervical disc disorders	7 (1.31)
Radiology of the spine and spinal cord (non-DCM)	7 (1.31)
Neurodegenerative disease of the CNS	7 (1.31)
Inflammatory spondylo-arthopathies	7 (1.31)
Cerebrospinal fluid disorders (leaks and syringomyelia)	5 (0.94)
Deforming dorsopathies	5 (0.94)
Metabolic diseases with spinal sequelae	4 (0.75)
Cervical radiculopathy	2 (0.37)
Subtotal	268 (50.19)
Non-DCM, nonspinal	
Diseases of the nervous system, cerebral	14 (2.62)
Diseases of the blood and blood-forming organs	9 (1.69)
Endocrine, nutritional, and metabolic diseases	9 (1.69)
Miscellaneous	8 (1.50)
Diseases of the ear, nose, upper respiratory tract, and head and neck	7 (1.31)
Disorders of the female genital tract	6 (1.12)
Diseases of the musculoskeletal system and connective tissue	6 (1.12)
Disorders of the urological tract and male genital tract	6 (1.12)
Pain	5 (0.94)
Diseases of the circulatory system	4 (0.75)
Mental and behavioral disorders	4 (0.75)
Infectious and parasitic diseases	2 (0.37)
Diseases of the digestive system	1 (0.19)
Diseases of the lower respiratory tract	1 (0.19)
Subtotal	84 (15.36)
Nonhuman	

Category and subcategory	Values, n (%)
Feline and Canine	6 (0.94)
Equine	2 (0.37)
Subtotal	8 (1.50)
Grand total	534 (100)

[a]DCM: degenerative cervical myelopathy.

[b]CNS: central nervous system.

[c]Miscellaneous: not specified in the International Classification of Diseases 11th Revision (rare genetic disorders, rare immunological disorders, and rare extrapyramidal disorders) and/or not fitting into the above categories.

Of note, our search strategy was formed from an amalgamation of strategies used by previous authors in the field and validated PubMed hedge. Resultantly, the search terms used included 2 additional terms (*DCM/Degenerative Cervical Myelopathy* and *OPLL/Ossification of Posterior Longitudinal Ligament*) to the original validated hedge by Davies et al [7]. The addition of these terms made no difference to the search results during Phase 1 or Phase 2.

Categories of Imprecision

In regard to the overlapping terms when considering non-DCM search results relating to the spine (268/534, 50.2% of results), the most common categories involved spinal cord injury (75/534, 13.67%), spinal neoplasms (44/534, 8.2%), infectious diseases of spine and CNS (18/534, 3.4%), and other spinal level (thoracic, lumbar, or sacral; 18/534, 3.4%). When considering nonspinal categories (8/534, 15.4% of results), diseases of the nervous system; cerebral diseases (14/534, 2.6%); diseases of the blood and blood-forming organs (9/534, 1.7%); and endocrine, nutritional, and metabolic diseases (9/534, 1.7%) were the most commonly encountered.

Inadequacy of PubMed Search Filters

Importantly, Phase 2, unlike Phase 1, was successful in identifying our prospectively collected reference DCM systematic review and meta-analysis articles [1,21], highlighting the unreliable nature of *human* and *adult* search filters, which were present in Phase 1.

The nonhuman category totaled to 1.5% (8/534), which does not reflect the 81 articles removed from the search results when the *human* filter is selected. Similarly, the inadequacy of the *adult* filter is demonstrated through the comparison of the relative paucity of results specific to pediatric populations. There were only 4 of these results within the result categories, compared with the removal of 358 articles on the application of this filter. In addition, the application of the English filter removed 22 articles; the distribution of these was as follows: 3 in Chinese, 4 in French, 9 in German, 4 in Japanese, 1 in Russian, and 1 in Spanish. Of these, 4 articles (all in German) were in the field of DCM but none were systematic reviews or meta-analyses. Thus, the removal of non-English articles did not decrease the sensitivity of our search. For pragmatic purposes, the *year range* and *text availability* (ie, full text availability) filters were not scrutinized.

Extended Literature Search

Related Articles Function (PubMed/Medical Literature Analysis and Retrieval System Online)

The *related articles* feature was tested in 2 searches of differing sensitivities, Phase 1 (low sensitivity) and Phase 2 (high sensitivity). In Phase 1, all 32 DCM systematic review and meta-analysis articles were examined in view of the known poor sensitivity of the search without this function. A total of 3830 articles were identified by the database. Of these, 2.7% (102/3820) articles remained after applying the Phase 1 filters: humans, full text available, last 5 years range, adults (>19 years old), English, meta-analyses, systematic reviews, and reviews. These filtered studies were reviewed, and 1.8% (67/3820) of the total *related articles* search were found to be relevant to the DCM category topic. Duplicates were included in the above analysis as each article's *related articles* were examined separately. However, after the removal of duplicates and comparison with the original 32 DCM articles, 5 relevant studies that fitted the inclusion criteria (all of which were systematic reviews or meta-analyses) were identified through this *related articles* search but were not found in the original Phase 1 search. Thus, 1 new DCM systematic review or meta-analysis was found per 6.4 articles examined. However, our selected reference articles were still not identified by this extended Phase 1 search strategy, further elucidating Phase 1's lack of sensitivity.

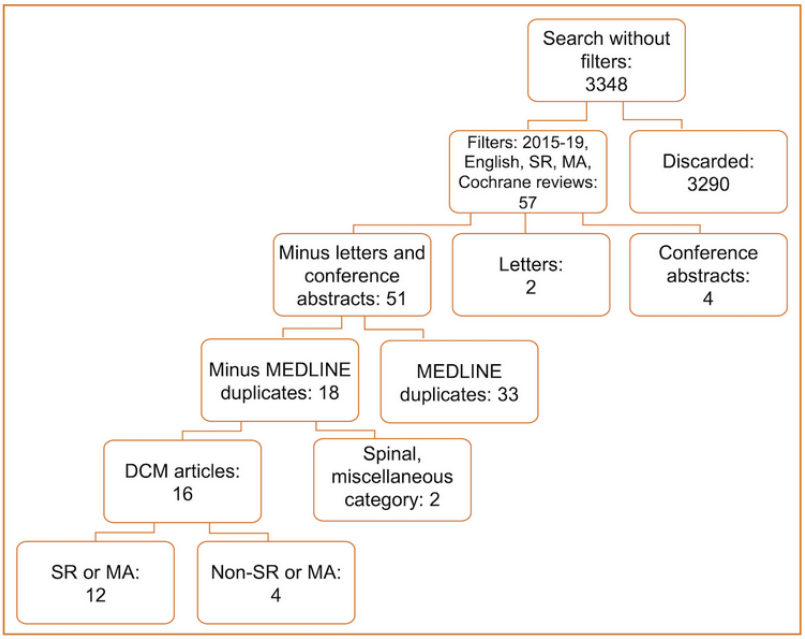
In Phase 2, the *related articles* function was used on a pragmatic a priori 10% of the DCM systematic reviews and meta-analyses. This equated to 10 articles examined, chosen by a random number table. A total of 980 articles were classed as articles related to the 10 DCM systematic reviews and meta-analyses. After the application of Phase 2 filters, 118 studies remained, with 105 of these being related to DCM and 87 being DCM systematic reviews or meta-analyses. Importantly, 91% (79/87) of these DCM systematic review and meta-analysis articles were identified by the Phase 2 strategy. Thus, 7 new articles (6 once duplicates were removed) were found via this extended search, equating to 1 new DCM systematic review or meta-analysis found per 1.67 articles examined.

Second Database Search (Excerpta Medica dataBASE)

The EMBASE database was searched on February 3, 2019, through the adaptation of the above search strategy (although originally developed for MEDLINE/PubMed) [7]. The following filters were applied to emulate the Phase 2 PubMed search: 2015-2019, humans, systematic reviews, meta-analyses, and Cochrane review (Figure 2). These filters narrowed down the

raw 3348 results to 57 results; 6 nonresearch articles were removed, 51 results were compared with the Phase 2 PubMed cohort, and 33 duplicates (all within the DCM category) were subsequently removed. This left 18 articles for review, 67% (12/18) of which were systematic reviews or meta-analyses in DCM and 22% (4/18) of which were nonsystematic reviews or non–meta-analysis DCM articles.

Figure 2. EMBASE search strategy and results. CNS: cerebral nervous system; DCM: degenerative cervical myelopathy; MA: meta-analysis; SR: systematic review.



Discussion

Principal Findings

Our study served to replicate an important step in research synthesis and evidence-based clinical practice, identifying systematic reviews or meta-analyses in the field. It was hypothesized that, without an agreed index term, MeSH, or an equivalent and accurate indexing of articles, this attempt at comprehensively searching the literature would be inefficient and imprecise. Specifically, only 18.2% (97/534) of search results concerned DCM systematic reviews or meta-analyses and commonly used PubMed search filters (such as *adult*) stratified studies incorrectly. Moreover, it is clear that expanding the search with *related articles* functions and searching additional databases will identify additional relevant studies. These results taken together indicate that systematic search in DCM is currently extremely labor-intensive.

The PubMed filters of *systematic reviews*, *reviews*, and *meta-analyses*, with proven satisfactory sensitivity and specificity [19,20], were applied to our search terms. The standard against which imprecision was judged was the percentage and number of DCM systematic reviews or meta-analyses found. This aimed to replicate common occurrence in clinical practice and the initial steps of research synthesis. It also served as a pragmatic approach to assessing imprecision. DCM systematic reviews and meta-analyses were 18.2% (97/534) of studies returned in our search (Phase 2), with principal categories of imprecision including spinal cord injury and spinal neoplasms.

The need to exercise caution when applying other generic filters in the field of DCM is illustrated in the results of the Phase 1 search. This included the additional filters of *adult* and *human* and a search that was less sensitive or specific than Phase 2 (searching without these filters applied). However, the addition of the English filter did not affect the number of DCM systematic reviews or meta-analyses found in our search. This is unfortunate as these filters have the potential to make this already labor-intensive process more efficient but fail to do so in DCM PubMed literature.

The *related articles* function on PubMed's displayed utility in the setting of both low- and high-sensitivity searches. In Phase 1, it was used to find 5 additional DCM systematic review and meta-analysis studies after searching the original 32 articles—1 new DCM systematic review or meta-analysis was found per 6.4 articles examined. In Phase 2, 6 extra articles were found via this extended search, equating to 1 new DCM systematic review or meta-analysis found per 1.67 articles examined. Thus, the common practice of using this function for the literature search is justified and recommended. In addition, it is important to note that the EMBASE database composed 14% (16/114) of the total EMBASE plus MEDLINE *DCM systematic reviewsand meta-analysis* yield of our search and 9.2% (18/195) of the total EMBASE plus MEDLINE *DCM* category results. This reiterates the potential value of searching multiple literature databases while performing systematic reviews or meta-analyses in the field of DCM, and DCM reviewers should be cognoscente of this [11].

Study Results in Context

The findings of our search reflect previous studies discussing systematic review or meta-analysis retrieval in other fields.

Specifically, they mirror the search precision generated by a DCM hedge. Overlapping terms and general imprecision have spurred the creation of search hedges, aiming to increase search efficiency when performing comprehensive literature retrieval [23]. However, there is a broad range of sensitivities and specifies that is achieved using these hedges [23,24]. This is compounded by the inaccuracy of generic search filters, for example, the *cross-sectional studies* filter [25]. There is an agreement that root problems to such search inefficiencies included interindexer inconsistency when labeling studies and a lack of natural language processing terms such as MeSH terms [26,27]. Regardless, searching of multiple databases and using *related articles*-type functions are widely accepted for their utility [28]. Importantly, the choice of databases must be carefully considered. For example, Google Scholar is another option commonly considered for literature retrieval. It holds advantages in its simplicity, familiarity, and ability to search a broader area of the literature (including multiple medical libraries and preprint articles) [29]. However, it has been criticized for being less comprehensive, less precise, and less sophisticated (in terms of advanced search functions and controlled vocabulary) [29,30]. Therefore, we elected dedicated literature search databases for the purposes of identifying imprecision.

Developing a Solution

As the rate of our primary research synthesis exceeds our ability to review it [31], it is imperative that our methods for systematically reviewing and analyzing data emphasize efficiency. Over the last decade, an average of 700,000 to 850,000 articles per year were published in MEDLINE [32], whereas 2500 systematic reviews are published yearly [12]. It is estimated that 10,000 Cochrane systematic reviews would be needed to sufficiently synthesize the information from 300,000 trials in the Cochrane Central Register of Controlled Trials literature database [33]. This was thought by Cochrane to be achievable by 2010 to 2015, but to date, this figure stands at approximately 7900 [33]. Furthermore, although Cochrane aspires to update these reviews regularly with new studies and analyses, it struggles to do so [12]. The suggested reason for this is the inefficiency of the systematic review or meta-analysis process [2]. Proposed methods to ameliorate this issue include standardization (eg, Preferred Reporting Items for Systematic Reviews and Meta-Analyses and International Prospective Register of Systematic Reviews) and availing of technology to streamline the process [15].

Although technology such as meta-search engines, machine learning platforms, and automated information extraction systems continue to develop, these solutions remain largely experimental [34-37]. Filter or hedge development has been proposed as one solution to this problem. However, as demonstrated in this study, this can have varying degrees of accuracy. When developing a DCM search filter with 100% sensitivity, this returned <20% precision values, and efforts to optimize its specificity using *NOT* functions reduced the sensitivity [7].

A more comprehensive change would be the development of an index term/ICD category with a paired MeSH term. This could deliver immediate search efficiencies. MeSH terms have been developed as natural language processing tools [38], streamlining the current literature search process, and will likely prove integral to a future machine-assisted and/or machine-led review of the literature [37]. Indeed, MeSH tags have the potential to solve the identified issues in DCM literature of heterogenous synonyms and overlapping terms with non-DCM literature. The hierarchal tree structuring of MeSH tags will allow encompassing the various index terms that exist for DCM without the inclusion of such a large body of the literature, which is unrelated but shares isolated overlapping words or phrases. The MeSH labeling process, once a MeSH term is created, has moved from a human-only process to a machine-assisted process, saving cost and time for literature libraries [27]. Each article is currently processed by using the Medical Text Indexer technology, suggesting MeSH labels (on the basis of the title, abstract, and related articles' labels) to human indexers [27]. However, the rate of comprehensive and accurate indexing struggles to keep up with high rates of research synthesis [27]. However, novel fully automatic MeSH indexing technologies (eg, MeSHLabeler and DeepMeSH) employ machine learning algorithms to make large-scale MeSH indexing cheaper, more efficient, and more accurate. Employing such technology should motivate us to aim for a fully indexed body of DCM literature [27,39].

Index terms are equally important in standardizing our language in both research and clinical practice. In addition to search inefficiencies, inconsistencies within the definition of DCM have prevented all retrieved studies being pooled for analysis [40]. Development of a universally agreed definition has been successfully done via consensus processes for other diseases, more specifically via a modified Delphi process [41]. Our group aims to establish this index term for DCM as part of our Research objectives and Common Data Elements for DCM study. For creation of an ICD entry, a proposal can be made via the World Health Organization web-based ICD-11 platform to be reviewed by a Topic Advisory Group and Revision Steering Group [42].

Limitations

This illustrative search excluded the vast majority of primary DCM research by using the systematic review, review, and meta-analysis filters. This was done to make the illustration of imprecision, a process that requires hand searching of articles, more pragmatic. Although this reduced the number of articles retrieved, given that the objective of this study was to consider the sources of imprecision, we do not feel that this would have limited our findings. Moreover, the practice of limiting research synthesis is reflective of day-to-day search practices.

In addition, a small number of results covered multiple categories of imprecision. In these cases, a review of the article's full text for the primary area of discussion was undertaken, followed by allocation to that imprecision category. We acknowledge that this is a relatively subjective process. However, imprecision because of overlapping terms was still identified, regardless of categorization, and thus, the primary aims of the study were fulfilled. Finally, we searched only 1 additional database, and only 10% of articles had their related

articles function tested. Again, this served to elucidate their known utility in a practical fashion, with further database evaluation not required.

Conclusions

This paper illustrates the difficulties encountered by past, current, and future reviewers of DCM literature. Overlapping and heterogenous search terms and inaccurate article indexing lead to an imprecise and wasteful process. Researchers in the field of DCM must be aware of the adverse effects that sensitivity and specificity common search functions (eg, *humans* and *adult*) may have on the retrieval of results. However, the common practice of using *related articles* functions and searching multiple databases is recommended in DCM literature. Looking forward, MeSH labeling, a standardized DCM definition, and comprehensive indexing of DCM literature will be crucial steps in ameliorating these hurdles.

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Authors' Contributions

DK performed literature searches, results review, and manuscript production. MK was involved in study design, protocol development, and manuscript review. MRK contributed via manuscript review. BD was involved in study design, protocol development, and manuscript review and production. All authors have read and approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Phase 1 Search Results Categorisation.
[DOCX File , 17 KB - resprot_v9i6e15922_app1.docx]

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Abbreviations

CNS: central nervous system
CSF: cerebrospinal fluid
DCM: degenerative cervical myelopathy
EMBASE: Excerpta Medica dataBASE
ICD-11: International Classification of Diseases 11th Revision
MEDLINE: Medical Literature Analysis and Retrieval System Online
MeSH: Medical Subject Headings

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Protocol

Digital Game Interventions for Youth Mental Health Services (Gaming My Way to Recovery): Protocol for a Scoping Review

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Abstract

Background: Digital or video games are played by millions of adolescents and young adults around the world and are one of the technologies used by youths to access mental health services. Youths with mental health problems strongly endorse the use of technologies, including mobile and online platforms, to receive information, support their treatment journeys (eg, decision-making tools), and facilitate recovery. A growing body of literature explores the advantages of playing digital games for improving attention span and memory, managing emotions, promoting behavior change, and supporting treatment for mental illness (eg, anxiety, depression, or posttraumatic stress disorder). The research field has also focused on the negative impact of video games, describing potential harms related to aggression, addiction, and depression. To promote clarity on this matter, there is a great need for knowledge synthesis offering recommendations on how video games can be safely and effectively adopted and integrated into youth mental health services.

Objective: The Gaming My Way to Recovery scoping review project assesses existing evidence on the use of digital game interventions within the context of mental health services for youths (aged 11-29 years) using the stepped care model as the conceptual framework. The research question is as follows: For which youth mental health conditions have digital games been used and what broad objectives (eg, prevention, treatment) have they addressed?

Methods: Using the methodology proposed by Arksey and O'Malley, this scoping review will map the available evidence on the use of digital games for youths between 11 and 29 years old with mental health or substance use problems, or both.

Results: The review will bring together evidence-based knowledge to assist mental health providers and policymakers in evaluating the potential benefits and risks of these interventions. Following funding of the project in September 2018, we completed

the search in November 2018, and carried out data screening and stakeholder engagement activities during preparation of the protocol. We will conduct a knowledge synthesis based on specific disorders, treatment level and modality, type of service, population, settings, ethical practices, and user engagement and offer recommendations concerning the integration of video game technologies and programs, future research and practice, and knowledge dissemination.

Conclusions: Digital game interventions employ unique, experiential, and interactive features that potentially improve skills and facilitate learning among players. Digital games may also provide a new treatment platform for youths with mental health conditions. Assessing current knowledge on video game technology and interventions may potentially improve the range of interventions offered by youth mental health services while supporting prevention, intervention, and treatment.

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KEYWORDS

mental health; mental disorders; biomedical technology; video games; virtual reality; mental health services

Introduction

Background

The risk of developing first-time mental health disorders is greatest among adolescents and young adults [1]. Early intervention provides a window of opportunity to promote detection, rapid access, monitoring, and treatment of youth mental health problems in the community [2-9]. Youth mental health programs designed to serve people between the ages of 11 and 25 years are rapidly emerging worldwide [6,9-13] and showing promising results in terms of improving mental health–related outcomes [5,14-16]. Several definitions of youth exist in the literature. For Statistics Canada and other international agencies, youth is considered to be a transition period in the life course between 16 and 29 years, involving a concentration of formative moments that occur in close succession (eg, achieving autonomy in relation to the family of origin, financial and residential autonomy, a stable couple relationship, family formation, and participation in society through full citizenship [17,18]). The literature on high-quality care in youth mental health programs calls for the following approaches: a community-based stepped care model of care; a youth-friendly physical space; stigma-free culture of care; and innovative information technology solutions to support the ability of programs to monitor the provision of high-quality care (measurement-based care) [6,9-13] and meet the needs of a generation that has grown up with digital technologies [19]. Youths in contact with mental health services strongly endorse the use of technology to receive information on medication, education, career, employment, and mental health, support their treatment journeys (eg, decision-making tools), and facilitate recovery [20].

Research in e-mental health is developing rapidly [21-23] despite slow uptake in clinical settings. Various reviews to date have identified how e-mental health tools may be effective in improving access to services, supporting evidence-based and personalized care, encouraging patient engagement, reducing stigma, and ensuring cost effectiveness [21-28]. These critical and comprehensive reviews have assessed various technologies, including telehealth, internet-based interventions or virtual communities, virtual reality and artificial intelligence, and video games or serious games [21-23,29]. What is needed, however, is a focused review that accurately assesses the treatment capacity, impact, and implementability of specific e-mental health solutions and technologies for youths. This review aims to address this need by exploring how digital game interventions may be integrated within current youth mental health services.

At any given moment, digital or video games are being played by millions of adolescents and young adults around the world. These games are among the preferred and most heavily used technologies among youths who access mental health services [30,31]. Not surprisingly, there is a growing body of literature that explores the advantages of playing digital games among players in different age groups, particularly in terms of improving attention span, memory, and problem-solving skills [32]; enhancing the ability of gamers to cope with failure [32] and manage emotions [32]; improving information retention [33]; facilitating deep learning [34]; supporting and promoting behavior change [35]; and promoting socialization [32]. Moreover, evidence suggests that games can be effectively used as therapeutic tools to support recovery from anxiety, depression, posttraumatic stress disorder (PTSD), and other disorders [36-42]. Finally, youths and primary care providers have identified video game technology as a valuable tool for early intervention and treatment [30,43].

Most studies have focused thus far on the negative impact of video games, describing potential harms related to aggression, addiction, and depression [44,45]. The World Health Organization, in the *International Classification of Diseases, 11th Revision*, recently identified a new classification of gaming disorder, defined as a pattern of gaming behavior ("digital-gaming" or "video-gaming") characterized by impaired control over gaming, increasing priority given to gaming over other daily life activities, and continuation or escalation of gaming despite the occurrence of negative consequences. This new classification leaves health care providers with unique challenges related to assessment, diagnosis, and treatment for this disorder [46,47].

In light of these two contrasting realities—the desire of youths to play games and the evidence for gaming disorder—there is a need for critical assessment of the existing evidence on the use of digital game interventions within the context of mental health services for youths and the ways in which such interventions can be implemented in a safe and effective way.

Objective

Systematic reviews and meta-analyses that assess the accessibility, feasibility, and effectiveness of serious video games for use in mental health have been published [36-42]. However, these reviews focused on specific mental health conditions, mainly depression and anxiety [36-42], without reporting on other mental illnesses affecting youths, such as psychosis, eating disorders, and substance misuse. Moreover, some of these reviews assessed the effectiveness of digital games for mental health in mixed-age populations, which often included older adults. Based on these gaps, the aim of the Gaming My Way to Recovery scoping review project is to identify and map the available evidence on the use of video game technologies for youths aged 11 to 29 years with mental health and substance use problems. This work complements and expands on existing systematic reviews by exploring the available evidence with respect to various mental health conditions affecting youths.

Methods

Objectives and Research Questions

This scoping review will use the stepped care model, a care delivery system in which treatment options are triaged based on relevant criteria (eg, severity) and shared decision-making practices [48,49], as a conceptual framework for mapping the available evidence on the use of digital game interventions. The stepped care model is often used in the youth mental health field to promote greater integration between mental health services, tailor treatments to youths, and ensure high-quality care.

In light of this model, our primary research question is as follows: For which youth mental health conditions have digital games been used and which broad objectives (eg, prevention, treatment) have they addressed?

Secondary research questions that will help generate a comprehensive picture of the available evidence are as follows: First, regarding equity, effectiveness, and impact: In which youth populations have digital game interventions been used and shown to be effective? What do we know about the experiences of youths and providers in receiving or providing mental health interventions through video game technologies? What are the current research gaps in this area? Second, regarding efficiency and process: How have digital game interventions been employed as prevention and treatment interventions in youth mental health services? What have been the outcomes of these programs? What barriers and enablers affect the use of digital or video games in clinical settings? Third, regarding engagement: What do we know about youth, family, and provider involvement in the creation and evaluation of digital game interventions for prevention and treatment of mental health conditions? Fourth, regarding relevance and sustainability: What evidence exists for the ability of digital game interventions to support youth mental health services? How can this evidence be used to support the integration of digital game interventions into youth mental health services? And fifth, regarding ethical practices: How may video game interventions be used in youth mental health services without doing harm?

Scoping Review Method

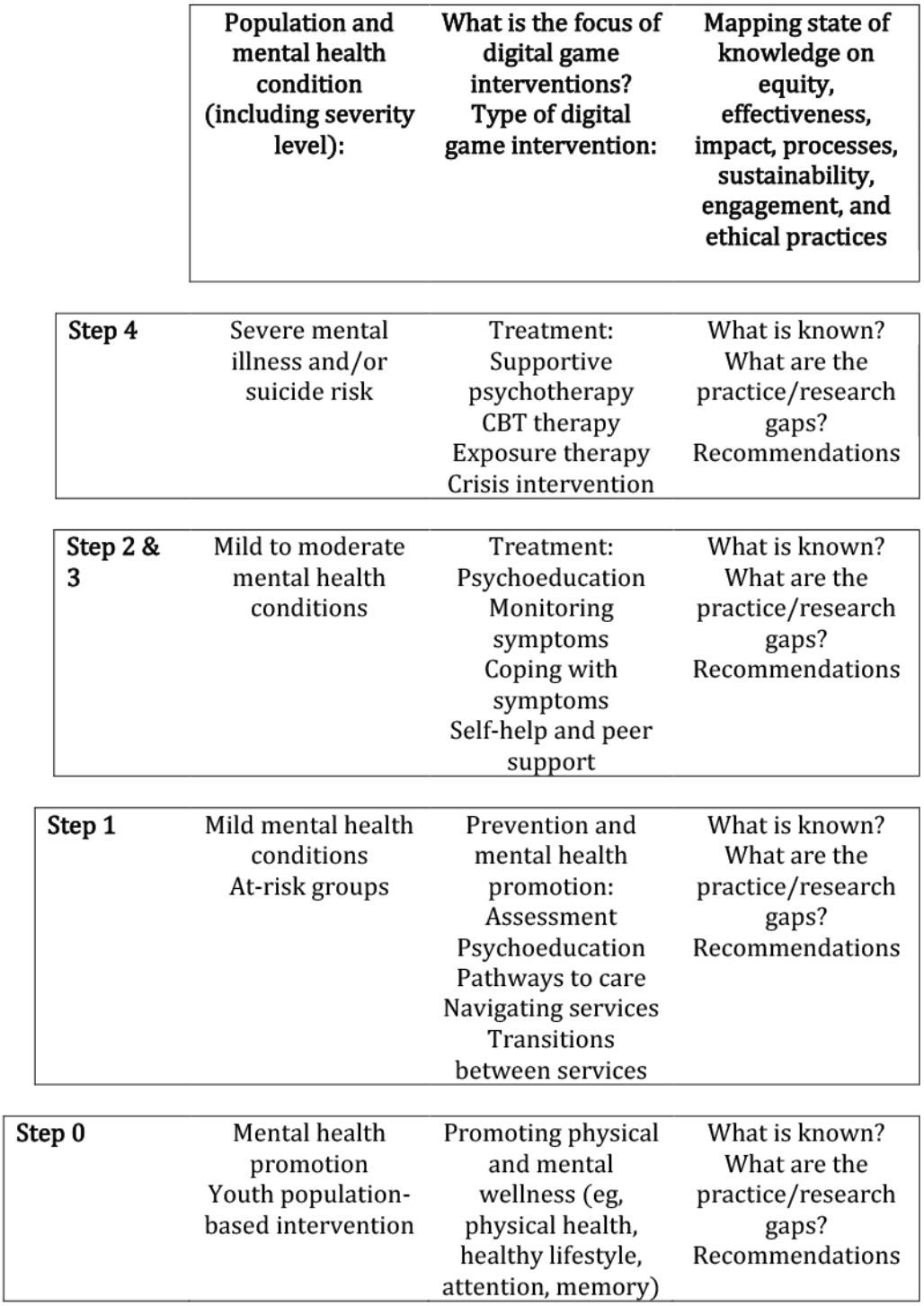
To answer these research questions, we will conduct a scoping review that will systematically capture the main evidence, types of evidence, key concepts, models, and gaps in research on the use of digital game interventions for youths 11 to 29 years old with mental health and substance use problems. Scoping reviews are useful for the assessment of emerging evidence when it is still unclear whether more specific questions might be posed. A scoping review is the most suitable method for knowledge synthesis, as it considers different types of evidence and publications (from empirical studies, to reviews, to coverage of a complete body of literature) while also reporting on the types of evidence that inform practice in the field and the ways in which research has been conducted.

We will use the scoping review methodology developed by Arksey and O'Malley to guide this process [50]. Building on the Arksey and O'Malley framework, Levac and colleagues [51] further suggested that the consultation stage provide opportunities for stakeholder involvement, where insights beyond those reported in the literature may be provided. Therefore, we will engage partners and knowledge users, acting as consultants, throughout the scoping review.

Stepped Care as a Conceptual Framework

This scoping review will use the stepped care model as a conceptual framework to systematically guide synthesis of the literature, identify existing evidence and gaps in knowledge, and provide recommendations for future studies and interventions. Model 1 (Figure 1) is our adaptation of the traditional stepped care model, which shows the targeted population and treatment options (from low-intensity to high-intensity treatment). This revised model brings together the aims and research questions posed in this knowledge synthesis project with the targeted population and treatment options. Using model 1, we will map the video game interventions that have been studied and the level of evidence for each video game intervention, looking at equity, effectiveness, impact, processes, sustainability, user engagement, and ethical practices, where possible.

Figure 1. Model 1 adaptation of the traditional stepped care model. CBT: cognitive behavioral therapy.



Stakeholder Engagement

This knowledge synthesis project will engage stakeholders and partners (youths, family members or caregivers, and health care providers) within key stages of the project: proposal development, statement of aims and objectives, and data analysis and synthesis, as well as, importantly, the dissemination and translation of findings. The involvement of 3 different stakeholder groups will increase the relevance of the scoping review while enhancing its quality, innovation, and potential for implementation in youth mental health care settings. We will invite youths experiencing mental health problems who are also video game players to participate in this project and share their knowledge and expertise. They have unique experience and insight into their own health conditions and treatment, as well as knowledge and opinions on video game technologies (including associated ethical considerations). Caregivers (eg, family members and friends) are experts in how to care for and

support those with mental illness or substance use problems and in knowledge of their needs. Thus, they may provide valuable perspectives on how video game interventions can help or hinder the recovery journey of affected family members and friends.

ACCESS Open Minds [16,52], a pan-Canadian network of 14 youth mental health service sites, will actively support this project. Youths and family members from the 3 ACCESS Open Minds Councils (National Youth Council, Family and Careers Council, and the Indigenous Council) and members of other youth networks will be invited to participate in the project. A project advisory group composed of 4 to 6 members (youths and family members interested in digital games as an intervention) will be established and meet 3 to 4 times over the course of the project. A peer researcher, a youth with lived experience and self-identified as a gamer, will help facilitate the meetings, which will cover the following topics: the nature of a scoping review, and a general discussion on project aims and how the knowledge of each advisory member may contribute to the project (first meeting); a review of data extraction forms and preliminary findings (second meeting); and the design of knowledge translation activities and materials, including contributions from the project advisory group (third and fourth meetings).

Stakeholders, especially youths, may provide insight on how to differentiate between playing video games for fun and the problems that may occur in relation to playing video games [53,54], suggesting which elements of the games should be further explored during the data extraction process. At the same time, stakeholders may benefit through their involvement in terms of their ability to access information and increase knowledge and skills concerning knowledge synthesis methodologies and processes.

Members of the project team are health care providers from 3 countries (Australia, Canada, and Denmark), who represent various youth mental health networks (ACCESS Open Minds, Youth Wellness Hubs Ontario, Frayme, Headspace, and Black Dog Institute). These youth networks will support dissemination of the project among their own members, as well as through professional associations such as the Early Psychosis Intervention Ontario Network and game research programs or groups (Participatory Research at McGill; Games and Gamification for Human Development & Well-being Working Group; and the Center for Computer Games Research at the IT University of Copenhagen).

Scoping Review Stages

The following section describes the 5 stages involved in the Arksey and O'Malley scoping review methodology.

Stage 1: Identifying the Research Question(s) and Revising the Protocol

We will present this scoping review protocol and proposed research questions to project partners and knowledge users, including youths, families, and providers, to gather feedback and identify missing elements. If required, we will revise the protocol to reflect the input of project partners and knowledge users during the different phases of the project.

Stage 2: Identifying Relevant Studies (Databases to be Searched and Strategies)

A systematic search strategy has been constructed by a health sciences librarian in consultation with the research team and reviewed by another librarian as recommended by the Peer Review of Electronic Search Strategies checklist [55]. This strategy will be run in MEDLINE (through Ovid) and adapted for CINAHL, EMBASE (Ovid), PsycINFO (Ovid), the Cochrane Library, and ProQuest Dissertations & Theses for all years from inception of each database to November 30, 2018. We will update the search of all relevant databases for the 12 months prior to publication of our results. No limits for language or publication type will be applied. We will not include gray literature in this project. We will use the citation software EndNote (Clarivate Analytics) to remove duplicate citations. Multimedia Appendix 1 presents the MEDLINE search strategy.

Stage 3: Study Selection

The review process will comprise 2 levels of screening: (1) a title and abstract review, and (2) a full-text review. We will use Rayyan (Qatar Computing Research institute) [56] to screen titles and abstracts. In the first phase, 2 research assistants will independently examine titles and abstracts for all retrieved citations according to the following inclusion criteria: (1) the intervention used a digital game delivered on any technical platform, including PCs, consoles (handheld console), mobile devices, and virtual reality; (2) the intervention targeted mental and substance use disorders, defined in terms of specific disorders, including mood disorders (eg, depression, bipolar disorders), anxiety disorders, obsessive-compulsive disorder, schizophrenia and related psychotic disorders, eating disorders, PTSD, and substance-related disorders; (3) the study pertained to an age group between 11 and 29 years [7,17,18,57]; (4) the study was published in English or French; and (5) the study was published between 2010 and 2020. Articles will be excluded if they (1) are theses or dissertations, (2) do not provide an abstract, (3) are conference presentations, (4) focus on a game intervention that targeted physical illnesses (eg, cancer, dementia, Alzheimer disease, epilepsy, and chronic pain), (5) primarily used telemedicine interventions, or (6) focused on commercial games for entertainment purposes only or were nondigital games (eg, board games).

We will retain studies identified as eligible for phase 2 (full-text review). In this phase, 2 raters will screen the full texts of articles to determine whether they meet the inclusion criteria listed above. We will retain eligible studies for data extraction in stage 4. Differences in ratings will be resolved through discussion until a consensus is reached. If agreement is not reached, the project team leader will intervene to make a final determination.

Stage 4: Data Collection and Extraction

A data extraction sheet will be developed by the research team and consulting partners by adapting relevant critical appraisal tools. This sheet will confirm the eligibility of each study and extract the relevant characteristics. Knowledge users will have the opportunity to provide input to confirm that the information for extraction is relevant. The variables to be extracted from the articles are divided into the following categories: (1) participant

characteristics, including age, (2) study characteristics and methodology, (3) game characteristics, (4) youth and family engagement in the design of the digital game intervention, (5) youth and family engagement in the evaluation process, (6) treatment settings, (7) treatment level (health promotion; treatment for mild, moderate, and severe mental illness), (8) level of integration with in-person treatment, (9) game costs, and (10) sustainability. Specific participant and study characteristics include variables such as target group, recruitment, treatment type (single- or multicomponent interventions), primary outcome measures, type and extent of guidance provided during the intervention, setting of the intervention, study conditions, attrition, and results. Game characteristics will comprise variables such as the title of the game used in the study, serious game type, game genre, purpose of the game, and country where the study took place (country identification, and whether it is a low- to middle-income country or a high middle- to high-income country).

Stage 5: Data Summary and Synthesis of Results

This scoping review will map knowledge, evidence, and overall findings aligned with the proposed research questions. We will analyze each variable captured on the extraction form based on the type of data and using descriptive statistics, for example, percentages and thematic analysis. We will summarize the data using statistical plots and graphics, as well as through the creation of text tables, to describe key characteristics for each revised study (see Results section). We will further integrate the review findings into model 1. A revised model 1 will provide a synthesis of results for the available evidence on equity, effectiveness, impact, processes, efficiency, sustainability, engagement, and ethical practices in the use of digital game interventions for mental health and substance use conditions in youth populations.

Quality Assessment

Throughout the data extraction process, we will use well-known critical appraisal tools to ensure the extraction of essential information from the articles and to promote rigor. The critical appraisal tools that we plan to use, if appropriate, include Preferred Reporting Items for Systematic Reviews and Meta-Analyses for meta-analyses [58] and Grading of Recommendations, Assessment, Development and Evaluations II for guidelines [59]. When appropriate, for example in the case of randomized controlled trials, systematic reviews, and meta-analyses, we will use critical appraisal tools to assess the risk of bias and report our findings as part of the final report.

Results

Stage 1

We began the identification of relevant studies in November 2018. Stakeholder engagement began in December 2018. Data extraction (stage 1) was slowly carried out during the publication process for this protocol. We expect that the completion of stages 2 to 4 will take 1 to 2 months. After completion of stages 1 to 3, we will confirm the number of studies that meet the inclusion criteria (title and abstract); the number of studies that meet the inclusion criteria (full-text review); and the number of studies included in full-text data extraction. Stage 5 will include the summary and synthesis of the results using the conceptual framework (model 1) and will take approximately one month to complete.

Anticipated Outcomes

The scoping review will provide knowledge on the use of digital game interventions for youths aged 11 to 29 years with mental health and substance use problems. More specifically, we will synthesize knowledge related to the following subthemes and subpopulations: (1) specific disorders (eg, anxiety, depression, psychosis, PTSD, eating disorders), (2) level of treatment (mental health promotion, prevention, treatment), (3) modality of treatment (self-help, psychoeducation, psychotherapy), (4) type of service (eg, mental health intervention, substance use treatment, primary care, employment or educational supports), (5) population (eg, indigenous; ethnoracial; lesbian, gay, bisexual, transsexual, transgender, intersexual, queer, questioning, 2-spirited; disabled, linguistic, low income), (6) settings (eg, community care, primary care, specialized services, rural or remote services), (7) ethical practices, and (8) level of user engagement.

We will revise and update this list of anticipated outcomes based on project findings.

In relation to specific knowledge mobilization outcomes, this review will (1) provide recommendations on how to best integrate video game technologies and programs into youth mental health settings and services, (2) identify research and practice gaps in the literature on video game technologies in youth mental health to inform future research projects, and (3) generate different knowledge dissemination materials to share project results with key knowledge users (eg, youths, caregivers, service providers), as well as pertinent partners, associations, and networks.

Discussion

Overall, digital game interventions and solutions hold promise as learning machines [60] because of their ability to build on pedagogical principles (eg, experiential learning, active engagement of learners). They may employ unique features that facilitate learning processes, introduce new modalities to increase knowledge, and improve coping strategies and skills, while providing a more interactive and youth-friendly way to deliver treatments. This review on digital game interventions will provide evidence to assist mental health providers and policymakers in evaluating the potential risks of digital game interventions for youths experiencing mental health and substance use problems. Providers working in youth mental health settings may promote the implementation of digital game interventions in their services, if appropriate, to support prevention and treatment.

Methodological knowledge gained from this scoping review process will be useful in the systematic assessment of other e-mental health technologies: virtual communities, telemedicine, etc. Moreover, this scoping review project will gather valuable knowledge on how to involve different stakeholders in knowledge synthesis activities so that future reviews on

e-technologies may use similar processes in seeking input from pertinent stakeholders.

Clinical knowledge gleaned from this review will also generate valuable knowledge on how, and for what purpose, video game interventions can be effectively implemented in youth services for mental health and substance misuse, as well as the appropriate conditions for doing so. The assessment of current knowledge on digital game interventions has the potential to improve treatment in youth mental health services.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
MEDLINE search strategy.
[DOCX File , 100 KB - resprot_v9i6e13834_app1.docx]

Multimedia Appendix 2
Peer review report summary.
[PDF File (Adobe PDF File), 233 KB - resprot_v9i6e13834_app2.pdf]

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Abbreviations

PTSD: posttraumatic stress disorder

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Proposal

Exploring the Effectiveness of an Integrated Physical Activity and Psychosocial Program Targeting At-Risk Adolescent Girls: Protocol for the Girls United and on the Move (GUM) Intervention Study

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Abstract

Background: Adolescents are highly susceptible to negative self-perceptions, likely due to their social cues and environment. The presence of these negative self-perceptions has been shown to adversely impact levels of physical activity (PA). Although PA has the ability to foster improved self-perceptions, the rates of PA among adolescents continue to descend, with girls appearing to be most susceptible to these declines. At-risk adolescent girls, who may experience a number of negative preceding lifestyle conditions, may be exceptionally vulnerable to declines in PA. There are a high number of adolescent girls from low-income and abusive households in British Columbia, Canada, thus indicating a need for a program to relay the importance of PA and healthy lifestyle behaviors.

Objective: This paper aims to describe the protocol of the Girls United and on the Move (GUM) pragmatic intervention, an integrated PA and psychosocial program aimed at improving self-compassion, social connectedness, and overall self-perceptions among at-risk adolescent girls.

Methods: Using a quasi-experimental mixed methods approach, the GUM intervention was conducted in 5 schools in British Columbia, Canada. Adolescent girls aged 11 to 15 years who were identified as at risk were included in the study. The 9-week intervention, co-delivered by a PA/health promotion–trained researcher and a registered social worker, involved a PA component and a psychosocial component with evidence-based topics addressing the concerns of the adolescent girls. The following outcomes were evaluated: PA, self-compassion, social support, leader supportiveness, and sport enjoyment and commitment. Program acceptability and satisfaction was also examined. Outcome measures were assessed at baseline (week 1), week 6, and postintervention (week 9), and interview data concerning program acceptability and satisfaction were collected at postintervention from a subsample of participants.

Results: A total of 101 participants were invited to participate in the GUM intervention. Reporting of the results is projected for the fall of 2020.

Conclusions: It is anticipated that the GUM intervention will enhance PA while also improving self-compassion, social connectedness, and overall self-perceptions among at-risk adolescent girls. The findings of this research will contribute to the literature concerning PA and various psychosocial factors that impact the physical and mental health of at-risk adolescent girls.

Trial Registration: Clinicaltrials.gov NCT03567200; https://clinicaltrials.gov/ct2/show/NCT03567200.

International Registered Report Identifier (IRRID): DERR1-10.2196/15302

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KEYWORDS

adolescence; girls; at-risk; self-compassion; sport enjoyment; physical activity; community-based intervention

Introduction

Worldwide levels of physical activity (PA) among adolescent girls have seen a substantial decline in past decades [1,2], with this decline being related to a number of physical and mental health issues (eg, increased risk of cardiovascular diseases, overweight and obesity, type 2 diabetes, depression, anxiety, poor emotional health, and overall mortality rates) [3-5]. Despite enhanced efforts to increase levels of PA among adolescent girls, only 33% of adolescent girls currently report being physically active, with only 16% meeting the PA recommendations put forth by the World Health Organization [6] (ie, a minimum of 60 minutes of moderate-vigorous intensity PA daily). The lack of participation in PA and sports among adolescent girls is thought to be influenced by a number of negative self-perceptions, including low levels of self-compassion, poor social support, and social isolation [7-10].

At-risk adolescent girls are especially vulnerable to these negative self-perceptions, as they may be faced with additional hardships, including low socioeconomic housing, exposure to substance abuse, sexual exploitation, etc [11]. At-risk adolescents have been known to have a higher prevalence of depression and low self-esteem compared with the general population of adolescents [9], possibly leading to a higher likelihood of adopting future problem behaviors, which consequently have more serious long-term consequences [12,13]. In fact, conditions such as low income, insufficient caregiving, and family breakup have all been identified as conditions predictive of youth delinquency [14,15]. Adolescents who are categorized as at risk in this regard are also at higher risk of compromised health outcomes, such as obesity, cardiovascular diseases, type 2 diabetes, and numerous other chronic diseases [2]. For the purposes of this study, at risk was operationally defined as one with a dysfunctional family life, socioeconomic instabilities, various forms of abuse, or mental health issues such as anxiety or depression [16,17].

By providing an emotionally supportive environment for this population, it is likely that enhanced physical and mental health outcomes will be exhibited, as a strong support system is able to establish a sense of belonging and aid in case of problems [18]. In particular, engaging in regular PA during adolescence has been directly linked to reduced rates of anxiety, depression, emotional disturbances, and psychological distress [19,20] and improved self-perception facets, such as self-esteem, self-confidence, self-compassion, and perceived social support [20-22]. For instance, Raudsepp and Vink [23] examined the longitudinal associations between girls' sedentary behavior and depressive symptoms and found that higher levels of depressive symptoms were predictive of greater sedentary behavior. Additionally, Kliziene and colleagues [24] investigated the influence of a 7-month exercise intervention on levels of anxiety among adolescents aged 14 to 15 years and revealed that the exercise intervention was related to decreased anxiety scores. Further, self-compassion, or the way in which an individual offers kindness and support to oneself [25], has been shown to increase in individuals who are physically active [26], and by increasing self-compassion, one is more apt to engage in other healthful behaviors (eg, healthy diet, stress-reducing practices) [27]. Social support provided from peers and significant adult figures has been shown to play a large role in the adoption of various health behaviors, and the critical role that program leaders play as personal role models has been vastly highlighted throughout the literature [28,29]. Positive self-perceptions and PA and sport enjoyment are also key emotional and motivational processes that have been linked to continued participation in PA [30].

There have been various interventions to date with the goal of improving PA behavior among adolescent girls; however, few have focused on at-risk girls. There is a need for tailored and targeted evidence-based programs focused on addressing specific physical, mental, and psychosocial health issues that at-risk adolescent girls may currently face in everyday life. To address these issues, Girls United and on the Move (GUM), an integrated PA and psychosocial program, was developed. The overarching purpose of the GUM study was to explore the effectiveness of an integrated PA and psychosocial program on PA behaviors and various identified psychosocial factors among at-risk adolescent girls. The purpose of this paper is to describe the intervention design and methodological protocol of the GUM program.

Methods

Study Design

The GUM study protocol was prepared according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines [31] and used an exploratory quasi-experimental pretest-posttest design. Data collection occurred at baseline (T1), week 6 (T2), and postintervention (T3) and included self-report questionnaires and semistructured interviews. Recruitment for the GUM program began in December 2017 and was completed in May 2019. Figure 1 provides a flow diagram of the GUM protocol, and Table 1 provides a detailed description of relative program recruitment dates.

Figure 1. Flow diagram of the GUM protocol. GUM: Girls United and on the Move.

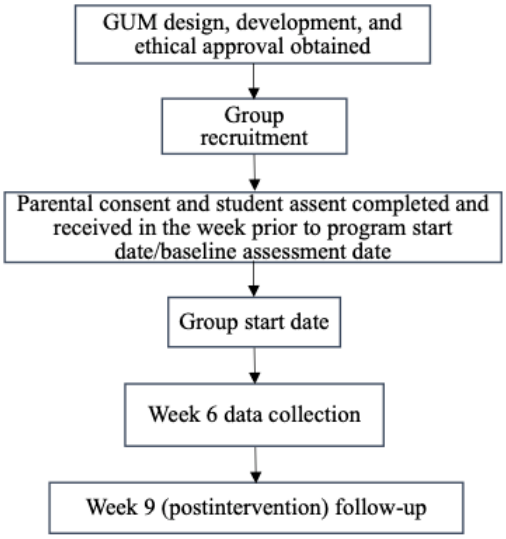

Table 1. Detailed description of relative program start dates[a].

Group No.	Number of participants	Program recruitment
1	13	January 2018
2	11	January 2018
3	13	April 2018
4	9	April 2018
5	7	July 2018
6	14	September 2018
7	10	September 2018
8	11	October 2018
9	13	May 2019

[a]Program commencement dates were consistent with program recruitment dates. Each program was 9 weeks in duration.

Ethical Approval

Ethical approval was obtained from the Behavioural Human Research Ethics Board at the University of British Columbia (H17-01540) and from School District 23. In all cases, both parental consent and student assent were obtained prior to data collection.

Objectives

The specific objectives of the GUM study were (1) deliver and explore the effectiveness of the 9-week GUM intervention program on the primary outcomes of PA, self-compassion, social support, and leader behavior; (2) explore the effectiveness of the 9-week GUM intervention program on the secondary outcomes of sport enjoyment and commitment; and (3) examine participant perceptions of the GUM program in terms of acceptability and satisfaction.

Participants, Setting, and Recruitment

Participants of the GUM study included adolescent girls from 5 middle schools in British Columbia, Canada, who were aged 11 to 15 years and identified as at risk. Guidance counselors from each middle school used these criteria to identify girls and invite them to participate, encouraging those whom they felt would benefit from participating in the program. The guidance counselors were exclusively responsible for recruitment because they had previous history working with the girls on a regular one-to-one basis due to the girls' behavioral inadequacies, issues with home life, or mental health–related concerns such as anxiety or depression. Counselors then provided interested individuals with further detailed information about the program (including parental consent and student assent forms) and prompted the students to discuss the program with their parents or guardians. Participants were asked to return the signed consent and assent forms to the guidance counselor or the research team prior to the start of the program or at T1. There were no specific exclusion criteria except that participants could not have been a participant of the previous pilot study, Girls on the Move (GoM) which took place from 2015 to 2016 [32]. A total of 101 participants forming 9 groups were recruited from 5 schools throughout the region, with group sizes ranging from 7 to 14 participants per school. Each group had a different start date, with some groups in different schools running simultaneously. However, no two groups from the same school

received the intervention at the same time. Recruitment was completed in May 2019.

Each GUM intervention session occurred at the participating school (eg, a classroom, gymnasium, or outside on school grounds) or off campus within the community, depending on the scheduled activity for the given day (eg, kickboxing occurred at a local community kickboxing and martial arts studio). The participants were provided with transportation to all off-campus activities by the trained researcher and social worker (ie, program facilitators). Both facilitators were authorized and insured to provide transportation for program participants. Participation was completely voluntary and all participants were informed that they did not need to participate in the research component to participate in the GUM program. Those who chose to participate in the research component were informed that they could withdraw from participation in the study at any time and without consequence.

Description of the GUM Intervention

Pilot Study

The GUM intervention was developed and refined based on the GoM pilot study. GoM was conducted from 2015 to 2016 and included 2 middle schools, with a total of 24 participants aged 11 to 17 years. The purpose of the GoM intervention was to examine program and methodological feasibility and gain further insight concerning PA experiences, preferences, and self-concept among at-risk adolescent girls [32]. Findings from the GoM program indicated that the assessments used were appropriate, program delivery (ie, duration, geographic setting, and facilitation) was acceptable, and participants were satisfied with the activities and content. The findings also suggested that adolescent girls are aware of the importance of proper PA and nutrition in relation to health outcomes, believe that peer social support is important for PA engagement, and feel that enjoyment is crucial when dictating PA participation. Based on these outcomes, minor refinements were made to the GUM intervention protocol and research methodology, including the addition of alternative physical activities on and off school grounds, the use of personalized journals for participants to write in, the addition of measures to assess different contexts of social support and the impact of the leaders and facilitators, and the name change from Girls on the Move to Girls United on the Move.

Program Components

The GUM intervention was a pragmatic PA and psychosocial program designed specifically for at-risk adolescent girls. Components of the self-determination theory, particularly autonomy, competence, and relatedness, were integrated throughout the intervention because these are known to affect intrinsic motivation and engagement in PA, especially among underserved youth [11,33]. The GUM intervention consisted of 9 weekly, group-based, 90-minute face-to-face sessions that were cofacilitated by a trained researcher and a registered social worker from a partnering community organization or key stakeholder. The partnering stakeholder was a nonprofit organization with the goal of bringing an end to violence and poverty and seeking justice for children and women. This nonprofit organization works extensively with adolescent populations, particularly those categorized as at risk. Each GUM group consisted of 7 to 14 at-risk adolescent girls from participating schools. Smaller groups were desired in order to create an intimate and supportive environment and provide a greater opportunity for participants to get acquainted with each other and the program facilitators.

Within each of the weekly 90-minute program sessions, 45 minutes of PA were delivered by a trained researcher and 45 minutes were allocated to social worker–led discussions on various psychosocial topics. Examples of physical/sport activities included on-campus activities such as yoga, team obstacle courses, and soccer, or off-campus activities such as rock climbing, self-defense classes, and fitness classes. Examples of psychosocial topics that were discussed within each group included healthy relationships, conflict resolution strategies, substance abuse issues, sexuality, and gender issues. Table 2 outlines the components of the GUM intervention.

In addition to the group discussions facilitated by the social worker, personal journals were distributed to each participant during week 1. These journals provided participants with an opportunity to disclose their thoughts and feelings about their current state, any personal struggles they may be undergoing, or anything to do with the GUM program itself. Participants returned the journals to the registered social worker at the end of each of the weekly GUM sessions, indicating if they wanted the social worker to read the entry and give a written response. This allowed participants to reach out and seek advice if they needed it, without requiring the participants to talk in person about their issues to either one of the program facilitators. Although not previously used in the GoM pilot study, disclosure journals have been used previously by the social worker and have been reported to be an important component of previous programs delivered to this population. The disclosure journals were used as a component of the intervention, but no data were extracted or evaluated from the journals. After program completion (ie, after week 9), a subsample of participants (30/101, 29.7%) were invited to participate in an individual semistructured interview so that the program facilitators could gain further information concerning program acceptability and satisfaction. Those who attended a minimum of 80% (7/9) of the program sessions were invited to participate in the voluntary semistructured interviews. Participants were informed that they were able to withdraw from the study at any time, for any reason, without consequence. All personal data were coded and handled with confidentiality.

Table 2. Components of the Girls United and on the Move (GUM) program.

Week	Physical activity component	Psychosocial component
Week 1 (T1)[a]	N/A[b]	N/A
Week 2	Yoga	Emotional wellness
Week 3	Dance	Self-awareness, self-esteem, and body image
Week 4	Self-defense	Healthy relationships
Week 5	Hike/walk outdoors	Healthy sexuality
Week 6 (T2)[c]	Rock climbing	Communication skills, conflict resolution, and boundaries
Week 7	Kickboxing	Sexual exploitation and abuse
Week 8	Free play and outdoor games (eg, capture the flag, scavenger hunt)	Media and gender issues
Week 9 (T3)[d]	N/A	N/A

[a]Introductions and questionnaires were completed. Baseline data were collected at T1.

[b]N/A: not applicable.

[c]The Learning Climate Questionnaire was the only self-report questionnaire administered at T2. See Outcome Measures for further information.

[d]Questionnaires and a wrap-up were completed. Follow-up data were collected at T3.

Outcome Measures

Mixed methods were used to collect and analyze data. Quantitative data measures consisted of self-report questionnaires to assess self-compassion, social support, leader supportiveness, and sport commitment and enjoyment. Qualitative data consisted of semistructured interviews with a subsample of program participants, which provided further insight concerning the acceptability and satisfaction of the program components, physical and psychosocial activities, resources, and overall delivery (ie, environment/facilities, facilitators, etc). Self-report measures were used because they are easy to administer, relatively inexpensive, and recognized as an acceptable means of recording participant responses and psychological constructs in youth populations [34]. Further, the guidance counselors advised us that handing out wearable measurement devices, such as accelerometers and pedometers, and having participants return them after the program could be very difficult, with a high likelihood that the devices would be lost, damaged, or stolen, which the counselors identified as an unfortunate reality within an at-risk population. The majority of the assessments occurred at T1 and at T3 at each participating school. Demographic information was collected during T1 and the Learning Climate Questionnaire (LCQ) [35] was completed at T2. Figure 2 provides the SPIRIT figure for the GUM trial.

Figure 2. Standard Protocol Items: Recommendations for Interventional Trials figure for the GUM study. GUM: Girls United and on the Move.

		Study period				
		Enrollment	Allocation			Closeout
Timepoint		*–2 to 0 weeks*	1 week	6 weeks	9 weeks	Postintervention
Enrollment						
	Parental consent	✓				
	Student consent	✓				
Interventions						
	GUM intervention		←	—	→	
Assessments						
	Demographics		✓			
	Physical activity		✓		✓	
	Self-compassion		✓		✓	
	Social support		✓		✓	
	Leader supportiveness			✓		
	Sport commitment and enjoyment		✓		✓	
	Program acceptability					✓

Demographics

Demographic information consisted of age, grade, number of siblings, housing location, mode of transportation to school, and whether the participant took part in any PA inside or outside of school.

Physical Activity

Level of PA was assessed using the Physical Activity Questionnaire for Children, a 10-item questionnaire that assesses the frequency of PA participation over a 7-day recall period [36]. This assessment has been reported to be a valid and reliable measure of PA among children and adolescents as it is able to accurately measure general PA patterns regarding intensity, frequency, and duration [36].

Self-compassion

The Self-Compassion Scale (SCS) was used to assess self-compassion through 6 subscales that include contrasting components: self-kindness vs self-judgement, mindfulness vs overidentification, and common humanity vs isolation [37,38]. The SCS is a 26-item scale that measures each of these components using a 5-point Likert scale (1=almost never, 5=almost always). The mean scores of each of the subscales can then be combined to yield a total score, which reflects a global self-compassion score [38].

Social Support

Perceived social support was assessed using the Child and Adolescent Social Support Scale (CASSS) [39]. The CASSS consists of five 12-item subscales that measure social support received from a variety of sources, including parents, teachers, classmates, close friends, and the school environment [39]. However, a condensed version without the school environment subscale was used, as the actual sources of social support received in the school environment were not well defined and were deemed unnecessary for the purposes of the GUM study [40]. The CASSS measures each of the items on a 6-point Likert scale, ranking each item on how often the participant feels they receive social support from the indicated source, from never (1) to always (6). Additionally, each item has a perceived importance scale, which is measured using a 3-point Likert scale ranging from not important (1) to very important (3). The CASSS has been represented as a valid and reliable measure for its intended purposes [40].

Perceived Leader Supportiveness

The LCQ [35] was used to assess participants' perceptions of support provided by the program facilitators. The LCQ is a 15-item measure with values ranging from strongly disagree (1) to strongly agree (7). It provides a good indication of the support that leaders provided for the 3 psychological needs (ie, autonomy, competence, and relatedness) [35]. Research shows that when these needs are supported, higher levels of psychological well-being are evident [35]. The LCQ has been shown to have extensive internal consistency and reliability, and it provides a valid indication of perceived supportiveness among youth outside of sporting contexts [41]. The LCQ was the only self-report questionnaire that was not administered at both T1 and T3; instead, it was distributed at T2.

Sport Commitment and Enjoyment

Sport commitment and enjoyment was assessed using the Sport Commitment Model [42], a questionnaire that has been shown to be a valid and reliable measure of sport commitment and enjoyment among youth [42]. The model addresses the 5 components related to sport commitment, namely sport enjoyment, personal investments in the self-indicated activity, involvement opportunities, social constraints, and involvement alternatives. Each of the 58 items is assessed using a 5-point Likert scale, with scores ranging from strongly disagree (1) to strongly agree (5).

Program Acceptability and Satisfaction

Face-to-face, individual, semistructured interviews were conducted with a subsample of participants (30/101, 29.7%) to gain greater knowledge concerning acceptability of and satisfaction with the GUM program. Participants were asked to share their thoughts, opinions, experiences, and recommendations concerning activities, education, and resources of the program. These interviews were conducted at postintervention by a trained researcher at a time that was convenient to the participants. Interview questions were informed by the study objectives and the research literature specific to this topic area and study population. Data from the interviews were audio recorded and transcribed verbatim with all possible identifiable information removed.

To enhance rigor, various verification strategies were used, such as having the data systematically checked by other trained researchers and closely monitoring gradually learned information as the research project progressed. Table 3 provides a summary of the measures used at the various data collection time points.

Table 3. Summary of measures and data collection time points.

Measure	Methods for data collection	Data collection time points
Demographics	Age, grade, number of siblings, housing location, main mode of transportation to school, participation in organized PA or sport inside or outside of school	Week 1 (baseline only)
Physical activity	Physical Activity Questionnaire for Children	Weeks 1 and 9
Self-compassion	Self-Compassion Scale	Weeks 1 and 9
Social support	Child and Adolescent Social Support Scale	Weeks 1 and 9
Perceived leader supportiveness	Learning Climate Questionnaire	Week 6 only
Sport commitment and enjoyment	Sport Commitment Model	Weeks 1 and 9
Program acceptability	In-person semistructured interviews	After week 9 (postintervention only)

Data Analysis

All data collected for descriptive purposes will be presented as means and standard deviations for all sample characteristics. All outcome variables, including changes in PA behavior, self-compassion, social support, perceived leader supportiveness, and sport commitment and enjoyment, will be analyzed using an analysis of covariance statistical design. The level of significance will be set at α=.05. Statistical analyses will be conducted using SPSS software (version 21.0; IBM Corp).

Inductive thematic analysis, as outlined by Braun and Clarke [43], will be used to analyze the interview data. Data analyses will be conducted by 2 trained researchers who will independently read the transcripts numerous times to become familiar with the data and generate initial codes by identifying important features of the data that are relevant to the study objective. Coded data will then be examined for similarities, grouped, and refined to identify potential themes [43]. Representative quotes will be used to provide evidence of the themes within the data.

Data Management

Data collection, as well as the handling and storage of data, will be coordinated within the Physical Health and Activity Behaviour (PHAB) Lab at the University of British Columbia. Demographic and self-report questionnaire data will be entered electronically by a trained researcher on the project. All paper-based data will be stored in a secure and locked filing cabinet located in the PHAB Lab. All electronic data will be stored on a password-protected computer also located in the PHAB Lab.

Results

The final recruitment phase for the GUM study was completed in May 2019, with the final study results projected to be published in the fall of 2020. The results of the GUM study will be disseminated through traditional avenues such as presentations at national and international academic meetings and publication in open-access, peer-reviewed journals. In addition, these results will be disseminated through plain language summaries to participants and through summary briefings to local stakeholders and government agencies.

Discussion

This protocol paper describes the methodology processes of a unique intervention encompassing both PA and psychosocial components, designed to help address the specific issues and barriers faced by an underserved subpopulation of adolescent girls. Through evidence provided in the literature, issues

revolving around self-compassion, social support, and social isolation are further amplified by lack of PA and sports participation. To make matters worse, adolescent girls who are considered to be at risk may experience magnified barriers to PA and lack interest in the potential benefits of a PA program. This is problematic because this specific population may experience significant benefits from a successful PA program compared with the general population of adolescent girls. PA has been shown to positively enhance self-perceptions of self-compassion and social support and to reduce social isolation, all of which are prevalent traits among at-risk adolescent girls [7,20,44]. Therefore, there is a need for an integrated PA and psychosocial program to help address these specific issues faced by this vulnerable population, as well as to foster at-risk girls' interests in the discussion of various psychosocial topics deemed important by them.

The GUM intervention was designed with these specific elements in mind. By providing a safe space for at-risk adolescent girls to talk about their issues and engage in fun, organized PAs that help emphasize the importance of a physically active lifestyle, the intervention's outcomes may be highly valuable to future research. However, this study does pose some potential limitations as a result of its noncontrolled environment, the population being studied, and the constraints based on budget and resources. First, the use of subjective self-report measures may be problematic, as the ability to recall PA engagement and other psychological factors can be imperfect among adolescents [45,46]. Second, this study was exploratory in nature and did not include a control group. Therefore, a true cause and effect cannot be determined and the outcomes may have been a result of some unforeseen variables. Additionally, the outcomes from this study will provide an estimate/exploration of effectiveness immediately after the completion of the intervention and do not include long-term follow-up, making it difficult to be certain of sustained behavior change. Lastly, the fact that the GUM study was specifically targeting at-risk adolescent girls means that the findings are only generalizable and applicable to this specific population.

In conclusion, given the lack of research around at-risk adolescents, the overarching goals and objectives of the GUM program may provide the current literature with promising results and aid in the future design and refinement of effective PA programs for at-risk adolescent girls.

Acknowledgments

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Authors' Contributions

CMC, CMS, SB, KCK, and LJF conceived the project and procured the project funding. CMC is leading the coordination of the trial. CMC, CMS, SB, KCK, LJF, and NH assisted with the protocol design. NH will manage the project, including participant recruitment, program delivery, and data collection, with assistance from CMC and SB. CMC and NH drafted the manuscript and all authors read, edited, and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer Review Report Summary SSHRC CRSH.
[PDF File (Adobe PDF File), 117 KB - resprot_v9i6e15302_app1.pdf]

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Abbreviations

CASSS: Child and Adolescent Social Support Scale
GoM: Girls on the Move
GUM: Girls United and on the Move
LCQ: Learning Climate Questionnaire
PA: physical activity
PHAB: Physical Health and Activity Behaviour
SCS: Self-Compassion Scale
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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