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Immediate and Long-Term Effects of an 8-Week Digital Mental Health Intervention on Adults With Poorly Managed Type 2 Diabetes: Protocol for a Randomized Controlled Trial

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Abstract

Background: Diabetes is a leading cause of years of life lost and accounts for approximately one-fourth of health care dollars spent in the United States. Many of these costs are related to poor medication adherence and lack of self-care behaviors and are thus preventable. Depression, which is more prevalent among people with diabetes than in the general population, predicts poorer management of one's diabetes, whereas positive affect predicts engaging in more positive health behaviors. Consequently, interventions that improve depression and positive affect may also improve diabetes-related outcomes among people with diabetes. Although preliminary research on the impact of such interventions among people with diabetes is promising, these studies focused primarily on in-person interventions, have had small samples, and lack long-term follow-up.

Objective: This study aims to examine the short- and long-term effects of a digital therapeutic platform focused on mental health among adults with poorly managed type 2 diabetes and elevated levels of depression.

Methods: This is a randomized controlled trial in which adults with a type 2 diabetes diagnosis, elevated hemoglobin A_{1c} (HbA_{1c}) levels ($\geqq 7$), and moderate to severe depressive symptoms will be randomly assigned to a positive emotion regulation skills intervention group or a sham digital intervention with only psychoeducational content. The study will take place over 14 months, including the 8-week intervention (or control) delivered via a digital therapeutic platform (Happify Health) and follow-up assessments at 3, 6, and 12 months postintervention. Throughout the intervention and for 1 week at each postintervention follow-up, participants will complete daily assessments of diabetes-related distress, diabetes regimen adherence, and mood. Our primary outcome, HbA_{1c}, will be self-reported every 3 months throughout the study. Secondary and exploratory outcomes will be assessed at baseline; at 8 weeks; and at 3, 6, and 12 months postintervention.

Results: Recruitment is expected to begin in June 2020. Participants will begin the study as they are recruited and will finish in waves. The final wave of data collection from the 8-week intervention is expected for winter 2020, with the completion of the 12-month follow-up in winter 2021.

Conclusions: Although previous research suggests that in-person psychological interventions have promising effects on both psychological and physical outcomes among adults with diabetes, digital interventions can be advantageous because they are easily scalable and reduce many barriers that prevent people from seeking treatment. This trial will provide important information about the effects of a digital mental health intervention among adults with type 2 diabetes, assessing both short- and long-term effects of this intervention on HbA1c, depressive symptoms, and other diabetes-specific outcomes. If successful, this may introduce a scalable intervention that would help reduce some of the preventable costs associated with diabetes.

Trial Registration: ClinicalTrials.gov NCT04068805; https://clinicaltrials.gov/ct2/show/NCT04068805.

International Registered Report Identifier (IRRID): PRR1-10.2196/18578

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Introduction

Prevalence and Costs of Diabetes

Diabetes is one of the most common chronic health conditions worldwide [1] and is considered to be a leading cause of years of life lost [2]. The prevalence of diabetes has also been increasing since the mid-1980s [3]. According to the Centers for Disease Control and Prevention, approximately 9.5% of the American population had diabetes in 2015 [4], most of which were type 2 diabetes diagnoses [4], and approximately 34% of the population met the criteria for prediabetes, suggesting that even more people are at risk of developing type 2 diabetes [4]. By 2030, 4.4% of the global population is estimated to have diabetes [5].

The economic cost associated with diabetes is also increasing because of the increased prevalence and the increased cost per patient [6]. The American Diabetes Association recently estimated the total annual cost of diabetes at US $327 billion when considering both medical costs and reduced productivity [7], and people with diabetes account for 25% of all health care dollars spent in the United States [7]. On an individual level, people with a diabetes diagnosis spend approximately US $16,750 annually for medical expenses, and more than 57% of those expenses are directly related to their diabetes [7]. The projected global costs associated with diabetes are estimated to increase from US $1.32 trillion in 2015 to US $2.12 trillion by 2030 [8].

However, many of these costs are preventable, resulting from poor diabetes management. In 2014, 577,040 diabetes-related hospitalizations in the United States were preventable [9], accounting for US $5.9 billion of the diabetes-related health care costs [10]. Previous research shows that many people with diabetes struggle with medication compliance [11], which puts them at an increased risk for hospitalization and mortality [12]. Similarly, adherence to physician-recommended self-monitoring of blood glucose levels tends to be low, particularly among people with type 2 diabetes [13].

Diabetes and Mental Health

People living with a chronic illness often report that depression is a major barrier to managing their condition and, worse, often do not seek treatment for their depression due to perceived stigma [14]. This is particularly relevant for people with diabetes, who are at a higher risk for depression than the general population [15]. Although depression does not appear to be directly related to hemoglobin A_{1c} (HbA$_{1c}$), a measure of average blood sugar levels over 3 months, in patients with diabetes [16,17], comorbid depression predicts poorer diet, poorer medication compliance, and greater functional impairment [18], which, in turn, predicts higher rates of diabetes-related preventable hospitalizations [19] and health care costs [18]. In addition, depression predicts higher levels of diabetes-related distress [20]. In turn, diabetes-related distress

predicts poorer HbA$_{1c}$ [16], and reducing diabetes-related distress leads to significant improvements in HbA$_{1c}$ level [17].

Conversely, higher levels of positive affect are associated with reduced mortality risk [21] and depression [22,23] among people with diabetes. Positive affect also promotes various health behaviors central to managing diabetes, including higher levels of physical exercise [24] and better diet [25]. Similarly, higher levels of self-compassion predict better behavioral and psychological outcomes among people with diabetes as well as better HbA$_{1c}$ levels [26]. Conceivably, self-compassion may lead to improved diabetes outcomes because it promotes greater well-being and better mental health [27]; however, self-compassion may also lead to more adaptive responses to difficulties patients face with managing their condition and, in turn, promote better diabetes management, including more effective health care use, healthy diet and physical activity, and better management of blood glucose levels [26].

Taken together, these findings suggest that better mental health among people with diabetes is associated with less diabetes-related distress and healthier lifestyles, which, in turn, predict better diabetes-related outcomes. Consequently, psychological interventions targeting mental health may lead people with diabetes to engage in healthier lifestyles, indirectly improving diabetes-related outcomes and reducing associated costs [22,28].

Impact of Mental Health Interventions on Diabetes

Research on the impact of mental health interventions applied specifically to people living with diabetes remains limited. Mindfulness and positive psychology (PP) interventions, which are effective in reducing depression and increasing well-being in the general population [29], have shown promise in improving depression, diabetes-related distress, and HbA$_{1c}$ levels among people with type 1 or 2 diabetes [30]. A recent systematic review showed that such interventions, particularly mindfulness-based interventions, led to improvements in psychological outcomes, including self-efficacy, self-compassion, well-being, mental health–related quality of life, positive affect, stress, diabetes-related distress, depression, and anxiety [30]. Mindfulness-based interventions also appeared to lead to improvements in HbA$_{1c}$ levels, although in some cases, the effects were not observed until 1 or 3 months postintervention [30]. Other research also suggested that mindfulness-based interventions have small to moderate effects on metabolic control [31].

Such interventions appear to be particularly successful when patients have higher baseline levels of diabetes-related distress and when interventions are delivered in a group format, draw on mindfulness-based stress reduction (MBSR), and include home practice assignments [32]. Although few of these studies have included long-term follow-up, there is preliminary evidence that the effects of mindfulness-based interventions on depressive

symptoms are maintained, or even stronger, after 6 months [30,32], although they may dissipate after 2 or 3 years postintervention [30]. Some findings also suggest that the effects of mindfulness-based interventions on HbA_{1c} levels may actually be stronger 1 or 3 months postintervention rather than immediately postintervention [30].

Preliminary research also suggests that cognitive behavioral therapy (CBT) may be effective in treating depression among individuals with diabetes, although the effects on diabetes-specific outcomes are mixed, and may be limited to people with high baseline depression scores [33]. In one study of adults with uncontrolled diabetes and unipolar depression, CBT designed for adherence and depression led to improvements in medication adherence and self-monitoring of blood glucose, HbA_{1c}, and depression, and these improvements were maintained for up to 12 months [34]. However, in another study, CBT was associated with improved depression relative to a control group, but the levels of glycosylated hemoglobin were better in the CBT group than in the control group only at 6 months posttreatment [35]. Similarly, a recent systematic review of 10 randomized controlled trials (RCTs) showed that CBT improved depression, quality of life, fasting glucose, and anxiety but not glycemic control or diabetes-related distress [36].

Digital Interventions

Although this research is promising, most of these studies have focused on the impact of in-person interventions. However, there are numerous barriers to in-person treatment that prevent people from seeking treatment [37], including stigma [38] and a shortage of mental health professionals [39]. Internet-based interventions offer a cost-effective means of providing access to large populations [40], while also reducing some of the other barriers to seeking treatment by increasing convenience [41] and anonymity [42]. Indeed, research suggests that people with comorbid depression and diabetes find web-based interventions attractive and may reach a population that would not otherwise seek treatment [43].

Although previous research supports the effectiveness of internet-based interventions in physical health [44] and mental health [45] domains, few studies have tested the impact of internet-based interventions among people with diabetes specifically, and what research has been done on the benefits of mobile health interventions among people with diabetes yielded mixed results [46]. Most studies on the effects of web-based interventions on people with diabetes found no significant effects on depression or distress [47,48], whereas research demonstrating effects on depressive symptoms found no effects on diabetes-specific outcomes [22]. However, unlike most studies of in-person CBT, these studies did not include a sample of patients with diabetes and elevated levels of depression. One study of individuals with a diabetes diagnosis and elevated depressive symptoms found that internet-based CBT reduced depression, although they found no benefits for glycemic control [49]. Therefore, additional research testing the effectiveness of digital mental health interventions specifically among people with diabetes and elevated depressive symptoms is necessary, particularly studies with long-term follow-up and larger sample sizes [47].

Objectives of This Study

This study aims to examine the effectiveness of a digital therapeutics platform named *Happify Health* on people with poorly managed type 2 diabetes and elevated depressive symptoms. Happify Health is a digital intervention platform focused on mental health and its impact on other diseases that can be accessed via the internet or mobile app. Unlike most other interventions tested in person or digitally, which draw on just one theoretical approach, Happify Health activities draw from each of the three major theoretical approaches: CBT [50], MBSR [51], and PP [52-54]. Therefore, Happify Health uses multiple pathways to improve users' mental health by incorporating strengths from all three theoretical approaches, while simultaneously improving person-activity fit relative to other singular approaches by offering users more opportunities to find types of activities that suit them.

Activities within Happify Health were developed by identifying evidence-based tasks and interventions that were shown to be effective in at least two separate studies and in different samples [55]. These activities fall into different themes: *savor* (building mindfulness skills), *thank* (gratitude), *aspire* (optimism, goal setting, and finding meaning and purpose), *give* (kindness, forgiveness, and prosociality), *empathize* (self-compassion and perspective taking), and *revive* (physical health). Activities from these different themes are then organized into *tracks*, developed to help users improve in a specific area of concern such as reducing stress. Within each track, users can select specific activities and may also switch tracks before completing them or access activities in a *free play* format. Consequently, users have the ability to choose tracks and activities that better fit them, which has been shown to improve outcomes [56].

Observational studies of Happify Health users demonstrate that usage over 8 weeks is associated with more than a 27% increase in positive emotions, and high-use participants see even greater improvement [57,58]. A later RCT also demonstrated that Happify Health users who completed at least two activities per week reported significantly more improvement in depression, anxiety, and resilience than those who completed fewer activities or participants assigned to the control group [59]. Similar effects were obtained from RCTs focused specifically on people with higher levels of emotional or workplace distress [60]. More recent research also suggests that Happify Health use improves subjective well-being among people living with chronic physical conditions, including, but not limited to, diabetes, at the same rate as those without chronic conditions [61]. Consequently, there is preliminary evidence to suggest that Happify Health could effectively improve subjective and psychological well-being among individuals diagnosed with type 2 diabetes. However, no research has examined whether Happify Health use could also positively improve outcomes associated with their diabetes, including how well they manage their condition, their level of diabetes-related distress, and physical outcomes such as HbA_{1c} levels.

Therefore, in this study, our goal is to examine whether Happify Health use over the course of 8 weeks also helps to improve

diabetes-specific outcomes. To do so, we plan to compare changes in HbA_{1c} levels among adults with poorly managed type 2 diabetes and elevated depressive symptoms who have completed 8 weeks of activities on Happify Health or 8 weeks of a sham digital intervention. Secondary outcomes include depression, positive affect, and other diabetes-specific outcomes such as medication adherence, diabetes-related distress, and diabetes-related self-care activities. In addition, although many other studies (particularly mindfulness and PP interventions) did not examine long-term effects, we plan to explore the long-term effects of Happify Health use on both primary and secondary outcomes at 3, 6, and 12 months postintervention.

Methods

Recruitment Strategy

We plan to recruit participants by capitalizing on the existing process used to draw new users to Happify Health, including advertisements on Facebook and other social media sources. To attract individuals with type 2 diabetes specifically, targeted advertisements will also be posted on websites that connect potential participants with research studies and clinical trials (eg, Research Match) and on websites relevant to people living with type 2 diabetes.

Interested participants will be directed to a web-based survey to determine eligibility. The survey questions will include questions on age, location, previous Happify Health usage, diagnosed chronic illnesses, self-reported HbA_{1c} level, the Patient Health Questionnaire (PHQ) [62], and contact information. Users who meet initial inclusion criteria will then be contacted directly by Happify Health research staff to discuss the study in more detail. During this call, all eligibility questions will be readministered to ensure that the potential participant still meets the inclusion criteria. Those who agree to participate after this call will be sent an email to begin a week-long run-in period; during this run-in period, participants will be instructed to answer a brief web-based survey including three questions assessing daily diabetes-related distress, diabetes regimen adherence, and mood. Participants who complete this run-in period will then be sent an email instructing them to download the Happify Health app and to begin the study.

Inclusion and Exclusion Criteria

Participants will qualify for the study if they are aged 18 years or older, currently living in the United States, have never used Happify Health before, and have a current diagnosis of type 2 diabetes. In addition, as we are targeting participants with poorly managed diabetes and recent recommendations are that below 7% is a reasonable glycemic goal for most adults with type 2 diabetes [63], participants will be included if their most recent HbA_{1c} level is at least 7%. Similarly, as we are also targeting participants with elevated depressive symptoms, participants will be included if their scores on the PHQ are at least 15, which is indicative of moderately severe depression [62]. Participants will also need to indicate their willingness to provide HbA_{1c} results throughout the study, complete daily assessments, and engage with the platform to qualify for the study. Finally, participants will also have to complete 5 of the 7 daily questionnaires during an initial qualifying period (refer to the *Procedures* section for more detail) to participate in the study.

Participants

This study is an RCT (NCT04068805) with an initial target sample size of 400 participants (200 participants per condition). Recruitment will continue until 400 participants have successfully completed pretesting and have been randomized to condition.

Although previous RCTs using Happify Health had response rates ranging from 56% to 72% for an 8-week posttest [60], as the first attempt to include long-term follow-up of Happify Health users, the level of attrition beyond the 8-week intervention is difficult to estimate. The few previous tests of mental health interventions on people with diabetes that included long-term follow-up reported relatively low attrition for 6-month [35,64] and 12-month [34,65] follow-ups; however, all these studies involved in-person interventions and often included booster sessions, thereby increasing the level of contact with participants and increasing response rates. The levels of attrition are much higher in research using digital interventions [66], although dropout rates are lower in RCTs than in open-access interventions [67]. Consequently, although we predict attrition for long-term follow-ups to be higher in this study than in previous research with in-person interventions, it is unclear what percentage of participants to expect for our 3-, 6-, and 12-month assessments.

Participant Compensation

Participants will receive three types of compensation throughout the study. After the baseline assessment (for which participants will not be compensated), participants will be compensated with Amazon gift cards valued at US $15 for completing each assessment. As separate compensation for completing daily assessments (as part of the 8-week intervention and during the 3-, 6-, and 12-month follow-ups), participants will earn US $1 for each daily assessment, for a possible total of US $56 for completing daily assessments during the intervention and US $28 for completing the week-long daily assessments at postintervention and during the 3-, 6-, and 12-month follow-ups. Finally, participants will be compensated with US $5 for obtaining and reporting each HbA_{1c} recording after baseline. Thus, participants will be compensated with a total of US $164 if they complete all assessments at all waves of data collection.

Outcome Measures

All assessments will be administered via Happify Health, and participants who do not complete measures will be sent email reminders; however, participants may withdraw from the study or skip assessments at any time. To link participant data across assessments and other data collections, each participant will be assigned a unique study ID number; participants will otherwise remain anonymous throughout the study. In addition to the primary and secondary outcome measures described in the following sections, other exploratory measures will also be included that are not reported here.

Primary Outcome: Hemoglobin A$_{1c}$

Participants will self-report their HbA$_{1c}$ levels, a measure of the average blood glucose levels over the past 3 months, 5 times throughout the study: at baseline, week 12 (3 weeks postintervention), week 24 (3 weeks after the 3-month postintervention assessment), week 36 (3 weeks after the 6-month postintervention assessment), and week 57 (at the 12-month postintervention assessment). At each assessment, participants will also report the date when they received this HbA$_{1c}$ reading to verify that it falls in the correct time frame.

Secondary Outcomes

Diabetes Distress Scale

Diabetes distress scale [68] is a 17-item scale that assesses the extent to which certain diabetes-related situations have been a problem for participants. Each item represents a potential problem area for individuals living with diabetes (eg, feeling that I am often failing with my diabetes routine), and participants indicate the extent to which they have been distressed or bothered by that issue during the past month on a scale ranging from 1 (*not a problem*) to 6 (*a very serious problem*). The responses are averaged so that scores can range from 1 to 6, where higher scores indicate higher levels of distress, and scores of 3 or greater are considered to be clinically significant levels of diabetes-related distress.

Measures of Medication Adherence Scale

Measures of Medication Adherence Scale [69] is a 4-item self-report measure of medication adherence and thus will only be shown to participants who indicate they are currently prescribed medication for diabetes on a preceding question. This scale will be modified slightly to ask participants specifically about adherence to diabetes medication over the past week. For each item (eg, Over the past week, did you ever forget to take your diabetes medicine?), participants indicate *yes* or *no*. All *yes* responses are coded as 0, and *no* responses are coded as *1*. The responses are then summed so that higher scores indicate greater medication nonadherence.

Summary of Diabetes Self-Care Activities

Summary of diabetes self-care activities [70] is an 11-item measure of self-reported adherence to diabetes self-care activities. For 10 items, participants indicate on how many days they engaged in self-care activities related to diet (eg, How many of the last 7 days have you followed a healthful eating plan?), exercise (eg, On how many of the last 7 days did you participate in at least 30 min of physical activity?), blood sugar testing (eg, On how many of the last 7 days did you test your blood sugar?), and foot care (eg, On how many of the last 7 days did you check your feet?) over the past week on a scale ranging from 0 to 7. One item also asks participants to indicate the frequency of smoking over the past week (ie, Have you smoked a cigarette, even 1 puff, during the past 7 days?) on a scale ranging from 0 (*no*) to 1 (*yes*); participants who respond yes are then asked to indicate how many cigarettes they smoked on an average day. Separate scores are then created for each subscale.

Patient Health Questionnaire

PHQ-9 [62] is a 9-item scale measuring depressive symptomology. Each item represents a depressive symptom (eg, feeling down, depressed, or hopeless), and participants indicate how often they have been bothered by each symptom over the past 2 weeks on a scale ranging from 0 (*not at all*) to 3 (*nearly every day*). The responses are then summed such that scores can range from 0 to 27, and higher scores indicate more severe depressive symptoms.

Patient-Reported Outcomes Measurement Information Systems: Positive Affect Subscale

Participants will also complete the positive affect subscale of the Patient-Reported Outcomes Measurement Information Systems [71] scale. This subscale asks participants to indicate how much they felt each of the 15 emotions (eg, "I felt cheerful") over the past 7 days on a scale ranging from 1 (*not at all*) to 5 (*very much*). Items are summed so that higher scores indicate greater positive affect.

Daily Assessments

Diabetes-Related Distress

We will assess daily levels of diabetes-related distress with a single item (ie, How would you rate your diabetes-related distress, on average, over the past 24 hours?) rated on a scale ranging from 1 (*very low*) to 7 (*very high*).

Diabetes Regimen Adherence

We will assess participants' daily regimen adherence using a single item (ie, Which of the following activities in your diabetes regimen did you complete over the past 24 hours?) where participants check any of the following options that apply to their situation: monitored blood sugar, ate according to healthy eating diet, engaged in physical activity, took diabetes medication as prescribed, or did not follow my diabetes regimen at all.

Daily Mood

We will assess participants' daily mood with a single item (ie, "How depressed did you feel, on average, over the past 24 hours?") rated on a scale ranging from 1 (*not at all*) to 7 (*extremely*) [72].

Procedures

Participation in this study will take place over approximately 14 months, including an 8-week intervention (or corresponding control) delivered via Happify Health as well as follow-up assessments at 3, 6, and 12 months postintervention. To ensure that HbA$_{1c}$ levels reported postintervention reflect average glucose levels only after starting the intervention, all participants will begin the study within 3 weeks of obtaining their most recent HbA$_{1c}$ levels. Participants who indicate that their most recent HbA$_{1c}$ levels were obtained before that when contacted by phone will wait to begin the study until they obtain their following HbA$_{1c}$ measurement and researchers confirm that they meet the inclusion criterion.

Once participants are ready to begin the study, they will be directed to complete 1 week of daily assessments without

exposure to either condition. Participants who complete fewer than 5 of these assessments will be disqualified from the study. Those who complete at least five of the daily assessments during this qualifying period will be directed to download the mobile app and complete the regular onboarding questionnaire for Happify Health; participants will be randomly assigned to either the positive emotion regulation skills intervention group or the control group upon completing these questions. Following randomization, participants will be prompted to complete the baseline assessment.

Participants will then be instructed to begin using their assigned version of Happify Health. Although participants will not be given explicit instructions on how often they should use the platform, they will be encouraged to engage with the platform daily. Participants will receive daily push notifications on their mobile device to remind them to access the platform and answer daily questionnaires, and they will also receive weekly emails as part of the Happify Health platform to help keep them engaged with the program. In addition, to improve use rates and participant retention, research staff will call participants to

inquire about problems when a participant has not engaged with the Happify Health platform at all for 1 week.

After 8 weeks, participants will be instructed to complete the postintervention assessment; this assessment will be identical to the baseline with the exception of HbA_{1c} assessment, which will occur 3 weeks later via the Happify Health app. After completing this assessment, participants will receive an email instructing them to answer daily questions for 1 week and to remind them that we will contact them again in 3, 6, and 12 months for follow-up assessments and that they should continue to use their assigned version of Happify Health as they see fit. Participants will then receive emails instructing them to complete each of the 3-, 6-, and 12-month assessments, which will also be accompanied by 1 week of daily assessments at each follow-up period. Table 1 provides the schedule of activities. To improve participant retention, participants who do not complete the postintervention, 3-, 6-, and 12-month assessments will also receive a reminder phone call from the research staff.

Table 1. Schedule of activities for prescreen, intervention period, and follow-up assessments.

Assessments	Time										
	Prescreen	Week 1: qualifying period	Week 2: baseline and first week of intervention	Weeks 3-9: intervention	Week 10	Week 12	Week 21: 3-month follow-up	Week 24	Week 33: 6-month follow-up	Week 36	Week 57: 12-month follow-up
Primary outcome											
HbA_{1c}[a]	X[b]	N/A[c]	X	N/A	NA/	X	N/A	X	N/A	X	X
Secondary outcomes											
Diabetes distress scale	N/A	N/A	X	N/A	X	N/A	X	N/A	X	N/A	X
Measures of Medication Adherence Scale	N/A	N/A	X	N/A	X	N/A	X	N/A	X	N/A	X
Summary of diabetes self-care activities	N/A	N/A	X	N/A	X	N/A	X	N/A	X	N/A	X
Patient Health Questionnaire	X	N/A	X	N/A	X	N/A	X	N/A	X	N/A	X
Positive affect subscale	N/A	N/A	X	N/A	X	N/A	X	N/A	X	N/A	X
Daily assessments	N/A	X	X	X	X	N/A	X	N/A	X	N/A	X

[a]HbA_{1C}: hemoglobin A_{1c}.

[b]X: assessment administered.

[c]N/A: not applicable.

Intervention Group

Participants assigned to the positive emotion regulation skills intervention will receive full access to the Happify Health platform. However, their version will feature a diabetes-related track focusing on building skills for greater happiness, reducing stress, and coping better with diabetes (Figure 1). Although the

description of the track cues them to think about the impact of negative emotions on their diabetes and the benefits of increasing positive emotions, activities within the track are not focused specifically on diabetes. Importantly, although participants will be encouraged to use this particular track, they will not be required to start or complete the diabetes-related

track and will be able to choose from all the other tracks available on Happify Health.

Figure 1. Screenshot of the featured track description for Developing Affective HeaLth to Improve Adherence intervention.

The featured diabetes-related track was designed by Happify Health and the second author, who is an expert on emotion and diabetes. The track is based on activities and content from the Developing Affective Health to Improve Adherence intervention originally developed by Moskowitz et al [21]. The version included in this study has four parts.

Part 1

This part contains 8 different activities and exercises focusing on savoring. For example, in 1 activity, *Today' s grateful moment*, participants are asked to spend a few moments writing about something they are grateful for. In another activity, *Let the good times roll*, participants make a plan to spend time doing simple things that promote positive affect and then write about how it went after completing the tasks they planned.

Part 2

This part contains 9 different activities and exercises focusing on reframing negative thoughts. For example, in *A week's worth of thanks*, participants keep a gratitude journal about someone they are close to and spend time writing about why they are grateful for that person. In another activity, *Savor the small stuff*, participants spend a week doing something mindfully (eg, eating a meal or taking medication) and then write about how it went.

Part 3

This part contains 11 different activities that build on parts 1 and 2 but includes exercises promoting goal orientation and optimistic thinking. For example, in *Give Myself a Break*, where participants practice self-compassion and then spend time

writing about how it went. In another activity, *Loving-Kindness Meditation*, participants verbalize good wishes when interacting with other people and then write about how it went.

Part 4

This part contains 11 different activities that promote resilience and helping others. For example, in *What am I proud of?*, participants spend some time thinking about something they are proud of and then write about it. In another activity, *Help Someone*, participants spend some time helping another person and then write about it.

Participants must complete one part before they can begin the following part, and they do so by earning either a silver medal (earned by completing all but 4 activities) or a gold medal (earned by completing all but 3 activities). Thus, participants will take varying lengths of time to complete a track, depending on their level of engagement with the platform. As participants will have access to the full Happify Health platform, if they complete the intervention track before the 8-week study period has elapsed or choose to change tracks before finishing, they will have access to all other available Happify Health tracks and instant-play activities (where they can choose to complete certain activities outside of dedicated tracks).

Sham Digital Intervention

Participants assigned to the control condition (Figure 2) will have access to a version of Happify Health that includes only polls on various mental health topics. After each poll, participants in this condition are provided with social comparison data about how their responses to the poll compared

with other users' responses and information about why this topic is important (including references to relevant scientific studies). For example, after responding to a poll question that asks participants to indicate how often they have a deep or meaningful conversation with someone, participants will view psychoeducational information about the benefits of

conversation, including that people who spend less time alone and more time talking to others tend to be happier [73] and that the happiest people have much less small talk, but many more meaningful conversations compared with the least happy people [74].

Figure 2. Screenshot of the track description in sham digital intervention.

Analysis Plan

We plan to analyze the changes in primary and secondary outcomes across the 2 conditions using hierarchical linear modeling (HLM). We will compute the change trajectories on each outcome over the course of the study assessments (ie, at baseline, immediately postintervention, and at 3-, 6-, and 12-month follow-ups). These trajectories will then be averaged together within each condition, so we can compare the trajectories for each outcome across the 2 conditions to determine if there was greater improvement in the positive emotion regulation skills intervention group relative to the control group.

We plan to use participants' daily assessments in 2 ways. First, we will compute growth trajectories for each participant using their daily assessments to explore when people tend to experience improvements in diabetes-related distress, diabetes regimen adherence, and mood during the intervention. Second, as retrospective reports can sometimes lead to inflated or inaccurate information compared with daily assessments [75], we will use daily assessments to compute weekly averages for diabetes-related distress, diabetes regimen adherence, and mood during and after the intervention. These weekly averages will then be used as outcome variables in the same HLM analyses described earlier.

Previous research on the impact of health care interventions on people with poorly managed diabetes suggests that effects may be most effective among people with especially poor glycemic control or HbA_{1c} levels above 9.5% [76]. Consequently, we plan to examine the effects of baseline HbA_{1c} as a moderator of the effects of the intervention on changes in the primary and secondary outcomes. Similarly, we also plan to examine the effects of baseline depressive symptoms as a moderator of the effects of the intervention. Finally, given that the effects of Happify Health use are typically moderated by usage [57-61], we plan to examine the effects of frequency of usage as another moderator of changes in the primary and secondary outcomes.

Ethics

This study was submitted and approved for ethical review by IntegReview (protocol HLS-07), an independent institutional review board.

Results

Recruitment for the trial is expected to begin during the second quarter of 2020, and participants will begin the 8-week intervention as they are recruited and consent to participate in the study. Consequently, the first wave of data collection is expected to be complete approximately 8 weeks after

recruitment, with an estimated intervention completion date for all participants in the fourth quarter. We plan to conduct data analysis for postintervention assessments once this initial data collection is complete, and these results may be shared at conferences or submitted for publication while we continue to collect data for the 3-, 6-, and 12-month follow-up assessments. Owing to the high cost associated with this research, we plan to conduct preliminary analyses once 20% of our target sample has completed the 8-week intervention. If we find no trends suggesting Happify Health use predicts primary outcomes, we plan to discontinue the study.

Recruitment, data monitoring for participant safety, data storage, protocol implementation, and research administration (participant follow-up, etc) will be under the purview of EB, GK, JS, and AP as employees of Happify Health. All data analyses will be conducted by JM and IK.

Discussion

Previous research suggests that many of the costs associated with diabetes are preventable when individuals with a diabetes diagnosis manage their condition more effectively [9,10,12]. One factor that appears to interfere with individuals' ability to manage their diabetes is depression [18], which is more common among people with a diabetes diagnosis than in the general population [15]. Interventions targeting depression among people with diabetes show promise in helping to improve psychological as well as physical health outcomes [30,31]. Research testing these interventions, however, focuses primarily on in-person interventions and has yielded mixed results, particularly on diabetes-specific outcomes. The purpose of the outlined study is to examine the effectiveness of a digital therapeutics platform (Happify Health) shown to improve mental health over the course of 8 weeks among general populations [59], distressed populations [62], and people living with chronic physical conditions [64], specifically in a population of adults with poorly controlled type 2 diabetes and elevated depressive symptoms.

Strengths and Limitations

Previous research demonstrated that 8 weeks of Happify Health use improved subjective well-being among people with chronic physical conditions, including type 2 diabetes, at the same rate as people without these conditions [61]. However, the previous study examined the effects of Happify Health use on users with at least one self-reported chronic condition but was unable to examine the impact on users with specific chronic conditions. Therefore, this will be the first attempt to examine the effects of Happify Health use specifically on individuals with type 2 diabetes. Moreover, the previous study assessed only well-being, whereas this study will examine depressive symptoms and, more importantly, diabetes-specific outcomes such as HbA_{1c}, frequency of self-care behaviors, and diabetes-related distress. Consequently, this study will provide a more comprehensive analysis of whether Happify Health use can improve physical health outcomes as well as psychological outcomes among individuals with poorly managed type 2 diabetes and elevated depressive symptoms.

This study also plans to include 3-, 6-, and 12-month follow-up assessments, providing important information about the longitudinal effects of this intervention. Longitudinal research on the impact of psychological interventions on people with diabetes remains limited [30], but research suggests that long-term follow-ups are important, as some effects may dissipate over time [30], whereas other effects may only emerge or become stronger over time [30,31].

Previous research has also been characterized by small samples, with sample sizes for in-person interventions ranging from 23 to 139 [30]. Sample sizes for research testing digital interventions have often been higher; however, most of these studies assessed only psychological well-being (depression and diabetes-related distress) and not physical health outcomes such as glycemic control [47]. Although the levels of attrition for long-term follow-up assessments are difficult to predict, based on response rates in previous RCT research using Happify Health ranging from 56% to 72% for 8-week interventions [60], our sample size postintervention is likely to be substantially higher than that in the previous studies. Given the mixed findings with glycemic control in previous research, it is important to examine these effects with larger samples to determine whether previous null findings are related to a lack of power.

However, one limitation of this study is that we are targeting a specific group of people with poorly managed diabetes and elevated depressive symptoms. Furthermore, because participants will have to successfully complete a run-in period before starting the study, our participants are also likely to differ from those who do not participate in terms of motivation, conscientiousness, etc. Thus, it is unclear whether our findings will generalize to a broader population of individuals with type 2 diabetes.

Another limitation of this study is that the intervention does not specifically focus on diabetes-related content. That is, participants in the positive emotion regulation skills intervention group may choose to complete the featured track, which includes a description cueing them to think about the impact of negative emotions on their diabetes, but activities within this featured track do not refer specifically to diabetes or incorporate diabetes-specific behavioral strategies. Furthermore, participants are not required to complete, or even begin, this track and may choose from any other available tracks that do not refer to diabetes whatsoever. Consequently, our intervention is similar to mindfulness or PP interventions that are broader in focus [30]. By comparison, CBT applied to people with diabetes typically has been modified to include specific information about adherence [34] or include supportive diabetes information [35]. Thus, our intervention may have weaker effects, particularly on diabetes-specific outcomes, than CBT modified for diabetes. However, there is preliminary evidence that completing regular activities (ie, not disease specific) on Happify Health is associated with improved subjective well-being among people with chronic physical conditions [61] and that mindfulness and PP interventions without behavioral strategies for managing diabetes can improve participants' health outcomes [30]. If we are able to demonstrate that Happify Health use can have physical as well as psychological benefits for people with

poorly managed type 2 diabetes and elevated depressive symptoms, without incorporating specific behavioral strategies for managing diabetes, the effects are also likely to have broader applicability.

Conclusions

Given the buffering effects of psychological well-being on diabetes outcomes [23], researchers and practitioners have become increasingly interested in whether psychological interventions can improve diabetes-related outcomes among people living with diabetes [30]. This trial would add to the emerging literature testing the effectiveness of such interventions. Importantly, however, although most previous research focused on interventions delivered in person [30], this study tests the efficacy of a digital intervention, which has the added benefit of reducing many of the barriers that prevent people from seeking treatment [77]. This study also addresses two important limitations of previous research: (1) small sample sizes and (2) lack of long-term follow-ups [30]. Consequently, this trial will not only provide information about the immediate effects of a digital therapeutic intervention on diabetes-related outcomes but also the extent to which these effects may persist for up to 12 months.

Authors' Contributions

EB contributed to designing the study and wrote the initial draft of this protocol. JM and AP contributed substantially to the study aims, scope, and design of the study. GK contributed substantially to the design of the study. JS contributed to designing the study and provided general manuscript support for this protocol. IK contributed to the study design.

Conflicts of Interest

EB, GK, JS, and AP are employees of Happify Health.

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Abbreviations

CBT: cognitive behavioral therapy
HbA$_{1c}$: hemoglobin A$_{1c}$
HLM: hierarchical linear modeling
MBSR: mindfulness-based stress reduction
PHQ: Patient Health Questionnaire
PP: positive psychology
RCT: randomized controlled trial

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<u>Protocol</u>

A Web-Based Positive Psychological Intervention to Improve Blood Pressure Control in Spanish-Speaking Hispanic/Latino Adults With Uncontrolled Hypertension: Protocol and Design for the ¡Alégrate! Randomized Controlled Trial

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Abstract

Background: Growing evidence links psychological well-being and resilience with superior cardiac health, but there remains a critical scientific gap about whether (or how) interventions that aim to cultivate psychological well-being reduce cardiac risk. Hispanic/Latino people in the United States have high cardiovascular disease risk and poorly controlled blood pressure (BP) compared with their peers of European ancestry, and they represent a population in need of new and innovative therapeutic approaches. As such, a focused intervention to boost psychological well-being holds promise as a novel therapeutic target for hypertension in Hispanic/Latino adults; to date, however, no research has explored whether a causal link is evident.

Objective: The aim of this paper is to detail the protocol for the *¡Alégrate! (Be Happy!)* intervention, a Phase II randomized controlled trial testing initial efficacy in improving BP of a web-based positive psychological intervention designed to boost psychological well-being in Spanish-speaking Hispanic/Latino people with hypertension.

Methods: A total of 70 Hispanic/Latino people aged ≥18 years, fluent in Spanish, and with elevated BP (≥140/90 mm Hg) will be recruited in person from a single Federally Qualified Health Center in Chicago. Enrollees will be randomly assigned to 1 of 2 trial arms: (1) web-based positive psychological intervention or (2) an active control condition (eg, 3 times weekly emotion reporting). Our 5-week Spanish-language *¡Alégrate!* intervention is web-based and delivers curricular content via didactic instruction, journaling, and assigned at-home practice—all accessed via our website using investigator-purchased tablet computers, with a unique username and password assigned to each enrollee. Targeted skills include noting daily positive events, positive reappraisal of stressful events, effective expression of gratitude, performing acts of kindness, and regular practice of mindfulness and meditation. The primary outcome is improvement in BP, both sitting values and 24-hour ambulatory readings, as measured at baseline and 5 and 12 weeks from baseline. Secondary outcomes include psychological well-being, engagement in healthy behaviors, and circulating levels of inflammatory markers. The outcomes of interest are collected by trained research staff through in-person interviews using the REDCap software.

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Results: Activities of the *¡Alégrate!* intervention were funded in August 2017, and data collection is ongoing. We expect to submit trial results for peer-reviewed publications in 2021, soon after recruitment has been concluded and statistical analyses are finalized.

Conclusions: Findings will provide evidence on whether interventions to boost psychological well-being and resilience have downstream effects on BP control and cardiovascular health, particularly as they are deployed in the Spanish language with cultural tailoring and via a web-based platform. If effective, we will have an easily disseminable application that can positively impact well-being profiles and BP control in Hispanic/Latino people, with the possibility of addressing health disparities of this US racial/ethnic minority group.

Trial Registration: ClinicalTrials.gov NCT03892057; https://clinicaltrials.gov/ct2/show/NCT03892057

International Registered Report Identifier (IRRID):   PRR1-10.2196/17721

Introduction

One in every 3 adults in the United States is classified as hypertensive and only around half maintain blood pressure (BP) under control [1-3]. Cardiovascular disease (CVD) is the leading cause of death in the United States, and hypertension exhibits the highest attributable risk for CVD morbidity and mortality [4]. Mounting evidence suggests that positive psychological well-being (hereafter, psychological well-being)—which includes positively valenced feelings or cognitive appraisals such as happiness, optimism, and purpose in life—is independently associated with favorable cardiac health, for example, reduced risk for incident hypertension, better lipid profiles, reduced inflammatory markers, and reduced odds of incident heart disease and cardiac-related mortality [5-7]. Nevertheless, while multiple studies link psychological well-being with better cardiac health [6-8], there is a need to investigate the most effective approaches to cultivate psychological well-being in an effort to reduce cardiac risk.

While scholars define psychological well-being in various ways [9,10], in the field of cardiovascular epidemiology, it encompasses positively valenced feelings or cognitive appraisals that individuals use to evaluate their lives favorably [7,8]. As such, 2 theoretical perspectives inform the characterization of psychological well-being: the hedonic approach, which focuses on pursuit and attainment of pleasure and happiness [11], and the eudaimonic approach, which defines well-being as the ability to practice meaningful life pursuits and striving to realize one's best self [11]. Other domains, which are less easily classified as hedonic versus eudaimonic (eg, optimism, emotional vitality), have consistently predicted cardiovascular outcomes. Common measures of psychological well-being include purpose in life, personal growth, self-acceptance, environmental mastery, autonomy, happiness, satisfaction in life, positive affect, optimism (and hope), and emotional vitality.

The Hispanic/Latino population in the United States is a racial/ethnic group that may benefit from novel treatment focused on improving psychological well-being [12]. There are 57 million [13] Hispanic/Latino people in the United States, and they represent the second fastest growing ethnic/racial minority group [14,15]. Hispanic/Latino people exhibit a disproportionately higher burden of cardiovascular disease risk factors [3,16]. In addition, the Hispanic/Latino population has a higher incidence rate for CVD-related comorbidities (eg, chronic kidney disease) when compared with non-Hispanic populations, with 30% mortality attributable to CVD and its sequelae [14,17,18]. Additional research is needed, however, to explore strategies that boost psychological well-being specifically in Hispanic/Latino adults and whether this leads to better heart health and BP management. To date, pilot trials highlight that Hispanic/Latino adults find interventions targeting psychological well-being both enjoyable and beneficial [19,20].

Observational evidence links psychological well-being with better overall health, more healthy coping tendencies, improved quality of life, and healthy longevity [8,21]. Psychological well-being focuses on positive thoughts and feelings at the individual level, which may be key in promoting healthy behaviors in hypertension management [8]. Evidence suggests that psychological well-being is related to healthier BP profiles and plays a protective role in disease incidence [7,22]. In over 1000 healthy non-Hispanic adults, a large prospective study found that higher levels of psychological well-being were associated with a decreased likelihood of incident hypertension at a one-year follow-up [23]. In 126 British civil servants, aggregate baseline levels of happiness were negatively associated with 3-year measures of systolic BP, independent of known confounders.

Approximately 22% [15] of Hispanic/Latino people have hypertension, and they tend to display lower compliance with treatment recommendations when compared with their non-Hispanic peers [15,17]. Adherence to antihypertensive treatment and effective BP control in Hispanic/Latino people was approximately 58% and 35%, respectively, compared with whites (71% and 48%, respectively) and blacks (71% and 43%, respectively) [24]. There are no specific clinical CVD guidelines addressing the unique characteristics of Hispanic/Latino people, which highlights the need for novel and more effective disease management efforts for this racial/ethnic group [14].

The use of web-based interventions in different clinical populations has grown significantly [25]. Web-based interventions tend to be less costly than face-to-face designs, offering flexibility and greater access [26]. Internet use has also

grown substantially among Hispanic/Latino adults, with 80% reporting use of the internet [26]. A majority of Hispanic/Latino people reported having a computer (78%) and reported owning a smartphone (71%) [27]. Web-based interventions have the potential for broad dissemination and may help eliminate common barriers to participation (eg, transportation, scheduling conflict, and lack of child care) [28]. Recent studies have used web-based interventions to promote psychological well-being in different patient populations [25]. For example, web-based delivery formats were found to be effective in the management of symptoms of depression, anxiety, and stress [29-33] in healthy and clinical populations. However, most of these studies have been conducted on non-Hispanic white samples. There is a need for better representation of underserved, racial/ethnic minorities in web-based psychological well-being interventions.

Empirical evidence suggests that effect sizes for web-based therapies are similar to those deployed using traditional face-to-face approaches, with high patient satisfaction reported across these high-tech platforms. Few evidence-based programs, however, have been developed specifically for and deployed with Hispanic/Latino adults using web-based platforms. Schueller et al [34] identified only 6 studies that deployed digital health technologies in Hispanic/Latino populations. Given the paucity of evidence, testing for feasibility is imperative to document whether insurmountable barriers are evident, for example, limited internet accessibility and low technology literacy, among others. For instance, in past years, Hispanic/Latino adults have reported low Wi-Fi accessibility when compared with their peers of European ancestry, but important strides have been made in recent years with 81% of Hispanic/Latino adults now reporting internet access—although, usually in the form of mobile-only internet access versus at-home networks. Nonetheless, with increased accessibility, web-based platforms can become viable avenues because of their low cost and potential for broad dissemination, particularly among marginalized, underserved, and minority populations that encounter multiple barriers in accessing care, such as lack of health insurance or shortage of Spanish-speaking clinicians. Indeed, the use of technology represents a promising opportunity as Hispanic/Latino people express high interest (ie, ~86%) in engaging health-related phone apps and related technologies [34].

¡Alégrate! (Be Happy!) is a Phase II randomized controlled trial (RCT) created to address these limitations by testing the initial efficacy of a Spanish language web-based intervention. The RCT intends to boost psychological well-being in Spanish-speaking Hispanic/Latino adults with hypertension by examining changes in BP, psychological well-being, healthy behavior adherence, and circulating serum inflammation. This web-based intervention is built on activities that target psychological well-being by promoting optimism, gratitude, and positive affect directly through activities such as recalling positive life events, identifying and employing personal strengths, and engaging in acts of kindness, among others. We hypothesized that compared with participants in the control condition, those in the active intervention group will show greater improvements in BP, higher scores for psychological well-being, greater engagement in healthy behaviors, and lower

levels of inflammatory markers at follow-up. The aim of this paper was to detail the procedures of the ¡Alégrate! Phase II trial: Focus on the design and protocol of the web-based intervention.

Methods

Overview and Study Design

This study, known as *¡Alégrate! (Be Happy!)*, is an RCT testing the initial efficacy of a 5-week web-based positive psychological intervention in Spanish-speaking Hispanic/Latino adults with hypertension. As such, the current Phase II pilot trial implements a parallel group design with a 1:1 allocation ratio, with 2 fixed factors: (1) sex (male and female) and (2) antihypertensive medication use (yes and no). Participants assigned to the treatment condition will be asked to visit the *¡Alégrate!* study website over a 5-week period in which they learn skills known to boost positive emotion and overall psychological well-being, while participants in the active control condition engage in emotion reporting 3 times weekly. Participants assigned to the active control condition will gain access to the web-based curriculum at the end of the 12-week assessment period, after all survey and clinical data has been collected.

Participant Eligibility

Spanish-speaking Hispanic/Latino adults are eligible to enroll in the *¡Alégrate!* trial if they meet the following criteria: (1) Hispanic/Latino heritage based on self-report; (2) aged 18 years or older; (3) fluent in Spanish, that is, ability to read, speak, and write Spanish; (4) elevated sitting BP (≥140/90 mm Hg); and (5) basic technological literacy with the ability to access the internet at home or in a public setting. The exclusion criteria were as follows: (1) cognitive impairment denoting dementia [35], (2) severely reduced life expectancy (eg, self-reported diagnosis of metastatic cancer, congestive heart failure, or end-stage kidney disease), and (3) severe psychopathology including active psychosis or untreated bipolar disorder. The Institutional Review Board at the University of Illinois at Urbana-Champaign (UIUC) approved the *¡Alégrate!* trial, and all subjects provided written informed consent.

Study Procedures

Recruitment

Participants were recruited from a single Federally Qualified Health Center (FQHC) located in Chicago and situated in a neighborhood with a high density of Hispanic/Latino residents. The attending physician and clinical staff (eg, registered nurse, medical assistant) identify potentially eligible patients and subsequently refer them to *¡Alégrate!* research staff who then follow-up via phone or in person; participant information is stored in a secure web-based portal. During phone or in-person exchanges, the staff inform participants that the goal of the study is to explore whether an intervention intended to boost positive emotions results in better cardiac-related health. Only initial eligibility is determined via phone, with an in-person visit scheduled to establish full eligibility based on sitting BP values. Research staff will also approach patients in the waiting area to provide information about the research study and offer an invitation to receive a no-cost BP screening; research staff will

collect contact information of those expressing interest to determine full eligibility. The consent form and study materials outline the design of the study and inform participants of random assignment into 1 of 2 groups, either the group where *they learn skills known* to *boost mood and heighten positive emotions* or the group where *they would report experiences of positive or negative emotions on a thrice weekly basis*. It is communicated that all curricular instruction occurs online by visiting our *¡Alégrate!* website. In addition, the staff inform participants that 3 in-person clinical visits are required, each 2 to 3 hours in length, where staff collect survey and clinical data including anthropometric information, blood spots, and 24-hour BP monitoring; home visits are also offered for data collection to increase rates of retention. Participants are informed that they can keep the investigator-purchased tablet computer at the end of the study as compensation for their participation and time invested [36]. To reduce the risk of bias, enrollees in both the treatment and control arms keep the tablet computer at the end of study participation, that is, immediately after providing follow-up survey and clinical data at 12 weeks postbaseline. Participants expressing interest in enrolling in the trial who are screened for full eligibility and ultimately qualify undergo a face-to-face consent process and complete the survey and clinical exams before randomization.

Consent, Assessments, and Randomization

Survey and clinical exams occur in tandem at 3 time points, as follows: Time 1 (baseline) at study enrollment; Time 2, immediately postintervention (5 weeks after baseline); and Time 3 (12 weeks after baseline). Figure 1 details the design of the study and the associated timeline for recruitment, enrollment, and assessment tasks.

Survey and clinical assessments are conducted in Spanish through in-person interviews by trained bilingual research staff in a one-to-one encounter at the participating FQHC. Questionnaires used and associated constructs assessed as part of the survey interview includes measures of psychological well-being (eg, optimism, positive affect), acculturation, self-reported health and medical comorbidities, engagement in healthy behaviors (eg, sodium intake, sleep quality, and duration), and medication adherence. Many survey instruments used in the current trial have undergone previous psychometric testing, showing adequate validity and reliability in the Spanish language. For those not previously translated, our team conducted thorough forward and backward translation procedures to craft a Spanish-language adaptation with linguistic equivalency. All survey data were collected using REDCap, a secure internet-based platform for building and managing web-based surveys. Finally, clinical examinations will be carried out by research staff to collect anthropometric data (eg, body mass index, waist-to-hip ratio), serum blood spots, sitting BP, and 24-hour ambulatory BP profiles. It should be noted that all data will be deidentified, stored in a password-protected computer, and/or stored in a locked cabinet in the principal investigator's office.

After determining full eligibility, participants will be enrolled in the trial by providing written informed consent. After completing baseline assessments, participants will be randomly assigned in a 1:1 ratio to the intervention or active control condition using block randomization alternating between varying block sizes of 4, 6, or 8. The principal investigator created a random allocation table using Sealed Envelope, after which it was uploaded to REDCap to define the randomization model of *¡Alégrate!* to ensure proper blocking and stratification by sex (male and female) and use of antihypertensive medication (yes and no). A trained research staff generated allocation assignment through REDCap. It should be noted that REDCap conceals the allocation table and associated sequencing from research staff to prevent selection bias. Finally, given the pilot nature of a Phase II trial, blinding occurs only at the level of data analysis.

Figure 1. Recruitment and assessment timeline for the ¡Alégrate! web-based intervention.
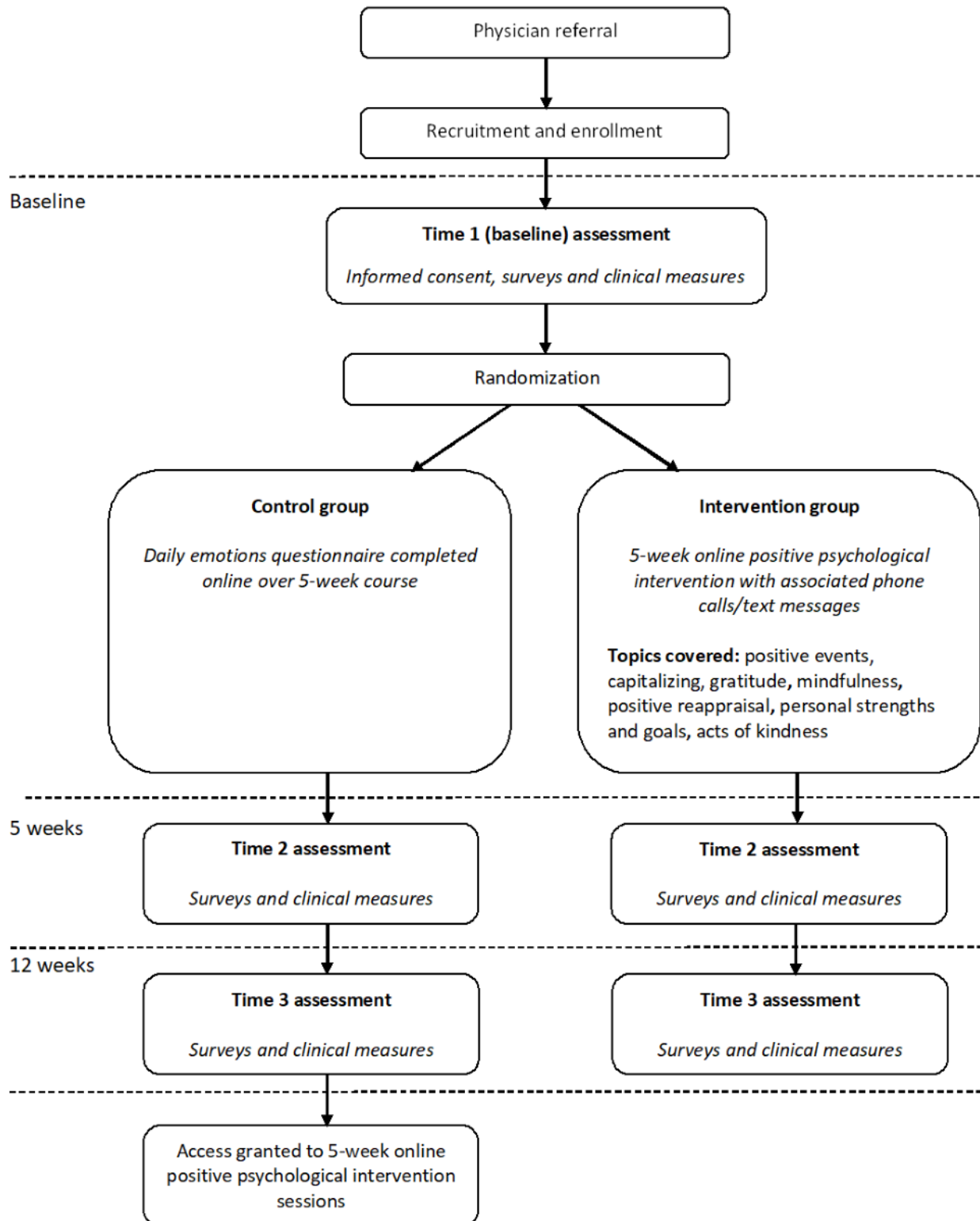
Content of the Intervention

Our Spanish-language web-based *¡Alégrate!* positive psychological intervention was adapted from previously published and empirically validated curricula of the Moskowitz MARIGOLD trial [37-41]. Our 5-week *¡Alégrate!* intervention delivers curricular content via didactic instruction (eg, text, videos), journaling, and assigned at-home practice—all accessed via our website using investigator-purchased tablet computers.

The website was designed and managed by Michael Cohn, a coinvestigator of the *¡Alégrate!* intervention. This 5-session, multicomponent web-based intervention instructs on 8 emotion regulation skills that have proven efficacious for increasing positive emotion and decreasing symptoms of depression and psychological distress in patients with varying chronic illness diagnoses, that is, those with metastatic breast cancer, HIV, and type 2 diabetes [38,40,41]. A detailed description of the curricula is published elsewhere [42]. Briefly, 8 empirically validated

behavioral and cognitive skills are taught via our web-based interface, and include the following: (1) identification and use of personal strengths; (2) noticing of positive events in daily life; (3) prolonged appreciation and relishing of positive events; (4) positive reappraisal of stressful events or situations; (5) gratitude; (6) regular practice of mindfulness and meditation; (7) setting and working toward pragmatic and achievable goals; and (8) planning and performing acts of kindness. We previously tested the in-person delivery of MARIGOLD in the Spanish language [19].

During each weekly session, participants will learn skills and then complete the assigned at-home exercises to actively integrate the acquired techniques into daily life. As such, participants are instructed to log-in to the ¡Alégrate! website for 30-min sessions at least three times per week. New skills are sequentially taught every week (see Table 1 for sequencing and content); to ensure successive instruction, new content becomes available only after a 7-day period, and once participants have completed the previous week's content and at-home practice. Table 1 summarizes the content of the ¡Alégrate! Spanish-language curricula, and Figure 2 presents screenshots of our web-based curricular interface [43]. Each participant logs in to the ¡Alégrate! website using a unique username and password assigned by research staff—the tablet interface is customized with shortcuts for ease of navigation. Participants are also instructed to password protect their tablet to mitigate any data breaches from external parties.

In addition to accessing our web-based positive psychological intervention, participants will also receive weekly phone calls and text messages to reinforce lessons learned and as a strategy to maximize retention and continued visitation to our study site. Weekly phone calls will be brief, 10 to 15 min in duration, in which study staff review highlights of skills taught that week—along with technical support on any issues in handling the tablet computer or in navigating the ¡Alégrate! site. Finally, participants with cell phone capability will receive a weekly text message from research staff highlighting the skills taught that week with the reminder to put them into daily practice—these sometimes take the form of a meme containing both images and text. For example, during Week 3 that focuses on mindfulness, they receive the following message:

> *Savoring requires that you slow down and pay attention to the positive events, large and small, that are happening in your day-to-day life. It can help you be more open, think more clearly, and appreciate things you have missed. It is important to be careful not to engage in thoughts that distract you from fully experiencing the present moment [La atención plena es una forma de prestar atención a los eventos positivos, grandes o pequeños, en su vida diaria. Lo puede ayudar a ser más abierto de mente, pensar más claramente y apreciar las cosas que quizás no noto. Es importante de no dedicarse en pensamientos que lo distraigan de experimentar plenamente el momento presente]*

Table 1. Positive psychology skills imparted in the 5-week internet-based intervention.

Weekly session	Skills	Goals of the session
Week 1	Positive events and capitalizing (Skills 1 and 2)	Individuals are equipped to note positive life events in their day-to-day encounters. Capitalizing is an expressive response to positive events and includes telling others about it, marking the occurrence in some way, or even thinking about the even again later on
Week 1	Gratitude (Skill 3)	Gratitude is defined as a feeling of thankfulness and appreciation expressed toward others, which may include other people, nature, or God
Week 2	Mindfulness (Skill 4)	Mindfulness is defined as the ability to intentionally pay attention to and maintain nonjudgmental awareness of one's thoughts, feelings, and physical sensations in the present moment
Week 3	Positive reappraisal (Skill 5)	Positive reappraisal is a form of coping in which the significance of the event is reinterpreted in a more positive way
Week 4	Focusing on personal strengths (Skill 6)	Identifying and focusing on one's strengths as a form of self-affirmation to evaluate the resources possessed to cope with a stressful event
Week 4	Attainable goals (Skill 7)	Setting of realistic goals and imparting techniques to increase their progression and attainment
Week 5	Altruistic behaviors/acts of kindness (Skill 8)	Engagement in volunteerism and other altruistic behaviors

Figure 2. Screenshots of our Spanish-language internet-based positive psychological intervention accessed via a web browser.

Content of Control Sessions

Participants randomly assigned to the active control condition will be asked to visit the study site where they report their emotions (eg, grateful, happy, guilty, relieved, ashamed, etc), 3 times weekly, using the Differential Emotions Scale (DES), but they will not be granted access to curricular content of our *¡Alégrate!* positive psychological intervention. It takes 5 to 10 min to complete the DES online. Emotion reporting for the control condition occurs for the duration of the active intervention period, that is, 5 weeks in total. Research has previously established effectual use of emotion reporting as a control condition, with documented benefits similar to that of a placebo effect, and with high rates of retention (approximately 80%). Concerted efforts are undertaken to promote retention among participants in the control arm, including postcard notices and phone calls to remind participants to engage in web-based emotion reporting and to appear, in person, for scheduled clinical assessments. Finally, participants in the control condition will be granted access to the web-based *¡Alégrate!* curricular content upon completion of their final follow-up assessment at 12 weeks postbaseline.

Participants in both the treatment and control arms will receive detailed handouts on how to operate the *Samsung Galaxy Tab A* tablet computer, along with instructions on connecting to Wi-Fi and accessing the *¡Alégrate!* website. Handouts display textual instructions along with detailed step-by-step visual screenshots, along with a listing of Wi-Fi locations in the local neighborhood, for example, coffee shops and public libraries or bookstores. In addition, staff will hold, in person, 15- to 20-min tutorials at baseline to familiarize enrollees on tablet use, with the assurance of continual availability via phone or in person to assist with any issues and to troubleshoot difficulties encountered with the technology.

Payment to the Participants

As compensation for their time invested and efforts in completing all trial-related tasks, participants in both trial arms (ie, treatment and active control) will be allowed to keep the investigator-purchased tablet computer at the end of the study period, which has a retail value of US $300. Participants who do not complete the full study, that is, those who drop out early, will be asked to return the tablet computer and will instead be given US $40 in cash for each assessment interview completed before dropping out. In addition, participants will receive reimbursement for travel-related costs (eg, parking, Uber, etc) and will be given light snacks while attending assessment interviews at the clinic site.

Training and Intervention Fidelity

The principal investigator and all research staff are bilingual (English and Spanish) and bicultural (Mexican-American), and each underwent extensive training (minimum 30 hours) before recruitment and data collection. Research staff are trained to accurately implement the recruitment protocol, to properly deploy assessment interviews, and to support detailed tracking of participants throughout the 12-week study period. Over

several weeks' time, research staff were trained in the following key component areas: (1) knowledge in the protection and privacy of patient-related health information through UIUC's Health Insurance Portability and Accountability Act Privacy and Security Compliance Program; (2) safe handling of Human Cell Lines/Materials in a Research Laboratory for the collection of blood spots, sponsored by the UIUC Institutional Biosafety Committee; (3) technological training, including electronic collection of survey data through REDCap, handling of tablet computers, and tracking of website visits and module completion across enrollees; (4) training in interview techniques, including building of rapport, interacting warmly and respectfully when working with Hispanic/Latino adults, that is, cultural value of *respeto*, consistency in ordering and wording of survey instruments, that is, quantitative methodology, (5) triggering of referrals to attending physician or distribution of resource listings when appropriate (eg, dangerously high levels of BP); and (6) protocol for weekly phone calls and text messages to reinforce web-based curricular content.

Multiple aspects of the intervention are manualized to strengthen the fidelity of the intervention and to ensure that the research staff are conveying identical content, particularly during weekly phone calls and when delivering messages via text. As such, research staff followed predrafted scripts, developed by the principal investigator, all of which followed a standard template as follows: (1) greet participants; (2) provide a brief summary (2-3 sentences) of the curricular content for that week; (3) from the participants' perspective, inquire of important lessons learned from weekly content; (4) ask of any difficulties in using a tablet computer; and (5) remind participants that the staff are available via phone or email to troubleshoot if any questions or difficulties arise. All weekly text messages were prewritten in Spanish and sent to participants without modification.

Finally, research staff are trained on handling circumstances requiring immediate action and a patient referral to the attending physician. Research staff have detailed instructions, depicted using a graphic decision support tool (ie, decision tree), on the protocol to alert the attending physician if participants displayed elevated symptoms of depression (Center for Epidemiologic Studies Depression Scale ≥16; denoting probable clinical depression) or if they present with exorbitantly high BP levels, that is, ≥180/120 mm Hg. Training of research staff occurs at the outset during study startup, with booster sessions throughout the trial to ensure proficiency, along with immediate guidance when procedural issues are evident.

Measures

Primary Outcome

Measures of sitting and ambulatory BP serve as the primary outcomes for the current *¡Alégrate!* trial. An ambulatory BP

monitoring (ABPM) method will be used to capture 24-hour daytime and nighttime BP readings in the natural environment (Ultralite 90217A ABPM from Spacelabs Healthcare); this device has shown adequate reliability and accuracy. We will consider 24-hour mean systolic and diastolic readings. Weighing in at 9 ounces, the ABPM monitors were fitted and preprogramed to automatically inflate over a 24-hour period—specifically, measurements are taken every 30 min during daytime hours (7:00 AM to 11:00 PM) and every 60 min at night (11:00 PM to 6:00 AM). We will additionally use an automatic sphygmomanometer to evaluate sitting BP. This measurement device has been validated across multiple cohort studies, including MESA, NHANES, and HCHS/SOL. Three systolic and diastolic BP readings will be taken with participants in the seated position; mean values will be obtained by averaging the last 2 readings.

Secondary Outcomes

Table 2 identifies the secondary outcomes and describes in detail the survey and clinical measures used to capture these constructs. Specifically, secondary outcomes include the following: (1) psychological well-being (depressive symptoms, perceived stress, positive and negative affect, optimism, emotional vitality, life engagement and meaning, happiness-inducing behavior, and social support), (2) healthy behaviors (physical activity, diet, sodium intake, smoking status, sleep quality and duration, and mediation use), and (3) biological materials (serum blood spots).

Antecedent Variables and Qualitative Data

In addition to the main outcomes of interest, we will also collect variables hypothesized to be antecedents or important confounders when exploring intervention effects. The list of antecedents or covariates is summarized in Table 2 and includes the following: (1) demographic factors, (2) anthropometric measurements, (3) acculturation, (4) level of religiosity, (5) self-reported mental and physical health, and (6) current or previous history of medical comorbidities. In addition, we will conduct qualitative exit interviews to capture facilitators and barriers in using the tablet computer to access *¡Alégrate!* curricular content. Indeed, qualitative process evaluation techniques further inform metrics of acceptability and utility for the modality of content distribution. Finally, we will also analyze data describing the overall use of the website by trial participants, including the number of website logins per participant, average length of screen time per site visit, and extent to which enrollees completed and recorded practicing of at-home exercises.

Table 2. Outcome, mediator, and intervention-based measures.

Measure	Description
Outcomes (exams 1 through 3 unless otherwise noted)	
Primary outcomes	
Blood pressure measurements	
Sitting blood pressure	We will use an automatic sphygmomanometer to evaluate sitting BP. This measurement device has been validated across multiple cohort studies including MESA, NHANES, and HCHS/SOL [44,45]. The 3 systolic and diastolic blood pressure readings will be taken with participants in the seated position; mean values will be obtained by averaging the last 2 readings
24-hour ambulatory blood pressure	An ambulatory BP monitoring (ABPM) method will be used to capture 24-hour daytime and nighttime BP readings in the natural environment (CONTECTM Automatic Blood Pressure Monitor [ABPM50]); this device has shown adequate reliability and accuracy [46]. We will consider 24-hour mean systolic and diastolic readings. Weighing 1.87 lbs, the ABPM monitors will be fitted and pretested before 24-hour use [47]
Secondary outcomes	
Psychological well-being	
Depressive symptoms	The 20-item Center for Epidemiologic Studies Depression Scale (CES-D) will be used to measure depressive symptomatology [48]. The CES-D uses a 4-point Likert scale to probe the extent to which an individual has been troubled by depressive symptoms in the last 7 days; scores range from 0 to 60
Perceived stress scale (PSS)	The PSS includes 10-items to assess self-perceived levels of stress over the previous month using a Likert scale ranging from never to always [49]. Previously validated in the HCHS/SOL cohort [50], overall scores range from 0 to 40 for the full scale and includes items such as, "How often have you felt confident about your ability to handle your personal problems?"
Positive and negative affect	Participants will be asked to recall emotions experienced in the past week using a modified version of the Differential Emotions Scale [51]. A list of 26 different emotions will be provided (eg, grateful, happy, guilty, relieved, ashamed, or humiliated) and participants will be asked to identify how often they have experienced each on a scale ranging from 1—Not at all to 9—All the time
Dispositional optimism	The revised Life Orientation Test (*LOT-R*) will be used to assess dispositional optimism. The LOT-R is a validated 6-item self-administered questionnaire with possible scores ranging from 0 (least optimistic) to 24 (most optimistic) [52,53]. The scale includes 3 positively worded items and 3 negatively worded items that are rated on a 5-point Likert scale
Emotional vitality	Emotional vitality is characterized as a sense of overall well-being through active engagement in day-to-day activities and effectual regulation of emotions. Borrowing items from the General Well-being Schedule, this construct will be captured using a 6-item measure previously used in published studies with available evidence of adequate psychometric properties [54,55]. Respondents are asked to think about the previous 30 days, and using an ordinal scale are instructed to rate statements such as, "Has your daily life been full of things that were interesting to you?" and "Have you been feeling emotionally stable and sure of yourself?"
Life engagement and meaning (LET)	The LET is a 6-item instrument that probes the extent to which an individual engages in activities which they personally value and find meaningful [56], for example, *To me, the things that I do are all worthwhile.* Scores range from 6 to 30 with respondents rating items on a 5-point scale. Higher scores characterize an individual that experiences greater life engagement and purpose
Happiness-inducing behavior	This 38-item survey inquires of the extent to which participant engage in behavior or prescribed strategies known to induce happiness, for example, relaying gratitude, engaging in mediation and religious practices, focusing on positive life events, among others [57]
Self-perceived social support	The Medical Outcomes Study Social Support Survey will be used to quantify social support as provided by family, friends, and acquaintances [58]. This 20-item instrument first directs participants to quantify the total number of close friends and relatives they possess, that is, defined as the people they feel at ease with and can talk about what is on their mind. Remaining items ask participants to rate statements using a 5-point Likert scale that inquire of the perceived availability of support from family, friends, or others, if or when needed. Sample statements include "someone you can count on to listen to you when you need to talk" and "someone to help with daily chores if you were sick"
Healthy behaviors	
Physical activity and dietary intake	Items of the Summary of Diabetes Self-Care Activities Measure will be used to assess engagement in physical activity and self-reported dietary intake. Items ask participants to report engagement across activities over a 7-day period and include queries such as, "On how many of the last SEVEN DAYS did you participate in at least 30 minutes of physical activity?" and "How many of the last SEVEN DAYS have you followed a healthful eating plan?"

Measure	Description
Sodium intake	The Scored Sodium Questionnaire will be used to measure dietary intake specifically targeting quantification of sodium consumption [59]. Participants will be asked to report dietary patterns over the last 7 days across multiple food groups (eg, breads, processed meats, tinned or packet soups) with response options indicating daily consumption to rare or never eaten items. Dietary intake will also include items of the Summary of Diabetes Self-Care Activities questionnaire [60]
Smoking status	Participants will identify whether they are current smokers, former smokers, or if they have never smoked before. Current smokers will report the average number of cigarettes they smoke per day
Self-reported sleep quality and duration	Two self-report items were used to capture subjective rating of sleep. The first inquired about the number of hours per night of sleep (ie, during the main sleep period) that participants were getting on weekdays or workdays. The second asked participants to rate their typical night's sleep during the past 4 weeks, with a Likert response option ranging from *very sound or restful* to *very restless*
Medication use and adherence	Participants will be asked if they were prescribed oral medication for their high blood pressure. Those indicating use of antihypertensive medication will be asked to identify the start date when they first initiated said use. We will also document whether participants had taken their blood pressure medication on the date of their clinical visit, and if so, the approximate time of day. Finally, medication adherence specific to antihypertensive drugs will be assessed using the Morisky Medication Adherence Scale [61]. At each scheduled assessment, participants will be instructed to bring all medications currently taken. Research staff will document details across medication (eg, dosage) and they will save a digital picture of associated pill bottles
Markers of cardiovascular disease	
Serum blood spots	Serum blood spots will be collected from each participant at baseline and immediately postintervention (8 weeks). A trained research staff will prick the participant's middle or ring finger using sterile procedures. After wiping away the first spot of blood, 5 subsequent drops will be collected using Whatman #903 filter paper. The blood spots will be stored for future analysis in a −20° freezer at the Institute for Minority Health Research at the University of Illinois at Chicago
Covariates	
Antecedent or confounding variables	
Demographic factors	We will gather basic demographic information from all participants including: age, sex, income, educational attainment, marital status, health insurance status, employment type, nativity status and number of years in the United States, and country of origin
Anthropometric measurements	Research staff will ascertain measures of height (to the nearest centimeter) and weight (to the nearest 0.1 kg) and will calculate BMI using these values. The waist-to-hip ratio will be derived from abdominal and hip girth obtained using a Gulick II 150- and 250-cm anthropometric tape measure with participants wearing light clothing
Acculturation/cultural factors	The Short Acculturation Scale for Hispanics will be used to capture the construct of acculturation in Hispanic/Latino adults [62]. The 10-item scale inquires of language use (Spanish vs English) across settings (home vs social life), language in which entertainment is consumed, and race/ethnicity of individuals across varied social circles. Derived from the Duke University Religion Index [63], religiosity will be assessed using a 5-items scale that includes questions such as, "My religious beliefs are what really lie behind my whole approach to life." It also assesses frequency of attendance to church services and engagement in religious practices
Current health status and medical comorbidities	Self-reported physical and mental health will be measured using the 12-item Short Form Health Survey [64]. Participants will also self-report previous or current existence of any of the following medical conditions: heart attack; congestive heart failure; stroke; diabetes; arthritis; moderate or severe renal disease; fracture of the hip, wrist, arm, or shin; asthma; cirrhosis of the liver or liver disease; cancer; bypass of arteries in the leg; Parkinson's disease; Alzheimer's disease or dementia; HIV or AIDS; depression; or anxiety disorder
Overall website use	We will also analyze data describing overall use of the website by trial participants, including the number of website logins per participant, average length of screen time per site visit, and extent to which enrollees completed and recorded practicing of at-home exercises

Planned Analyses

The primary outcome of the *¡Alégrate!* trial focused on prospective changes in B*P* values, that is, both sitting BP and 24-hour ambulatory readings. The first aim was to examine the efficacy of the intervention in reducing B*P* values immediately postintervention (ie, 5 weeks) and at the 12-week follow-up period, that is, Exams 2 and 3. The second aim was to explore whether the intervention leads to significant improvements in psychological well-being and greater adherence to healthy behavioral practices. We will additionally test whether psychological well-being and healthy behaviors serve as mediators when exploring intervention effects on BP control. The third aim is to test intervention effects on circulating markers of inflammation, specifically high-sensitivity C-reactive protein.

Descriptive statistics, at baseline, will summarize participant characteristics for the full sample and stratified by intervention arm. Bivariate tests will be conducted to compare the intervention and control conditions to ensure compatibility

across key variables (eg, demographic factors, well-being profiles, etc) and to test the success of the randomization protocol. Discrepancies in baseline values across conditions will inform covariates for inclusion when testing our main hypotheses of interest. In addition, we will document the number of missing observations over time to assess the potential for bias resulting from significant dropout and differential attrition by condition. We will perform independent sample two-tailed *t* tests and/or Fisher exact tests to compare baseline characteristics of enrollees who completed the trial versus those who prematurely dropped out, allowing us to test possible predictors of attrition.

Given our design and main objective of treatment evaluation, an intent-to-treat analysis will be conducted, where we will consider the data of all participants randomized, with retention of their original intervention assignment. Sensitivity analysis will use multiple imputation procedures across missing values to ensure inclusion of all observations, particularly those resulting from participants who withdraw, are lost to follow-up, or do not complete all assessments. In a supplementary analysis, we will use ordinary or logistic regression (as appropriate, given variable distribution) to implement a dose-response analysis to test whether participation-related factors (eg, number of sessions viewed, rate of homework completion) impact outcomes of interest.

We estimated the sample size requirements of a two-arm randomized trial to evaluate whether our web-based positive psychological intervention resulted in differential and clinically meaningful improvements in systolic BP of 6 mm Hg compared with an attention control condition. A repeated-measures design with systolic BP determination at baseline and 5 and 12 weeks was used. In addition, the following operating characteristics were assumed: (1) a between-subject standard deviation for BP of $\sigma=12\ mm\ Hg$; (2) a within-subject correlation, $\rho=0.60$ (3) a two-sided type I error probability of 0.05; and (4) 80% statistical power. Frison and Pocock [65] argue that adjusting for baseline measures (analysis of covariance) results in a more efficient analysis for a given sample size (larger statistical power). This approach yields an estimate of the required sample size of 28 participants per study arm under equal allocation. Furthermore, assuming a conservative attrition rate of 20%, an updated estimation produces the following sample size of participants per study arm.

Stata 15 was used for sample size calculation (*sampsi* command) and all statistical analyses, with effect size estimation derived from published data on the clinical effectiveness of psychotherapeutic interventions to treat hypertension [47,66,67].

Aim 1: Determine the Efficacy of the ¡Alégrate! Web-Based Positive Psychological Intervention in Improving BP Control in Hispanic/Latino People With Hypertension From Baseline, Immediately

Postintervention (5 Weeks), and at 12 Weeks After Baseline

Independent samples *t* tests will be performed using 5-week systolic BP and diastolic BP as the dependent variables, with treatment condition serving as the grouping variable. Other model-based approaches to handle missing data, such as weighted estimating equations, will be implemented. We will also use mixed-effects models to compare changes in BP between the control and intervention arms as measured at baseline, 5 weeks, and 12 weeks. The independent variables include a time variable t (t=0, 5, 12), a dummy variable N (N=1, if PP intervention group; N=0, if attention control), and a cross-product term (t×N). For ambulatory data collected across a 24-hour period, sensitivity analyses will compare mean overall daytime versus nighttime values of BP. All data analyses were conducted using SAS 9.4 software (SAS Institute).

Aim 2: To Test Intervention Effects on Psychological Well-Being and Adherence to Healthy Behaviors and to Subsequently Explore Whether Improvements in Psychological Well-Being and Adherence to Healthy Behaviors Are Responsible for Better BP Control, That Is, Mediation Testing

Similar analytic techniques will be implemented for Aim 2 as used for Aim 1. The interaction of Group×Time will test if greater improvements are evident for psychological well-being and engagement in healthy behaviors (eg, dietary intake and self-reported physical activity) at 5 weeks postbaseline for the treatment arm as compared with the active control group. RM-ANOVA will also be used to examine whether the *¡Alégrate!* intervention is associated with greater improvements in psychological well-being and engagement in healthy behavior. In addition to reporting nominal *P* values, we will document the number of tests conducted and associated Bonferroni correction. Finally, we will conduct mediation analysis to test whether psychological well-being and healthy behaviors serve as intermediates (or mediators) through which *¡Alégrate!* impacts BP control. Tests of mediation will follow the recommendations of Shrout and Bolder to bootstrap product terms using Mplus. Given the dependency of indirect effects on the time interval, for multiwave models, we will compute overall, rather than time-specific, indirect effects.

Aim 3: Evaluate Intervention Effects on High-Sensitivity C-Reactive Protein

Similar analytic techniques as previously described will be used when testing intervention effects on chronic inflammation. Specifically, the term capturing Group×Time interaction will test whether lower levels of inflammation are evident at 8 weeks postbaseline for the intervention group versus the active control arm.

Results

Activities of the Spanish-language *¡Alégrate!* intervention were funded in 2017, and data collection is ongoing. We expect to submit the trial results to peer-reviewed publications in 2021,

soon after recruitment has been concluded and statistical analysis is finalized.

Discussion

Principal Findings

This paper describes the design and protocol of the *¡Alégrate!* program, which is a web-based positive psychological intervention tailored for Hispanic/Latino people with hypertension—with the curricular content and evidence-based skills disseminated fully in the Spanish language. Novel interventions specifically geared toward Hispanic/Latino adults are greatly needed, as this racial/ethnic group constitutes the largest minority group in the United States and they experience continued and ever-growing health disparities and high burden of cardiovascular disease risk factors [12,18]. As such, our Spanish-language web-based *¡Alégrate!* program has the potential to positively impact cardiovascular health profiles of Hispanic/Latino adults, particularly when it comes to BP control. Moreover, it offers a more cost-effective alternative to face-to-face delivery of our intervention through dissemination using a web-based platform—accessed through the comfort of an individual's home.

Strengths and Limitations

Limitations are evident in the design and eventual deployment of the *¡Alégrate!* web-based trial. Selective enrollment has the potential to introduce bias as Hispanic/Latino people with limited technological proficiency may decline to participate in the trial, or if enrolled, may have difficulty in connecting to Wi-Fi or in navigating the study site. Future trials may want to explore more user-friendly modalities that require little to no coaching that may be more appealing to less technologically savvy community members. We are recruiting in a Chicago-based neighborhood with a large population of Hispanic/Latino adults, the majority of which are of Mexican ancestry. Thus, the findings of the trial may not generalize to the wider, more heterogeneous Hispanic/Latino population across the United States with differences by country of origin, nativity status, and level of acculturation. Our design includes an active control condition where participants are asked to report their emotions, thrice weekly, via our web-based platform. This may not adequately adjust for effects derived from social support and contact with research staff as imparted in the treatment group. Future trials may want to deploy a more active control condition where participants' access to web-based content is unrelated to the outcome of interest, for example, money management skills. Finally, blinding occurs only at the level of data analysis, and both trial participants and assessors (research staff collecting outcome data) are aware of randomization assignment, which can introduce unintended bias.

Despite these limitations, the strengths of our design are evident. We are the first to design and deliver a Spanish-language positive psychological intervention to Hispanic/Latino adults using a web-based platform. Second, we are collaborating with a Chicago-based clinic located in a neighborhood with residents predominantly of Hispanic/Latino origin, that is, approximately 21,500 Hispanic/Latino people, primarily of Mexican-American descent. Our partnering clinic is also a federally qualified site servicing the most vulnerable, including those with limited income and those with no health insurance. Finally, we provided all enrollees with an investigator-purchased tablet computer and developed detailed Spanish-language user guides (with screenshots) to assist participants in accessing our website, with research staff available via phone for additional tech support.

Conclusions

Hispanic/Latino people are a vital population for testing our *¡Alégrate!* web-based programs due to an overwhelming need for interventions to improve cardiovascular health and evidence that psychological well-being may be a particularly relevant target. This is especially true within the context of a cultural group that values building of positive emotional bonds and encourages *personalismo* (ie, emphasis on agreeableness, politeness, or courtesy)—and, who despite these positive cultural inclinations, constitutes a collective group that experiences widening cardiac-related health disparities. Our team previously tested our positive psychological curriculum as delivered face-to-face by a psychologist/social worker in a group setting and in the Spanish language [19,42]. We found significant improvement when examining pre-post intervention changes in emotional vitality, subjective happiness, and engagement in happiness-inducing behaviors (eg, meditation). However, rates of retention were particularly low and often involved the inability to attend on-site sessions because of shifts in work schedules, inclement weather, and/or travel outside of the country. Offering an alternative to access our intervention content via a website, from the comfort of home and in a self-paced manner, may prove to be a viable and more effective alternative for Hispanic/Latino adults. This new delivery modality may also prove to be more cost-effective when compared with in-person delivery by a highly trained clinician.

As the use of technology continues to expand, it is imperative that vulnerable populations and ethnic/racial minorities are taken into account during its inception and expansion. How might technology be deployed within a more user-friendly interface for those with limited exposure to technology or those with little formal educational training who experience literacy challenges? For instance, the website for the current *¡Alégrate!* trial was created using inclusive design principles and usability testing to create a simple, straightforward interface to foster high rates of retention and acceptability. The home screen for our tablets was clutter-free with only 1 to 2 apps available that directly linked participants to our study website—with parameters imposed that restricted the addition of new apps and/or the visitation to entertainment sites, for example, Netflix and YouTube. Finally, websites and clinical apps developed from evidenced-based curricular content should be made available in the Spanish language, and other languages for mass and equitable consumption. Tech companies and their employees (eg, software engineers) will need to be creative to ensure that emerging technology is accessible to all—even those with limited technology experience, low literacy, and limited economic resources.

Acknowledgments

Authors' Contributions

RH and JM initiated and designed all phases of the *¡Alégrate!* trial. MC designed the web-based platform where enrollees accessed the intervention content of the *¡Alégrate!* trial. LM, AM, and IM coordinated study activities at the clinic site, including recruitment, data collection, and retention efforts. All authors assisted in developing the study and finalizing the associated study protocol. RH and AH wrote the first draft of the manuscript. All authors reviewed and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-eHEALTH (V 1.6.1).
[PDF File (Adobe PDF File), 361 KB - resprot_v9i8e17721_app1.pdf]

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Abbreviations

ABPM: ambulatory blood pressure monitoring
BP: blood pressure
CVD: cardiovascular disease
DES: Differential Emotions Scale
FQHC: Federally Qualified Health Center
NIH: National Institutes of Health
RCT: randomized controlled trial
UIUC: University of Illinois at Urbana-Champaign

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Protocol

Evaluating the Effectiveness of an Intervention Integrating Technology and In-Person Sexual Health Education for Adolescents (In the Know): Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: Access to a smartphone is nearly universal among American adolescents, and most of them have used the internet to seek health information. Integrating digital technologies into health program delivery may expand opportunities for youth to receive important health information, yet there are few rigorous studies assessing the effectiveness of this type of intervention.

Objective: The purpose of this study is to assess the effectiveness of *In the Know* (ITK), a program integrating in-person and technology-based sexual health education for underserved adolescents.

Methods: Youth were engaged in the development of the intervention, including the design of the digital technology and the curriculum content. The intervention focuses on 3 main areas: sexual health and contraceptive use, healthy relationships, and educational and career success. It includes an in-person, classroom component, along with a web-based component to complement and reinforce key content. A cluster randomized controlled trial is in progress among adolescents aged 13-19 years living in Fresno County, California. It is designed to examine the differences in self-reported health and behavioral outcomes among youth in the intervention and control groups at 3 and 9 months. Primary outcomes are condom and contraceptive use or no sex in the past 3 months and use of any clinical health services in the past 3 months. Secondary outcomes include the number of sexual partners in the past 3 months and knowledge of local clinical sexual health services. We will use mixed-effects linear and logistic regression models to assess differences between the intervention and control groups.

Results: Trial enrollment began in October 2017 and ended in March 2020 with a total of 1260 participants. The mean age of the participants is 15.73 (SD 1.83) years, and 69.98% (867/1239) of the participants report being Hispanic or Latino. Study results will be available in 2021.

Conclusions: ITK has the potential to improve contraceptive and clinic use among underserved youth. This trial will inform future youth-focused health interventions that are considering incorporating technology.

International Registered Report Identifier (IRRID): DERR1-10.2196/18060

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Introduction

Background

Technology-based health interventions are growing in popularity for youth. Recent promising evidence supports the feasibility and acceptability of digital interventions for knowledge and behavior change, particularly with adolescents. However, evidence of the effectiveness of this approach remains limited, with few rigorous studies assessing medium- and long-term outcomes.

Youth and Technology

Smartphone ownership is nearly universal in the life of American adolescents: 95% of adolescents now report either owning or having access to a smartphone, over 90% of adolescents use the internet daily, and 45% say they are online on a near-constant basis [1]. Recent statistics suggest comparable smartphone ownership among teens across gender, race and ethnicities, and socioeconomic backgrounds, with 93% of low-income adolescents reporting access to a smartphone [1]. However, research suggests key demographic differences in how youth use the internet for health. In a nationally representative survey in the United States, over 80% of adolescents reported that they had ever sought health advice on the internet, with African American and Hispanic adolescents reporting the use of web-based platforms for health information more frequently than white adolescents [2]. Lesbian, gay, bisexual, transgender, and queer (LGBTQ) youth report searching for health information online more often than heterosexual youth due to privacy-related reasons, lack of health education inclusive of their sexual orientation or gender identity, and not having anyone to ask for accurate information [3]. Integrating digital technologies into health program delivery presents an enormous opportunity to connect with youth who rely on digital health information.

Recent research assessing technology-based interventions for health has shown promise in a variety of topics and settings, including increased adherence and knowledge [4]. One systematic review of mobile apps for health and fitness found high acceptability but limited rigorous research to determine efficacy and establish evidence for best practices [5]. There is growing evidence that technology-based sexual and reproductive health (SRH) interventions can be effective [6,7]. A recent meta-analysis of 15 years of research found that technology-based interventions for youth had a significant effect on improving condom use, delaying sex, and increasing sexual health knowledge, although the effects on other sexual health outcomes were more limited [8]. Online HIV prevention interventions have shown similar efficacy as their in-person equivalents; online programs have been found to increase condom use, reduce the number of sexual partners, and reduce sexually transmitted infection (STI) incidence [9]. Similarly, Bedsider.org, a web-based educational network that provides

peer feedback on birth control methods and lists youth-friendly locations to access contraceptives, has been shown to reduce unprotected sex and increase contraceptive use [10]. The enormous potential of technology-based interventions has led to the proliferation of youth-focused SRH interventions that incorporate social media, texting, and other digital components.

However, gaps remain in the research into the effectiveness of technology-based SRH interventions, particularly with certain youth populations. The analysis of long-term efficacy and the use of randomized controlled trial designs thus far are limited [8,11,12]. One systematic review of text and mobile phone app interventions for adolescents found no significant improvements in preventative sexual health behavior [13]. Furthermore, a review of apps designed for sexual health education found that the majority narrowly focused on STIs and pregnancy prevention and did not integrate evidence-based components of effective sexual health education [14]. Blended learning, which combines online and in-person instruction, is also increasing in popularity in sexual health education with mixed results [15]. Further research is needed to determine if technologies can reinforce the messaging and skill development provided in person. In addition, it is important to evaluate the viability of technology as a mechanism to reach marginalized youth populations who may not receive adequate SRH information through traditional approaches.

Sexual health education can provide critical information, but the content and quality of the curricula vary substantially [16]. Furthermore, traditional programming that focuses on pregnancy prevention often ignores the broader health and developmental issues that youth face. Incorporating educational and career success, healthy life skills, and healthy relationships into sexual health education may build youth self-efficacy in making positive life choices that impact sexual health and overall well-being [17]. However, few sexual education programs cover these more comprehensive topics [18].

Underserved Youth Populations

Although the adolescent pregnancy rate is declining nationwide, substantial disparities persist [19]. In addition, the rates of STIs are increasing among adolescents and disproportionately affect youth from certain racial, ethnic, geographic, and socioeconomic backgrounds [20]. Too often, sexual health education and services do not reach these youth or do not reflect their experiences and backgrounds [21]. In many cases, youth who are at the greatest need for comprehensive programming are less likely to receive it. For example, youth who frequently move, are unstably housed, or in foster care may miss school-based programming [21,22]. Similarly, few sex education curricula are designed to be inclusive of same-sex partners, sexual orientation, or gender identity [23]. In addition, many of the most common sexual health curricula were developed decades ago with limited adolescent input during the design

phase. These curricula often seem dated and culturally irrelevant to youth [21].

Youth who are unstably housed, homeless, or in foster care are at a higher risk of unplanned pregnancy and STIs [24,25]. These young people often have limited access to consistent health care, are more at risk for coerced sexual activity, are more likely to have experienced trauma, and are more likely to exchange sex for money or other basic resources [24]. As a result, the rate of STI and HIV infection in homeless youth is 2 to 10 times higher than that of other adolescents [26]. Youth of color and sexual minority youth also have an elevated risk for adolescent pregnancy and STIs [19,25].

Many vulnerable youth who may need SRH services worry about provider attitudes, privacy and confidentiality, and stigma [27]. Providers are rarely competent in LGBTQ-specific health concerns, so LGBTQ youth often face discrimination when seeking health services [27]. Providing relevant information about accessible, confidential, and respectful health services for these youth can increase their use of contraceptives and improve the overall health service utilization [28].

Objectives

The primary objective of this study is to evaluate the effectiveness of *In the Know* (ITK), an integrated in-person and technology-based sexual health education intervention, on its ability to increase contraceptive use and use of clinical health services among adolescents. The secondary objectives are to evaluate the impact of ITK on sexual risk behavior and knowledge of local clinical sexual health services as well as healthy relationship skills, career and education skills, and goal-setting skills. We hypothesize that sexually active youth who participate in the intervention will demonstrate higher contraceptive use and greater use of clinic health services as compared with youth in the control arm.

Intervention

ITK is an innovative SRH intervention that incorporates positive youth development and a youth-centered design. ITK combines in-person sexual health education with a web-based component to provide the necessary and timely skills, information, and resources to improve the SRH and overall well-being of adolescents aged 13-19 years. In particular, it is designed to address the needs of homeless and unstably housed youth, LGBTQ youth, and youth of color.

ITK has 5 key objectives:

1. Increase use of condoms and contraceptives among those who are sexually active
2. Improve awareness about healthy relationships and decrease the incidence of sexual, physical, and emotional violence among youth
3. Improve educational and career skill development and attainment
4. Develop healthy life skills, including goal setting and stress management
5. Increase access to health care and other services through referrals and information

Development

Adolescents representing the diverse target populations helped to develop ITK by engaging in a user-centered design process, which recognizes that youth are the experts in their own lives [29,30]. Through a series of workshops, youth brainstormed ideas for intervention content and design and developed rapid prototypes alongside the design team. Youth then reviewed ideas and provided feedback on multiple design and content iterations.

ITK was designed using a trauma-informed approach and a positive youth development framework. This behavioral approach to adolescent development views youth as having assets that can be cultivated to reach their full developmental potential [31,32]. It focuses on creating an environment that supports protective factors, which promote personal strengths and resilience.

Classroom Component

The in-person, classroom component of the intervention is divided into 3 modules that can be implemented in 1 day or over the course of a few days. The total implementation time is approximately 6.5 hours, with each module lasting approximately 2 hours. *Module 1: Sexual health and contraceptive use* teaches youth the functions of the sexual and reproductive system; sexual orientation and inclusivity of all gender and sexual identities; how pregnancy occurs; birth control methods and correct condom usage; and STI prevention, symptoms, testing, and treatment options. *Module 2: Healthy relationships* helps youth understand healthy relationships, including communication, consent, and sexual violence prevention, and teaches life skills, such as stress management, identifying strengths, and goal setting. *Module 3: Educational and career success* informs youth of education and career options and teaches them about financial aid, resume and cover letter writing, interview skills, and budgeting.

Web-Based Component

The web-based component incorporates digital technologies to complement and reinforce the key content covered in the classroom intervention. It uses technology-based strategies to digitalize the components of the existing curricula, including text message reminders, gamification, geo-location, and web-based resources such as videos. Youth can access this information through a downloadable app or a website (Figure 1).

Figure 1. Sample screenshot from mobile application.
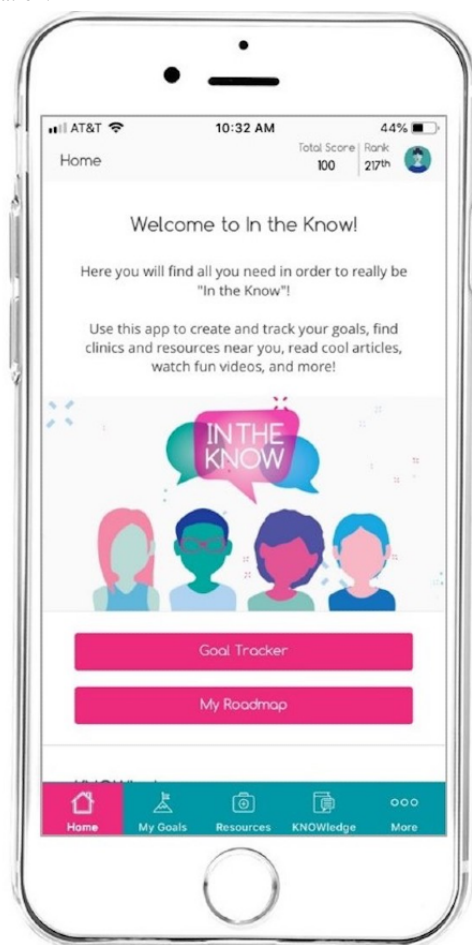
This enables health educators to engage with youth on platforms easily accessed by them (such as mobile phones and tablets) to provide high-quality education and training while offering supportive tools that allow youth to practice new knowledge and skills. In addition to introducing the app and explaining how the app works at the beginning of the cohort, health educators demonstrate and support the participants in using one or more key features of the app during each session. Health educators remind participants that the app supplements the in-class education, offers reinforcement of messaging, and has additional resources that youth can access after the session. Taking the knowledge gained in the classroom, participants can generate health or career goals and set reminders to keep them on track. Participants can also complete short quizzes for points. Under the *Resources* tab, users can search for and find local services and resources using a Yelp-like feature that allows them to locate clinics on a map and rate the services after they have used them. In addition, in the *Knowledge* section of the mobile app, users can explore curated articles and videos. Youth are able to take this information and resources with them after completing the class, enabling them to refer to materials and locate services as needed. Participants also sign up to receive text messages for 1 month after the in-person sessions end, with information and reinforcement of key messages. They can also schedule reminders to complete activities to achieve their personal sexual health, relationship, and career development goals that they selected.

Methods

This study follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines [33].

Trial Registration and Institutional Board Approval

The Institutional Review Board for the Human Research Protection Program of the University of California, San Francisco (UCSF), approved this study (IRB# 17-22381) and its protocols on September 3, 2017. This study is also registered at ClinicalTrials.gov (NCT03765255).

Study Design

The study uses a cluster randomized controlled trial design with treatment and control groups randomized at the level of the cohort, which are defined as groups of 5 to 20 youth recruited at the same site. Researchers at the UCSF follow a simple randomization procedure. Cohorts are randomized using a computer-generated random number assignment with a 1:1 allocation. Participants in cohorts assigned to the intervention group receive ITK and those in cohorts assigned to the control group receive standard services provided at the site.

Study Setting

The trial will be implemented by the Fresno Economic Opportunities Commission (EOC) in approximately 50 sites of youth-serving agencies in Fresno County, California.

Participating agencies represent a variety of settings in which youth receive services or activities, including school and afterschool settings, employment and training sites, youth development centers, clubs, foster care sites, housing authorities, tribal agencies, and LGBTQ programs. Youth recruited in these settings generally already receive some other type of service or activity, including sports programs and clubs.

Eligibility Criteria

Youth are eligible to participate in the study if they are aged 13-19 years, English-speaking or Spanish-speaking, and living within Fresno County at the time of enrollment.

Recruitment

Participants will be recruited at the study sites between October 2017 and March 2020 through 3 primary mechanisms: (1) printed flyers posted at the sites, (2) EOC staff setting up a table at the site to share information about the study, and (3) staff at the participating agencies making announcements about the study.

Youth who are interested in participating in the study complete a paper-based screening form to determine their eligibility. All potential participants receive a consent form, which is available in English and Spanish. A trained member of the Fresno EOC staff reads the consent form aloud to potential participants to ensure understanding. Participants provide informed consent before completing the baseline survey.

Each cohort's allocation to the treatment or control group is concealed to participants and staff until enrollment and baseline data collection are complete (Figure 2). Then, a health educator opens an envelope to reveal whether the cohort has been assigned to the treatment or control group. Due to the nature of the intervention, neither the participants nor the staff can be blinded to the allocation.

Figure 2. Consolidated Standards of Reporting Trials (CONSORT) flow diagram.
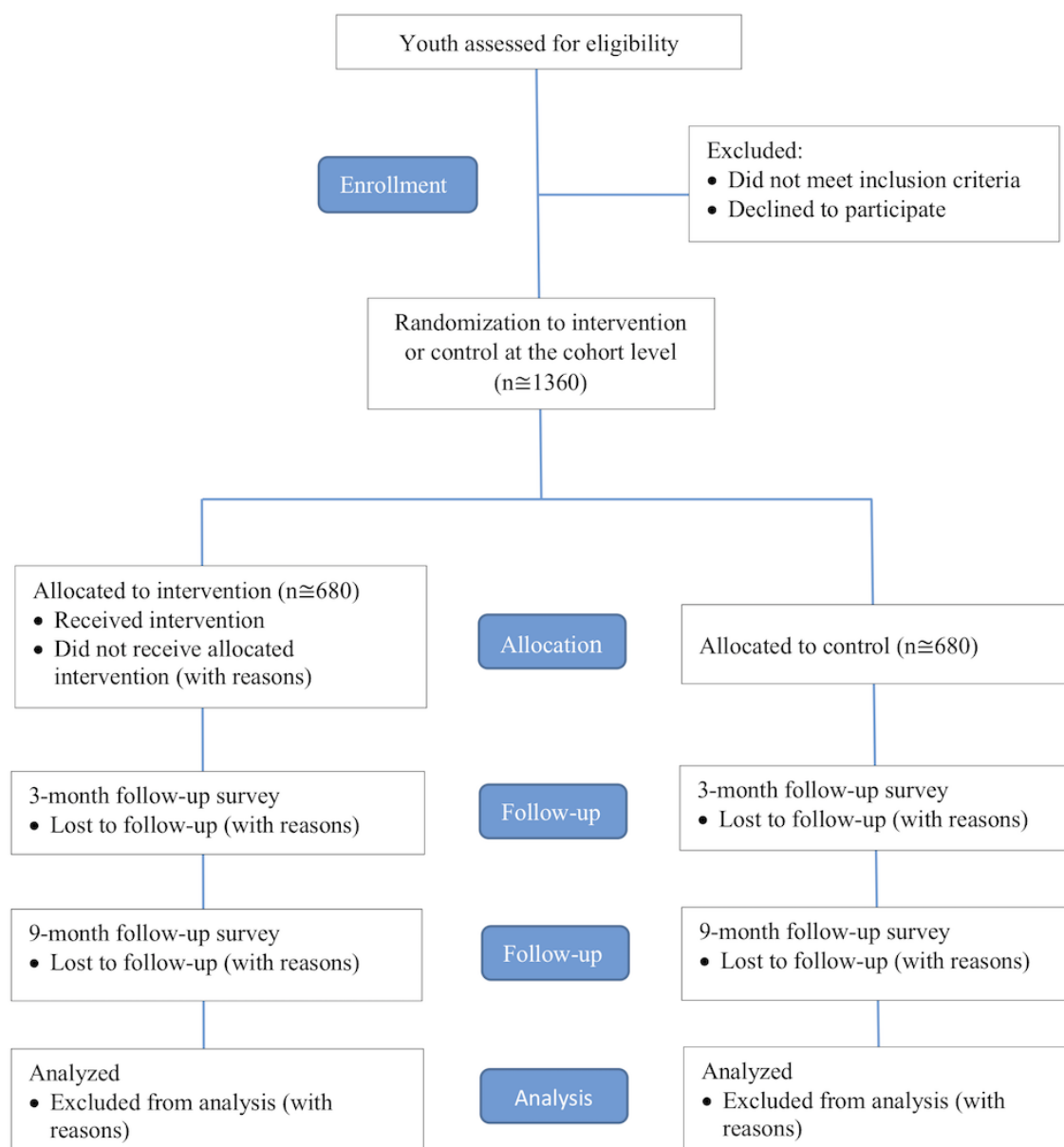
Outcomes

Primary Outcome Measures

The first primary outcome is condom/contraceptive use or no sex in the last 3 months. This is assessed at 3 months by asking participants how often they used birth control, including condoms, when they had vaginal sex in the past 3 months; and how often they used a condom when they had anal sex in the past 3 months. The second primary outcome is the use of any clinical health services in the last 3 months. This is assessed at 9 months by asking participants whether they have received mental health services or counseling, substance abuse treatment, or sexual health services from a doctor, counselor, therapist, social worker, or clinic in the past 3 months.

Secondary Outcome Measures

The secondary outcome measures are as follows:

- Number of sexual partners in the past 3 months
- Knowledge of local clinical sexual health services, which is assessed by asking "Have you heard of a clinic or doctor in your community where teens can get sexual health information and services such as condoms, birth control, pregnancy tests, STI tests/treatment, and/or HIV tests?" Response options included "yes," "no," and "I'm not sure."

The outcomes and covariates are shown in Table 1. All measures are collected at baseline, 3 months, and 9 months, except where noted in the table.

Table 1. Outcomes and measures for In the Know.

Domains	Description
Primary outcomes	
Condom/contraceptive use or no sex	Past 3 months
Use of clinical health services	Past 3 months
Secondary outcomes	
Number of sexual partners (oral, vaginal, and anal)	Past 3 months
Knowledge of clinical sexual health services	Knows where to get sexual health information or services (yes, no, or not sure)
Other outcomes	
Healthy relationship skills	Perceived ability to refuse sex and ask partner for HIV/STI[a] testing
Career and educational success	Current school enrollment and participation in job training or vocational program
Goal-setting skills	Frequency of working on educational or career goal and making plans to reach goals
Moderators and covariates	
Demographics	Age, race/ethnicity, and language spoken at home[b]; gender identity and sex[c]; and grade level, sexual orientation, living situation, and housing instability
Sexual health education	Ever received and topics covered[b]
General health education	Ever received and topics covered[b]
Life skills education	Ever received[b]
Technology ownership and use	Technology owned, used technology to access sexual health information and health services; location where accesses internet[b]; and websites or apps used to find health information and services[d]
Arrest or juvenile detention history	Ever and past 3 months
Gang-related activities	Past 3 months
Dating violence	Past 3 months
Cyberbullying	Ever experienced
Sexual behavior (oral, vaginal, and anal)	Ever, frequency in the past 3 months, and drug or alcohol use before sex in the past 30 days
Sexual and reproductive health services	Likelihood of seeking
Tested positive for STI	Ever and past 3 months
Pregnancy and childbearing history	Ever pregnancy and number of children
Sexual and reproductive health knowledge	Sexual and reproductive health knowledge scale
Communication with adults	Frequency of talking with trusted adults and comfort level talking about sex with parent
Employment skills	Perceived skills writing a resume, cover letter, budget, or interviewing for job
Life skills	Successfully managing stress, resolving conflict, respectful toward other, and confidently communicating ideas in the past 3 months

[a]STI: sexually transmitted infection.

[b]Measured at baseline only.

[c]Measured at baseline and 3 months.

[d]Measured at 3 and 9 months.

Sample Size

A target sample of 1360 youth (680 per study arm) will be enrolled in the study. The number of cohorts to be enrolled in the study is 68 per study arm, with an estimated 10 youth per cohort. We estimate 85% (1156/1360) retention at 3 months (578 per arm) and 80% (1088/1360) retention at 9 months (544 per arm).

Sample size calculations were based on the first primary (binary) outcome, which is condom/contraceptive use or no sex in the past 3 months (assessed at 3 months). We selected an intracluster

correlation coefficient (ICC) of 0.02, which is within the range of previous group-randomized trials of school-based HIV, STI, and pregnancy prevention interventions in the United States [34]. With a two-sided significance level of 5% and a power of 80%, this sample size is sufficient to detect an increase in condom/contraceptive use or no sex from 60% to 67% at 3 months, with an estimated 15% loss to follow-up.

We have also planned for adequate study power for the second primary (binary) outcome, any use of clinical services in the past 3 months (at 9 months). With a two-sided significance level of 5%, a power of 80%, and an ICC of 0.02, this sample size is sufficient to detect an increase in use of clinical services from 30% to 38% at 9 months, with an estimated 20% loss to follow-up.

Data Collection Methods

Baseline Survey

Participants complete the baseline survey on a tablet, although paper surveys are available as needed. The baseline survey includes questions from all domains, as shown in Table 1.

Follow-Up Surveys (3 and 9 Months)

All participants are asked to complete web-based follow-up surveys 3 and 9 months after baseline. A link to complete the follow-up surveys is sent via email and/or a text message to their mobile phone; participants are asked to state their preferred method of survey delivery at baseline. When the follow-up surveys are due, participants receive the survey via the method of their choice.

The 3- and 9-month follow-up surveys collect repeat measures of the outcomes measured at baseline. They also ask youth to report what websites and apps they have used to search for health information and services in the past 3 months.

Confidentiality

Protocols have been established to ensure the confidentiality of personal information about participants. Data are encrypted and transmitted securely through Qualtrics, a tool for collecting web-based surveys that meets the security requirements for UCSF research. Surveys are void of participant identifiers such as names and addresses. Participants are only identified through their study identification numbers. Electronic data are stored on encrypted, password-protected computers within a secure network, inside a building with limited access. Audio-recorded data, such as focus groups and interviews, and any paper-based surveys are stored in a secure and locked file cabinet. Only authorized personnel have access to the data, and all data are de-identified before analyses.

Retention

We expect that retention may be challenging due to the high mobility of the study's target population. We developed a protocol to maximize retention via incentives and reminders. Study participants can receive up to US $60 for completing all surveys. The following is the incentive structure:

- US $20 for completing the baseline survey
- US $10 for completing the immediate follow-up survey (intervention only)

- US $10 for completing the 3-month follow-up survey
- US $20 for completing the 9-month follow-up survey.

At baseline, detailed contact information, including telephone numbers, email addresses, and mailing addresses, is collected. Participants are asked to provide this information for themselves as well as at least two alternative contacts, such as a parent, case manager, relative, friend, or other trusted adult. Alternate contacts are only used if the contact information for the participant is no longer accurate. EOC staff give participants small cards with the dates they will receive their follow-up surveys. Participants receive ongoing reminders about the study through text messages approximately every 2 months.

When youth are eligible to receive their follow-up survey, they are sent the survey link through their choice of text message or email. They receive two additional requests to complete the survey, at 3 and 7 days. If participants do not complete the follow-up survey during the initial outreach period, researchers call youth or their alternate contacts and offer to resend the survey or have the youth complete the survey verbally over the phone.

If the researchers are unable to contact the youth via email, text messages, or phone, EOC staff return to the implementation site, administer paper-based follow-up surveys, and collect new contact information for the youth. Surveys are mailed to the UCSF for processing.

Statistical Methods

Our study will follow the Consolidated Standards of Reporting Trials guidelines for reporting of randomized trials, including reporting the flow of study participants through the trial (Figure 2) [35,36]. Our analysis will retain participants in their original assigned groups (intention to treat analysis) and will be conducted by a researcher who is blinded to the study arms. We will use up-to-date versions of Stata (StataCorp) to conduct all analyses. For all tests, we will use two-sided P values with $P<.05$ level of significance.

Refusal and Attrition Analysis

We will compare participants who refuse to participate and those lost to follow-up with the baseline sample to assess whether they vary by study arm, sociodemographic factors, or site. We will report any nonrandom loss to follow-up and consider the impact on the interpretation of our results.

Missing Data

We will report rates of and reasons for missing data, and we will assess whether participants with missing data differ systematically from others on sociodemographic characteristics, site, or trial arm. We plan to use multiple imputation to impute missing values for the predictor variables.

Analysis of Primary and Secondary Outcomes

The intervention arm (ITK) will be compared with the control arm (standard of care) for all primary analyses. The analysis population will include all enrolled participants. We will compare changes in condom/contraceptive use or no sex in the last 3 months from baseline to 3-month follow-up. We also will compare changes in the use of any clinical health services in

the last 3 months from baseline to 9-month follow-up. We will use mixed-effects logistic regression analysis with random effects at the individual, cohort, and site levels to account for clustering. Unadjusted models will include a variable for the study group, time, and interaction between study group and time. Additional models will be estimated adjusting for sociodemographic characteristics known to be associated with the primary outcomes (age, race/ethnicity, gender, sexual orientation, rural or urban location, and housing status). We will conduct a correlation analysis among the control variables and consider the directionality of the relationship between control variables and outcome variables. For subgroup analyses, we will also test the interactions of the study group with age, race/ethnicity, gender, sexual orientation, rural or urban location, and housing status.

The analysis of the secondary outcomes will be similar to that of the primary outcomes. To compare outcomes between the treatment and control arms longitudinally, we will use mixed-effects logistic regression analyses for binary outcomes and mixed-effects linear regression for continuous outcomes.

Implementation Evaluation Data

In addition to the outcome data, we collect a variety of measures to verify fidelity to the curriculum, identify potential challenges, and receive feedback from youth participants. Data sources and methods include the following: immediate post survey, attendance logs, implementation logs, interviews, focus groups, site observations, and web-based analytics.

Immediate Post Survey

Participants in the intervention group are asked to complete a survey on the last day after all intervention activities have been completed. The immediate post survey is generally administered on tablets but is available in a paper-based format if needed. It assesses reproductive health knowledge and perceptions of the in-person and technology-based components.

Attendance Logs

Health educators collect attendance data for each participant. The UCSF uses this to measure the number of youth served and the amount of the intervention (dosage) they receive. The UCSF reviews attendance logs in conjunction with the number of surveys collected to ensure accuracy.

Implementation Logs

Conducted for each intervention cohort, this information tracks the fidelity of ITK delivery and any adaptations made. The UCSF reviews these fidelity checklists and provides technical assistance as needed.

Interviews

The UCSF interviews health educators annually to assess their perception of the program and identify implementation challenges and successes.

Focus Groups

The UCSF conducts 6-8 youth focus groups annually. A subset of participants (purposively sampled to ensure different backgrounds are represented) are invited to share their perceptions of the program and provide feedback on how it can be improved.

Site Observations

The UCSF conducts quarterly site observations, with sites purposively selected to represent different youth populations. They focus on factors that may affect the quality of implementation, the extent to which the intervention is delivered with fidelity, implementation challenges, and needs for additional technical assistance or training.

Web-Based Analytics

Web-based analytics capture the extent and type of technology used by participants, including the use of tools, resources, and referrals on the app and website at the aggregate level. This provides an important measure of dosage and utility.

Results

This study began enrollment in October 2017, and preliminary study results will be available in 2021. As of February 2020, 1260 participants have been enrolled. Due to coronavirus (COVID-19) concerns and restrictions, cohorts scheduled for March 2020 could not be completed.

The average age of the participants is 15.73 (SD 1.83) years, and 69.98% (867/1239) of the participants report being Hispanic or Latino. When asked about their gender identity, 55.70% (694/1246) identify as female; 42.30% (527/1246) as male; 0.64% (8/1246) as transgender; and 1.36% (17/1246) as gender-queer, nonbinary, or other. In terms of sexual orientation, 81.53% (1002/1229) identify as straight and 15.79% (194/1229) identify as LGBTQ.

Study staff and their collaborating partners will share results with community members; local, state, and federal governmental officials; and other stakeholders. We will disseminate programmatic and policy implications through presentations, peer-reviewed journal articles, and social media.

The datasets generated during this study will be available from the corresponding author after completion of the study analysis on reasonable request.

Discussion

Strengths and Limitations

The *ITK* study has the potential to improve contraceptive and clinic use among underserved youth. Youth have been actively involved in the design and continuous improvement of the intervention, helping to ensure that the intervention is relevant and applicable to youth. Prior research suggests that the target populations' input in the development of technology-based health interventions should be sought early in the design process to ensure short- and long-term engagement [37,38]. To our knowledge, this is one of the first longitudinal studies to examine the integration of mobile technology into a sexual health intervention, allowing us to assess program impact on youth over time. In addition to longitudinal survey data, the study will triangulate results using multiple qualitative and quantitative data sources to document implementation and provide context

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to the findings. A particular strength of this study is its implementation in low-income communities with youth who are often unstably housed.

This study also has some limitations. Outcomes cannot be attributed specifically to the in-person or technology component but rather are based on the combination of the two. In addition, given that the study population is highly mobile, extra measures are required to improve retention. Finally, the longitudinal study relies on self-reports of health and behavioral outcomes.

This study has faced some implementation challenges, including (1) low response rates of follow-up surveys at 3 and 9 months, particularly among early cohorts; (2) low enrollment numbers, particularly in the first months of the intervention; and (3) challenges using the mobile app technology, including internet connectivity issues, broken links within the app, youth having limited access to mobile phones, and limited mobile data plans.

Successful strategies to address these challenges include diversification of follow-up strategies, such as in-person survey administration; expanded recruitment to multiple sites and scheduling cohorts 6 months in advance; and having back-up tablets and a web-based version where youth can access the app content.

Conclusions

The results of this study can inform the development and implementation of future youth-focused health interventions that are considering incorporating technology. In addition, this study will increase the evidence regarding best practices of integrating youth-focused technology into sexual health education. Future research should compare the outcomes with populations of varying socioeconomic status and housing stability and also compare both the outcomes and cost-effectiveness of an integrated intervention with a tech-only or to an in-person–only intervention [39].

Authors' Contributions

MD is the principal investigator of the study, and is one of the primary authors of the manuscript. AG provides support to this study's evaluation activities and is one of the primary authors of the manuscript. JY provides statistical and analytical support to this study and contributed to the *Methods* section. BS oversaw the design, development, and pilot testing of the app. MP provides training and oversight for fidelity monitoring and supported pilot testing efforts. JR helped develop the curriculum and app content and is the study implementation coordinator. JY, MP, BS, and JR reviewed and edited the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

Fresno EOC: Fresno Economic Opportunities Commission
ICC: intracluster correlation coefficient
ITK: In the Know
LGBTQ: lesbian, gay, bisexual, transgender, and queer
SRH: sexual and reproductive health
STI: sexually transmitted infection
UCSF: University of California, San Francisco

Protocol

Notifications to Improve Engagement With an Alcohol Reduction App: Protocol for a Micro-Randomized Trial

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Abstract

Background: *Drink Less* is a behavior change app that aims to help users in the general adult population reduce hazardous and harmful alcohol consumption. The app includes a daily push notification, delivered at 11 am, asking users to "Please complete your mood and drinking diaries." Previous analysis of *Drink Less* engagement data suggests the current notification strongly influences how users engage with the app in the subsequent hour. To exploit a potential increase of vulnerability of excess drinking and opportunity to engage with the app in the evenings, we changed the delivery time from 11 am to 8 pm. We now aim to further optimise the content and sequence of notifications, testing 30 new evidence-informed notifications targeting the user's perceived usefulness of the app.

Objective: The primary objective is to assess whether sending a notification at 8 pm increases behavioral engagement (opening the app) in the subsequent hour. Secondary objectives include comparing the effect of the new bank of messages with the standard message and effect moderation over time. We also aim to more generally understand the role notifications have on the overall duration, depth, and frequency of engagement with *Drink Less* over the first 30 days after download.

Methods: This is a protocol for a micro-randomized trial with two additional parallel arms. Inclusion criteria are *Drink Less* users who (1) consent to participate in the trial; (2) self-report a baseline Alcohol Use Disorders Identification Test score of 8 or above; (3) reside in the United Kingdom; (4) age ≥18 years and; (5) report interest in drinking less alcohol. In the micro-randomized trial, participants will be randomized daily at 8 pm to receive no notification, a notification with text from the new message bank, or the standard message. The primary outcome is the time-varying, binary outcome of *"Did the user open the app in the hour from 8 pm to 9 pm?"*. The primary analysis will estimate the marginal relative risk for the notifications using an estimator developed for micro-randomized trials with binary outcomes. Participants randomized to the parallel arms will receive no notifications (Secondary Arm A), or the standard notification delivered daily at 11 am (Secondary Arm B) over 30 days, allowing the comparison of overall engagement between different notification delivery strategies.

Results: Approval was granted by the University College of London's Departmental Research Ethics Committee (CEHP/2016/556) on October 11, 2019, and The London School of Hygiene and Tropical Medicine Interventions Research Ethics Committee (17929) on November 27, 2019. Recruitment began on January 2, 2020, and is ongoing.

Conclusions: Understanding how push notifications may impact engagement with a behavior change app can lead to further improvements in engagement, and ultimately help users reduce their alcohol consumption. This understanding may also be generalizable to other apps that target a variety of behavior changes.

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Introduction

Excessive alcohol consumption inflicts an array of harms, causing various mental and physical illnesses, loss of productivity, and an increase in violence and traffic accidents [1,2]. There remains a large gap in delivering interventions to at-risk individuals despite the availability of screening and effective interventions [3,4]. As many as four out of five heavy drinkers who attend primary care do not receive screening and brief interventions [5], and this is in part due to barriers to large-scale implementation [6,7]. These barriers include time pressures within general practice, as well as a lack of support and training to successfully shift the consultation from treating the main presenting condition to offering a screening opportunity for hazardous drinking [8].

Behavior change apps promise to reduce this gap by providing real-time data capture and interventions [9-11]. Such behavior change apps, which aim to reduce excessive alcohol consumption, build onto a large body of literature demonstrating the effectiveness of text messages [12-15]. Similar to text messages, behavior change apps can be delivered at a low incremental cost per additional user (high scalability) and offer support to users in real-time. In addition, behavior change apps have the ability to gather data on users, thus enabling them to learn and evolve to become personalized to each individual user. However, a prime challenge for many behavior change apps is poor levels of engagement, with the frequency (number of sessions) and amount (time spent per session) sharply declining over time for the majority of users [16-18].

Engagement with a behavior change app can be considered in two dimensions, behavioral engagement, which can be measured as the amount, frequency, duration, and depth of use, and experiential engagement, characterized by attention, interest, and affect [19]. The behavioral aspect of engagement can be objectively measured through app use data. The effectiveness of a behavior change app can be moderated by a user's engagement with the intervention's active ingredients, and engagement fluctuates within and across users over time [20,21]. A push notification is a message that pops up on the phone, and may also vibrate, make a sound, or lock the screen to gain the user's attention. Push notifications can be sent as a feature to enhance engagement and effectiveness by directing users to engage with the intervention's modules when users likely need it the most [22]. The message can provide a connection between the moments of "point of care" when a user seeks an assessment and intervention, and "point of choice" when a user makes the decision to drink or not to drink [10,23,24].

Drink Less is a behavior change app for the general population of adults seeking to reduce hazardous and harmful alcohol consumption. The research and development of *Drink Less* has been described elsewhere [25-28]. Currently, users receive a daily push notification at 11 am, asking them to "Please complete your mood and drinks diary." Following the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [29], the protocol reports our design for a micro-randomized trial (MRT) that aims to improve behavioral engagement (ie, frequency and amount of use) with *Drink Less* through the push notification.

MRT as an Experimental Design for Optimizing Behavior Change Apps

The MRT design is a useful trial design for optimizing the *timing, content,* and *sequencing* for push notifications in a behavior change app [30-34]. During an MRT, individuals are repeatedly randomized to actionable notifications, or no notification, at prespecified decision points (Textbox 1). Along with longitudinally measuring a near-term outcome after each decision point, covariate data provided by wearables, sensors, or self-report may also be continuously gathered. Data evolves as a collection of time-varying covariates, treatments, and outcomes. A distinguishing feature of the MRT, compared to a parallel-group randomized controlled trial (RCT), is the repeated randomization over time. This repeated randomization aids further causal inferences that cannot be made when undertaking a parallel-group RCT.

Textbox 1. What does the repeated randomization of notifications in a micro-randomized trial (MRT) offer?

MRT is an experimental design that provides information for developing more optimized policies or decision rules for delivering notifications. The repeated randomization within each individual in an MRT, which is absent in a parallel-group RCT, allows us to understand:

- If the notifications have a near-term effect on engagement, averaging over (i) the course of the study, (ii) all individuals, and (iii) the time-varying contexts individuals experience during the study.

- If the near-term effect of the notifications changes over time or depends on other time-varying covariates of the individual.

- If the notifications have a long-term effect on engagement, in addition to the possible near-term effect.

By understanding the above, researchers can build a more effective and less burdensome policy for delivering notifications, in order to improve users' engagement with a behavior change app [35].

The Drink Less App

Drink Less is a stand-alone app to help people reduce hazardous and harmful alcohol consumption [25-28]. The app was developed in line with the Multiphase Optimisation Strategy Framework [36] and the United Kingdom (UK) Medical Research Council guidance on complex interventions [37]. *Drink Less* contains seven different modules based on behavior change theory and evidence. These modules are (1) Normative Feedback, which is personalized feedback on how an individual's drinking behavior compares to the recommended drinking levels; (2) Goal Setting, which allows users to set weekly "drinking reduction" goals, with brief advice on setting achievable goals; (3) Cognitive bias retraining, delivered through a game which targets users' automatic biases by avoiding cues of alcoholic drinks and approaching nonalcoholic drinks; (4) Self-monitoring and Feedback, which users monitor and reflect on their alcohol consumptions, along with their mood, productivity, sleep and progress on goals; and (5) Action Planning, in which users create plans for dealing with difficult drinking situations. As of January 2, 2020, two new modules were added: (1) Behavioral substitution, which promotes substitution of drinking with a neutral behavior; and (2) Information about Antecedents, which provides users with information about social and environmental situations and events, emotions and cognitions that reliably predict drinking.

Drink Less launched in 2016 and is freely available on iTunes. At onboarding, users are asked to report their age, gender, type of employment (nonmanual, manual, or other) and to complete the Alcohol Use Disorders Identification Test (AUDIT) score [38,39]. The AUDIT is a 10-item screening tool for assessing alcohol consumption that helps identify people who would benefit from reducing or ceasing drinking. Users are also asked why they are using the app ("interested in drinking less alcohol" or "just browsing").

In the existing version of the app, a push notification is sent daily at 11 am asking users to "Please complete your mood and drinks diary." Accessing the app through the notification opens up the app and prompts users to complete their mood and drinks diary.

User Engagement With Drink Less

An Ecological Momentary Assessment study with *Drink Less* users found that establishing a daily routine is important for maintaining engagement and that the daily notification supports such routines [20]. This study also found that perceived usefulness of the app (the belief that using the app will help the user to achieve their goal(s) and an indicator of users' reflective motivation to engage) was associated with increased engagement for some users. The push notification may hence be most effective in improving engagement if it (1) supports the establishment of a routine (being sent at a set time), and (2) motivates to use particular intervention modules.

We visually explored patterns of engagement among a sample of 19,233 existing users of *Drink Less*. Further details of these results are available elsewhere (manuscript submitted). Data analysis from this cohort showed four important findings: (1) use over time decreased, with 50% of users disengaging (no use

for seven or more consecutive days) after 22 days since download; (2) the existing daily notification, delivered at 11 am, is likely to have the strongest effect of near-term engagement in the subsequent hour; (3) the breadth of engagement is poor, with 85% of sessions occurring within the "Self-monitoring and Feedback" module; and (4), outside the 11 am notification period, a natural maximum of both frequency and length of sessions appeared in the evenings.

If and how to intervene at "peak-risk" moments is a key research priority [9,10,40,41]. Evenings are a time of day when people with a history of harmful alcohol consumption are the most vulnerable to continued, harmful drinking [42]. Additionally, the visual exploration of engagement patterns over time suggests evenings are an acceptable and opportune moment to engage with *Drink Less*. We decided to exploit the potential increase in vulnerability, opportunity, and acceptability of users in the evenings [43] and to test the marginal effect on near-term engagement of a bank of 30 new push notifications (see Multimedia Appendix 1) delivered at 8 pm. The new messages aim to promote the benefit of using specific intervention modules by targeting users' reflective motivation to use the app.

We will undertake an MRT, with a single decision point of 8 pm, to assess the marginal effect of the new notifications on near-term engagement—use of the app in the hour following the notification—compared with both no notification and to a notification using the existing wording "Please complete your mood and drinking diaries." Within the MRT, we aim to balance the objectives of learning how to optimize the push notification strategy, with the need to trial a good quality app that does not annoy users. Generally, in an MRT, the risk of annoying users with too many notifications over time could be mitigated with lower randomization probabilities. However, there are two reasons why we chose a single decision point to randomize notifications (8 pm), and not test multiple decision points within the day. Firstly, a single decision point allows users to establish an important routine with *Drink Less*, and secondly, this avoids asking users, through the design of the trial, to "Please complete your mood and drinking diaries" more than once within the day.

In order to explore how notifications influence overall engagement, the MRT will be complemented by two parallel trial arms; users will receive the standard notification daily at 11 am in one arm and will receive no notification on any day in the other. The two parallel arms provide us with (1) a momentary assessment of how engagement with *Drink Less* evolves over time when no notification is provided and (2) an exchangeable sample to compare the current policy of delivering a fixed notification daily at 11 am, to randomly varying the content and sequence of notifications at 8 pm.

Aims and Objectives

Aim

This study aims to assess the push notification strategy and to improve engagement with *Drink Less* during the first 30 days following download.

Primary Objective

The primary objective of the study is to estimate the marginal effect of a notification (pooling both types of messages, the standard wording and the new bank of messages) on near-term engagement, defined as the use of the app in the hour following the notification decision point (8 pm to 9 pm).

Secondary Objectives

The secondary objectives are as follows:

1. Compare the marginal effect of the new bank of 30 messages to the standard wording of "Please complete your mood and drinking diary" on near-term engagement, defined as the use of the app in the hour following the notification decision point (8 pm to 9 pm).
2. Explore whether the effect of a notification (pooling both types of messages) on near-term engagement decreases over time.
3. Estimate the lagged effect of prior notifications on near-term engagement.
4. Understand how the notification effect is moderated by time-varying covariates (use before 8 pm, use on the previous day, weekend/weekday effect).
5. Investigate if the effect of the notifications depends on baseline characteristics (gender, age, employment type, AUDIT score).
6. Examine overall engagement during the 30 days following download in users receiving no notifications, those who receive the standard notification daily at 11 am, and those who receive a mix of notifications at 8 pm.

Trial Design

This study is an MRT with two additional parallel arms. Multimedia Appendix 2 illustrates the participant flow through the trial. It also shows which outcomes will be obtained from either the MRT or the two additional trial arms.

The MRT will test the effect of both delivering standard message content and a bank of varied message content on near-term engagement, compared to receiving no message.

Sixty percent of eligible users will be randomly assigned to participate in the MRT. The remaining eligible users will be randomized in equal numbers to the two parallel arms of either receiving no notifications (Secondary Arm A) or daily notification of the standard message of *"Please complete your mood and drinking diary"* (Secondary Arm B).

Among users assigned to the MRT, every day at 8 pm (the "decision point"), each user will be randomized to receive one of three options: no notification, the standard message, or a notification selected at random from the bank of new messages. The randomization probabilities for the decision points each day are 40% to receive no notification, 30% to receive the standard message, and 30% to receive a randomly selected message from the bank of new messages.

Methods

Participants, Interventions, and Outcomes

Study Setting

Drink Less is freely available on the iTunes Store. This trial will recruit eligible new individuals who download the *Drink Less* app during the trial recruitment period, from January 2, 2020, to April 1, 2020 (app version: 2.0.1).

We extended the informed consent process for this trial to comply with ethics requirements. At onboarding, users will be first asked to read the privacy notice and participant information sheet, then provide informed consent (see Multimedia Appendices 2 and 3), before proceeding. Users who do not consent to take part in the research will be provided the standard version of the app.

Eligibility Criteria

Users who download *Drink Less* during the recruitment period will be eligible to participate if they: self-report a baseline Alcohol Use Disorders Identification Test (AUDIT) score of 8 or above, indicating excessive alcohol consumption [39,44]; reside in the UK; are aged 18 years or over, and report themselves to be interested in drinking less alcohol.

Intervention

A bank of 30 novel messages was developed with the aim of increasing users' reflective motivation to engage with the app (see Multimedia Appendix 1). All messages contain the phrase "(using a particular module in the app) *can help you drink less*." As perceived usefulness of the app has previously been found to be associated with increased engagement, we hypothesized that new messages which highlight the benefits of using the app would increase users' reflective motivation to use the app and hence generate higher rates of engagement compared with the standard, existing message.

Measures

Outcome measures for the MRT will be collected continuously over the 30 days following the download of *Drink Less*. These measures collected over time are: when users open the app, when each module is used, the length of time (seconds) spent on the app and drinking records, with the date of drinks consumed and date and time of records made. Outcomes for the wider comparison between the parallel trial arms are defined over the whole 30-day follow-up period.

Outcomes

Primary Outcome (MRT)

The primary outcome measure in the MRT is a time-varying, binary proximal (ie, near-term) measure of engagement (use of the app). Specifically, the primary outcome for the MRT is whether the user opens the app in the hour (8 pm to 9 pm) following the randomization of receiving a notification at 8 pm.

Secondary Outcomes Collected Daily Through the Trial Period (MRT)

Within the MRT, the two secondary outcomes below will be defined in the hour following the decision point (8 pm to 9 pm):

1. whether or not the user creates an entry in their drink calendar (by either recording a drink record or recording a drink-free day);
2. the time, in seconds, spent on the app;

Secondary Outcomes Over the Whole Trial Period (MRT and Parallel Arms)

In the parallel trial arms, secondary outcomes that will be explored are:

1. the number of days to complete disengagement, defined as the first day of at least seven consecutive days of no use from day of download;
2. the total number of sessions over the 30 days following download;
3. the total time, in seconds, spent on the app over 30 days since download, overall, and by intervention module.

Time-Varying Covariates

Measured covariates which vary over time within individuals are the use of the modules (Action Planning; Cognitive Bias Re-Training; Self-monitoring and Feedback; Behavioral Substitution; Goal Setting; Normative Feedback; Information About Antecedents); entry of drink (or alcohol-free) record in each session; if the user opened the app before 8 pm that day; and if the user opened the app the day before.

Time-Fixed Covariates

Measured time-fixed covariates are age, gender, type of employment (manual, nonmanual, or other), day of the week of download, and baseline AUDIT score.

Sample Size

We aim to randomly assign 1200 users to the MRT arm, 400 users to the standard daily notification arm (Secondary Arm A), and 400 users to the no notification arm (Secondary Arm B), resulting in a total of 2000 participants. The sample sizes were calculated as follows:

To estimate the sample size required for the MRT arm, we used a simulation-based approach to determine the sample size required to attain a prespecified power level, because currently there is no off-the-shelf software to calculate the sample size for MRTs with binary outcomes. Our primary objective is to understand the marginal effect of receiving a push notification at 8 pm on engagement, with an important secondary objective towards the tailoring of the notification policy is identifying effect moderation over time. Plausible estimates of a treatment effect and effect moderation were obtained by exploring patterns of use with *Drink Less*. With 80% power and 5% type I error, we have sized this trial to detect a marginal treatment effect of 2.16, which decays by a factor of 0.911 by day since download. This is close to 100% power for our primary objective, the marginal effect. See Multimedia Appendix 4 for more details.

The sample size of the two additional parallel arms was determined based on the secondary outcome of time to disengagement (no use for seven or more consecutive days). Analysis of the current app shows that 55% of users have disengaged by day 30. We powered this sample size based on a minimal relevant change in disengagement of 10%, such that we expect 65% of users to disengage by day 30 when no notifications are delivered. With a 5% type I error and 80% power to detect an increase in disengagement to 65% of users by day 30, we would require 372 users per arm. To simplify the allocation process, we rounded-up the sample size for the parallel arms to 400 users per arm each, resulting in an overall sample size of 2000 and an allocation ratio of 60% to the MRT and 20% to each parallel arm.

Anticipated Recruitment Rate

The available recruitment window with the app was January 2, 2020, to April 1, 2020. All new app users who meet the eligibility criteria, provide consent, and complete app onboarding during this period will be recruited into the trial. Previous analyses of cohort data of existing users suggest that the average number of downloads by eligible users will be 33 per day, through the 59-day recruitment period. If the number of participants exceeds the minimum required sample stated above, we will continue to recruit until the end of the predefined recruitment period.

Assignment of Interventions

Sequence Generation

At recruitment, 60% of participants will be randomized to the MRT. The remaining participants will be randomly allocated 50:50 to receive no notifications or to receive standard notifications daily at 11 am.

Among the participants randomized to the MRT, at 8 pm each participant will be randomized daily to receive one of three options: no notification, the standard notification wording, or a message randomly selected from the new message bank. The randomization probabilities for these three options will be 40%, 30%, and 30%, respectively.

The randomization probabilities are fixed across all individuals and do not depend on individuals' time-varying treatment, outcomes, or covariates.

Allocation Concealment Mechanism

Users will be aware of whether or not they have received a push notification each day. They will be informed in the consent procedures that they are part of a research study testing how different versions of the app affect use. However, they will not receive explicit information that we are interested in the effect of the notification, about which arm of the study they have been allocated to, the full design of the study, or the planned schedule of their notifications. The standard request for users to enable notifications at the end of the onboarding process was disabled for this trial. Users were still able to turn off the notifications through their phone settings.

Implementation

Simple randomization was used, with no stratification or blocking. The code to generate the randomization sequencing was developed and coded into the app by an external app developer. Members of the trial team verified the randomization process.

Data Collection, Management, and Analysis

Descriptions of the trial participants, in terms of their available baseline data, will be reported for all MRT participants and participants in the two additional arms.

Primary Analysis (MRT)

Our primary analysis will estimate the marginal effect of the notifications on the binary, time-varying outcome of whether or not a user opens the app between 8 pm and 9 pm. The marginal effect is averaged over all days and all participants in the MRT arm.

The effect of notifications, quantified as a relative risk, with a 95% confidence interval, will be assessed using the estimator for marginal excursion effect for MRTs with binary outcomes [45]. The excursion effect is a causal effect concerning what would happen if an individual followed the notification scheduled used in the MRT up to day t–1 and then deviated from the schedule to receive a notification at day t, versus deviated from the schedule to receive no notification at day t. The notification schedule used in the MRT is the delivery of push notifications with 40%, 30%, 30% probability every evening at 8 pm (see the last paragraph of the subsection Trial Design). The marginal excursion effect we consider in the primary analysis will marginalize (ie, average) overall days and all individuals. Because the near-term outcome is binary, we will estimate the marginal excursion effect on the log relative risk scale.

For this analysis, both types of notification—the standard wording and the messages drawn from the new bank of messages—will be pooled; the comparison will be between any notification versus no notification. P values less than .05 will be considered statistically significant. Models used in the primary and secondary analyses for the MRT arm will adjust for age, gender, employment type, baseline AUDIT score, the number of days since download, if the user opened the app before 8 pm, and if the user opened the app the day before.

Secondary Analyses (MRT)

Our secondary analyses will assess the effect of sending a notification from the bank of 30 new messages compared to the standard message "Please complete your mood and drinking diaries" on the primary outcome; that is, whether the user opened the app between 8 pm and 9 pm. We will use the same analysis method here as for the primary analyses, which is the estimator for the marginal excursion effect. We will also assess the effect notifications have on users creating an entry to their drinks calendar.

We will investigate the effect moderation of the notification by day in the study, quantified as an interaction, and expressed as a relative risk. We will also examine the sensitivity of the result when day-in-study is replaced by splines or its log-transformation. Lagged notification effects will be similarly quantified.

The continuously valued secondary outcome in the MRT relating to time spent on the app (seconds) will be analyzed using a centered and weighted least-squares estimation method [46] with the effect quantified using the mean difference. All secondary outcomes will be explored by comparing any notification versus none and then separating the two types of notifications.

Secondary Analyses (Parallel Arms)

Time to complete disengagement will be analyzed using the Kaplan-Meier estimator. A Cox proportional hazards model will be used to estimate the hazard ratio for disengagement comparing the three parallel arms. The proportional hazards assumption will be assessed graphically and using tests based on Schoenfeld residuals. If nonproportionality is detected, methods allowing for this will be applied and presented as exploratory analyses alongside the previous Cox model analysis.

Linear regression models with robust standard errors will be used to compare the time spent on the app, both overall and on specific modules, between the three parallel trial arms. Similar models will be used to compare the total number of days of app use between arms.

No adjustment will be made for multiple testing. Outcomes and analyses are categorized by the degree of importance (primary and secondary), and results will be interpreted in the light of that ordering.

Results

This study received funding from the MRC Network of Hubs for Trials Methodology Research (MR/L004933/2- R18) in January 2019. As of early March 2020, at the date of manuscript submission, the trial is ongoing, with 452 users recruited.

Data Collection and Data Monitoring

Data collection began on January 2, 2020, and will end on May 1, 2020. Due to the rapid nature of this research, and relatively very low risk of adverse events due to the intervention, there will be no interim analysis or Data Monitoring during the trial.

Ethics and Dissemination

Ethical approval was granted by the London School of Hygiene and Tropical Medicine Interventions Research Ethics Committee (17929) and the University College London Departmental Research Ethics Committee (CEHP/2016/556); an amendment was granted by the Ethics Amendment Request to Work Package One *"The application of digital technologies to advance the understanding, and improve the implementation of behavior change."*

Confidentiality

No identifiable data will be collected during this study.

Discussion

The study will determine whether sending a notification at 8 pm increases engagement in the subsequent hour with *Drink Less* and whether the impact of the notification changes over time. Previous research has found that the perceived usefulness of the app is a predictor of both the amount and frequency of engagement with *Drink Less* [20]. Building on these findings, secondary analyses will systematically explore if messages which aim to increase the perceived usefulness of the app by encouraging users to try out various modules are more effective at increasing engagement than the standard request to record drinking and mood diary entries. We will also explore potential effect moderation, lagged effects, and overall summaries of use over 30 days since download. This study will provide evidence of how notifications affect engagement, as well as considerations towards further improvement of the push notification policy.

Our research is limited by the lack of outcomes to understand a change in alcohol units consumed, meaning we could not investigate whether receiving notifications had any effect on hazardous and harmful alcohol consumption. Generally, gathering valid and reliable health outcome measures over time, solely through self-reports, is a prime challenge for the digital health community [47,48]. *Drink Less* prompts users to complete the AUDIT-C one month after downloading the app, but the proportion of users to do so is low [49]. Our primary aim is to improve engagement with the app, and future research can investigate whether any effectiveness is mediated through engagement. Importantly, research into effective strategies to collect real-time outcomes on substance abuse through other apps is emerging [50-52], including an MRT with an "engagement-first" strategy to increase the rate of self-reported data [53]. This research is a valuable step towards developing more effective behavior change apps. Another limitation is that we do not understand if users subsequently turned off their notifications during the trial through their phone's settings.

Methodologies for tailoring notification policies, either as a stratified intervention based on time-varying or time-invariant covariates (eg, day of the week, age, past moods, previous app use or drinks reported), or strictly personalized policies, in which user's own responses to prior notifications inform the future policy, are becoming increasingly more refined [54,55]. After establishing whether there is a marginal effect of the push notifications and gaining a better understanding of the push notification's role in the dynamic nature of engagement, subsequent studies may address the more ambitious aims of creating a sequence of decision rules. Such decision rules could capitalize on dynamic states of opportunities within users' current environment or adapt to a user's history. This may be achieved by better understanding how the between- and within-person effects of the notification [56] change under varying circumstances, as well as any lagged effects of notifications.

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Authors' Contributions

All authors conceptualized the research and designed the trial. LB acquired project funding and wrote the first draft. OP and CG developed the content of the new notification bank. CG performed data extraction and management for past use of *Drink Less*. LB derived estimates to inform the sample size calcuation. TQ performed sample size simulations. All authors reviewed and edited the manuscript, revising it for intellectual content. All authors gave their final approval for publication and agreed to be accountable for all aspects of the work.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Bank of 30 newly developed messages and their link to the relevant behavior change module.
[DOCX File , 14 KB - resprot_v9i8e18690_app1.docx]

Multimedia Appendix 2
User flow chart for the micro-randomized trial with two additional parallel arms.
[PNG File , 63 KB - resprot_v9i8e18690_app2.png]

Multimedia Appendix 3
Privacy notice.
[DOCX File , 14 KB - resprot_v9i8e18690_app3.docx]

Multimedia Appendix 4
Information sheet.
[DOCX File , 14 KB - resprot_v9i8e18690_app4.docx]

Multimedia Appendix 5
Sample size calculation.
[DOCX File , 295 KB - resprot_v9i8e18690_app5.docx]

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Abbreviations

AUDIT: Alcohol Use Disorders Identification Test
MRT: micro-randomized trial
NIHR: National Institute for Health Research
RCT: randomized controlled trial
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Evaluation of a Stepped-Care eHealth HIV Prevention Program for Diverse Adolescent Men Who Have Sex With Men: Protocol for a Hybrid Type 1 Effectiveness Implementation Trial of SMART

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Abstract

Background: Adolescent men who have sex with men (AMSM), aged 13 to 18 years, account for more than 80% of teen HIV occurrences. Despite this disproportionate burden, there is a conspicuous lack of evidence-based HIV prevention programs. Implementation issues are critical as traditional HIV prevention delivery channels (eg, community-based organizations, schools) have significant access limitations for AMSM. As such, eHealth interventions, such as our proposed SMART program, represent an excellent modality for delivering AMSM-specific intervention material where youth *are*.

Objective: This randomized trial aimed to test the effectiveness of the SMART program in reducing condom-less anal sex and increasing condom self-efficacy, condom use intentions, and HIV testing for AMSM. We also plan to test whether SMART has differential effectiveness across important subgroups of AMSM based on race and ethnicity, urban versus rural residence, age, socioeconomic status, and participation in an English versus a Spanish version of SMART.

Methods: Using a sequential multiple assignment randomized trial design, we will evaluate the impact of a stepped-care package of increasingly intensive eHealth interventions (ie, the universal, information-based SMART Sex Ed; the more intensive, selective SMART Squad; and a higher cost, indicated SMART Sessions). All intervention content is available in English and Spanish. Participants are recruited primarily from social media sources using paid and unpaid advertisements.

Results: The trial has enrolled 1285 AMSM aged 13 to 18 years, with a target enrollment of 1878. Recruitment concluded in June 2020. Participants were recruited from 49 US states as well as Puerto Rico and the District of Columbia. Assessments of intervention outcomes at 3, 6, 9, and 12 months are ongoing.

Conclusions: SMART is the first web-based program for AMSM to take a stepped-care approach to sexual education and HIV prevention. This design indicates that SMART delivers resources to all adolescents, but more costly treatments (eg, video chat counseling in SMART Sessions) are conserved for individuals who need them the most. SMART has the potential to reach AMSM

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to provide them with a sex-positive curriculum that empowers them with the information, motivation, and skills to make better health choices.

Introduction

Background

Adolescent men who have sex with men (AMSM) in the United States account for 83% of all new HIV occurrences among those aged 13 to 19 years. The majority of these cases (86%) are among racial and ethnic minority youth [1]. Despite these health disparities, there have been no prevention interventions targeted specifically at this population [2]. Current evidence-based HIV prevention programs focus primarily on adults and heterosexual youth [3]. However, as the issues affecting sexual health decisions among AMSM are unique (eg, access to affirming care) [4,5], interventions should be designed with their needs in mind to ensure that the content resonates with them. Moreover, prevention programs need to be responsive to racial and ethnic minority AMSM who experience reduced access to HIV or sexually transmitted infection (STI) prevention services [6,7] and, as a corollary, increased HIV incidence [1]. eHealth interventions represent a critical modality for delivering AMSM-specific intervention material where youth *are*, considering that 97% of adolescents across all races and income levels are on the web every day [8]. Combining web-based recruitment with intervention delivery across a range of devices could overcome many access barriers to the engagement of AMSM in HIV prevention. Here, we describe a hybrid type 1 effectiveness-implementation protocol [9] aimed at testing the SMART Program's effectiveness and informing future implementation as a service. Our study uses a sequential multiple assignment randomized trial [10,11] to examine the effectiveness of each component of SMART, which consists of three eHealth HIV prevention interventions.

HIV Acquisition Risk in AMSM

AMSM are the most at risk for HIV infection compared with all other subgroups of adolescents because of specific risk factors [1]. Some of these factors that contribute to inconsistent condom use are common to AMSM and adult men who have sex with men (MSM) alike, such as substance use before or during sex [12], familiarity with partners [13], and negative affective states such as loneliness or depression [14,15]. Other factors are more unique to AMSM, such as access to and cost of condoms [16], inconsistent sexual health education [17,18], sexual inexperience [14], sex with older partners [19,20], and underage use of sexual networking apps for adults [21]. Adult MSM have had increasing access to pre-exposure prophylaxis (PrEP) since it was approved by the Food and Drug Administration in 2012 [22]; however, adolescents, for whom PrEP was only recently approved in mid-2018, report extremely

low uptake [23-25]. Knowledge about PrEP, self-efficacy to access it, fear of lack of parental support or punishment, state-level requirements of parental consent to use it, and regimen upkeep (including quarterly HIV testing) have been cited as reasons for this difference between AMSM and adult MSM [23-26].

Despite engagement in HIV transmission risk behaviors and representing a large proportion of adolescent HIV diagnoses, AMSM have not achieved sufficiently high rates of HIV testing. A recent study found that only 23% of AMSM aged 13 to 18 years reported testing at least once for HIV in their lifetime [27]. Adolescents, especially AMSM, fail to test because of fears about family or pediatrician and health care provider judgments, being closeted, or being afraid of testing positive [28-31]. Lack of adolescent-friendly testing sites, barriers to transportation, and fear of being seen by friends also contribute to reduced testing rates [32,33]. Even among those who test, failure to repeatedly test or establish a testing regimen has been noted [27]. This suggests that existing sexual health education may be insufficient, lack relevance or depth, or simply may not be reaching AMSM [17,18].

AMSM HIV Prevention Programs and eHealth

The delivery of relevant HIV prevention measures for AMSM through traditional channels (eg, schools, parents) is extremely restricted. For example, the vast majority of school-based sexual education programs do not address the needs of sexual and gender minority adolescents [17,34], and many schools have explicit policies prohibiting the discussion of homosexuality [35,36]. Parent-child HIV prevention programs are efficacious in reducing sexual risk among heterosexual youth [37-41]. However, even in an era of greater acceptance, many parents of the most at-risk AMSM [42,43] reject their teen's sexual identity [44-46] or refuse to discuss same sex behaviors [47]. eHealth, or the use of electronic technologies to promote health [48], has the potential to circumvent these barriers. It represents a relatively anonymous manner to easily access knowledge that may otherwise be stigmatizing or endangering if sought using in-person methods (eg, information on sexual orientation, engaging in anal sex, PrEP) [49-51]. Considering that 95% of teens report having a smartphone and 45% report being on the web constantly [8], web-based programs that provide sexual health information regardless of location have excellent potential to reach AMSM.

Several noteworthy eHealth interventions have already targeted AMSM. Queer Sex Ed (QSE) was tested in 2013 with AMSM aged 16 to 20 years and young adult MSM [52]. This web-based program emphasized sexual health as more than just the absence

of disease and included information on healthy romantic relationships, having pleasurable sexual experiences, and acceptance of one's sexual orientation and gender identity. Intervention content also explained HIV or STI transmission and how to acquire and use condoms. A total of 15 of the 17 primary outcome measures significantly improved from baseline to posttest (2 weeks later), including the knowledge of safer sex practices. Guy2Guy (G2G) was a text message–based intervention that provided 14- to 18-year-old sexually experienced and inexperienced sexual minority males with text messages on safer sex, having sex in the context of a relationship, and HIV testing [53]. G2G also paired participants with each other so they could practice program skills and provide social support. A 2014 efficacy trial showed that participants in the intervention arm of G2G reported a three-fold increase in HIV testing relative to those in the information-only control group; however, condom-less anal sex did not differ between the groups.

Hybrid Type 1 Effectiveness Implementation Design

These previous eHealth interventions [52,53] suggest that web-based programs can be effective for sexual minority adolescents. However, none of these programs have systematically examined factors critical to their real-world implementation. The traditional, stepwise pipeline of intervention development to implementation is estimated to take 17 years and takes only a fraction of interventions from research to practice [54,55]. Hybrid designs serve to accelerate this process by concurrently examining effectiveness and implementation outcomes, thereby shortening the time needed to study both [9]. Our adaptation of pre-existing effective interventions also improves this acceleration by reducing the likelihood of null findings and increasing the ease of scale-out. As we are using a hybrid type 1 effectiveness implementation design, the primary aim of our study is to establish evidence of effectiveness for SMART; however, we will also gather preliminary implementation data to inform future selection of implementation strategies to scale our program. Specifically, we are utilizing the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) outcomes framework [56-58] to measure implementation outcomes by focusing on reach, effectiveness, cost, ongoing delivery, and program sustainment. In addition, we are drawing from the Consolidated Framework for Implementation Research (CFIR) [59] to assess contextual determinants that may impact future implementation (eg, implementation readiness, barriers, facilitators, and ease of integration). These data can provide convincing information for decision makers about how to implement SMART once effectiveness testing ends [9,60].

Objectives

SMART is a suite of stepped-care interventions, following the Institute of Medicine's prevention model [61,62]. This model suggests increasing the intensity of prevention techniques according to risk factors or specific risks exhibited by a given population. The first step in SMART is a low-cost universal intervention offered to all participants regardless of HIV risk (ie, SMART Sex Ed, SSE). The second more intensive selective intervention (ie, SMART Squad) is offered to those who report HIV risk intentions or behaviors following SSE. Finally, a higher cost indicated intervention (ie, SMART Sessions) is designed for those who continue to report HIV risk intentions or behavior following the two previous interventions. We are testing for individual intervention and cumulative intervention effectiveness at reducing condom-less anal sex and increasing condom use intentions, self-efficacy, and HIV testing among AMSM participants. Additionally, we are testing whether SMART has differential effectiveness across subgroups of AMSM based on race and ethnicity, urban versus rural residence, age, socioeconomic status, and preference for an English versus a Spanish version of the intervention. Our use of a hybrid type 1 design simultaneously allows us to collect data that will provide critical insight into factors that may impact SMART's real-world implementation. In the following section, we describe the protocol for all 3 components of SMART.

Methods

Study Design

This study uses a hybrid type 1, sequential multiple assignment randomized trial [10,11,63] evaluating the impact of a package of increasingly intensive, stepped-care interventions (Figure 1). The advantage of using a sequential design is that it can help determine which of a wide variety of intervention strategies (or combinations therein) will be best suited to a given individual, thus maximizing efficacy. Previous versions of SMART intervention steps have already shown evidence of efficacy with diverse young adult MSM [52,64,65] and were further developmentally and linguistically adapted to accommodate the unique social experiences and health barriers of English- and Spanish-speaking adolescents in this study [66]. All participants received the universally relevant SSE intervention at baseline. Response to the intervention, as defined in the section below, will be measured at the 3-month follow-up assessment. Those who respond to SSE will be randomized to receive either SMART Squad or a follow-up only condition. Those who do not respond to SSE will be randomized to receive 1 of 4 treatment packages, 2 of which include the control condition, SMART Sex Ed2.0 (SSE2.0). As shown in Figure 1, these treatment packages represent pathways a participant could take through the trial contingent on their responder status and are thus termed *embedded regimes* [63,67,68].

Figure 1. SMART participant intervention progression. Survey assessments are conducted at baseline (0 M), 3 months (3 M), 6 months (6 M), 9 months (9 M), and 12 months (12 M). An embedded regime is the path or sequence of specified interventions to which a participant may be randomized. The circled letter "R" refers to the point at which participants are randomized to an embedded regime, or in the case of responders to SSE (see R*), either follow-up only or access to SMART Squad after the 6-month assessment. Dashed embedded regime paths represent responder pathways. AMSM: adolescent men who sleep with men; SSE: SMART Sex Ed.
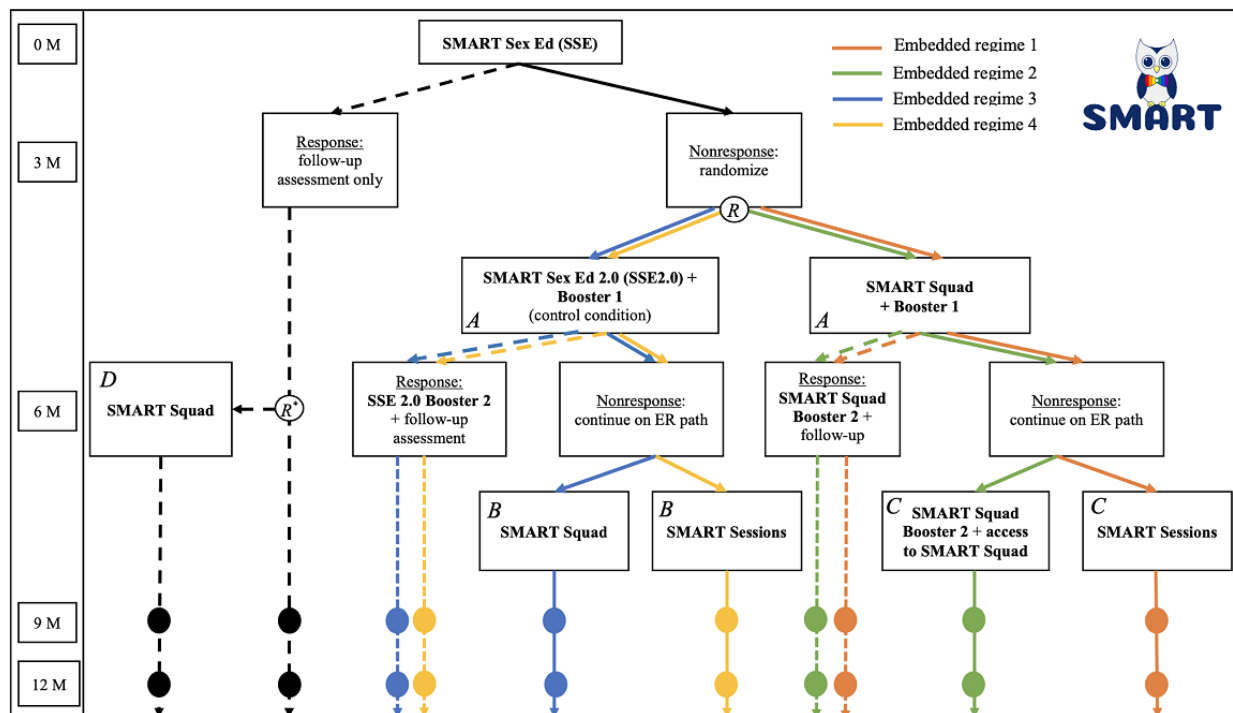
A: Efficacy of SMART Squad (including booster) relative to control (SMART Sex Ed 2.0) for AMSM who did not respond to general web-based sex education (SSE).
B: Efficacy of SMART Sessions relative to SMART Squad content for AMSM who did not respond to web-based sex education (SSE) or additional web-based sex education (SSE2.0).
C: Added benefit of SMART Sessions above an extended dose of SMART Squad for AMSM who did not respond to web-based sex education (SSE) or intensive HIV education (SMART Squad).
D: Added benefit of SMART Squad for AMSM who responded to web-based sex education (SSE).

Embedded regime 1 assigns the participant to the selective SMART Squad initially; if the participant is a nonresponder at 6 months, then it assigns the participant to SMART Sessions. If the participant is a responder at 6 months, then it assigns the participant to SMART Squad Booster 2 and follow-up.

Embedded regime 2 assigns the participant to a selective SMART Squad initially; if the participant is a nonresponder at 6 months, then it assigns the participant to SMART Squad Booster 2 and continued access to SMART Squad. If the participant is a responder at 6 months, then it assigns the participant to SMART Squad Booster 2 and follow-up.

Embedded regime 3 assigns the participant to receive SSE2.0 initially; if the participant is a nonresponder at 6 months, then it assigns the participant to SMART Squad. If the participant is a responder at 6 months, then it assigns the participant to SSE2.0 Booster 2 and follow-up.

Embedded regime 4 assigns the participant to receive SSE2.0 initially; if the participant is a nonresponder at 6 months, then it assigns the participant to SMART Sessions. If the participant is a responder at 6 months, then it assigns the participant to SSE2.0 Booster 2 and follow-up.

Randomization by embedded regimes is mathematically equivalent to running separate randomizations at each stage; however, from an implementation perspective, randomization to embedded regimes is often easier with clinical trial software (ie, REDCap, Research Electronic Data Capture), especially when randomization is stratified or subject to other constraints.

Defining Response to the Intervention

At each time point, the response threshold is defined as meeting each of these 3 criteria: (1) 100% condom use, if the participant is sexually active in the assessment period, (2) intentions for condom use during all instances of penetrative sex (regardless of reported sexual activity), and (3) reporting a high degree of self-efficacy for achieving condom use during all instances of penetrative sex (regardless of sexual reported activity). Condom use intentions are assessed using the 11-item Condom Use Intentions Scale [69,70]. This scale measures the likelihood of condom use under varying situations. An example item is, "If you have a boyfriend, how likely would you be to use condoms with him?" Each item has a 4-option response scale ranging from *very unlikely* to *very likely*. The self-efficacy of condom use is assessed using the Condom Use Self-Efficacy Scale [69,70]. This scale measures perceived confidence in being able to engage in safer sex practices under varying circumstances. An example item is, "How confident are you that you would be able to refuse to have anal sex without a condom?" Each item has a 7-option scale ranging from *not at all confident* to *extremely confident*. A mean score of 4 for condom use intentions and a mean score of 7 for condom self-efficacy would indicate 100% condom use intentions and self-efficacy.

Calibrating condom use intention and self-efficacy thresholds specifically for SMART was necessary to establish values that were meaningful in terms of prevention impact. The threshold calibrations also needed to be stringent enough to err on the side of escalation to a more intense intervention. Overall, the calibration process sought to establish the optimal treatment sequence in this stepped-care design. To do this, we tested the condom use intentions and self-efficacy items on a sample of 204 AMSM who were enrolled in a separate study to establish the distribution of values for these scales. As the aim was to select *a priori* thresholds for SMART's sample that would reflect a 90% nonresponse rate before SSE, we calculated the 90th percentile values from the 204 AMSM for condom use intentions and self-efficacy. A 90% nonresponse rate was required and calculated from an initial power analysis to ensure that the second- and third-tier interventions would be sufficiently powered. These values then became the initial responsiveness threshold for condom use intentions (ie, scores >3.76) and self-efficacy (ie, scores >6.50) for SMART. When enrollment into SMART opened in April 2018, study statisticians monitored the first 58 participants enrolled to verify the reliability of the condom use intention and self-efficacy thresholds between actual SMART participants and the previous sample of 204 AMSM. Most (51/58, 88%) of the first 58 SMART participants did not exceed the score set for responding. This finding was deemed acceptably close to 90% to retain those criteria.

As such, SMART participants are considered responsive to any intervention if they report all of the following: (1) 100% condom use, if sexually active in the assessment period, (2) a condom use intentions score >3.76 (ie, *very likely* to use condom), and (3) a self-efficacy score >6.50 (ie, *extremely confident* at using condoms). It is important to understand that with this type of research design, *responsive* is the threshold for participants to be considered for randomization to the next intervention step; this is not the same value that defines the success of the intervention in terms of the effectiveness outcomes.

Inclusion and Exclusion Criteria

Potential participants are eligible for this study according to the following inclusion criteria: (1) they were assigned male at birth, (2) they identify as a sexual minority (ie, report their sexual orientation as gay, bisexual, queer, lesbian, or pansexual) or report attraction to cisgender males, (3) they report an HIV negative or unknown HIV status, (4) they have engaged in sexual contact with another person (defined as having touched another person's genitals or performed oral, vaginal, or anal sex), (5) are between the ages of 13 and 18 years (inclusive), (6) have access to or use the internet, (7) are able to read and speak English or Spanish at a sixth grade level or better, (8) and

reside in the United States, including Puerto Rico, Guam, and the US Virgin Islands. Current gender identity was not an inclusion or exclusion criterion. Those assigned male at birth could identify as any gender identity (eg, transgender, nonbinary, genderqueer, genderfluid) provided they met the 8 inclusion criteria. Those identifying as intersex or assigned female at birth were excluded to comply with the trail's specific aim to curtail HIV spread in AMSM.

Potential participants are ineligible if the study staff identify discrepancies between the eligibility screener and the baseline assessment. Such discrepancies may include reporting 2 different ages on the screener and baseline assessment, reporting different zip codes or locations, and/or not reporting lifetime sexual contact on the baseline assessment.

Recruitment, Eligibility Screening, and Enrollment Into SMART

English- and Spanish-speaking AMSM are recruited using paid advertising on social media (eg, Instagram, Facebook) and through active web-based engagement using geospatial dating apps and other social media outlets (eg, Reddit, Tumblr). Advertisements, posts, and direct messages direct potential participants to a brief web-based eligibility survey, available in English and Spanish. Participants who complete the survey in English are given access to the English-only version of SMART. Those who complete it in Spanish are given access to the Spanish-only version of SMART, in which all study consent, communications or reminders, intervention content, and assessments are provided in Spanish. Figure 2 displays participant flow from advertisement to enrollment. All study surveys are administered via REDCap [71]. The Northwestern University Institutional Review Board granted SMART a waiver of signed documentation of informed consent or assent as well as a waiver of parental permission for participants under 18 years. Participants are routed to a consent page with 4 decisional capacity questions, which assess their comprehension of study tasks, risks, and benefits, as well as how to exit the study [72]. They also submit a username for study staff approval on the consent page. Usernames cannot have any personally identifying information (eg, name, email). If they provide consent, study staff email and/or text prospective participants to set up a video chat to verify participant identity, review the study tasks, and answer any of their questions. During this 5-min video chat, AMSM are also asked to explain back to study staff what they will be asked to do as a SMART participant. Finally, if a participant has submitted a username with personally identifying information, the study staff will work with the participant to revise the username while on the video chat.

Figure 2. Participant entrance into SMART: from advertisement to enrollment. SSE: SMART Sex Ed.
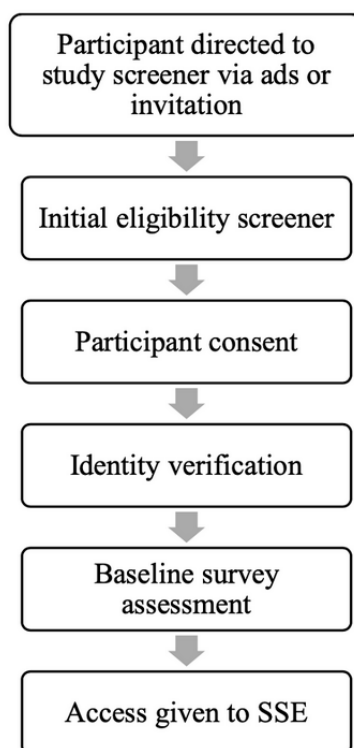
Once the video chat is complete, participants are sent their web-based baseline assessment survey, which has all pertinent primary and secondary study measures. Completion of the baseline assessment triggers an automatic email inviting the participant to login to SMART by going to the website, resetting their password using their username, and then logging in to access the first tier of the intervention. All participants, regardless of demographic characteristics or responses to their baseline assessment, are given access to SSE.

Randomization of Treatment Arms

Nonresponders to SSE are randomized to 1 of 4 embedded regimes, which determines the interventions that a participant receives and the order in which they occur. This assignment is performed using stratified block randomization [73]. Through stratification, we avoid an imbalance of prespecified factors that may be related to the primary outcomes and/or to the intervention delivery itself. We randomized within 8 strata comprising all combinations of the following 3 binary factors: language preference (English or Spanish), rurality (living in an urban or rural zip code), and lifetime anal sex experience (any or none). Within each stratum, embedded regimes were assigned using a permuted block design, with blocks of size 4. This ensures that at any point during the study, each embedded regime assignment is protected against large imbalances in language preference, rurality, and sexual experience. The R package *blockrand* [74] was used to create the randomization allocation table.

We selected these stratifying factors for several reasons. The SMART program is delivered in either English or Spanish depending on participant preference. Although the content is identical across language delivery, cultural factors may lead AMSM to be differentially responsive to the content and style

of the interventions [75-78]. As such, we wish to ensure that English and Spanish speakers are equally represented in each randomization assignment. Rurality is included as a stratifying factor because of potential differences in lived experiences when comparing rural AMSM with nonrural AMSM. Rural AMSM may feel less comfortable coming out, have less family support, and have less access to the lesbian, gay, bisexual, transgender, queer (LGBTQ) community organizations and providers who are knowledgeable about LGBTQ health and HIV [16,79,80]. Rural residence is assessed by categorizing participant-reported zip codes into rural-urban commuting area codes [81]; zip codes with 30% or more of their workers going to a census-defined *Urbanized Area* were considered urban and all others were considered rural. Finally, a lifetime penetrative sexual experience is included to account for differential HIV risk among those who have engaged in anal sex with a male and those who have not. Additionally, elements of the intervention content may be differentially applicable to those who have had penetrative sex based on their lived experiences.

Treatment Conditions

All tiers of SMART were built from the information-motivation-behavioral (IMB) skills model for HIV prevention [82]. This model suggests that individuals are likely to enact behaviors if they are knowledgeable or informed about the behavior, motivated to enact it, and have the corresponding skills to enact the behavior. In adult MSM [83-85], this model has shown that individuals with accurate HIV knowledge, sufficient motivation (eg, fear, HIV vulnerability), and know where to screen for HIV are more likely to complete HIV testing. Similarly, IMB constructs have been associated with condom use consistency and PrEP use among MSM [64,69,86-89]. These studies indicate that knowledge is

necessary but not always sufficient to move MSM toward prevention and testing behaviors, and individuals who report higher levels of the 3 IMB components tend to be more likely to engage in HIV prevention and testing. SMART builds on this evidence by taking a tiered approach to HIV prevention messaging to AMSM, that is, for some, merely providing basic information on HIV prevention will be sufficient to improve condom use. SSE (tier 1) is therefore built as an information-only intervention to which all participants will be granted access. For those who do not respond to HIV-related information, providing situational and contextual HIV prevention motivations, and training in HIV behavioral skills to prevent transmission can increase behavioral enactment. As such, we built SMART Squad (tier 2) and SMART Sessions (tier 3) to provide all 3 theoretical constructs from IMB to participants who continue to report inconsistent condom use intentions and behaviors.

SMART Sex Ed

SSE represents the first-tier intervention for SMART. It is exclusively informational in nature and was adapted from an intervention previously tested on LGBTQ youth showing preliminary efficacy (ie, QSE) [52]. As part of the adaptation process [90], core sexual health competencies and learning objectives from the Centers for Disease Control and Prevention (CDC) [91] and Sexuality Information and Education Council of the United States [92] were incorporated and, if necessary,

were updated to suit a sexual minority audience (eg, coming out strategies). We assembled a diverse, standing web-based youth advisory council of AMSM (13- to 18-year olds) to review our adapted content and answer questions about the relevance of information we were considering incorporating. Members of the council acted as an asynchronous focus group and were compensated monthly for their time [93]. Besides ensuring that SSE content would resonate with AMSM, this focus group allowed community member stakeholders (ie, AMSM) to participate in the intervention creation. SSE contains 4 modules that participants can navigate in their preferred order (Figure 3). Media assets used across the modules include full-page scroll screens (resembling social media feeds), slideshows with narration recorded using near-peer voice actors, videos, games, quizzes, and graphic interchange format images. Emojis are liberally used to make topics and lessons more tangible to participants who commonly use emojis in peer-to-peer web-based communication to discuss sexual behavior. *SMART Facts* are used to segue between modules. They describe LGBTQ historical moments (eg, the Stonewall riots) and LGBTQ racial and ethnic identity intersectionality (eg, pictures and a historic description of the Native Hawaiian LGBTQ experience). All modules end with a content quiz for participants, which helps them identify areas they may want to review. When participants select an incorrect response, they are given messaging that explains why their choice is incorrect and why another answer may be the better option.

Figure 3. Overview of the 4 SMART Sex Ed modules. STI: sexually transmitted infection.

Module 1. Your guide to sexual orientation & gender identity	Module 2. Unfiltered sex ed: sexual activity, pleasure & consent	Module 3. Sex ed in the real world	Module 4. Single? Taken? It's complicated?: healthy relationships
1.0 - Introduction	2.0 - Introduction	3.0 – Introduction	4.0 - Introduction
1.1 - How do you know your sexual orientation?	2.1 – Sexual activity and pleasure	3.1 – Viral STIs	4.1 – Dating and being single
1.2 - Gender identity and expression	2.2 - Consent	3.2 – Bacterial STIs	4.2 – Communication skills
1.3 – Coming Out to Parents	2.3 – Sexting	3.3 – Barrier methods	4.3 – Relationship expectations
1.4 – Sexual Orientation Labels, Coming Out, & Support	2.4 – Adolescent sexual health rights	3.4 – Substance use and sex	4.4 – Relationship agreements
1.5 – Connecting to the Community	2.5 – State laws	3.5 – HIV risk calculator	
		3.6 – Getting an HIV test	
		3.7 – Finding an HIV testing site	

Figure 3 gives a visual overview of modules and their subsections. The first module covers sexual orientation and gender identity in detail. The differences between the 2 are identified, with both being further framed as continuous social constructs (eg, what transgender means relative to nonbinary,

what distinguishes someone identifying as gay from pansexual, and why people describe their sexual or gender identity on a continuum). *Coming out* is explained and participants are given tips for how to disclose sexual orientation or gender identity to family. Finally, community resources and LGBTQ-friendly

organizations are suggested for participants who may want more specific help regarding understanding their sexual or gender identities.

The second module explores sexual behaviors (eg, receptive anal sex), including how to minimize discomfort and maximize pleasure. Detailed discussions of sexual consent are provided as well as an explanation of the sexual health rights of adolescents (eg, a state-by-state map explaining laws about sexual health testing and access to services without parental consent).

The third and longest module introduces participants to biological and behavioral sexual health. Although traditional topics such as differences between bacterial and viral STIs are discussed in detail, this section elaborates on the sexual health needs of AMSM. For example, the role of lubrication during anal sex is explained as a protective factor when used with condoms, PrEP is described, relative differences in sexual risk behaviors are visually depicted using an HIV risk calculator, and how to find a friendly LGBTQ-oriented HIV or STI testing site is provided.
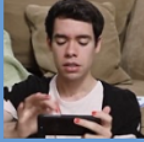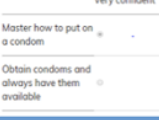
Finally, participants were introduced to the topic of healthy relationships in the fourth module. Different relationship configurations are described (eg, being single, dating, being in multiple relationships) and the differences between monogamy and nonmonogamy are explained. Suggestions for enacting direct communication about relationship expectations are given.

SMART Squad

SMART Squad represents the experimental second-tier intervention for SMART. Differing in many ways from the SSE, SMART Squad focuses on improving participants' motivations to concentrate on their sexual health and behavioral skills to enact protective measures to prevent HIV or STIs. This intervention was adapted from *Keep it Up!*, a CDC best-evidence effective intervention previously tested on young adult MSM [64,94] using intervention mapping as a systematic approach [66]. All the adapted content, including all scripted videos, were reviewed by our web-based youth advisory council. SMART Squad contains 6 episodes and 2 booster episodes; the first booster is delivered 1 month after the completion of episode 6, and the second is delivered 3 months after the completion of episode 6. Participants were forced to break for 8 hours between episodes 3 and 4. Figure 4 [66] describes the main concepts and active learning components within each episode.

Figure 4. Overview of the 8 SMART Squad episodes: main concepts and active learning components. Main concepts refer to learning objectives or topics covered by episodes. Interactive lessons refer to activities that provide positive motivations and skills for sexual health. Reflection refers to open-ended questions asked of participants as an activity within an episode. Decision support refers to skills-based activities to identify solutions to health barriers. PEP: postexposure prophylaxis; PrEP: pre-exposure prophylaxis; STI: sexually transmitted infection.

The educational modalities used are different in SMART Squad relative to SSE. This intervention relies on a scripted video soap opera delivered across the episodes. It features interactive activities that encourage participants to reflect on their motivations and help them build behavioral skills. SMART Squad also has a forum where participants can post asynchronous messages to each other under topics like *breaking the mold and being yourself*, *best/worst dates you've had*, and *parents/guardians*. The forum has a topic called, *ask the Sexpert*, where participants can post questions, which are directly answered by study staff who provide health education but not medical advice. Finally, after episode 6, participants complete a goal-setting activity where they select 3 prevention or risk-reduction goals to accomplish in the next 1 and 3 months. These goals include, but are not limited to getting an HIV test, obtaining a condom, using condoms during every sexual encounter, and talking to a health care provider about PrEP. Once selected, the activity helps users think through how to

overcome likely barriers using suggested strategies to achieve the goals. Briefly, SMART Squad encourages participants to consider their own sexual identity, sexual health, and psychological challenges, and identify the best ways to overcome them.

The video soap opera follows 4 main characters who are in geographically different high schools across the United States. These characters meet each other in a web-based space called *SMART Squad* and become fast friends. They share with each other different sexual orientation, sexual behavior, and relationship problems they encounter in their daily lives and ask each other (and other characters) for advice. Participants follow their storylines as the characters make healthy and unhealthy decisions and learn from their successes and failures. In addition to the video soap opera, there are activities that conceptually and visually align with the videos. For example, one of the video characters is about to have sex for the first time. His older partner is pressuring him to have condom-less sex, and the character does not know how to respond. At that moment in the video, an activity pops up for participants to help the character by rating potential *condom comebacks* as weak or strong. The strongest response from the activity is spoken by the character when the video restarts, enabling successful condom use.

These examples demonstrate how changes in motivations and behavioral skills are enacted throughout SMART Squad using interconnected videos and activities. Peer norms and tension for change are instilled through the storylines, and skill-building exercises support self–re-evaluation, stimulus control, and reinforcement management. In terms of specific content, episode 1 focuses on health, emotional, life, and physical needs, as well as tips for dating. Episode 2 delves into the social and emotional consequences of HIV infection (eg, stigma, disclosure) and shows how to have difficult conversations in a relationship (eg, discussing infidelity with a main partner). Episode 3 is the longest episode and covers how to resist peer pressure to use drugs, how and when to choose to have anal sex with a partner, how to talk to health care providers about sexual health, HIV or STI testing, condom use norms, and behavioral and biomedical prevention strategies (eg, PrEP). Episode 4 introduces participants to societal pressures around gender norms, features a condom demonstration, itemizes the steps to consider before meeting an unfamiliar or anonymous partner for sex, describes how to reinitiate condoms into a relationship, and shows how alcohol and drug use contributes to sexual risk behaviors. Episode 5 outlines the steps to take if condoms are not used or if the condom breaks (ie, postexposure prophylaxis). It also shows how to negotiate condom use before sex with a partner. Finally, episode 6 concludes the main intervention by covering the intrinsic and extrinsic pressures to have sex, sexting, control/agency surrounding sex with partners, and overcoming barriers to obtaining condoms. This last episode also has the characters reiterate the overall importance of condoms, PrEP, and consistent HIV or STI testing.

The 2 boosters (ie, episodes 7 and 8) do not introduce new concepts but reinforce main themes from the first 6 episodes, continue the storyline of the characters several months later, and conclude the plotlines. The 2 boosters also serve as

check-ins for participants regarding the goals they made after episode 6. Participants provide feedback whether they accomplished their goals. If they have, they are asked to select a new goal. If they have not, they are asked to provide reasons for not completing the goal, and then SMART Squad provides additional strategies to help.

SMART Sex Ed 2.0 (Control Condition)

SSE2.0 represents the second-tier control arm for SMART. One of the main hypotheses driving the design of this study was that some AMSM would need more than information to reduce their HIV risk. SMART Squad reflects this by addressing motivations and behavioral skills. The logical control condition for SMART Squad would be the continuation of an information-based intervention but without HIV prevention motivational and skill-building content. SSE2.0 was developed as an expanded version of the SSE (with 6 modules and 2 boosters). One key difference between SSE and SSE2.0 is that participants must go through the SSE2.0 modules in a specific order to match how participants advance through SMART Squad. Participants start with a module that reviews what sex and sexual behaviors are, the importance of pleasure, and health communication. Module 2 provides additional facts about STIs that were not covered in SSE. Module 3 is exclusively about HIV and shows the epidemiology of the disease, including which groups are more at risk of infection. Module 4 outlines the different types of barrier methods to prevent HIV or STI infection (eg, traditional condoms, internal or receptive condoms, lube, dental dams). Module 5 discusses PrEP, postexposure prophylaxis, and treatment as prevention. The final module in SSE2.0 provides an overview of HIV testing and HIV treatment. The first booster, which opens 1 month after the completion of module 6, discusses drugs or alcohol and their relationship with sexual consent and sexual risk taking. The second booster, which opens 3 months after the completion of module 6, identifies HIV risk factors and the steps participants can take to avoid those factors.

SMART Sessions

SMART Sessions represent the third-tier intervention for SMART. Similar to SMART Squad, this intervention focuses on motivations, skill building, and goal setting for participants. However, where SMART Squad uses an automated web platform, SMART Sessions rely on one-on-one video chat motivational interviewing (MI) counseling between participants and SMART coaches. This program was adapted from the Young Men's Health Project, an effective intervention previously tested on young adult MSM [65]. SMART Sessions are delivered by clinical professionals with postgraduate training in counseling or psychology. All coaches receive extensive training in MI techniques and conduct mock sessions to be cleared to deliver the intervention to SMART participants [95]. Coaches receive weekly individual and group supervision by a licensed clinical psychologist to ensure quality delivery of MI principles. Participants who are randomized to SMART Sessions participate in 3 to 4 video chat sessions over the course of 4 to 6 weeks via Skype or FaceTime. The number of sessions is determined by the coach, based on whether the participant reports engagement in condom-less sex and/or is a strong

candidate for PrEP. Video chats last between 20 and 45 min, on average, and participants remain with the same coach for all their sessions. The minimum time for being considered a completed session is 15 min.

The 4 sessions focus on increasing motivation to engage in safer sex behaviors, including using condoms during sexual intercourse, receiving an HIV or STI test or creating a routine around testing, and PrEP use. The first session begins with introductions, an explanation of the overall timeline and content of SMART Sessions, limits to confidentiality, and a *priorities* activity. This activity asks the participant to list the most important priorities in their lives and asks about the following 5 priorities and how they might fit into the priorities that the participant has already listed: family, independence, sexuality, school, and health. The coach then asks the participant to select their top 3 priorities from the list and discuss how these priorities might be related to the decisions that they make around sexual health. The purpose of this activity is to consider how HIV prevention may fit in with the participant's broader goals and values and to serve as a jump-off point for discussing the participant's sexual health practices. At this point, the coach collaborates with the participant regarding what topic they would like to explore first—HIV prevention or HIV testing. Using MI strategies, the coach works with the participant to identify changes that they may want to make to their sexual health plan and encourages the participant to brainstorm ways in which they may begin to make those changes. Participants are asked to take into account past successes that they might have had regarding sexual health. The first session ends with a summary of their discussions and scheduling the second session. The second session mimics the first, but focuses on whichever topic was not previously addressed (HIV prevention or HIV testing). By the end of the first 2 sessions, the participant and coach would have discussed both topic areas, identified moments for potential behavior change regarding prevention and testing, and developed potential sexual health goals for consideration.

The third session takes a different direction by focusing on PrEP education and PrEP navigation. The session begins with a review of sessions 1 and 2 and a recount of any successes or failures surrounding HIV prevention and/or testing. Following this, the coach provides the participant with a brief educational overview of PrEP, including its usefulness and navigation options (ie, who prescribes it, where to find providers). Together, the coach and participant explore ideas about whether PrEP might be a right fit or identify future milestones for the participant that may signify it might be right to start PrEP (ie, becoming sexually active, having multiple sex partners). If PrEP is a good choice for the participant, the coach and participant discuss strategies and goals to move the participant toward PrEP acquisition and use. The session ends with a review of PrEP and the coach

answering any additional questions from the participant. If this is the final session, there is also a review of all the material covered in the previous sessions, a discussion regarding what sexual health resources are available to the participant and the coach saying goodbye to the participant. The fourth session, for those designated in advance (ie, those actively engaging in condom-less anal sex), begins with the participant describing progress made since initiating SMART Sessions. The coach spends time highlighting the changes in the participant's thinking and describes the progress that the coach perceives the participant has made. Together, they discuss obstacles to past change and steps to take toward future change regarding HIV prevention, testing, and, if applicable, PrEP uptake. The coach works with the participant to identify commitment statements, which the participant should consider before enacting risk behaviors, if applicable. Goals are finalized, and any concluding questions or concerns are answered before this last session is completed.

If a participant reports a safety concern (eg, they are experiencing suicidal or homicidal ideation, they are currently being abused or maltreated by a caregiver), the coach will conduct a safety assessment with the participant to determine the level of risk involved. The coach will then consult with their supervisor to determine whether further action, including mandatory reporting, needs to be taken.

All sessions conducted are audio-recorded by the coaches. Weekly supervision occurs within SMART Sessions, in which coaches' sessions are reviewed and analyzed by a clinical psychologist with advanced proficiency in MI and Motivational Interviewing Treatment Integrity (MITI) 4.2.1 coding [96]. Coaches are provided with guidance on how to enhance their delivery of MI techniques. SMART Session recordings (20%) are coded for MI fidelity using the MITI coding system [96]. Sessions are individually coded by a group of trained MITI coders.

Study Assessments and Other Measures

Whether participants graduate from 1 intervention tier to the next is contingent on how they answer the previously described condom use attitudinal questions (ie, condom intention and self-efficacy items) and the behaviors they report. To prevent participant anticipatory effects (ie, misreporting with the intent to receive more or less treatment), they are not told the criteria for intervention response. Participants complete self-reported questionnaires at all follow-up time points (ie, 3, 6, 9, and 12 months post-SSE). They are compensated US $25 for completing each assessment, for a total of up to US $125 per participant. Figure 1 shows the flow of events for participants, and Table 1 provides a list of the primary and secondary outcomes by assessment time point.

Table 1. Primary, secondary, and other outcome measures: operationalization and schedule.

Constructs	Measures and operationalization	Measurement schedules				
		Baseline	3 months	6 months	9 months	12 months
Sexual risk (P[a])	Condom-less anal sex partners as well as sex acts with the most recent 3 partners [97]	x[b]	x	x	x	x
Condom use intentions and self-efficacy (P)	Condom Use Intentions Scale–11 items; Condom Use Self-Efficacy Scale–5 items [69,70]	x	x	x	x	x
HIV testing (P)	Self-reported history of testing for HIV in the previous 3 months [98]	x	x	x	x	x
HIV knowledge (S[c])	Knowledge of HIV transmission and prevention [99]	x	x	—[d]	—	x
Motivation and behavioral skills (S)	Motivation (eg, motivation to become safer), social norms (eg, partners', friends', or family members' opinions about condom use), and behavioral skills (eg, negotiating condom use) [69]	x	x	x	x	x
Condom errors (S)	Adapted condom errors questionnaire–15 items [100]	x	x	x	x	x
Substance use (O[e])	Alcohol use disorders identification test, cannabis use disorders identification test, past 3-month use of illicit drugs [101]	x	x	x	x	x
PrEP[f] (O)	PrEP knowledge, current and past 3-month PrEP use, PrEP adherence, motivation to start PrEP, and reasons for discontinuation [102,103]	x	x	x	x	x

[a]P: primary outcomes.

[b]Measure is assessed.

[c]S: secondary outcomes.

[d]Measure is not assessed because the first-tier intervention was the only one to focus on HIV information. As such, HIV knowledge was assessed before and after this intervention (baseline and 3-month assessments), as well as the final time point (12-months) to assess knowledge retention.

[e]O: other outcomes.

[f]PrEP: pre-exposure prophylaxis.

Implementation Science

As this is a hybrid type 1 implementation trial, we are measuring additional constructs from the CFIR [59] and RE-AIM models (eg, reach, adoption, integration) [56,58,104] to help improve future implementation and dissemination of SMART. Internal accounting for costs, recruitment activities, staff and investigator effort, resources, and stakeholder attitudes have occurred during the intervention development and the ongoing trial. With respect to enrolled participants, we actively and passively collect key data on their interactions with the different interventions, attitudes toward them, and the amount of time they spend within them. Within interventions, participants can give a *thumbs-up* or *thumbs-down* on each activity and overall module or episode; we also provide an open-ended textbox to allow them to provide feedback about an activity, a section, or an overall module or episode. We follow all interventions with an adapted version of an HIV intervention acceptability and tolerability battery [105], which includes open- and closed-ended items. This battery assesses participant engagement, impact, usefulness, and usability per intervention. Additionally, for SMART Sessions, we assess participants' perceived quality of interaction with SMART coaches [106]. Finally, after participants have

graduated from the randomized controlled trial and completed their 12-month survey, participants are invited to complete a 30-min exit interview with the study staff. These participants explain their overall attitudes toward SMART (as a suite of interventions), identify areas for overall improvement, and provide suggestions for ways to publicly implement the program.

The SMART platform has sophisticated backend software to collect analytics or *paradata*. Time spent on every page of intervention content is measured per participant per intervention. This allows us to assess the overall time for each of the interventions, whether participants are rushing through or taking too long to complete any interventions and whether participants are engaged with specific pieces of any given intervention relative to others. SMART Sessions have different passive measurements that are collected by the SMART coaches. These include the duration and frequency of a session, session notes, and overall impressions of the session; the MITI coding previously mentioned also serves as implementation data.

Analytic Plan

Our primary aim is to compare the differential effects of 2 web-based interventions, the active treatment of SMART Squad and the control condition of SSE2.0 among nonresponders to

SSE in terms of the 3 primary outcomes: condom-less anal sex, intentions to use condoms or condom self-efficacy, and HIV testing behaviors (Table 1). Outcomes will be assessed at all time points, allowing for initial differences to be compared as well as the longevity of these differences over the 9 months

following the second intervention completion (ie, finishing SMART Squad or SSE2.0). Overall, 13 hypotheses were suggested within this primary comparison of SMART Squad versus SSE2.0 (Table 2).

Table 2. Power analysis by hypothesized group.

Hypothesis	Groups	Full (N)	80% reduction of full N after SSE[a] due to response	Alpha values[b]	Power	Cohen effect size
1	All	1632	1306	.00207	0.999	0.52
2	Native American/Alaskan Native	200	160	.0083	0.830	0.52
3	Asian	200	160	.0083	0.830	0.52
4	Black	300	240	.00417	0.920	0.52
5	Latinx (English-speaking)	182	146	.00417	0.920	0.52
6	White	300	240	.00417	0.920	0.52
7	Native Hawaiian/Other Pacific Islanders	200	160	.0083	0.830	0.52
8	Latinx (Spanish-speaking)	250	200	.00102	0.939	0.52
9	Urban (nonrural)	1224	979	.00207	0.999	0.52
10	Rural	408	326	.00207	0.960	0.52
11	Low SES[c]	408	326	.00207	0.960	0.52
12	Mid/high SES	1224	979	.00207	0.999	0.52
13	Age	1632	1306	.00207	0.999	0.52

[a]SSE: SMART Sex Ed.

[b]The total alpha after Bonferroni adjustment was .05. The full sample size will be increased by 15% to account for projected attrition to a final total of 1878. The 15% increase will be equally distributed across all subgroups (ie, Native American/Alaskan Native, Asian, Black, Latinx-English, White, Native Hawaiian/Other Pacific Islander, and Latinx-Spanish).

[c]SES: socioeconomic status

Specifically, we will test the hypothesis (H1) of no difference in actual condom use or intentions/self-efficacy to use condoms in the SMART Squad group relative to the control group (SSE2.0; Figure 1, letter A). To understand the potential effects of the interventions on health disparities, we will test the hypothesis of no difference in actual condom use or intentions/self-efficacy to use condoms in the SMART Squad group relative to the control group separately within each of the 6 National Institutes of Health (NIH)–defined racial and ethnic categories (Table 2, H2-H7). Furthermore, we will test this hypothesis for the SMART Squad group relative to the control group among subjects: residing in nonrural areas (H9), residing in rural areas (H10), identified as low socioeconomic status (SES) according to a family affluence scale (H11), identified as medium or high SES according to a family affluence scale (H12), and with younger and older ages (H13). As we offer SMART and its interventions in Spanish, we will also test the effectiveness of SMART Squad (in Spanish) specifically among Spanish speakers (H8) relative to the control group (SSE2.0 in Spanish).

We will test each of these hypotheses using a 2-sided difference of proportions *t* test. For age, we seek to enroll approximately equal numbers of each age, and we will test for a significant interaction between treatment (SMART Squad vs SSE2.0) and age using a logistic regression model. We will use a Bonferroni

multiplicity adjustment to ensure that the family-wise error rate of testing H1 to H13 is no greater than 0.05. Power calculations displayed in Table 2 show that even after this multiplicity adjustment, there is sufficient power to detect a moderate difference (ie, a Cohen effect size of 0.52) [107] in the proportion of responders with 80% power at the proposed sample size within each subgroup considered. All power calculations were performed using the *pwr* package in the R programming language. Table 2 shows that we have apportioned the Type I error inversely with the anticipated size of each subgroup, thereby ensuring sufficient power in the smaller subgroups. Finally, to account for attrition, we inflate each group's sample size shown in Table 2 by 15% for a total proposed sample size of 1878.

We will also conduct a series of exploratory (ie, hypothesis generating) comparisons between interventions applied to nonresponders to SSE and SSE2.0. First, we will compare the response rates at 9 months among those assigned to SMART Squad with those assigned to SMART Sessions. This may provide evidence about whether the more intensive and costly SMART Sessions are more effective than SMART Squad among those that did not respond to the control condition/SSE2.0 (Figure 1, letter B). Second, we will compare response rates at 9 months among nonresponders to SMART Squad assigned to SMART Squad Booster 2 relative to those assigned to SMART

Sessions. This will provide evidence about whether those who do not respond to SMART Squad will benefit from SMART Sessions or whether continued access to SMART Squad content would be sufficient (Figure 1, letter C). Finally, among responders to SSE, we will compare response rates at 9 months among those assigned to SMART Squad relative to follow-up only. This will provide evidence about whether those that respond to information only, web-based HIV education intervention (eg, SSE), will see additional benefits from SMART Squad (Figure 1, letter D). Unlike the primary comparisons, secondary analyses will not involve statistical tests of significance, but rather will consist of descriptive statistics, visualizations, and (unadjusted for multiplicity) confidence intervals. These results will be reported as exploratory.

In addition to these preceding exploratory hypotheses, we will use the data collected in this trial to estimate optimal individualized treatment strategies. An individualized treatment strategy is a sequence of decision rules, one per stage of intervention, which maps up-to-date patient information to a recommended intervention [108-110]. An optimal individualized strategy maximizes the total response rate by compounding the interventions' effects (eg, SSE with SMART Squad or no SSE with SMART Squad and SMART Sessions), resulting in the best outcome for a potential user. A primary advantage of sequential multiple assignment designs is that they facilitate the estimation of an optimal individualized strategy. We will apply Q-learning [108,111,112] to estimate an optimal individualized strategy. To ensure that the strategy is interpretable given easily measurable data (eg, sexual activity, age) and thereby maximally informative for subsequent research, we will estimate an individualized strategy composed of decision rules represented as a sequence of if-then clauses [113]. For example, decision rules might be: if a subject is 16 years of age or older and has not experienced anal sex yet, assign them to SSE followed by SSE2.0, otherwise assign them to SMART Squad.

Our hybrid type 1 trial will also analyze data collected around the implementation of SMART. Guided by the RE-AIM framework [56,58,104], we will describe our ability to reach diverse AMSM through our recruitment efforts during the trial. We will also interview potential future implementers (ie, community-based organizations, CBOs) to understand what implementation strategies they might need to reach this population. AMSM ratings of acceptability and engagement with SMART (eg, completion rates, time through interventions, SMART coach satisfaction, and qualitative feedback) will supplement the primary efficacy outcomes as well as inform updates and improvements to the intervention over time. Determinants of adoption will be examined primarily through interviews and surveys with AMSM and CBOs to identify, respectively, actual and potential barriers and facilitators of uptake, drawing on the CFIR for key constructs [59]. We will assess the implementation needs of SMART by tracking workflow, operations, and other process metrics. Finally, to inform maintenance, we will assess the potential cost savings associated with implementing SMART using an HIV mathematical model that factors in the construction and delivery of the program, costs of future medical care, HIV incidence projections, quality of life weights, and other necessary inputs

[114]. The model will estimate the 5-year and 10-year flow of fund differences for example individuals, Medicaid, private insurers, and other payers under specific assumptions, as well as cost utility estimates.

Results

Between April 2018 and June 2020, 1285 AMSM had completed all baseline assessment components and were considered enrolled in the study. Of those enrolled, 357 AMSM have completed their 12-month follow-up survey and have finished participating in SMART. We proposed enrollment of 1878 AMSM, with recruitment concluding at the end of June 2020. The final sample will be diverse in terms of race and ethnicity, primary language spoken (ie, English and Spanish), geographic region, socioeconomic status, and urban versus rural location.

Discussion

Principal Findings

This hybrid type 1 evaluation of SMART, a promising stepped-care eHealth HIV prevention intervention for AMSM, is an important contribution to the field of HIV prevention and implementation science for several reasons. It also represents the first HIV prevention intervention to overcome linguistic barriers and target monolingual, Spanish-speaking adolescents. To begin, SMART delivers sexual health education on the web and directs to AMSM, circumventing many of the individual and structural barriers of traditional in-person curricula. SSE and SMART Squad, the first two intervention tiers, are available on any smartphone or internet-ready device at any time of day, and can be completed at the participants' own paces. SMART Sessions are available via Skype and FaceTime, 2 readily used video chat platforms among teens, and allow participants to set up their sessions on their own terms and schedules. This level of availability and usability also helps reduce fears about being outed by the intervention itself.

Second, SMART provides a tailored curriculum for AMSM that addresses topics and concerns that are more prevalent among sexual minorities. SSE was modeled from a previously developed and tested intervention for AMSM [52], covering topics such as HIV risk differences between receptive and insertive anal sex, using a receptive or internal condom, water-based lubrications and their use during anal sex, how to come out to parents, and how to find support as a sexual minority. SSE and SMART Squad were developed with continuous input from a web-based youth advisory council of racially and ethnically diverse 13- to 18-year olds. Several members of that same youth advisory council read and helped revise the 120-page soap opera script for SMART Squad. Both interventions were beta-tested with AMSM. Sessions were pilot-tested before the randomized trial with 13- to 18-year olds and workshopped according to feedback from pilot coaches.

Third, SMART is the first trial testing the IMB model with AMSM and using intervention responsiveness as a benchmark before providing additional content or treatment to participants. Because interventions can be costly and potentially unnecessary if participants are already enacting change [115], it is necessary

to find the right dose for AMSM regarding HIV information, situational and contextual behavioral motivations, and prevention skills. Sequentially designed programs that increase in intensity, such as SMART, may be the best way to maximize positive behavioral health change while minimizing overall cost [116]. They may also be an excellent means to identify moderating individual conditions that make some more likely to need increased prevention education (eg, if AMSM come from school districts that teach abstinence-only sexual education).

Finally, our use of a hybrid type 1 design will be the first-time implementation science data that will be prioritized during the creation and testing of an HIV intervention for AMSM. The NIH has invested heavily in developing eHealth HIV prevention programs; however, few to date have seen widespread use and none have targeted AMSM. This formative work helps us identify appropriate and feasible implementation strategies needed in the future to deploy SMART in the real world. Implementation data allow us to explore contextual determinants (ie, barriers and facilitators) to future dissemination, as well as preliminary implementation outcomes. It also indicates how we might update the content and technology of SMART over time to avoid obsolescence. More broadly, the data collected on SMART's reach, engagement, cost, adoption, and maintenance will be invaluable for future researchers as they create web-based and in-person sexual health curricula. It can also provide insight and direction for CBOs and other institutions (eg, schools) that may be interested in upgrading their prevention programs to a web-based platform and to target AMSM.

Limitations

There are several limitations that SMART faces in its current form while we actively enroll AMSM. SMART is an eHealth intervention, which means that for SSE, SMART Squad, and SSE2.0, study staff are not present when participants access and move through intervention content. If participants have questions or concerns while viewing materials, there is no synchronously available moderator to help. Similarly, if participants encounter technical problems while viewing any content, the onus is on the participant to contact the study staff and report the issue. To counteract these potential issues, we include feedback pages across all the interventions, at multiple points within modules, to elicit questions, concerns, and participant attitudes. Open-ended textboxes are available, along with clickable rating buttons. We also have an active process to catalog the feedback, change content when appropriate, and respond to participants. Similarly, if a participant encounters a technical issue, the SMART toolbar has a dedicated button called *Technical Help*, which allows participants within the intervention to send study staff reports of the issue. The SMART

platform automatically codes the message with the participant's browser, device, platform, and device operating system version.

Participant attention during the intervention is another potential concern. During SSE, SMART Squad, and SSE2.0, how intently participants are focusing on the content cannot be measured precisely. Given other web-based (eg, social media and television) and offline distractions (eg, homework, chores, and extracurricular activities), it may be possible that participants are focusing less on SMART content than if delivered in person using a traditional modality such as lectures or discussions. We do measure time-through-intervention; although few participants appear to rush through the intervention (eg, viewing for 10 min or less), overall focus may be inconsistent and an unmeasured individual participant difference. During SMART Sessions, SMART coaches have anecdotally indicated several cases in which they suspected participants were multitasking using other apps while engaging in discussions. In these cases, coaches acknowledge that the participant may be distracted and attempt to refocus the individual or reschedule the session.

In addition to these operational limitations, there is a larger issue of trying to test a SMART intervention with such a young population. This type of trial requires participants to engage with multiple interventions of varying intensities and lengths. More than 90% of the participants will ultimately receive at least 2 interventions, if not 3, over the course of 12 months. Considering that many of these participants might not be intrinsically motivated or interested in sexual health education, this amount of content may exceed participant interest. Granted, months transpire between interventions; this remains to be a potential problem when working with adolescents who already are saturated with formal and informal education on a daily basis.

Conclusions

Despite these limitations, the randomized trial of SMART currently shows that eHealth, stepped-care sequenced interventions are implementable for AMSM. The trial is planned to finish in the fourth quarter of 2021. Providing sexual education to AMSM, an underserved population for HIV prevention interventions, recognizes the importance of attending to their unique needs if we will end the domestic HIV epidemic [117]. Reducing the number of HIV infections for this youngest at-risk population dramatically reduces lifetime HIV costs and decreases the overall number of HIV quality-adjusted life years [118]. Most importantly, programs such as SMART may ultimately prevent or delay HIV infection among AMSM. Considering this is a population that consistently fails to test for HIV and inconsistently uses HIV protective measures, preventing infections for AMSM is a high-priority public health activity.

Multimedia Appendix 1
CONSORT-EHEALTH checklist (V. 1. 6. 1).
[PDF File (Adobe PDF File), 2008 KB - resprot_v9i8e19701_app1.pdf]

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Abbreviations

AMSM: adolescent men who have sex with men
CBO: community-based organization
CDC: Centers for Disease Control and Prevention
CFIR: Consolidated Framework for Implementation Research
G2G: Guy2Guy
IMB: information-motivation-behavioral skills
LGBTQ: lesbian, gay, bisexual, transgender, queer
MI: motivational interviewing
MITI: motivational interviewing treatment integrity
MSM: men who have sex with men
NIH: National Institutes of Health
PrEP: pre-exposure prophylaxis
QSE: Queer Sex Ed
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
REDCap: Research Electronic Data Capture
SES: socioeconomic status
SSE: SMART Sex Ed
SSE2.0: SMART Sex Ed 2.0
STI: sexually transmitted infection

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Protocol

Increasing Awareness and Use of Mobile Health Technology Among Individuals With Hypertension in a Rural Community of Bangladesh: Protocol for a Randomized Controlled Trial

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Abstract

Background: Hypertension remains one of the foremost noncommunicable diseases that most often lead to cardiovascular diseases and its different complications. The prevalence of hypertension in Bangladesh has been increasing. However, there are very limited studies that have evaluated the impact of health education and awareness development in mitigating the burden of hypertension and its complications in Bangladesh.

Objective: This study aims to increase awareness, enhance knowledge, and change lifestyle behaviors through health education and the use of mobile health (mHealth) technology among individuals with hypertension living in a rural community of Bangladesh.

Methods: A randomized controlled trial is underway in a Mirzapur subdistrict of Bangladesh. This trial compares two groups of individuals with hypertension: The comparison arm receives health education and the intervention arm receives health education and a periodic mobile phone–based text message intervention. The trial duration is 5 months. The primary end point is participants' actual behavior changes brought about by increased awareness and knowledge.

Results: Enrollment of participants started in August 2018, and collection of follow-up data was completed at the end of July 2019. A total of 420 participants volunteered to participate, and among them, 209 and 211 were randomly allocated to the intervention group and the control group, respectively. Among them, the ratio of males/females was 12.0/88.0 in the intervention group and 16.1/83.9 in the control group. Data cleaning and analyses have been completed and the results have been submitted for publication.

Conclusions: Periodic short education using mHealth technology in addition to face-to-face health education may be an effective method for increasing awareness and knowledge about behavioral changes and maintaining healthy lifestyle behaviors.

Trial Registration: Bangladesh Medical Research Council (BMRC) 06025072017; ClinicalTrials.gov NCT03614104, https://clinicaltrials.gov/ct2/show/NCT03614104; University hospital Medical Information Network (UMIN) R000033736, https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_his_list.cgi?recptno=R000033736

International Registered Report Identifier (IRRID): DERR1-10.2196/15523

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Introduction

Background

Hypertension is one of the most significant modifiable risk factors for cardiovascular diseases (CVDs) worldwide [1], with increasing pervasiveness in low- and middle-income countries [2]. Currently, high blood pressure (BP) has been reported to cause 7.5 million deaths, which account for approximately 12.8% of the total deaths occurring globally [3]. Of these CVD deaths, 53% are due to complications of hypertension. High BP is called the "silent killer" because often, it has no warning symptoms or signs, and many people do not know that they have it [4]. Factors attributed to the increased prevalence of hypertension include population growth; aging population; and behavioral risk factors such as smoking, low-quality diet, harmful alcohol consumption, less physical activity, and overweight or obesity [5].

A review of community-based interventions for CVD implemented in low- and middle-income countries recommends that patient education can have a positive effect on treatment adherence and BP control among individuals with hypertension [6]. The literature provides ample information on health education programs to support self-management for individuals with hypertension living in high-income countries [7]. However, information on the impact of the best possible education programs for individual with hypertension in low-resource countries is not available [8]. To fill the gap, in this study, we provide periodic health education aimed at increasing awareness on the relationship between BP level and salt intake, and knowledge about behavioral changes related to hypertension for positively influencing patients' perceptions of hypertension and their adherence to treatment remedies [9].

However, the current status of the knowledge, attitudes, and perceptions of hypertension among participants indicates the significance of awareness buildup with respect to various features of hypertension, basic changes in lifestyle, and detailing of procedures in improving health education. Moreover, participants' knowledge about hypertension and the benefits of lifestyle modifications by all means is important for successful management of hypertension [10]. Nevertheless, lifestyle changes are not effectively accomplished. Hence, a combination of health education, knowledge of behavioral changes, and periodic use of mobile health (mHealth) technology could be provided in a patient-centered manner [11], as adherence to treatment is likely to increase when participants have positive attitudes toward controlling hypertension. Subsequently, well-structured educational interventions along with active participation of the patients are vital to increasing the knowledge, self-monitoring, and control of hypertension.

To expand awareness of the target population, innovative techniques are introduced in this study. One is regular BP checkup by the use of a Portable Health Clinic system (developed by Kyushu University, Japan, and Grameen Communications, Bangladesh) during home visits by community health workers (CHWs), in light of the fact that a routine health checkup system at the community level is yet to be established in Bangladesh, particularly in its rural areas. For example, medical personnel such as community nurses, during their field visits, may routinely check the BP of hypertensive individuals, who do not have any BP self-checking facility at home.

The second extraordinary contraptions are used to measure food and urine salinity to alert the participants. The third strategy is the persuasive motivating approach and social capacity building using mHealth technology for behavioral change.

We hypothesize that awareness development and knowledge acquisition can enhance behavioral change, and periodical mobile phone–based SMS intervention will be significantly beneficial in modifying lifestyle changes among hypertensive individuals. Thus, this approach could minimize the hypertension status of participants as well as its complications.

Study Objectives

The objectives of this study are to develop awareness and enhance knowledge through health education, the use of mHealth technology, and change in lifestyle behaviors among hypertensive individuals in a rural community of Bangladesh.

Methods

Design

This is a single-center, randomized (1:1), open-label, parallel-group study, conducted in a rural community of Mirzapur, Bangladesh. The intervention period was 5 months for each individual, and the total study duration was 12 months.

Study Population and Sampling

Individuals with hypertension living in the study site were identified as follows. One group of individuals were identified from a tertiary-level health facility (Kumudini Hospital, Mirzapur, Bangladesh). The principal investigator and CHWs visited the tertiary facility and checked the database records as well as the registered notebook including current remedies from the facility and collected household contact information (ie, home address and phone number) with the permission of the hospital authorities. Afterwards, CHWs visited homes of the participants and obtained their consent to participate in this study. The other group of individuals were identified from the neighborhood rural communities arbitrarily by CHWs reviewing the registered clinician's prescriptions and current remedies by household visits, and obtained their consent for the study.

A purposive sampling method was followed for enrolling study participants who met the eligibility criteria and were willing to participate voluntarily in the study.

Participants who met the following criteria were eligible for enrollment into the study:

Individuals of either sex who have hypertension and are aged 35 years or above, have 1-5 years of schooling, reside within a radius of 3 miles from the Kumudini Women's Medical College

and Hospital, are likely to stay in the community for the ensuing 5 months, have a personal cell phone or access to a shared phone, are open and can exchange their views freely, are willing to participate in the study, and consented to comply with the health education and periodic text messages for the entire study period.

Individuals with mental illnesses or serious comorbidities such as progressive diabetes, chronic pulmonary disease, malignancy, and pulmonary tuberculosis that might cause periodic absence were excluded from this study.

Randomization

A randomization schedule was prepared following the permuted block randomization technique using a block size of 4 based on a computer-generated series of numbers. An experienced researcher (third party) who was not involved with the study generated the random allocation by sequence and distributed that in serially numbered sealed opaque envelopes, which are kept in locked file cabinets in a site away from the trial's location. Sealed envelopes containing group assignment were given to the eight CHWs who were involved in participants' enrollment under the guidance of a principal investigator.

Enrollment took place during morning hours for 6 consecutive days (except Friday) in a week, and the principal investigator of the study was present at the site every day to ensure compliance with the study protocol. Once eligibility for randomization was determined, written informed consent was obtained. CHWs opened the envelope in the presence of participants. Participants were allocated to either of the groups,

after enrollment, CHWs collected their demographic information and performed physical examination of the participants.

Study Procedure

For the Intervention Group

To develop awareness, enhance knowledge, and motivate behavioral changes using mHealth technology, the intervention group received the 5-month health education including health education materials and SMSs (Figure 1). At the time of enrollment, CHWs visited participants' households or asked participants to come to the nearest health facility such as Kumudini Women's Medical College and Hospital or Health and Family Welfare Center (HFWC) in the morning. CHWs interviewed them; performed physical examination (measurement of BP, height, weight, mid-upper arm circumference, waist-hip circumference) of the participants; and measured random blood sugar for about 30 minutes. Along with these, CHWs checked food salinity by measuring salt from liquid foods and urinary salinity by spot urine and first morning urine. Along with this, they checked urinary glucose and protein levels for another 30 minutes. Subsequently, CHWs explained the data and provided health education by researcher-developed booklets based on the dietary approach to stop hypertension (DASH) diet and lifestyle-changing behaviors like salt intake reduction, smoking cessation, exercise, and medication (in Bangla or English; Multimedia Appendix 1). Participants of the intervention group were followed up every month up to 5 months (twice in the first month and once in the rest of the months). Text messages were sent 5 times in the first month and once a week for the remaining 4 months (a total of 16 text messages).

Figure 1. Awareness development process and contents of study outline.
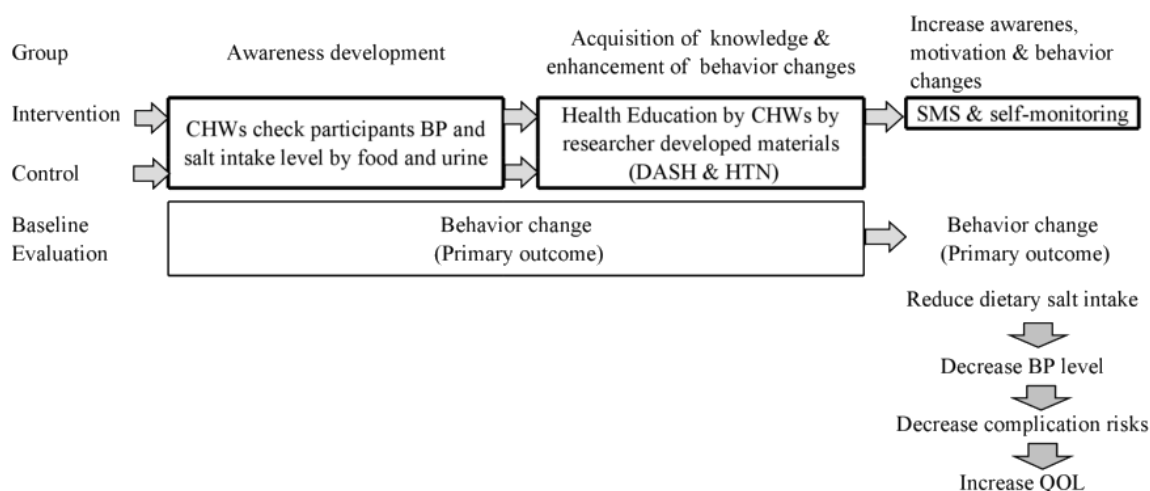
For the Control Group

The control group received the same health education booklet as the intervention group at the time of enrollment. After that, CHWs visited and provided health education at participants' households or asked them to visit the nearest health facilities such as Kumudini Women's Medical College and Hospital or HFWC. They were followed up every month for up to 5 months

(twice in the first month and once the rest of the months) for receiving health education only.

Sample Size

Sample size calculation was based on the behavioral changes of study participants. In this study, investigators compared two interventions (health education with and without text messaging). Investigators expected the compliance of the intervention group to be higher than that of the control group.

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We assumed that the proportion of patients in compliance is at most 10%-12% better in health education with text messaging group.

The sample size was calculated with a two-tailed 5% significance level and a power of 80%, with a 95% CI (1–α) to detect varying differences in the effectiveness of the two intervention groups. Adherence rates were assumed to differ by 10%-12%, that is, rates of 90% in the study group and 78%-80% in the control group, with a presumption that 6% of the participants would be lost during the follow-up (for example, if the intervention group adherence rate is 10% higher than that of the control group, then the difference will be 90%–80%=10%; if the intervention group adherence rate is 11% higher than that of the control group, then the difference will be 90%–79%=11%). The sample size for each group was estimated to be between 153 and 210 participants. Thus, considering the largest calculated sample size, the study finally had a sample size of 210 in each group.

Outcome Measures

Once the participants were made aware of the importance of lifestyle changes and obtained knowledge about lifestyle modification, they could change their lifestyles. Thus, increased awareness and knowledge was measured by the actual behavior change in them. Following the lifestyle change, their BP level was expected to decrease, the risk for complications would be reduced, and their quality of life would be improved. Therefore, we set the following end points.

Primary End Point

The primary outcome was the evaluation of the behavioral changes using the researcher-developed questionnaire (Table 1).

Table 1. Questionnaire for the evaluation of behavioral changes.

Evaluation questions	5[a]	4[b]	3[c]	2[d]	1[e]
1. How many days do you eat fruits in a week?	Everyday	5-6 days/week	3-4 days/week	1-2 days/week	0 day/week
2. How many days do you eat vegetables in a week?	Everyday	5-6 days/week	3-4 days/week	1-2 days/week	0 day/week
3. How much salt do you take per day in a week?	42 g (<6 g/day)	5-6 days/week (7-8 g/day)	3-4 days/week (9-10 g/day)	1-2 days/week (11-12 g/day)	0 day/week (13-14 g/day)
4. How many days do you do 30-minutes physical activity/exercise in a week?	Everyday	5-6 days/week	3-4 days/week	1-2 days/week	0 day/week
5. How frequently do you check your blood pressure in a month?	8 times/month	6 times/month	4 times/month	2 times/month	Never/month
6. How frequently do you monitor your body weight in a month?	8 times/month	6 times/month	4 times/month	2 times/month	Never/month

[a]5: Excellent.

[b]4: Good.

[c]3: Fair.

[d]2: Poor.

[e]1: Very Poor.

Secondary End Points

Secondary outcomes were (1) the actual salt intake (measured by a salinity tester [TANITA electronic salinometer SO-313]) and dietary salt excretion (measured by KME-03, KOUNO ME Institute), (2) BP value, (3) blood glucose level (measured by EasyMate G, Model no. ET-111, Bioptik Technology Inc) and urinary protein and glucose (measured by urine test strip uric 2v Glucose Protein, Changchun Merydi Bio-Tech Co, Ltd) for checking complications, and (4) quality of life measured by EQ-5D-5L quality of life questionnaire [12].

Primary and secondary outcomes were measured every month including baseline and up to 5 months for both intervention and control groups.

Feasibility Evaluation

As a secondary outcome, the feasibility of utilizing mobile phones in hypertensive individuals using field-testing questionnaires was checked by the researcher-developed questionnaire.

Economic Evaluation

Researchers have strongly recommended economic evaluation of health promotion interventions such as health education and mHealth technology [13]. For this purpose, all costs were classified according to major activities or resources. Costs were derived from two phases of the intervention named start-up costs and implementation costs, which are directly related to the study. Total costs were considered as the summation of capital and recurrent cost items for each phase [14].

Study Preparation

Training of Community Health Workers

CHWs were oriented on hypertension of rural community people every month till the completion of the study. Through this training, they understood the pathology and mechanisms of hypertension, dietary practices, behavioral changes, and physical

activities that are needed for controlling hypertension. Moreover, they could perform physical measurements and acquire motivational skills that are useful for drug and instructional compliances by the rural community people and are essential for the prevention of complications.

Health Education and the Material/Notebook

Health education materials were developed based on the DASH diet (4 to 5 servings a day of vegetables and fruits, fat dairy foods, avoidance of excessive smoking and drinking), with advice to walk every day for at least 30 minutes and to take medicine regularly. DASH diet and suggestions to reduce hypertension are stop smoking and drinking, walk at least 30 minutes every day, and take medicines regularly [15-18].

Focus Group Discussion on Individual's Hypertension Perception

An exploratory qualitative study was conducted to comprehend the knowledge level in relation to hypertension in a rural community of Bangladesh. The study assessed the level of understanding of individual's perception regarding symptoms, causes, and consequences of hypertension, the importance of lifestyle modifications, and regular checkups. One of the critical aims was to investigate the practice of hypertension management, adherence to drugs, barriers and challenges that keep them away from seeking regular clinical consultation, laboratory investigation, and medication adherence.

Text Messaging Development and Testing

SMS text messages have been developed in native language by the members of the research team representing different professional backgrounds; these messages were sent to 15 people (randomly) for their comprehension and acceptability as part of the field-testing procedure. Individuals in the wired intervention group received SMS text messages, and they had the liberty to participate additionally in a two-way communication system (between intervention individuals and research team members). After receiving the feedback, messages were finalized. The SMS consisted of simple health education information to aid in the behavioral change of participants. Attempts were made so that all the participants in the study could read the SMS messages by themselves or by someone in the family who could read and explain the contents of messages to them if they do not understand. Contents of the text messages are presented in Table 2.

Table 2. Content of text messages. Text messages were scheduled to send 5 times for first month and once a week for the rest of the 4 months.

Message content	Examples
Reduce sodium intake (salt)	• Sodium intake is < 6 g/day (just under a teaspoon). • No extra salt, not even with fruits or green leafy vegetables, pickles, milk, or any other foods. • It keeps your high blood pressure under control.
Avoid taking oily and fatty foods	• Like beef, mutton, poultry, pastries, cakes, and other junk foods. • You can gain weight.
Eat more fruits and vegetables	• 80 g per servings (fruits small size—full; large size—half; per meal) per day. • It makes you healthy.
Do exercise regularly	• Regular exercise (walking, running, cycling, household work) for 20-30 minutes most days of the week. • It keeps your heart well.
Take your medicine regularly	• Do not change and stop your hypertensive treatment without your doctor's guidance.

Measuring Predictor Variables for Intervention and Control Groups

At baseline, a standardized pretested questionnaire was administered to obtain information on the sociodemographic profile such as age; gender; religion; financial dependency; educational qualification; occupation; monthly family income and expense; type of housing; possessions of household land and properties; type of family; marital status of the respondent; living arrangements; health status; health care–seeking behavior; family history; hypertension-related information; hospitalization history; food consumption practices; lifestyle behavior such as tobacco use; alcohol consumption; food habits; the level of physical activity; and mHealth-relevant information.

Nutritional status assessments such as height, weight, mid-upper arm circumference, hip circumference, and waist circumference were measured by CHWs. BP, random blood sugar, urinary protein and glucose, and salinity of food and urine were measured using the standard procedure starting from the enrollment day till the end of the follow-up. Follow-up visits and physical examinations were performed at households, at Kumudini Hospital, or in the nearest HFWC.

Ethical Consideration

All participants were explicitly informed about the objectives, importance, and risks and benefits of the research before recruitment. Participation was completely voluntary, and written informed consent was obtained from all participants.

This study was approved by the Bangladesh Medical Research Council (BMRC; Registration No. 06025072017), with Clinical Trial Registration No. NCT03614104 and UMIN Registration No. R000033736. This study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies of the Ministry of Health, Labor and Welfare

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of Japan. Enrollment of participants started in August 2018, and collection of follow-up data was completed at the end of July 2019.

Quality Control

In 5% of the study participants, the quality control team independently checked data collected on the same day using a field-tested methodology. Errors detected were corrected immediately at the field site. Later on, scoring was completed for each question of the repeated interview (eg, 1=same, 2=different but possible, 3=different and not possible, 4=impossible to judge, and 0=not applicable). The sum of all the scores was divided by the total number of questions/variables asked. The ideal score was 1 or a score as close to 1 as possible. If the score exceeded 1.5, the CHW responsible for the interview was questioned regarding the differences. The findings of the quality control team were considered for necessary corrections if any major discrepancies were found.

Statistical Analysis

The intend-to-treat analysis was used to compare the outcomes of the intervention and control groups. To ensure comparability of randomized samples, all baseline indicators at the time of registration were analyzed. The data will be expressed as the mean±standard deviation or median (minimum-maximum) and cross tabulation (with the range or percentage with 95% CI where appropriate) for continuous variables and as frequencies and percentages for discrete variables. The differences in continuous variables between the groups were examined using the t-test or Mann-Whitney U test. The differences in categorical variables between groups were examined using χ^2 test. For primary and secondary endpoint analyses, Mann-Whitney U test was performed to assess the changes in health behaviors at baseline, and analysis of covariate was performed to assess the changes in health behaviors at baseline and 5 months after the follow-up. Analysis of covariance was used to check the correlation between a dependent variable and the covariate independent variables and to remove the variability from the dependent variable that can be accounted for by the covariates. A multivariate regression analysis was then performed to evaluate the simultaneous effects of various exposure variables after adjusting for any confounding variables. Data were analyzed using the statistical software packages SPSS for Windows version 25.0 (IBM Corp) and Epi Info version 7.0 (Centers for Disease Control and Prevention). Values of $P<.05$ are considered statistically significant.

Results

Currently, the study is in the active implementation phase (participants' follow-up is ongoing) after the completion of recruitment. A total of 420 participants have agreed to participate and among them, 209 and 211 are allocated to the intervention group and control group, respectively (Figure 2). The proportion of males/females is 12.0/88.0 in the intervention group and 16.1/83.9 in the control group.

From August 2018 to July 2019, the following processes were completed: recruitment, intervention, and data collection. Subsequently, data cleaning was completed, and from the results, data analysis (eg, of baseline sociodemographic data) was performed. Preliminary analytical results are presented in Table 3.

Figure 2. Enrollment procedure of the study.
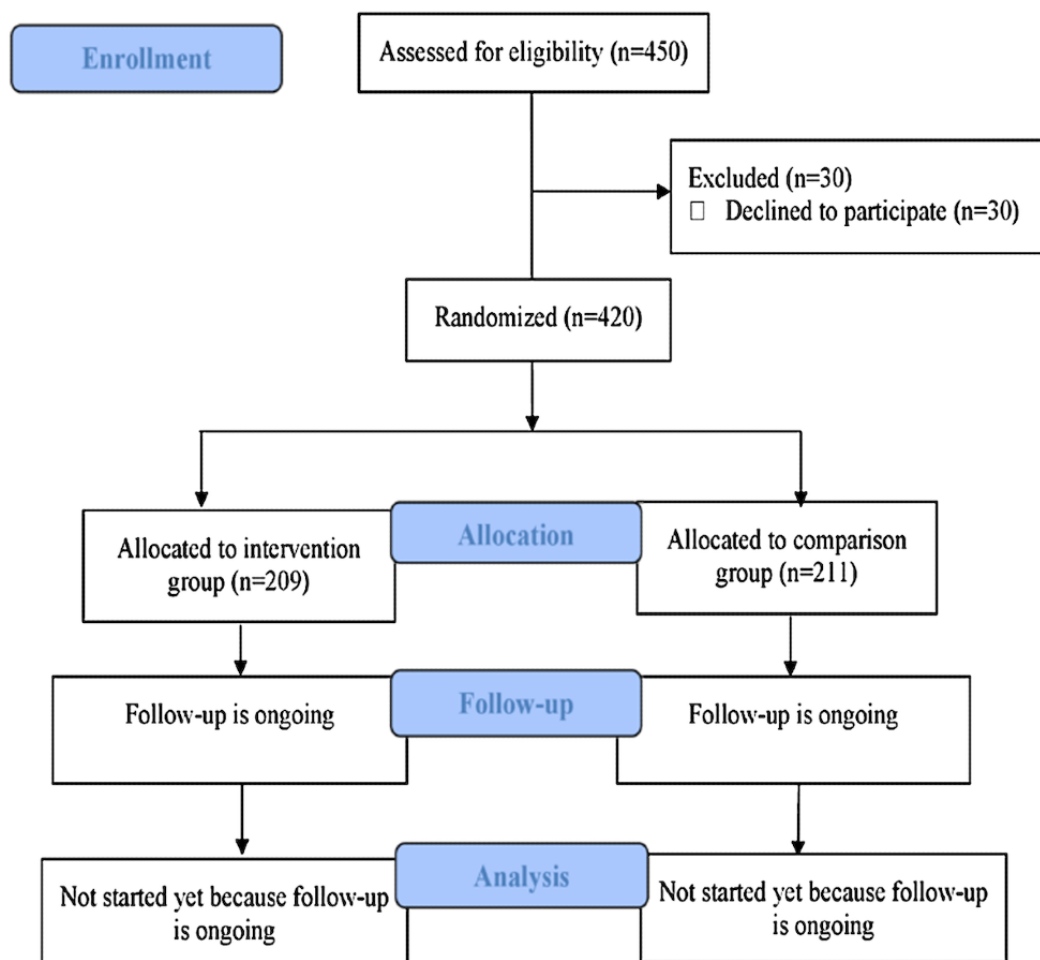
Table 3. Age-sex breakdown of study participants.

Variable	Intervention group (n=209), n (%)	Control group (n=211), n (%)
Age group (years)		
35-44	84 (40.2)	70 (33.2)
45-54	83 (39.7)	91 (43.1)
55-64	34 (16.3)	39 (18.5)
≥65	8 (3.8)	11 (5.2)
Gender		
Male	25 (12.0)	34 (16.1)
Female	184 (88.0)	177 (83.9)

Discussion

Principal Findings

This paper describes the protocol for a randomized control trial that aims to develop awareness, enhance knowledge, and make behavioral changes using health education and mHealth technology among individuals with hypertension in a rural community of Bangladesh. To our knowledge, this is the first study conducted in Bangladesh to measure the impacts of mobile phone SMS as a tool for reducing the burden of hypertension. One of the most significant barriers to effective treatment of hypertension is the lack of awareness and education about hypertension, its complications, and the optimal way to treat hypertension, which can be addressed by mobile phone interventions for knowledge generation as well as awareness and behavior change communications.

Strengths

In this study, we sent SMSs to participants through mobile phones (two-way communication). As the SMS is written in *Bengali* using *Bangla* alphabets, we assume that it will not be very difficult for the participants to read and understand, as the ability to read the SMS messages has been considered in the

inclusion criteria. Using SMS as a tool for health education, health information and lifestyle messages can be easily disseminated by persons with minimum technical knowledge and skills.

Moreover, in our study, we have used the following three unique devices to improve the self-management skills of individuals with hypertension.

Portable Health Clinic

Portable Health Clinic [19] is a handy, portable box that contains devices to measure BP, blood sugar, and urine protein and glucose and has an automatic transmission function to provide results (Multimedia Appendix 2). During their home visits, CHWs measure the parameters, and after checking that the data are fed immediately and used for health education.

Urine Salinometer

This is a handy, instant measurement device that can estimate the participant's salt intake of the previous day at home (Multimedia Appendix 3). Participants' baseline urine is analyzed as a proxy for daily salt intake and follow-up urine in the morning is analyzed using a KME 03 salinometer (developed by KOUNO ME Institute) [20].

Food Salinometer

We also check the participants' food salinity as a proxy for their daily salt intake by using an electronic salinometer for measuring food (TANITA white waterproof salinometer SO-313, which has three different types of level sensors; Multimedia Appendix 4). It starts from level 0.4 to 0.7 (yellow color), 0.8 to 1.1 (green color), and 1.2-1.4 (red color). It is a three-level salinity tester for food items. A range of 0.4-1.4 g of salt in the food can be measured using this device.

Limitations

Because of purposive sampling, this study does not represent hypertensive individuals of a rural community as a whole. To check the feasibility and reliability of urine and food salinity results, it is better to compare them with laboratory data, which cannot be evaluated in this study. CHWs were consented not to share the random allocation status of hypertensive individuals with the family members as well as their neighbors during the study period. However, chances of disclosure, although small, cannot be ruled out. Moreover, data contamination due to neighborhood as well as family members and obtaining consent from CHWs to not disclose the data may be other limitations of the study.

Conclusions

This study was conducted in rural Mirzapur, Bangladesh. This study aimed to determine the effectiveness of SMS-based interventions for health promotion and to determine whether it will be well accepted by beneficiaries. The results of the study indicated that SMS is an effective method for building awareness toward the prevention and control of hypertension and its consequences in a rural population of Bangladesh [21-23].

Conflicts of Interest

None declared.

Multimedia Appendix 1
Health education material.
[PNG File , 1039 KB - resprot_v9i8e15523_app1.png]

Multimedia Appendix 2
Portable health clinic device.
[PNG File , 173 KB - resprot_v9i8e15523_app2.png]

Multimedia Appendix 3
Urinary salinity check by salinometer.
[PNG File , 137 KB - resprot_v9i8e15523_app3.png]

Multimedia Appendix 4
Food salinity check by food salinometer.
[PNG File , 708 KB - resprot_v9i8e15523_app4.png]

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Abbreviations

BP: blood pressure
CHWs: community health workers
CVDs: cardiovascular diseases
DASH: Dietary Approach to Stop Hypertension

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HFWC: Health and Family Welfare Centers
mHealth: mobile health

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Protocol

Reducing Emotional Distress for Childhood Hypoglycemia in Parents (REDCHiP): Protocol for a Randomized Clinical Trial to Test a Video-Based Telehealth Intervention

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Abstract

Background: Despite the introduction of new insulin analogs, insulin pumps, and continuous glucose monitoring (CGM), young children with type 1 diabetes mellitus (T1D) remain vulnerable to episodes of hypoglycemia because of their unpredictable eating and activity patterns and high degree of insulin sensitivity. Caregivers and young children living with T1D learn to fear hypoglycemia because it is uncomfortable, unpredictable, and dangerous. Up to 60% of caregivers of young children with T1D report moderate to severe levels of fear of hypoglycemia, and caregiver fear of hypoglycemia relates to lower quality of life for families and suboptimal child glycemic control. Yet, until recently, there have been no studies reporting on a targeted intervention to treat caregiver fear of hypoglycemia in families of young children.

Objective: The aim of this project is to conduct a randomized clinical trial of an innovative, video-based telehealth intervention to treat fear of hypoglycemia in caregivers of young children with T1D versus a relevant, age-appropriate attention control intervention.

Methods: We created the Reducing Emotional Distress for Childhood Hypoglycemia in Parents (REDCHiP) intervention by merging age-appropriate T1D education and behavioral parenting strategies with cognitive behavioral therapy strategies that are effective for reducing fear and promoting adaptive coping. REDCHiP uses 10 video-based telehealth sessions that are a combination of group and individual sessions. We will recruit up to 180 families of young children with T1D to participate in this clinical trial from two pediatric diabetes clinics located in the midwestern and southern United States. Once families have been enrolled, we will randomize caregivers based on child age (age 2-3 years or 4-5 years), child sex, and family CGM use to participate in the REDCHiP or attention control intervention. Families will complete 3 assessment visits that coincide with study entry, end of treatment, and 3-month posttreatment. At each assessment visit, we will collect questionnaire data from caregivers, accelerometry data from caregivers and children, CGM data from children, and a blood sample to measure glycated hemoglobin levels from children.

Results: Recruitment began in July 2019, and enrollment is ongoing. The first wave of intervention delivery began in December 2019. We anticipate completing enrollment in 2023. Final reporting of results will occur within 12 months of the primary completion date.

Conclusions: If the REDCHiP intervention is efficacious, next steps will be to examine multiple implementation strategies to determine how best to disseminate the intervention to pediatric diabetes clinics around the world.

Trial Registration: ClinicalTrials.gov NCT03914547; https://clinicaltrials.gov/ct2/show/NCT03914547

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Introduction

Background

Type 1 diabetes mellitus (T1D) is a common pediatric chronic condition characterized by the loss of natural insulin production and inability to regulate blood glucose levels. Incidence rates of T1D are increasing in children aged younger than 6 years internationally [1], and data also demonstrate a 1.7% average annual increase of new cases among children aged 5 to 9 years in the United States specifically [2]. Achieving near-normal glycemic control (glycated hemoglobin [HbA_{1c}] <7.5%) early in the course of T1D may reduce economic burden to the health care system, and most importantly, can reduce the risk for later T1D-related complications [3]. This goal, however, is difficult for young children with T1D and their families to achieve as only 20% of young children in the United States and 58% of young children in Europe currently meet the HbA_{1c} target of <7.5% [4]. Managing T1D is particularly challenging in young children because of their heightened insulin sensitivity, unpredictable eating behaviors, inconsistent physical activity levels, and limited communication skills [5], which lead to extreme glycemic variations and severe hypoglycemic episodes [6].

Hypoglycemia events, or low blood glucose levels, are an immediate and dangerous complication of T1D [7]. Symptoms of hypoglycemia may include headaches, dizziness, impaired consciousness, irritability, weakness, sweating, racing pulse, and, in extreme cases, seizure, coma, or death [8,9]. Prevalence rates for severe hypoglycemia in young children with T1D are 2-fold higher than older children and adolescents and 3-fold higher than adults [10]. Not surprisingly, it is common for caregivers of young children with T1D to report elevated stress and anxiety regarding the probability of their child experiencing a hypoglycemia event [11]. Unfortunately, the introduction of new technologies such as shorter and longer acting insulin analogs, insulin pumps, and continuous glucose monitors (CGMs) have not eliminated the occurrence of hypoglycemia events in young children [11-13] or reduced caregiver fear of hypoglycemia [11,14].

Up to 60% of caregivers of young children with T1D report fear of hypoglycemia, which directly affects caregiver psychological and emotional well-being [15]. Additionally, in young children with T1D, caregivers may perceive hypoglycemia as unpredictable, exacerbating their level of fear [16]. Building on past research, we developed a theoretical model for caregiver fear of hypoglycemia (Figure 1) which identifies child and caregiver variables that may underlie caregiver fear of hypoglycemia. For example, we have data suggesting that a child's T1D history, including past experience with hypoglycemia, and a child's sleeping behavior may relate to

caregiver fear of hypoglycemia [15,17,18]. In addition, in older youth with T1D, there is evidence that child physical activity levels relate to caregiver fear of hypoglycemia [19-22].

For caregiver variables, several studies suggest that T1D-related distress, parenting stress, caregiver depressive and anxiety symptoms, and decreased caregiver sleep may exacerbate their perceptions of fear of hypoglycemia [23-27]. Our theoretical model of caregiver fear of hypoglycemia then proposes that greater caregiver fear of hypoglycemia relates to hypoglycemia avoidance behaviors, including maintaining blood glucose levels above the recommended range, treating blood glucose levels that are within the target range, and delaying or reducing insulin doses [16,28]. Our theoretical model of caregiver fear of hypoglycemia suggests that when caregivers engage in more hypoglycemia avoidance behaviors, these maladaptive coping strategies lead to chronically higher blood glucose levels, more glycemic variability, and increased risk for T1D-related complications for children [29,30]. Thus, our model suggests that caregiver fear of hypoglycemia may function as a barrier to optimal glycemic control and should be a target of behavioral interventions for families of young children with T1D.

In-person clinic visits have been a mainstay of behavioral interventions for families of youth with T1D, but this approach also presents logistical barriers (eg, travel, time, and cost). For this reason, the use of technology-based delivery methods has increased both in research and clinical settings. Access to mobile technology and the internet is ubiquitous in the United States. Current estimates suggest that 90% of American adults use the internet, 81% own smartphones, and 73% have high-speed internet access at home [31,32]. To date, most technology-based T1D interventions have focused on T1D management in adolescents and young adults versus families of young children, and the interventions have used email and text message support [33-35], websites and phone apps [36-44], and telephone counseling or video-based telehealth [45-51]. Yet these technology-based interventions suggest that it may be highly feasible and efficacious to use technology to intervene in families of youth with T1D. Moreover, using technology to intervene may be more scalable than in-person clinic delivery and enable behavioral interventions to reach a broader patient population, including families living in rural and underserved locations.

This study will fill an existing gap in the current T1D literature by developing and testing a video-based telehealth intervention to reduce caregiver fear of hypoglycemia in families of young children. Reducing Emotional Distress for Childhood Hypoglycemia in Parents (REDCHiP) uses a cognitive behavioral framework, T1D education, and behavioral parenting support to directly address caregiver fear of hypoglycemia and reduce their reliance on maladaptive coping strategies (including hypoglycemia avoidance behaviors) with the potential for

downstream positive effects on young children's T1D management and glycemic control. This paper outlines how we intend to examine the effectiveness of REDCHiP in reducing parenting stress and fear of hypoglycemia compared with an attention control intervention in a randomized clinical trial and obtain information about the intervention's feasibility, acceptability, and impact on child glycemic control.

Figure 1. Theoretical model of caregiver fear of hypoglycemia.
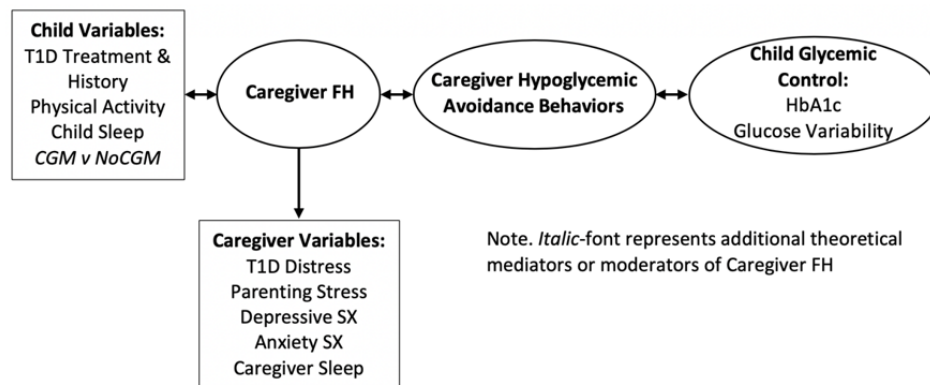
Objectives

The aims of this randomized clinical trial are to (1) evaluate whether caregivers who receive the REDCHiP intervention report reductions in parenting stress and fear of hypoglycemia immediately posttreatment compared with caregivers who receive the attention control intervention; (2) evaluate whether children of caregivers who receive the REDCHiP intervention have lower HbA_{1c} and less glycemic variability posttreatment compared with children of caregivers who receive the attention control intervention; and (3) examine whether maintenance reductions in parenting stress and caregiver fear of hypoglycemia and child HbA_{1c} occur 3 months' posttreatment for families receiving the REDCHiP intervention. Based on preliminary data, our primary hypotheses are (1) caregivers who receive REDCHiP will report reductions in parenting stress and fear of hypoglycemia compared with caregivers who receive the attention control intervention and (2) children of caregivers who receive REDCHiP will achieve more optimal glycemic control than children of caregivers who receive the attention control intervention.

Methods

Development of the Reducing Emotional Distress for Childhood Hypoglycemia in Parents Intervention

REDCHiP includes a cognitive behavioral framework based on the conceptualization that caregiver fear of hypoglycemia is a type of specific phobia. Individuals with specific phobias are "fearful or anxious about or avoidant of circumscribed objects or situations" and experience "fear, anxiety, or avoidance [that] is almost always immediately induced by the phobic situation, to a degree that it is persistent and out of proportion to the actual risk posed" [52]. Cognitive behavioral therapy plus systematic desensitization and exposures is a well-studied, evidence-based treatment for specific phobias in adults and demonstrates reductions in fear to a subclinical level in 90% of cases [53]. In REDCHiP, caregivers learn to recognize and alter thoughts and behaviors driven by fear of hypoglycemia and gain new behavioral parenting strategies and coping strategies to help them manage their fear. REDCHiP consists of 7 group and 3 individual sessions that are each 30 to 60 minutes in duration (Table 1).

We previously pilot-tested REDCHiP using a video-based telehealth approach. A total of 36 families completed the pilot intervention with low attrition (ie, 14%), high attendance (ie, 94%), and high caregiver-reported satisfaction [54]. Qualitatively, caregivers reported positive increases in knowledge, fear awareness, coping, and confidence and satisfaction with the support they received and the new behavioral parenting skills they learned from the REDCHiP intervention [54]. Quantitatively, caregivers experienced significant reductions in fear of hypoglycemia, parenting stress, and T1D-related distress [55]. Moreover, REDCHiP significantly reduced caregiver fear of hypoglycemia as compared against a waitlist control group, thus establishing preliminary efficacy for the REDCHiP intervention [55].

Table 1. Overview of the Reducing Emotional Distress for Childhood Hypoglycemia in Parents intervention.

Session No.	Format	Content
1-3, 5, 7, 9-10	Group	Hypoglycemia fear is a type of phobia and behavioral parent training, cognitive behavioral framework (eg, cognitive and behavioral responses to fear) and adaptations, diabetes education (eg, managing blood glucose levels and recognizing patterns in blood glucose)
4, 6, 8	Individual	Building a fear hierarchy and guided exposure, diabetes education (eg, recognizing your child's symptoms of high and low glucose), challenging nighttime fear, problem-solving type 1 diabetes mellitus challenges

Attention Control Development

We used two approaches to determine the content of our attention control intervention. First, parents of young children (ages 1 to 6 years) provided input by reviewing a list of potential topics and rating each topic on a 3-point scale according to its degree of relevance to them (not relevant, somewhat relevant, or very relevant). We then selected the topics identified as very relevant by the majority of caregivers. Second, we asked 5 experts in young child development and clinical psychology to review our initial list of topics and the list of topics caregivers provided and provide recommendations for additional developmentally and age-appropriate topics. The final list of sessions includes topics relevant to young children (eg, developmental milestones, child health and safety, starting school), positive parenting strategies, and early literacy; caregivers do not learn about T1D-related topics. To complement the REDCHiP format, the attention control intervention consists of 7 group and 3 individual sessions that are each 30 to 60 minutes in duration (Table 2).

Table 2. Overview of the attitude control intervention.

Session No.	Format	Content
1-3, 5, 7, 9-10	Group	Behavioral parent training, early childhood milestones and experiences, literacy, communication, learning through play
4, 6, 8	Individual	Early childhood safety topics (eg, injury prevention, car seat safety), creating a learning environment, establishing childhood routines and structure

Design Considerations and Potential Challenges

We carefully designed the trial to reduce the impact of several potential challenges. First, we anticipated a challenge in recruiting an adequate sample because in very young children, T1D occurs at a prevalence of 0.29 per 1000 patients [56]. Therefore, we designed a multisite trial, which should enable us to adequately recruit our anticipated sample. Second, we anticipated barriers related to family availability and scheduling. To minimize this barrier, we designed the trial to deliver treatments via telehealth and include an option for families to complete study visits from home. Third, based on our pilot trial, we anticipated that a few eligible families (<10%) might not own a compatible device or have internet connectivity. Therefore, we have the flexibility in our trial design to loan web-enabled tablets to families. Fourth, we considered the possibility that some families might not find the intervention content or telehealth delivery favorable and will withdraw. To minimize negative trial effects due to attrition, we plan to recruit 180 families, which allows for a 20% attrition rate.

Ethics and Dissemination

This is a multisite trial and follows National Institutes of Health guidelines to establish and operate within a single institutional review board (IRB) for final study monitoring. All research personnel will complete certification in responsible conduct of research, good clinical practice, and safe handling of biological samples. To minimize risk for participating families, we will inform all potential families of the purpose, procedures, and amount of time required to participate in the trial. We will minimize risk of breach of confidentiality by using a Health Insurance Portability and Accountability Act (HIPAA)-compliant telehealth platform and reviewing a group confidentiality agreement at the first session. We will minimize the risk of child pain or emotional discomfort when collecting blood samples by allowing families to use their own lancet and/or coordinating the sample collection to occur just after a clinic-based finger stick. Finally, we will protect caregivers by reviewing their responses on the study surveys within 24 hours of completion and contacting those who report concerning levels of depressive or anxiety symptoms to provide information on treatment resources. The trial was registered at ClinicalTrials.gov [NCT03914547].

The REDCHiP intervention builds on our previous research examining fear of hypoglycemia in caregivers of young children with T1D and fills a critical gap in behavioral intervention research in these understudied families. Moreover, the group-based telehealth approach is relatively novel for pediatric T1D interventions and may be easily scalable if the trial results confirm efficacy. We plan to disseminate the results of this trial to the pediatric diabetes community and broader medical community through national and international presentations at relevant scientific meetings and peer-reviewed manuscripts. We believe that there will be greater use of telehealth to deliver behavioral treatments for families of youth with T1D in the future because of the increasing adoption of telemedicine parity laws across the United States [57] and increased affinity for technology-enabled solutions to common needs in younger generations [58], including the need for convenient health care access [59]. We believe the format and general content of REDCHiP may be amenable to caregivers of older youth with T1D who also struggle with fear of hypoglycemia. Last, we expect that REDCHiP is in line with initiatives from the National Institute of Diabetes and Digestive and Kidney Diseases, which call for the development of more family-centered, efficacious, cost-effective, and easily scalable behavioral health interventions [60].

Participants

For this randomized clinical trial, we will recruit 180 families of young children with T1D. Inclusion criteria are child aged from 2 to 5.99 years, T1D diagnosis ≥6 months, and use of an intensive insulin regimen (eg, insulin pump or multiple daily injections). Exclusion criteria are caregivers of children on a conventional insulin regimen, children who have an allergy or sensitivity to the adhesive and/or skin preparation used for a CGM, children with a comorbid chronic condition (eg, renal disease), and caregivers who do not speak English.

Recruitment

We will recruit into the study at least one caregiver (mother, father, or guardian) who is primarily involved in the child's daily T1D management. Each site will apply standardized recruitment procedures approved by a single IRB to achieve the target sample. We will use a combination of in-clinic and telephone recruitment. Families who express interest in participating via telephone will complete IRB-approved telephone informed consent procedures including an approved eConsent developed in the Research Electronic Data Capture (REDCap) system [61,62]. Families recruited in person may complete an eConsent or standard paper consent.

Randomization

This study will use a 2-arm randomized attention control design with 90 families recruited to each of the REDCHiP and attention control intervention conditions. We will stratify caregivers based on their child's sex, child age (2 to 3 years versus 4 to 5 years) and CGM use (CGM or no CGM) and randomize to condition using blocks of eight. Recruitment and randomization will occur simultaneously across all participating sites using site-specific randomization envelopes prepared by the study biostatistician. This strategy will allow us to populate groups using caregivers from any site, thereby improving our recruitment efficiency and minimizing possible clinic effects.

Study Visit Procedures

After informed consent and randomization, all families will complete study visit 1, during which caregivers will complete online surveys in REDCap and we will show caregivers (via a short video) how to place the research-grade accelerometer on their child's nondominant wrist (to measure child physical activity) or ankle (to measure child sleep) and how to place the accelerometer on their own nondominant wrist to measure caregiver sleep. We will also teach caregivers how to upload glucometer and insulin pump data from home to a central study database using a commercially available data aggregating system (Glooko). In cases where caregivers cannot use the data aggregating system because of problems with device compatibility, we will collect .csv files. To measure children's daily glucose levels, we will place a FreeStyle Libre Pro (Abbott Laboratories) CGM sensor on the child's upper nondominant arm. We will collect a finger stick blood sample from children using a reliable mail-in kit to measure a baseline HbA_{1c} level. Finally, we will determine if caregivers need to borrow any equipment to participate in the intervention (eg, web camera, microphone, or tablet). After study visit 1, caregivers will begin participating in video-based telehealth sessions according to their group assignment (eg, REDCHiP or attention control intervention). Caregivers will participate in 10 video-based telehealth sessions administered during 13 weeks via a HIPAA-compliant telehealth platform that permits multiparticipant video teleconferencing so that each caregiver can both see and hear other caregivers. During weeks 14 to 15 of the trial, all families will engage in study visit 2 to complete posttreatment surveys online, collect accelerometry data from children and caregivers, collect child CGM data and finger stick blood sample to measure child HbA_{1c}, and recover any loaned study-related devices. Approximately 12 weeks after study visit 2, all families will complete study visit 3, which will involve final data collection: online surveys, child CGM data, and a finger stick blood sample to measure child HbA_{1c} (Figure 2 and Table 3).

Of note, the study protocol will enable families to complete study visits either in their home, at the diabetes clinic, or at another location (eg, library). Additionally, our protocol includes strategies to retain families in the study in the rare event that they move away (eg, telehealth, online surveys, mail-in HbA_{1c} kits) or recruit families who self-refer based on word of mouth or ClinicalTrials.gov. All participating caregivers and children will receive compensation for study visits 1 through 3. As needed, the study will use prepaid postage boxes for families to return study-related devices (eg, accelerometers and CGM sensors) to further reduce the burden on participating families.

Figure 2. Participant timeline.
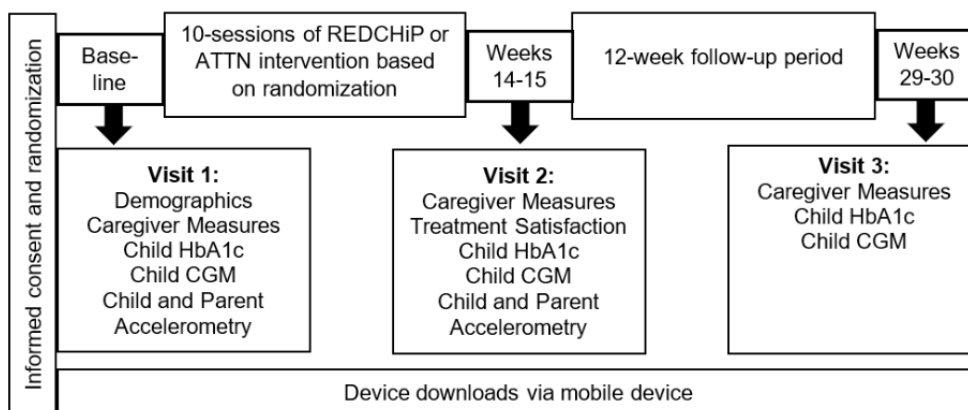
Table 3. Study outcome measures.

Outcome	Measure	Assessment schedule
Child		
T1D[a] treatment and history	Collect demographics; caregivers complete T1D History Questionnaire including caregiver report of family/child demographics, child insulin regimen, CGM[b] use, and history of T1D complications	Visit 1
Child physical activity	Calculate daily moderate to vigorous physical activity and sedentary time based on age-specific cutoffs using accelerometer data	Visits 1, 2
Sleep	Calculate TST[c], sleep latency, and sleep efficiency (TST/total time in bed); caregivers complete online sleep log to verify child sleep versus periods of wakeful inactivity	Visits 1, 2
Glycemic control	Collect children's blood samples using a finger stick capillary sampling kit (with or without mail-back box) developed at one of the study sites and record hemoglobin A_{1c}; we will send samples to a central laboratory for processing using an automated G8 Analyzer[d] with a reference range of 4.0% to 6.0%; this method has demonstrated reliability with a correlation of 0.98 relative to fresh venous samples	Visits 1, 2, 3
Glucose variability	Calculate percentage above, below, and within target range (target: 70 to 180 mg/dL) and mean and standard deviation of daily glucose using FreeStyle Libre Pro[e] data	Visits 1, 2, 3
Child treatment engagement	Calculate frequency of self-monitoring blood glucose and mealtime (bolus) insulin use [63] using device data (eg, glucometer and insulin pump)	Visits 1, 2, 3
Caregiver		
Hypoglycemia fear	Calculate total, worry, and behaviors scores from the HFS-PYC[f] [15,26]	Visits 1, 2, 3
Parenting stress	Calculate stress frequency and stress difficulty scores from the PIP[g] [64]	Visits 1, 2, 3
Depressive symptoms	Calculate total score from the CES-D-R[h] [65]	Visits 1, 2, 3
Anxiety	Calculate total score from PROMIS-A[i] [66]	Visits 1, 2, 3
Psychopathology	Calculate the depression, anxiety, and somatization scores and the Global Severity Index from the BSI-18[j] [67]	Visits 1, 2, 3
Sleep	Calculate TST, sleep latency, and sleep efficiency (TST/total time in bed) using accelerometer data; caregivers will also complete an online sleep log and the PROMIS-S[k] [68], and we will calculate total score	Visits 1, 2 (Visits 1, 2, 3 for PROMIS-S)
Treatment satisfaction	Calculate total score from the Treatment Satisfaction Questionnaire	Visit 2

[a]T1D: type 1 diabetes mellitus.

[b]CGM: continuous glucose monitor.

[c]TST: total sleep time.

[d]G8 analyzer: G8a High-Performance Liquid Chromatography Hemoglobin A_{1c} Analyzer (Tosoh Bioscience Inc).

[e]FreeStyle Libre Pro: FreeStyle Libre Pro Flash Glucose Monitoring System (Abbott Laboratories).

[f]HFS-PYC: Hypoglycemia Fear Survey–Parents of Young Children.

[g]PIP: Pediatric Inventory for Parents.

[h]CES-D-R: Center for Epidemiological Studies–Depression Scale Revised.

[i]PROMIS-A: Patient-Reported Outcomes Measurement Information System–Anxiety short form.

[j]BSI-18: Brief Symptom Inventory–18.

[k]PROMIS-S: PROMIS Sleep Disturbance and Sleep-Related Impairment.

Data Analysis Plan

We will measure parenting stress and caregiver fear of hypoglycemia using the Pediatric Inventory for Parents [64] and the Hypoglycemia Fear Survey–Parents of Young Children [15,26], respectively. We will use child HbA_{1c} levels and percentage of time in range (eg, 70 to 180 mg/dL) to examine child glycemic control and glycemic variability, respectively. To test for treatment outcomes, we will model study visit 2 scores as a function of visit 1 scores, condition (REDCHiP versus attention control intervention), and selected covariates (eg, race/ethnicity, pump use) in mixed models that include a random intercept to account for clustering of participants within group cohorts. We will accommodate nonnormal outcome variables with log transformation, modeling with an appropriate generalized mixed model or nonparametric test. We will test the effect of condition based on whether the 95% confidence interval for the condition coefficient includes zero (equivalent to a 2-sided test at $\alpha=.05$). To determine long-term treatment effects, we will test for sustained improvement on outcome

variables by modeling scores at study visit 3 as a function of visit 1 scores and condition (REDCHiP versus attention control intervention). To control the overall rate of type I errors, we will conduct these analyses only for variables with a statistically significant condition effect in our primary analysis of treatment outcomes.

Power Analysis

We anticipate recruiting 180 families, allowing for a 20% attrition rate and resulting in a final goal of completing the trial with at least 144 families. We assessed power using a simulation study; each simulated dataset contained 40 clusters (20 REDCHiP, 20 attention control intervention) of 4 to 5 participants each. We simulated posttreatment scores using the following model: $Y_{ij} = rX_{ij} + u_i + ES \times Condition_i + \varepsilon_{ij}$, where Y_{ij} is the posttreatment score for the jth participant in the ith cluster, r is the within-cluster correlation between baseline and posttreatment scores (set to .72 based on pilot data), X_{ij} is the ijth participant's baseline score, u_i is the normally distributed random intercept for the ith cluster, ES is the standardized effect size (set to 0.6 standard deviations based on pilot data), Condition is an indicator (1 for REDCHiP, 0 for attention control intervention), and ε is a normally distributed error term. The variances of u_i and ε_{ij} were set to yield a within-condition intraclass correlation coefficient of .10. We fit a mixed model with a random cluster intercept and baseline score and condition as predictors to each of 1000 simulated data sets. To compute estimated power we took the average number of data sets for which the condition was statistically significant in a 2-sided test at $\alpha=.05$. Based on the indicated parameter values and sample size, estimated power was 83%. For 40 groups averaging 3.6 families each, estimated power was 90%. Recognizing this trial will include a control group, which could attenuate our REDCHiP effect, if we conservatively reduce the standardized effect size to 0.4 standard deviations, estimated power is 85%.

Results

Recruitment began in July 2019, and enrollment is ongoing. The first wave of the intervention began in December 2019. We anticipate completing enrollment in 2023. Final reporting of results will occur within 12 months of the primary completion date.

Discussion

Limitations

This trial will focus on families of young children with T1D and exclude children who are on conventional insulin therapy, which could limit some of its generalizability. However, we anticipate little negative impact from this decision because intensive insulin therapy is now the gold standard regimen for individuals with T1D. An examination of maintenance effects of REDCHiP up to 3 months' posttreatment will occur, but we will not be able to draw inferences regarding longer term effects. Our trial includes numerous outcome measures, which increases the risk of missing data. We have attempted to reduce the risk of missing data through device use (eg, accelerometry to measure physical activity and sleep) and online questionnaire access and data sharing. We intend to give caregivers free and accessible technology support before and during telehealth visits in order to reduce any disruptions due to difficulties with the telehealth platform. We intend to stratify our samples according to child sex, age, and CGM status to control for any effect of these variables in our final models. Yet there may be other demographic variables we will not be able to control for a priori that moderate caregiver fear of hypoglycemia, and we may need to adjust for those in our final analyses. In addition, we intend to identify whether young children are using a hybrid closed loop or predictive low-glucose management system via caregiver report or electronic health record review and may adjust for these variables in our final analyses.

Conclusions

Our experience studying fear of hypoglycemia in families of young children with T1D reveals that this is a common fear for caregivers that is related to poorer quality of life and suboptimal child glycemic control. Our initial pilot study revealed promising effects for using cognitive behavioral techniques and a group-based telehealth approach to reduce caregiver fear of hypoglycemia. If this larger, multisite trial confirms the efficacy of REDCHiP and the acceptability and feasibility of our telehealth delivery method, future directions will focus on widespread dissemination of the REDCHiP intervention and implementation across a variety of clinic settings.

Conflicts of Interest

MAC is the chief medical officer for Glooko and has consulted with Medtronic Diabetes and Eli Lilly. All other authors have nothing to disclose.

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Abbreviations

CGM: continuous glucose monitor
HbA$_{1c}$: glycated hemoglobin
HIPAA: Health Insurance Portability and Accountability Act
IRB: institutional review board
REDCap: Research Electronic Data Capture
REDCHiP: Reducing Emotional Distress for Childhood Hypoglycemia in Parents
T1D: type 1 diabetes mellitus

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Protocol

Mobile Health App (AGRIPPA) to Prevent Relapse After Successful Interdisciplinary Treatment for Patients With Chronic Pain: Protocol for a Randomized Controlled Trial

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Abstract

Background: To facilitate adherence to adaptive pain management behaviors after interdisciplinary multimodal pain treatment, we developed a mobile health app (AGRIPPA app) that contains two behavior regulation strategies.

Objective: The aims of this project are (1) to test the effectiveness of the AGRIPPA app on pain disability; (2) to determine the cost-effectiveness; and (3) to explore the levels of engagement and usability of app users.

Methods: We will perform a multicenter randomized controlled trial with two parallel groups. Within the 12-month inclusion period, we plan to recruit 158 adult patients with chronic pain during the initial stage of their interdisciplinary treatment program in one of the 6 participating centers. Participants will be randomly assigned to the standard treatment condition or to the enhanced treatment condition in which they will receive the AGRIPPA app. Patients will be monitored from the start of the treatment program until 12 months posttreatment. In our primary analysis, we will evaluate the difference over time of pain-related disability between the two conditions. Other outcome measures will include health-related quality of life, illness perceptions, pain self-efficacy, app system usage data, productivity loss, and health care expenses.

Results: The study was approved by the local Medical Research Ethics Committee in October 2019. As of March 20, 2020, we have recruited 88 patients.

Conclusions: This study will be the first step in systematically evaluating the effectiveness and efficiency of the AGRIPPA app. After 3 years of development and feasibility testing, this formal evaluation will help determine to what extent the app will influence the maintenance of treatment gains over time. The outcomes of this trial will guide future decisions regarding uptake in clinical practice.

Trial Registration: Netherlands Trial Register NL8076; https://www.trialregister.nl/trial/8076

International Registered Report Identifier (IRRID): DERR1-10.2196/18632

Introduction

Background and Rationale

Chronic pain is a major contributor to worldwide disability, affecting approximately 20% of the global population [1-3]. For many patients, ongoing or recurrent pain severely impacts their physical, social, and mental health, as it interrupts ongoing activities and thereby continuously interferes with daily life functioning. Over time, this impacts patients' sense of self and quality of life [4].

In many cases, there is no monodisciplinary treatment available that can cure the persisting pain. Instead, the multifaceted nature of chronic pain, including biomedical as well as psychological and social factors, often requires a comprehensive treatment approach focusing on improving daily life functioning rather than reducing pain [5-7]. To realize this, interdisciplinary multimodal pain therapy (IMPT) programs have evolved that aim to support patients in learning to live a meaningful life irrespective of pain. These programs share a biopsychosocial orientation toward chronic pain and often include both neuroscientific models of pain physiology as well as (cognitive) behavioral treatment principles [6,8].

Although the effectiveness of IMPT programs has been well established [9-12], maintaining the positive effect of the treatment on patients' daily lives over time remains a major challenge [13,14]. The problem of relapse is not unique to the domain of pain treatment but has been observed across all health behavior domains (eg, [15,16]). In response, many treatment programs have added relapse prevention strategies that aim to preserve treatment gains over time (eg, [17,18]). In the context of chronic pain treatment, examples of such strategies include self-practice exercises [19,20], booster sessions [21,22], or encouragement of patients to take notes during treatment [23,24]. However, the integration of these particular strategies within the treatment program as well as an underlying theoretical rationale regarding how it may prevent relapse are often not described in clinical studies. Moreover, the effectiveness of these behavior regulation strategies remains unknown because they are usually evaluated as a part of the full program or with a limited follow-up period.

Mobile Health

The emergence of mobile health (mHealth) provides new opportunities to support behavior regulation to maintain or enhance the long-term treatment effect of IMPT programs. Despite substantial variations concerning study quality, interventions, and outcomes, mHealth apps are generally regarded as a promising strategy to facilitate adherence to treatment principles or to increase self-management skills (eg, [25,26]). A specific advantage is that an app can include multiple interacting behavior regulation strategies within its digital environment (eg, automatically linking personalized goal setting regarding physical activity to accelerometer output). Moreover, mHealth strategies can integrate other smartphone functionalities such as digital calendars, instant messaging services, or a camera, thereby offering personalized behavior regulation strategies that support the transfer of treatment insights into each patient's personal environment.

Despite the potential and current popularity of mHealth apps, the effectiveness on health-related outcome measures varies greatly [27]. Factors such as engagement—defined as the extent of app use as well as the corresponding subjective experience [28]—and usability—defined as the relative ease with which users can use an app to achieve a particular goal [29,30]—may account for this variability [27,30]. For example, patients that use an app to change their health behaviors may use the app in a different way than intended or stop using the app after several days, which prevents facilitating the intended behavior change [28]. Therefore, evaluations concerning the effectiveness and clinical importance of mHealth apps on health outcomes should take evaluations on user engagement and perceived usability into account [30,31].

Previous Studies

In 2015, we initiated the SOLACE research project to develop strategies to prevent relapse after IMPT programs. Because there was little research available on this topic [13,14], we started with an 18-month co-design project, in which patients, health care providers, researchers, and designers shared their expertise and collaborated to develop ideas, concepts, and strategies to prevent relapse after successful treatment. This resulted in a prototype paper workbook that contained the two most promising strategies: a valued-based goal-setting procedure, and a method for storing and facilitating retrieval of meaningful treatment experiences. Subsequently, we performed a feasibility study in which the prototype workbook was tested at two different IMPT programs for 6 months. Overall, patients and health care providers were willing and able to use the workbook and regarded the strategies to be in line with the IMPT treatment principles (see personal communication, first author SE; manuscript under review). The evaluations also yielded specific suggestions for further improvements, including a preference for a mobile app instead of a paper workbook, along with more interaction between both strategies and a modified goal-setting procedure. In the ensuing research project (ie, the AGRIPPA project), we used the insights of the feasibility study to improve both strategies and transferred the content of the workbook prototype to an mHealth app. Similar to the initial co-design project, patients, health care providers, designers, and researchers collaborated to optimize usability and intervention components of the app. For example, we explored direct user experience through think-aloud sessions with digital mockups, and we organized cocreation sessions to prioritize app features and to prepare a list of requirements.

Study Objectives

The present trial has three main objectives. Our first objective is to evaluate the effectiveness of the AGRIPPA intervention

(ie, enhanced treatment condition) on pain disability for patients with chronic musculoskeletal pain who participate in an IMPT program compared to a usual care control group with a follow-up period of 12 months. Our second objective is to determine the cost-effectiveness of the AGRIPPA intervention relative to usual care. Our third objective is to explore the level of engagement and perceived usability of patients that use the app. We have formulated three hypotheses: (1) the maintenance of improvement in pain-related disability over time after IMPT will be more favorable for the enhanced treatment condition compared to usual care; (2) the effect of the app on pain disability will translate to less health care utilization and less societal costs (eg, less absenteeism), leading to a cost-effective intervention compared to treatment as usual; and (3) for participants in the enhanced treatment condition, the perceived usability, frequency of use, duration of use, and reported adherence to the AGRIPPA app will be positively associated with a favorable change over time of pain-related disability.

Methods

Design

We will perform a randomized controlled multicenter superiority trial with two parallel groups in the Netherlands. Both groups will receive standard IMPT, but the experimental group will be provided with the AGRIPPA app that they can access both during and after the treatment program. The nature of the intervention does not allow for masking the condition for health care providers or patients. The allocation ratio will be 1:1.

Ethical Approval

The study activities have been reviewed and approved by the Medical Research Ethics Committee Utrecht (19/406/D). Protocol modifications that will result in significant changes of study objectives, design, or procedures will require approval by the AGRIPPA steering committee and the Medical Research Ethics Committee.

The trial will be coordinated by a senior researcher of the Lifestyle & Health Research Group of the University of Applied Sciences Utrecht. The AGRIPPA consortium that consists of all project partners (including the participating treatment centers) meets twice per year to discuss overall progress and topics such as dissemination. The AGRIPPA steering committee consists of researchers who meet four times per year to oversee the quality of the research and to decide on any substantial amendments to the initial project idea.

Study Setting

Six treatment facilities that provide IMPT programs participate in this study (2 hospital units and 4 rehabilitation clinics). All locations provide an interdisciplinary biopsychosocial-oriented treatment program to patients within the region, leading to a mixed rural and urban population throughout the Netherlands (ie, Arnhem, Eindhoven, Hoensbroek, Roermond, Maastricht, and Wijk aan Zee).

Eligibility Criteria

Patients

All patients who participate in one of the treatment programs will be eligible to participate in this study. To be admitted to one of the treatment programs, patients must be over 18 years of age and referred by a general practitioner or medical specialist for IMPT. Furthermore, patients must have received a diagnosis of chronic musculoskeletal pain (ie, pain localized in the muscles, tendons, bones, and joints) that lasts or recurs for more than 3 months, and significantly interferes with physical, psychological, and social functioning. Patients have to consent to a biopsychosocial form of treatment and to participate actively throughout the treatment program. Patients with dominant psychiatric comorbidities (eg, severe depression) and pending legal procedures that are thought to interfere with rehabilitative success will not be eligible for treatment. In all participating treatment facilities, this standard screening procedure is performed by a physician in rehabilitation medicine.

Health Care Providers

To qualify for participation, treatment teams will be required to attend a workshop where they will receive instruction on how to adhere to the study protocol and how to use the app. In addition, health care providers will be instructed to document notable or unexpected events and to participate in a focus group after the study period. Each treatment location is also required to provide a research assistant who is not involved with the treatment program. This research assistant will be responsible for performing the treatment allocation procedure.

Recruitment

All patients who will start an IMPT program during the study inclusion period will be contacted by their treating physician in rehabilitation medicine and will receive a patient information letter. The patient will then have 1 to 2 weeks to consider participation and to ask any additional questions before signing the informed consent form. Instruction of the app will follow when a signed informed consent form has been provided to the research assistant. An independent research counselor will be available to all participating patients for any questions and general support during the study. Her email address will be provided via the patient information letter.

Randomization

In participating treatment centers, treatment programs either consist of group sessions, individual sessions, or their combination. To prevent contamination, we will perform group randomization when treatment is predominantly provided in groups. When treatment is provided in individual sessions, we will randomize each patient individually using a simple randomization procedure. The randomization will be performed using random allocation cards based on computer-generated random numbers. The randomization procedure will be executed by a research assistant who is not providing treatment, and will be concealed from health care providers and patients using a set of sequentially numbered opaque and sealed envelopes. The group randomization procedure will be performed in a similar manner for each group that contains at least one participating patient.

Interventions

Standard Treatment

Although there is variation in the content of each treatment program, they all adopt a similar biopsychosocial perspective on pain management [6,32]. Furthermore, each program includes (cognitive) behavioral treatment modalities (eg, graded activity, exposure in vivo, acceptance, and commitment therapy) as well as pain neuroscience education, active patient involvement, and structured team meetings to coordinate treatment and evaluate each patient's progress. All programs are supervised by a physician in rehabilitation medicine who is responsible for patient screening, assessment, and monitoring of overall progress. The treatment team always includes a psychologist and a physical therapist or occupational therapist. At each location, patients start with pain education, where a biopsychosocial orientation toward pain will be explained. Patients also receive a manual that provides general information about the treatment program. All therapies are delivered at the location of the treatment center, except for optional workplace visits. Relapse prevention is part of regular treatment and is addressed during group treatment, individual counseling, or through specific assignments (eg, composing a relapse prevention plan).

Enhanced Treatment

In addition to the regular treatment condition, patients in the enhanced treatment condition will be provided access to the AGRIPPA app that is available on the Android and iOS operating systems for mobile devices. The app consists of three components: two behavioral strategies and an education module. "Insight Cards" and "Value-Based Goals" are specific behavior regulation strategies that have been derived from the SOLACE study and aim to prevent relapse. In addition, an information and education module has been developed in response to patient and health care provider preferences that were expressed during the app design phase.

Component 1: Insight Cards

Patients can use "Insight Cards" to document any personally meaningful experience, thought, or idea that relates to their treatment or corresponding personal development. The main aim is that these "insights" remain accessible after treatment and thereby support the transfer of key treatment principles to each patient's personal context. When capturing an insight, patients first type a title and a short description. Subsequently, they have the possibility to assign a corresponding value and a related picture to the insight (see Figure 1). When patients routinely save their experiences in the app during their treatment period, this will result in a chronologic overview of key experiences over time. During treatment, health care providers will be able to discuss this content with patients to check whether the treatment was received as intended. For patients, the app provides a means to reflect on important experiences during and after treatment. The app also enables patients to mark specific experiences as "favorite" and to share their Insight Cards via email or WhatsApp with their relevant others. After treatment, patients have continuous access to their personal collection of Insight Cards to recover specific insights, to explain specific insights of their condition or treatment to other people, or to reflect on their experiences. Moreover, they can add new Insight Cards to their collection after treatment completion if they have experienced relevant events or insights.

Figure 1. Three screenshots from the AGRIPPA app. Left: example of an insight card, including a related photo, title, two associated values, and description. Middle: Overview of a fictitious goal to go for a hike, including three steps and a related insight. Right: Overview screen of the education and information module. The first row includes treatment-specific exercises, the second row includes general information about the app, and the third row includes links to other support materials.
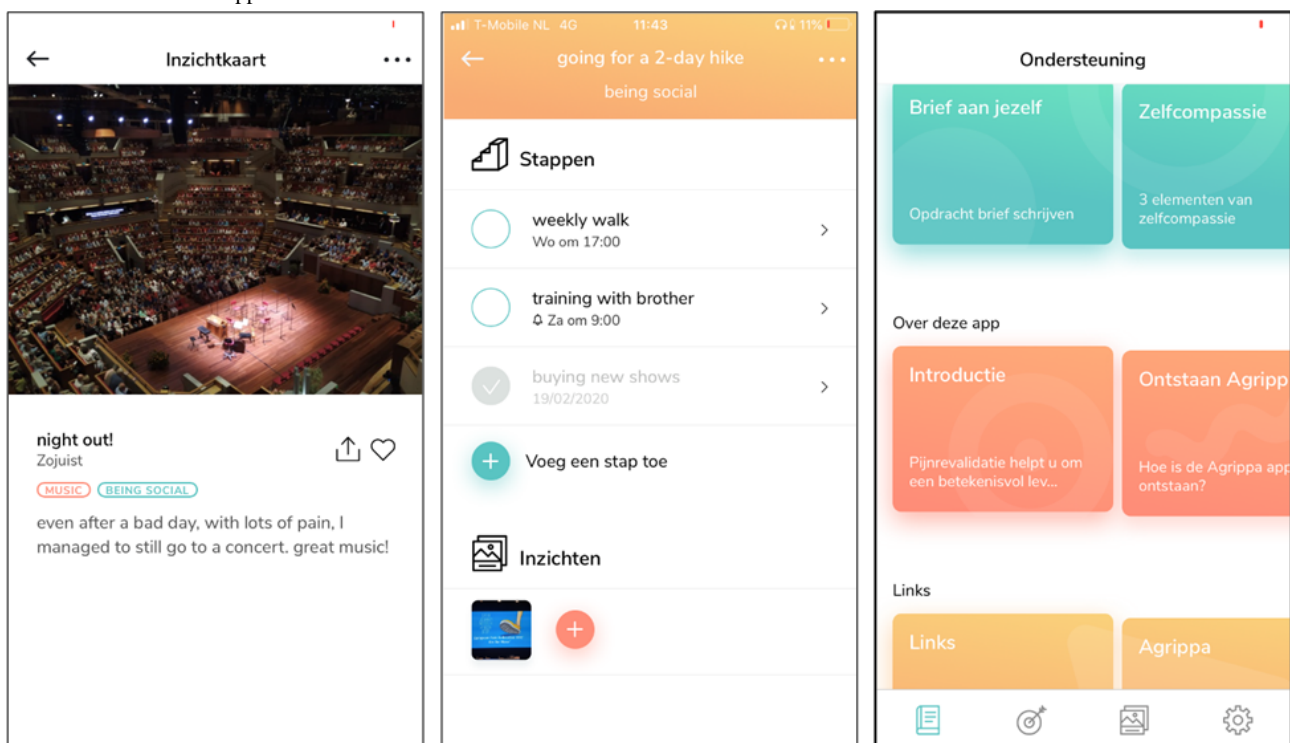
Component 2: Value-Based Goals

The Value-Based Goals module facilitates the formulation of meaningful goals (eg, going for a hike with friends on Saturday morning to be sociable) and subsequent action planning of each consecutive step toward this goal. The procedure is divided into four steps. First, patients formulate their overall goal. Second, patients reflect on desirability, self-efficacy, estimated time to achievement, and social support concerning this goal. Third, patients formulate a corresponding higher-order value (eg, values such as loyalty, friendship, or adventurousness in relation to a goal of going hiking with old classmates), and, optionally, a reward once the goal has been achieved. In the final part, patients can plan multiple "steps," comprising single or recurrent activities that need to be performed to achieve the corresponding goal (eg, buying hiking shoes or planning a weekly training session). For each step, patients plan where and when the specific activity will be performed. They can also add reminders or schedule each step in their mobile calendar. In the final part of the step-planning sequence, patients reflect on potential barriers and formulate coping strategies in anticipation of these barriers (eg, preparing dinner in advance to avoid missing a training session). If a goal has been achieved, patients can directly create an Insight Card of this particular experience. Figure 1 (middle) shows an overview of steps within a specific goal.

Component 3: Information and Education

By default, the Information and Education module includes general information about the AGRIPPA project and instructions on how to use both strategies. In addition, each treatment center can add specific content to this section, including information materials, website links, figures, embedded videos, and assignments. The main reason for including this module is to create a single environment for all supplementary materials of the treatment program. Figure 1 (right) depicts the main screen of this module.

Modifications

During the training session, we recommend health care providers to regularly discuss the app during treatment. However, due to expected variations in digital literacy and other urgent topics,

health care providers are allowed to modify the intensity according to their clinical judgement.

Adherence to the Intervention Protocol

The app will be made available to the members of the treatment teams to become accustomed to the content. The training will be provided by two researchers (JP and ES) and include an overview of the purpose and rationale of the study, as well as detailed instructions on how to use the app within the context of the treatment program. This includes identifying an appropriate moment within the treatment program to introduce the app, determining which member of the team will be responsible for the introduction and encouragement to regularly evaluate the app content, and provide feedback to the participant. During the study, a researcher will have biweekly contact with the treatment team to obtain feedback and discuss progress. Furthermore, two audit sessions will be planned at each location. The researcher will schedule an appointment to discuss overall progress, protocol adherence, and to share examples of good practice with the treatment team. During these sessions, the researcher will also inquire about substantial deviations from the protocol or discontinuation of the app during treatment.

Concomitant Care

During the treatment program, patients are not allowed to be treated elsewhere for their chronic pain unless the treatment team decides to refer the patient for a specific reason.

Outcomes

All six treatment facilities routinely collect outcome data with an electronic survey to monitor their patients [33]. All demographics, baseline measurements, as well as the primary outcome will be obtained by this procedure. Any outcome measures that are not part of the routine assessment will be obtained through an additional electronic survey. Table 1 includes an overview of all outcome domains, measures, and planned analysis methods. The participant flow that is depicted in Figure 2 includes all time points of data collection in this study. A researcher who is not involved with the treatment program will monitor all incoming data and will promote study retention using email reminders after 7 days and telephone reminders at 15 and 21 days postmeasurement.

Table 1. Planned outcome domains, outcome measures, and statistical methods.

Outcome	Hypothesis/research question	Outcome measure	Method of analysis
Primary			
Self-perceived pain disability	The development of pain disability over time after IMPT[a] will be more favorable for the enhanced treatment condition compared to usual care.	PDI[b,c]	Multilevel analysis
Planned subgroup analysis on patients that scored 1 ("very much better") or 2 ("much better") on the GPE[d] scale at t_1[e].	For patients that experienced meaningful treatment success, the development of pain disability over time after IMPT will be more favorable for the enhanced treatment condition compared to usual care.	1. PDI[c] 2. GPE[f]	Multilevel analysis
Secondary (quality of life)			
Health care costs	The enhanced treatment condition will be cost-effective compared with usual care at 3 and 6 months posttreatment.	1. SF-12[f,g] 2. iPCQ[f,h]	Cost-effectiveness analysis
Illness perception	The development of illness perceptions over time after IMPT will be more favorable for the enhanced treatment condition compared to usual care.	IPQ-K DLV[c,i]	Multilevel analysis
Pain self-efficacy	The development of pain self-efficacy over time after IMPT will be more favorable for the enhanced treatment condition compared to usual care.	PSEQ[c,j]	Multilevel analysis
Pain intensity	The development of outcome measures over time may be affected by the level of pain intensity	NRS[c,k]	Multilevel analysis
Engagement and usability			
Overall engagement	The level of engagement and usability will be positively associated with a change in pain disability during follow up ($t_4^1 - t_1$).	1. System usability scale[f] 2. System usage data of AGRIPPA app (see below)	Multiple linear regression
Frequency of engagement	How does the frequency of engagement vary over time after treatment?	Average number of logins per week	Descriptive statistics
Depth of engagement	How does the average number of features accessed per login vary after treatment?	Average number of features accessed per log-in	Descriptive statistics
Duration of engagement	How do the average minutes spent at each login as well as the total time spent with the app per week vary after treatment?	1. Average minutes spent at each login. 2. Total time spent with the app	Descriptive statistics
Active engagement with Insight Cards	To what extent will the number of created Insight Cards increase or decrease after treatment?	Number of Insight Cards created	Descriptive statistics
Active engagement with VBG[m]	To what extent will the number of created VBG cards increase or decrease after treatment?	1. Number of VBGs created. 2. Number of steps created	Descriptive statistics

[a]IMPT: interdisciplinary multimodal pain therapy.

[b]PDI: Pain Disability Index.

[c]Outcome measure is part of routine care.

[d]GPE: global perceived effect.

[e]t_1: immediately postintervention.

[f]Outcome measures will be obtained with an additional electronic survey.

[g]SF-12: 12-item short-form health survey.

[h]iPCQ: iMTA Productivity Cost Questionnaire.

[i]IPQ-K DLV: Dutch language version of the Illness Perception Questionnaire.

[j]PSEQ: Pain Self-Efficacy Questionnaire.

[k]NRS: numeric rating scale.

[l]t_4: 12 months postintervention.

[m]VBG: Value-Based Goals.

Figure 2. Schedule of enrollment, interventions, and assessments. Adopted from SPIRIT (2013). -t1: prior to treatment; t1: posttreatment; t2: 3 months posttreatment; t3: 6 months posttreatment; t4: 12 months posttreatment; PDI: pain disability index; IPQ-K (DLV): Dutch language version of the Illness Perception Questionnaire; PSEQ: Pain Self-Efficacy Questionnaire; NRS: numeric rating scale; SF12: 12-item short-form health survey; GPE: global perceived effect.

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			
TIME POINT	$-t_1$	0	t_1	t_2	t_3	t_4
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS:						
Standard treatment		●——————●				
Enhanced treatment		●——————●				
ASSESSMENTS:						
Patient characteristics	X					
PDI	X		X	X	X	X
IPQ-K (DLV)	X		X	X	X	X
PSEQ	X		X	X	X	X
NRS Pain intensity	X		X	X	X	X
SF12				X	X	
GPE			X	X	X	X
System usage data		●————————————————————●				
System Usability Scale			X			
Cost-effectiveness* (iMCQ)				X	X	

Primary Outcome

Self-perceived pain disability will be measured with the Pain Disability Index (PDI) [34]. This questionnaire consists of 7 items ranging from 1 (no disability) to 10 (maximum disability). Each item relates to the self-reported disability in the context of family/home, recreation, social, occupation, sexual, self-care, and life support. The PDI score (0-70) is obtained by summing all individual items. The PDI score is evaluated as responsive, with a change of 8.5 to 9.5 points considered to be clinically important [35].

Secondary Outcomes

iMTA Medical Cost Questionnaire

The iMTA Medical Cost Questionnaire (iMTQ) measures all health care costs that have been made during a specific period [36]. The questionnaire contains 18 items that refer to 11 primary care components (eg, medication use, general practitioner visits) and 5 secondary care components (eg, hospital visits). Two optional questions will be added that relate to informal care by relatives and health care–related travel expenses. Furthermore, we will add two questions from the iMTA Productivity Cost Questionnaire (iPCQ) to acquire an indication of the productivity losses, as the number of hours work lost due to the disease [37,38].

Twelve-Item Short Form Health Survey

The 12-item short-form health survey (SF-12) contains 12 multiple choice items that cover 8 health status domains. Raw item scores are combined and transformed into two summary scores: a physical and a mental component score [39]. Higher scores reflect better mental or physical functioning. The SF-12 is considered valid and reliable and has been previously used in patients with chronic pain [40-43].

Pain Self-Efficacy Questionnaire

The Pain Self-Efficacy Questionnaire (PSEQ) assesses self-efficacy beliefs regarding daily life goals in the context of chronic pain [44,45]. The questionnaire includes 10 items that ask a patient to indicate the degree of confidence to perform specific activities (eg, socializing with friends) despite the pain. Responses are obtained using a Likert scale, ranging from 0 (not confident at all) to 6 (completely confident). The sum of individual scores indicates the total pain self-efficacy. A study on the psychometric properties in a Dutch population of patients with chronic pain demonstrated that the PSEQ is an internally consistent unidimensional instrument [46].

Brief Illness Perceptions Questionnaire Dutch Language Versions

The Dutch language version of the Illness Perception Questionnaire (IPQ-K [DLV]) measures how patients evaluate their current health condition with respect to 8 areas of cognitive perception [47]. The questionnaire includes 9 items, with 8 items covering a different cognitive area (eg, controllability) with a Likert-scale response option, ranging from 0 (absolutely no control) to 10 (extreme amount of control). The last item requires the patient to list the 3 most important causes for their current condition. A systematic review on the clinimetric properties of the IPQ-K (DLV) concluded that the questionnaire is appropriate to explore the illness beliefs of various patient groups, including acceptable test-retest reliability. However, the smallest detectable change of 42 (on a maximum of 80 points) implies that the use of an IPQ sum score to detect individual changes is not recommended [48]. Therefore, we will not use the sum score but instead evaluate each item separately [49].

Pain Intensity

We will measure current pain intensity on a numerical rating scale ranging from 0 (no pain) to 10 (worst pain imaginable).

Global Perceived Effect

The global perceived effect (GPE) evaluates to what extent the patient's current condition has improved or worsened compared to the period prior to the treatment program. Patients respond with a 5-point Likert scale, ranging from 1 (very much improved) to 5 (very much worsened). The psychometric properties of this questionnaire have been tested in the context of various musculoskeletal disorders and are considered adequate [50].

System Usability Scale

The system usability scale is a 10-item questionnaire that is frequently used for evaluation of the perceived usability of software apps [51,52]. Each item is scored on a range from strongly disagree (1) to strongly agree (5). The total usability score is expressed on a 0-100 scale with higher scores indicating more usability.

System Usage Data

To obtain insight into the frequency, intensity, and duration of engagement, we will obtain the following system usage data for each time point: average number of logins per week, average number of features accessed per login, average minutes spent with the app at each login, total time spent with the app per week, number of Insight Cards created, number of value-based goals created, and number of steps created within the Value-Based Goals module.

Intervention Reporting

We will ask each center to provide a detailed overview of their intervention according to the Template for Intervention Description and Replication checklist [53]. This checklist aims to provide a set of items to describe an intervention for enhancing understanding and replication. Although the interdisciplinary interventions are not the main focus of this study, we will use this intervention to provide an indication of between-center heterogeneity and to assess to what extent the interventions will be modified during the study (item 10).

Data Management

All study data will be obtained via three electronic sources. The questionnaires will either be collected through routine monitoring procedures within the treatment centers or via additional electronic surveys. System usage data will be provided by the app developer. All study data will be stored within the firewall of the University of Applied Sciences Utrecht (UAS) in a folder on a network drive that is protected by permission rights and will only be available to researchers that

are assigned by the project team to analyze the data. Data will be automatically backed up (daily) by the UAS Utrecht. To protect the identity of individual participants, we will perform the following procedures for personally identifiable information. During the data collection phase, we will pseudonymize all incoming data. In the main dataset, we will replace identity data with a unique number (ie, identifier). Date of birth will be transformed to age in years and address information will not be included in the dataset, except for province and place of residence (rural/urban). To add additional measurements to the dataset and to delete data upon participant request, we will create a correspondence table that contains both the identifier and patient personal information. This table will be stored in a separate folder that only the principal investigator (JP) and the head of the Lifestyle & Health Research Group (HW) can access. Any unforeseen data collection issues that may threaten to reveal an individual's identity will be solved according to the recommendations of Tessier and Bonnemains [54].

Harm

We do not expect any serious adverse events as a result of using the app. However, we will monitor any negative consequence that results from usage. During the training of the treatment team, we will instruct the health care providers to report negative experiences of the app (eg, frustration due to low digital literacy skills). During biweekly contact with treatment teams, the researcher will also actively ask for any adverse event. In the unlikely event of harm, patients can appeal to the liability insurance of the sponsor that covers any damage to research subjects caused by the study within 4 years after the end of the study.

Data Analysis

During all analyses, the treatment condition will be masked to the researchers. We will analyze the data according to the intention-to-treat principle and include patients in the analysis regardless of their adherence to the treatment protocol. We will perform no interim analysis. We will collect data at the following time points: $-t_1$ (baseline), t_1 (immediately postintervention), t_2 (3 months postintervention), t_3 (6 months postintervention), and t_4 (12 months postintervention). Prior to the main analysis, we will check the randomization by examining the distribution of baseline characteristics between both groups.

Sample Size Calculation

The sample size calculation is based on a 2-factor repeated-measures analysis of variance with within-factor time (5 levels) and between-factor treatment (2 levels) conditions on the outcome variable PDI. We have set the α to .05, the power $(1 - \beta)$ to .95, and assumed a moderate treatment effect (f=0.2). To account for the expected dependencies of patients within each of the 5 participating treatment locations, we applied the Donner et al [55] formula for the variance inflation factor, assuming an intracorrelation coefficient of 0.2 [56,57]. Furthermore, we corrected the analysis for an expected attrition of 20%, which is based on the average attrition of similar studies that used the PDI [21,58,59]. Based on these calculations, a minimum sample size of 157 participants, equally divided over 5 treatment locations, will be required.

Primary Analysis: Pain Disability

In our primary analysis, we will test the difference in the development of pain disability over time between patients in the enhanced condition and patients in the treatment condition. To account for the assumed dependence of the repeated observations and treatment locations, we will perform a multilevel analysis. In our hierarchical model, time points (level 1) will be nested in patients (level 2) and patients nested in treatment locations (level 3). Our main analysis will include the effects of time, treatment condition, treatment location, and the interaction between time and treatment condition, with a random intercept for patients. In addition, the model will be adjusted for sex, age, pain intensity, and pain duration. In the case of a significant 2-way interaction between time and treatment condition, posthoc contrasts between the treatment conditions at 3, 6, and 12 months will be calculated. We will also perform a subgroup analysis for patients that report a positive treatment effect at t_1 (ie, a GPE score of 1 or 2).

Analysis of Secondary Outcomes

Perceived Usability and App Engagement

Based on the results of the feasibility study and the nature of the behavior regulation strategies, we expect an engagement pattern in frequency, type, and depth of engagement that differs for each behavior change strategy and changes over time. Specifically, for Insight Cards, we believe that patients will actively engage with this component during treatment (ie, creating Insight Cards during use), but shift to more passive engagement (ie, reading the input, but only creating new content at limited occasions) during follow up. For Value-Based Goals, we expect that the formulation of goals and steps will increase during the final part of treatment, together with a growing emphasis within the treatment program on integrating newly learned strategies into daily life routines. After treatment, we anticipate that patients will engage in a reflective (eg, documenting progress) and active (ie, formulating new goals) manner with this strategy. In general, we expect a decreasing trend of the number of logins over time, but an increase in the "depth" of use (ie, the average number of features accessed per login) as well as an increase in the duration of a login. We will calculate descriptive statistics to explore patterns of engagement. Furthermore, to examine the extent to which user engagement and usability are negatively associated with the change of pain disability during follow up, we will perform a multiple regression analysis, with the change score of pain disability ($t_4 - t_1$) as the outcome variable and engagement and usability measures as predictors. We will adjust for age, sex, pain intensity, and baseline PDI.

Cost Effectiveness

To investigate the efficiency of the intervention, we will perform a cost-effectiveness analysis at 3 and 6 months posttreatment according to the intention-to-treat principle. We hypothesize that patients in the enhanced treatment condition will have more quality-adjusted life years (QALYs) relative to the health care expenses compared to the regular treatment condition within

the 6-month study period. Expected health gain will be expressed in QALYs and calculated using the procedure of Brazier and colleagues [60] to estimate the 6-dimensional health state form (SF-6D) using the SF-12 assessment at 3 and 6 months posttreatment [39,61]. Intervention costs will be determined by the standardized cost prices for rehabilitation treatment [62]. Other health expenses will be obtained using the iMTQ at 3 and 6 months posttreatment. This questionnaire includes visits to health care providers, prescribed and over-the-counter medication, and alternative health care. We will also calculate the productivity loss due to pain-related absence from work, adopting the gross human capital approach [63]. Productivity loss will be obtained with two questions of the iPCQ at 3 and 6 months posttreatment. Total costs are calculated using the Dutch manual for cost analysis in health care research [62,64]. Following the procedure of Den Hollander and colleagues [65], a standardized cost price will be used for each hour of productivity loss. Total costs and total health gains for each condition will be used to calculate the incremental cost-effectiveness ratio (ICER). Furthermore, we will construct cost-effectiveness acceptability curves based on mean costs and using incremental costs and incremental effects, employing nonparametric bootstrapping with 5000 replications. This will result in a scatter plot over four quadrants, where each quadrant indicates a different implication for economic evaluation (ie, a combination of positive or negative costs and effects) [66].

According to the National Institute for Health Care and Excellence guidelines, all intervention costs in cost-effectiveness analyses should relate to health care or social services funding [67,68]. This excludes the development costs of the AGRIPPA app because this project has been funded with research grants. However, to account for future development and maintenance costs, we will perform a sensitivity analysis and explore various cost scenarios. We will calculate multiple ICERs, each with a different cost input value that corresponds to a possible future pricing scenario (eg, subscription, pay to download).

Missing Data

Following recommendations of Twisk and colleagues [69], we will perform the multilevel analysis on incomplete data, rather than using multiple imputation procedures. However, we will use the R MICE package to search for patterns of missing data across the included variables and to perform t tests to explore the relationships between the amount of missingness of each variable and all other variables [70].

Participant Timeline

Patient eligibility screening, informed consent, and treatment allocation procedures, as well as the baseline assessment, will be completed prior to the start of the treatment program. Patients in the enhanced treatment condition will receive instruction on how to download and use the app, and both strategies will be explained by a member of the treatment staff. To match the existing treatment content and procedures, the moment that the app will be introduced to patients can vary between locations. During the treatment phase, the app is considered a supplement to the main treatment activities and patients are free to decide how and when to use the app. Health care providers will be instructed to encourage and facilitate using the strategies when

they expect it will reinforce the treatment process. However, both strategies can largely be used independently of any treatment activity and are expected to minimally affect direct treatment time. A member of the research team will be available to the treatment staff throughout the experimental phase for additional questions, support, and discussions regarding optimal use. Following treatment, there will be no additional monitoring in the enhanced treatment condition. Patients will continue to be able to use the app at their discretion. Posttreatment data will be obtained directly posttreatment (t1), and at 3 months (t2), 6 months (t3), and 12 months (t4) posttreatment.

Results

The trial has been registered in the Netherlands Trial Register under the identifier NL8076. The study is ongoing. The patient inclusion period started in October 2019 and is expected to end in November 2020. As of March 20, 2020, we have recruited 88 patients. Results are expected to be released in the final quarter of 2021. In the last meeting of 2020, the steering committee will initiate the formation of writing teams that will be responsible for the final trial report.

Discussion

Study Goals

This study will evaluate the AGRIPPA app in the context of interdisciplinary multimodal pain treatment programs. Specifically, we will investigate the effect of app use on long-term pain disability and efficiency by means of a cost-effectiveness analysis. To discover how patients interact with the app, we will also explore usability and engagement and test the impact of these variables on pain disability. Together, these analyses will help to demonstrate to what extent the AGRIPPA app contributes to preventing relapse in pain-related disability.

In contrast to prevailing intervention development guidelines, the AGRIPPA development project adopted a co-design approach and started with collecting qualitative data from end users (eg, patients and health care providers) rather than with formulating a theoretical framework. Although co-design is increasingly acknowledged in the health care domain as a method to integrate stakeholder input into the intervention design, more robust evaluations of co-design–based interventions are required to determine its additional value to existing development practices [71,72]. A similar point can be made for the evaluation of mHealth apps. A recent systematic review revealed that health care apps to promote self-management in chronic conditions have seldom been evaluated by randomized controlled trials over a prolonged study period [27]. This study will help understand if an mHealth app that has been developed by co-design methods not only contributes to an acceptable and user-friendly intervention but also leads to maintenance of treatment gains for patients with chronic pain.

Strengths and Limitations

Because IMPT programs often substantially vary in dose and content, the inclusion of multiple treatment centers will

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positively influence generalization. Furthermore, this study builds on a feasibility study where evaluations related to form, content, and integration within treatment programs have been incorporated into the current app and study procedures.

The exploratory analysis of engagement variables in this study is expected to provide preliminary insight into patient adherence to the behavior regulation strategies within the app. According to Sieverink and colleagues [73], insight into adherence to mHealth apps can be acquired by combining usage behavior data with a description of intended use and a well-substantiated justification for this intended use. Although this may be difficult to quantify as the intended usage of the app depends on fluctuations of patients' functional status in the posttreatment phase, the comparison of system usage data with our expectations regarding the use of the strategies will at least provide an indication of adherence to the app. Possible follow-up studies that include qualitative evaluations of patient input may lead to a more sustained insight into adherence.

This study includes several challenges and compromises that can potentially bias the outcomes. First, including patients with both treatment conditions within one center increases the risk of contamination. Second, health care providers have a large influence on participant engagement. Our feasibility study indicated that health care provider involvement varied greatly between patients, and that patients with limited health care provider feedback did not always use the intervention as intended (see personal communication, first author SE; manuscript under review). By scheduling regular contact moments to discuss progress, we aim to minimize the impact of this potential threat. Third, the limited project duration and funding resulted in a maximum follow-up period of 12 months. Although this first year may be crucial for integrating the newly learned management strategies into a daily life routine, the effect of the AGRIPPA app on late-onset occurrences of relapse will not be monitored in this study. Limited funding also prevented the development of an active (mHealth) control condition. Although opting for a treatment-as-usual condition as a comparator is a widely used method, this does not control for the potential placebo effect of receiving an mHealth app. Fourth, to minimize the impact for patients to participate in this study, we have selected a limited number of outcome measures and measurement time points in addition to routine assessments. This may result in an increased recall bias or limited insight in potential factors that could explain a possible effect of the app. Finally, patients will require sufficient digital literacy skills to effectively use the app, which may lead to self-selection during the recruitment phase. The selection bias may threaten generalization.

Implications for Practice

Maintaining behavior change is notoriously difficult to achieve and every small step toward decreasing relapse or understanding the specific mechanisms by which relapse occurs or is prevented will be important to the field of pain rehabilitation. Implementation of this intervention in treatment programs may also positively empower patients to take a more proactive role in their treatment program and increase sharing their experiences, thoughts, and beliefs with health care providers and significant others. This may not only lead to a better patient–health care provider relationship and improved mutual understanding but is also expected to positively influence adherence to newly learned pain management strategies [74].

Authors' Contributions

SE prepared the manuscript; JP, HW, AK, ES, and RS provided feedback; JP and HW are grant holders; JP obtained medical ethical approval, is the principal investigator, and is responsible for the day-to-day management of the "AGRIPPA" research project; HW, AK, and RS are steering committee members of AGRIPPA and monitor overall progress; ES is the contact person for the treatment locations.

Conflicts of Interest

None declared.

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Abbreviations

GPE: global perceived effort
ICER: incremental cost-effectiveness ratio
IMPT: interdisciplinary multimodal pain therapy
iMTQ: iMTA Medical Cost Questionnaire
iPCQ: iMTA Productivity Cost Questionnaire
IPQ-K (DLV): Illness Perception Questionnaire- Dutch language version
mHealth: mobile health
PDI: Pain Disability Index
PSEQ: Pain Self-Efficacy Questionnaire
QALYs: quality-adjusted life years
SF-6D: 6-dimensional health state form
SF-12: 12-item short-form health survey
UAS: University of Applied Sciences Utrecht

Original Paper

Improving Retention in Care and Promoting Adherence to HIV Treatment: Protocol for a Multisite Randomized Controlled Trial of Mobile Phone Text Messaging

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Abstract

Background: The World Health Organization has prioritized the use of new technologies to assist in health care delivery in resource-limited settings. Findings suggest that the use of SMS on mobile phones is an advantageous application in health care delivery, especially in communities with an increasing use of this device.

Objective: The main aim of this trial is to assess whether sending weekly motivational text messages (SMS) through mobile phones versus no text messaging will improve retention in care and promote adherence to treatment and health outcomes among patients receiving HIV treatment in Fako Division of Cameroon.

Methods: This is a multisite randomized controlled single-blinded trial. Computer-generated random block sizes shall be used to produce a randomization list. Participants shall be randomly allocated into the intervention and control groups determined by serially numbered sealed opaque envelopes. The 156 participants will either receive the mobile phone text message or usual standard of care. We hypothesize that sending weekly motivational SMS reminders will produce a change in behavior to enhance retention; treatment adherence; and, hence, health outcomes. Participants shall be evaluated and data collected at baseline and then at 2, 4, and 6 months after the launch of the intervention. Text messages shall be sent out, and the delivery will be recorded. Primary outcome measures are retention in care and adherence to treatment. Secondary outcomes are clinical (weight, body mass index), biological (virologic suppression, tuberculosis coinfection), quality of life, treatment discontinuation, and mortality. The analysis shall be by intention-to-treat. Analysis of covariates shall be performed to determine factors influencing outcomes.

Results: Recruitment and random allocation are complete; 160 participants were allocated into 3 groups (52 in the single SMS, 55 in the double SMS, and 53 in the control). Data collection and analysis are ongoing, and statistical results will be available by the end of August 2019.

Conclusions: The interventions will contribute to an improved understanding of which intervention types can be feasible in improving retention in care and promoting adherence to antiretroviral therapy.

Trial Registration: Pan African Clinical Trial Registry in South Africa PACTR201802003035922; https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=3035

International Registered Report Identifier (IRRID): DERR1-10.2196/15680

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Introduction

In patients infected with HIV, viral replication can be effectively suppressed with antiretroviral therapy (ART), allowing the body's immune system to restore and function adequately [1]. Suppressed viral replication in HIV infection has been proven to dramatically reduce mortality and morbidity rates, leading to improved quality of life and improved perceptions on HIV/AIDS from a death sentence to a manageable chronic disease [2]. Yet, the population effect of ART depends on high coverage and sustained adherence to treatment among people living with HIV [3].

The SMS of the mobile phone is an inexpensive and suitable means of communication that can be used in conveying health messages to persons who own or have access to mobile phones. In 2013, 97% of the world's population were mobile phone subscribers [4]. Moreover, by 2015, 71 per 100 inhabitants of Cameroon were accessing mobile phones [5].

Study protocols on the use of SMS technology to promote adherence to ART have been developed in Kenya [6], India [7], and Cameroon [8]. In 2005, the World Health Organization spelled out the use of new technologies to assist health care delivery in resource-limited settings [9]. Since then, the SMS has shown promising results in improving HIV health care delivery and communication between health personnel and clients, and as an appointment reminder in trials conducted in Kenya [10], Cameroon [11,12], South Africa [13], and elsewhere [14].

The use of text messages in improving adherence to primary care has been found to be more profitable than phone calls [15]. Patient-centered mobile health (mHealth) interventions have had promising outcomes in sickle cell disease management [16]. Systematic reviews have pointed to the success of mobile phone text messaging interventions in improving medication adherence among people living with chronic diseases [17-19]. These findings suggest the use of SMS as a more advantageous application of the mobile phone in health care delivery especially in communities with increasing use of these devices.

Only a single mHealth intervention has been conducted in Cameroon and included only one hospital and 198 participants for a period of 6 months [11]. This lone Cameroonian mHealth intervention together with those conducted elsewhere [10,13,15] has shown promising results on ART adherence and retention in HIV care. Thus, further research involving patients from different treatment centers, and most especially in the phase of government efforts to fight HIV/AIDS, is warranted in Cameroon. This study is timely as it is based on this strategy to improve and promote ART adherence and retention in care in Cameroon. Furthermore, the study will enhance our understanding of the extent that mHealth intervention promotes healthy behaviors and supports psychosocial well-being among patients receiving treatment for chronic diseases. Therefore, this study will contribute to an improved understanding of which

text message frequency can be feasible when, why, and for whom.

The goal of this trial is to determine whether sending weekly motivational text messages through mobile phones versus no text messaging will improve retention in care and promote adherence to treatments and health outcomes among patients receiving HIV treatments over a 6-month period. We hypothesize that sending weekly motivational text message reminders will produce a change in behavior to enhance retention; treatment adherence; and, hence, health outcomes.

Participants will be recruited from two hospitals approved to provide free HIV treatment services in Fako Division of the South West Region of Cameroon.

Methods

The trial was registered with the Pan African Clinical Trial Registry [20] in South Africa on February 1, 2018. The unique identification number for the protocol is PACTR201802003035922.

Study Design

The design rests on a three-arm, randomized controlled trial with two intervention arms and one control group. The trial shall be single-blinded where the investigators and participants shall not be blinded to the intervention, whereas interviewers and data analysts will be blinded to group allocation. The intervention shall include the use of mobile cellphone SMS in addition to the standard of care provided to the clients. Participants shall be randomly allocated in a 1:1:1 ratio to one of three arms prior to the beginning of the intervention: (1) once weekly mobile phone SMS, (2) twice weekly mobile phone SMS, and (3) a control group that shall not receive mobile cellphone SMS. Clients will be recruited from the government-approved centers of the Regional Hospital Buea and Regional Hospital Limbe providing HIV treatment services.

Randomization

This is a parallel-group design evaluating the effects of adding once-weekly mobile phone text messages and twice-weekly mobile phone text messages to the usual standard of care (intervention) versus usual standard of care alone (control) among HIV clients receiving ART. Eligible and consenting participants shall be randomized to interventions and control arms using a 1:1:1 allocation ratio by the opaque sealed envelope method. A computer-generated randomization list will be produced using random block sizes of 2, 4, and 6 by the research biostatistician. The allocation codes shall then be put in serially numbered opaque sealed envelopes and administered by the research staff at the various hospitals. Trained interviewers, who shall be blinded to group allocation, will collect data using pretested questionnaires containing sociodemographic data, clinical information, retention, and adherence measures at baseline and at 2, 4, and 6 months. The biostatistician shall also be blinded to group allocation. Blood samples will be collected

and analyzed for viral load during the trial once a participant has been on ART for at least 6 months. The time schedule of enrollment, interventions, and assessments are summarized in Figure 1.

Figure 1. Recruitment and random allocation into the text messaging and control groups. AFB: acid-fast bacilli; ART: antiretroviral therapy; TB: tuberculosis; WHO: World Health Organization.
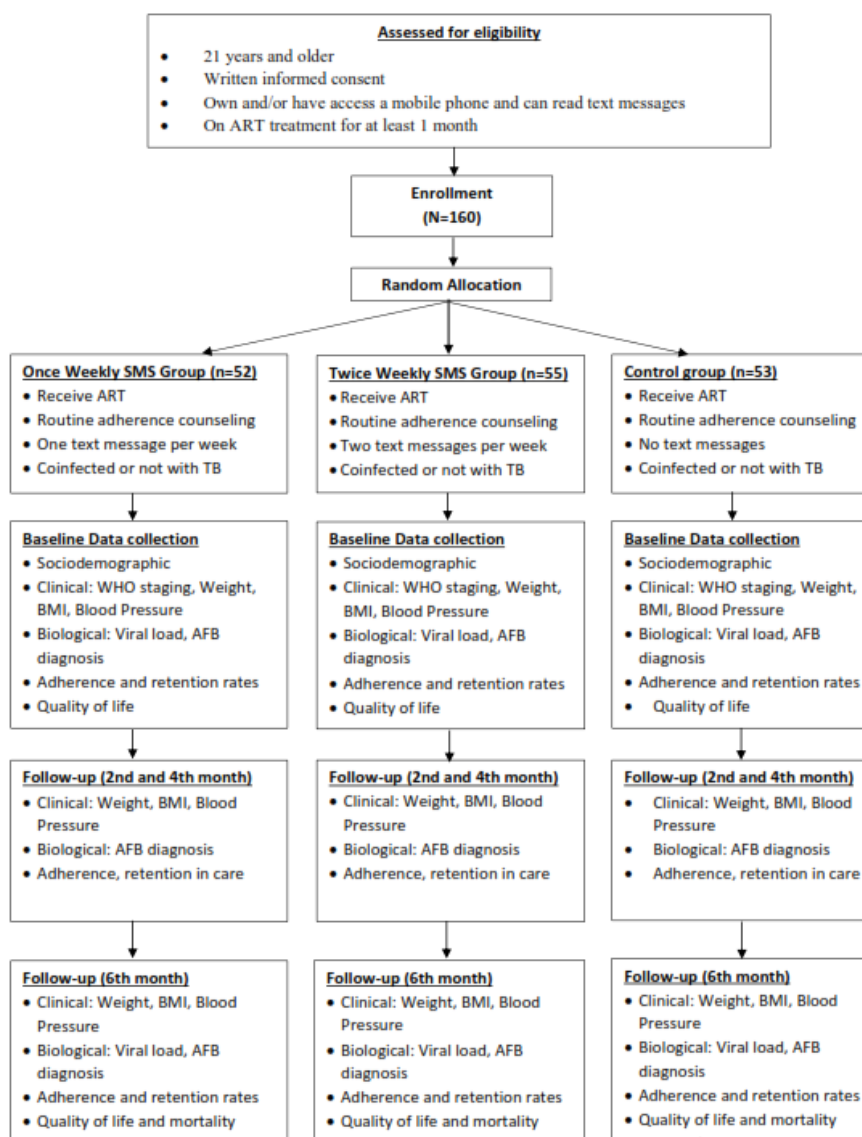
Trial Setting

Cameroon is a sub-Saharan central African country made of ten regions and a population of over 24 million inhabitants [21]. The study will be implemented in Fako Division of the South West Region of Cameroon. The adult prevalence of HIV in the country was 3.4% in 2018 [22]. The adult prevalence of HIV in the South West Region was 3.6% in 2018 [22]. Most inhabitants practice agriculture as the main economic activity. The region has two seasons: the dry season from October to March and the wet season from April to September. Almost all ethnic groups in Cameroon are represented in the region, attracted by the fertile volcanic soil and the Cameroon Development Corporation, a giant agricultural corporation that

seconds the state of Cameroon in employment. The two hospitals selected for the trial have government-approved centers offering free treatment and care services for HIV to the population of the region. Participants will be residents in their various communities and support groups while visiting these treatment hospitals for routine care during the entire study period. As per the Cameroonian Ministry of Public Health national guidelines, newly diagnosed clients are initiated on free nonnucleotide reverse transcriptase inhibitors–based ART irrespective of their viral load count or CD_4^+ T cell count [11]. Recently, HIV clients initiating ART were systematically placed on isoniazid prophylaxis for the first 6 months of their ART. These are the largest treatment centers in the region and offer enormous potential for recruitment.

Participants: Inclusion and Exclusion Criteria

The study population shall include HIV clients either coinfected with or without tuberculosis who come to the hospital for a routine health evaluation. Participants shall be consecutively recruited and randomly allocated to the intervention and control groups.

We shall include clients who are 21 years or older, have access to or own a mobile phone and can read text messages, and who have been on ART for at least a month and planned to live in Cameroon during the period of the study. We shall place more emphasis on clients who have started ART for at least 1 month to measure the differential effects for clients initiating ART versus those who have been under treatment for longer durations. Informed consent is a prerequisite for participating in the study and shall be provided orally and in writing.

We shall exclude clients who have been on ART for less than a month and who are younger than 21 years. Clients who have used ART for at least 1 month are chosen to enable us to be able to calculate a baseline figure for treatment adherence.

Intervention

The HIV clients will be receiving ART for free from the hospital staff at the HIV treatment centers. The HIV clients who shall be coinfected with tuberculosis shall also receive directly observed treatment short-course for free. This is the usual standard of care for people living with HIV/AIDS and tuberculosis in Cameroon [23]. Patients with HIV on any of these treatments shall be randomized to receive mobile phone text message reminders. The trial shall comprise 2 intervention groups and 1 control group to investigate the impact of text message reminders on retention in care and adherence to treatment and health outcomes.

A short text message will be sent to the participants in the intervention groups in English or French depending on the preferred language of each client. The content of these text messages has been developed and pretested in focus group discussions involving people living with HIV/AIDS, their caregivers, and health care workers. The construct of the health belief model was used to develop these text messages that are sociocultural acceptable and targeted at improving retention in care and promoting adherence to treatment [24]. The messages are motivating and shall act both as reminders and a cue to action. Participants unanimously agreed that the messages should not contain the name of the disease. It was also concluded that the word "food" should be used in place of medication or drug when sending the messages (Textbox 1). The message shall also contain a phone number that the participants can call back if they need directives on their treatment and care. The content shall be varied so as to retain participants' attention and interest throughout the period of the study and to explore the various aspects of behavior change. There shall be a list of phone numbers that the messages targeted at improving retention in care shall be sent midway before the next clinic visit schedule and then 2 days before each clinic visit appointment. The messages targeted at promoting adherence to treatment will be sent twice every week. The "delivery report" function of the mobile phone shall be used to verify and to record whether the messages have been delivered to the clients. Clients will be contacted through the phone numbers of their contact persons in the event of undelivered messages. The issue of missing phone numbers shall be resolved by replacing clients' existing contracts with their recent phone numbers. One message will be sent per week in the evening between 6 PM and 7 PM of a day chosen by the client in the once-weekly SMS intervention arm. In addition, two messages shall be sent per week in the evening between 6 PM and 7 PM of 2 days chosen by the client in the twice-weekly SMS intervention arm. The mobile phone text messaging shall be provided as add-ons to the usual standard of care, which includes rare ART counseling and occasional home visits.

Textbox 1. Examples of the text messages that will be sent in the intervention group.

Sample SMS to improve retention in care

- You are so loved. Handle your health with care, visit us on xx-xx-xxxx.

- You are very important. Do not forget your visit on xx-xx-xxxx.

- Are you busy? This is why I remind you to come for your visit on xx-xx-xxxx.

- Your health is important. Come for your appointment on xx-xx-xxxx.

Sample SMS to promote adherence to treatment

- Your health is important. Take your food.

- You are very important. Do not play with your health. Take your food.

- You are so loved. Handle your health with great care. Take your food.

- Are you very busy? This is why I remind you to regularly take your food.

Control

The routine practice in Cameroon is that, at ART initiation, the responsibilities of the treatment centers usually explain the side effects of medications and problems associated with poor adherence to the clients prior to dispensing drugs. All participants including those in the control arm have received this educational message during their routine hospital visits. Participants randomly allocated to the control group shall not receive mobile phone SMS. However, they shall receive ART, be screened for tuberculosis coinfection, and be interviewed alongside the other participants.

Study Objectives

Primary Objective

The main aim of this trial is to investigate the impact of adding mobile phone SMS to the usual standard of care versus usual standard of care alone in improving retention in care and promoting adherence to treatment among HIV clients on treatment at 2, 4, and 6 months. Retention in care shall be defined as the proportion of clients who had started on ART, enrolled in the study, and attended clinic visits at the second, fourth, or sixth months. There is no gold standard in the measurement of adherence because the majority of the tools currently used cannot meet all the features of an ideal tool [25]. However, a multi-method tool is recommended and can include self-report and different combinations of other tools including pill count, the pill identification test (PIT) and visual analog scale (VAS), electronic methods, and drug levels. Therefore, a composite adherence measure shall be used in this study to reduce the errors associated with using a single adherence measure [25]. The adherence score shall be built on four adherence measures including a self-report questionnaire with 4 items, supplement of pill pick up from pharmacy refill records, a PIT consisting of 5 items, and a 30-day VAS. Adherence shall first be estimated by each measure and classified into three categories as high, moderate, and low before finally combining the results of the four measures into the composite adherence score.

Secondary Objectives

The secondary objectives include comparing health outcomes such as weight, BMI, opportunistic infections such as tuberculosis, and quality of life. These comparisons will be performed between the groups at baseline and at 2, 4, and 6 months. In addition, the viral load will be determined for participants who have been receiving ART for at least 6 months to ascertain virologic suppression.

Outcome Measures

Primary outcomes

The primary outcomes will be retention in care and adherence to treatments, measured using self-reports (supplemented by PIT, pharmacy refill data, and VAS; Table 1).

Table 1. Overview of outcome measures.

Outcome measures	Scale	Type	Measure	Analysis method
Primary				
Retention at 2, 4, and 6 months	Nominal	Binary	Number retained in care	Risk ratio
Adherence at baseline and at 2, 4, and 6 months				
Self-report	Ordinal	Binary	% adherence in last month >95%	Risk ratio
Pill identification test	Ordinal	Binary	% of pills identified >95%	Risk ratio
PRD[a]	Ordinal	Binary	% of complete refills >95%	Risk ratio
VAS[b]	Ordinal	Binary	VAS percentage >95%	Risk ratio
Secondary				
Weight	Ratio	Continuous	Change in weight	t test
BMI	Ratio	Continuous	Change in BMI	t test
Viral load	Ratio	Continuous	Change in viral load	t test
OIs[c] (AFB[d] diagnosis)	Nominal	Binary	Occurrence of new OI (AFB positive smear)	Chi-square test
Mortality	Nominal	Binary	All deaths	Chi-square test
Satisfaction with care	Ordinal	Categorical	Change in satisfaction scores	t test
QoL[e]	Ordinal	Categorical	Change in QoL scores	t test
Overall				
	Nominal	Binary	Number retained in each group	Risk ratio
	Ordinal	Binary	Change in composite adherence measure	Risk ratio

[a]PRD: pharmacy refill data.

[b]VAS: visual analog scale.

[c]OI: opportunistic infection.

[d]AFB: acid-fast bacilli.

[e]QoL: quality of life.

Secondary Outcomes

The secondary endpoints shall comprise clinical (weight and BMI), biological (viral load and AFB diagnosis), quality of life (measured with the self-functioning–12 quality of life assessment form), and all-cause mortality. Treatment discontinuation, reasons for discontinuation, and risk factors of treatment discontinuation shall also be determined. The trial endpoints are summarized in Table 1.

Duration

The trial shall run for 6 months. Outcome assessments will be conducted at baseline, 2 months, 4 months, and 6 months.

Sample Size Determination

The sample size determination is based on the test of the null hypothesis that the rates of adherence to ART in the intervention and control groups are equal. The primary measure of effect is the rate of adherence to ART as measured by using the VAS over 6 months. Given the information from previous studies [10,11], it is estimated that approximately 60% of participants would maintain adherence ≥95% without intervention and that the interventions would help 82% of the participants maintain ≥95% adherence. A two-sided test is assumed where an effect in either direction will be interpreted at a significance level of 5%. The study will have a power of 80% to yield a statistically significant result using a chi-square test (assuming an intention-to-treat principle for the analysis) of the relative risk at an alpha level of 5% to detect a 25% difference (60% vs 85%).

The formula for calculating the sample size for randomized controlled trials by Chan [26] is used.

where c=7.9 for 80% power and p1 and p2 are the proportion estimates (60% for the control group and 85% for the intervention group).

It is assumed that 10% of the participants shall drop out of the study due to loss to follow-up and mortality. A total of 52 participants shall be randomized to each arm to allow for the 10% drop out. Therefore, the required sample size will be 156 (52 x 3 = 156) participants.

Analysis Plan

The CONSORT (Consolidated Standards of Reporting Trials) guidelines will be used in reporting the results. The biostatistician shall be blinded to the group allocation. The process of client selection and flow throughout the study will be summarized using a flow diagram. The analysis of client demographics and outcome variables shall be summarized using descriptive summary measures, expressed as mean (standard deviation) or median (range) for continuous variables and number (percentages) for categorical variables. All outcomes shall be analyzed using an intention-to-treat principle where data from participants shall be analyzed according to the group to which they were randomized even if they do not receive the allocated intervention. Missing data shall be handled using the multiple-imputation method. The student *t* test and analysis of variance for comparing group means will be used. All statistical tests shall be performed using two-sided tests at the 5% level of significance. The Bonferroni method shall be used to adjust the level of significance for testing of secondary outcomes to keep the overall level at an alpha of 5%. For all group comparisons, the results shall be expressed as an effect (or risk ratio for binary outcomes), corresponding two-sided 95% confidence intervals, and associated *P* values. *P* values shall be reported to three decimal places with values less than .001 reported as <.001. Adjusted analyses using baseline variables shall be performed using regression techniques to determine the continuing influence of key baseline characteristics on the outcomes. The Kaplan-Meier survival analysis will be used for timed variables like mortality. All analyses will be performed using SPSS version 25.0 (IBM Corp) for Windows. Adherence will be measured both as a continuous outcome (change in adherence) and as a binary outcome (ie, adherent, 95% of pills taken, or nonadherent, <95% of pills taken) following the composite adherence score method. Adherence data shall be handled in a number of ways, reported as the number of doses respected, and shall be combined into a composite score. The effects of the intervention shall be reported on all the measures of adherence used and will be compared for discrepancies.

Patient and Public Involvement

This study was conceived and designed to address gaps in the care and support available to people living with HIV/AIDS who are receiving ART. The intervention was designed with the active involvement of patients with HIV, their caregivers, and health workers through focus group discussions. Our randomized controlled trial offers participants the opportunity to provide feedback regarding the burden of the intervention through focus group discussions involving a cross-section of participants.

Ethics and Dissemination

Ethical clearance for this trial was obtained from the Institutional Review Board of the Faculty of Health Sciences of the University of Buea in Cameroon (Reference number: 2018/147/UB/SG/IRB/FHS). Administrative authorization was obtained from the Regional Delegation of the Ministry of Public Health for the South West Region and the District Health Services. The purpose of the study and the role of the participants will be well explained in the consent form to the participants and participation shall only take place after the participant has read and signed the informed consent forms voluntarily. The informed consent shall include signed permission to consult the client's medical records over the duration of the study.

Dissemination efforts shall target individuals and institutions that will have the most impact on local, national, and international HIV and AIDS policies. Therefore, dissemination plans shall include the presentation of research findings in seminars, conferences, and scientific publications in peer-reviewed journals. A summary of the findings will be made available to participants.

Results

Recruitment of participants in the trial took place in May and June 2018. Recruited participates were randomly allocated to the intervention and control arms at the start of the intervention in July 2018.

A total of 160 participants have been recruited and randomly allocated into the intervention and control groups. Participants were allocated into 3 groups (52 in the once weekly SMS, 55 in the twice weekly SMS, and 53 in the control). Data collection and analysis are ongoing, and statistical results will be available by the end of August 2019.

Discussion

Since the launch of the fast track approach to end the AIDS epidemic by 2030, Cameroon is far from reaching the 90-90-90 treatment target in 2020, whereby 90% of people living with HIV know their HIV status, 90% of people who know their HIV-positive status are accessing treatment, and 90% of people on treatment have suppressed viral loads [27]. Only 58% of people living with HIV know their HIV status, 37% of those living with HIV are on treatment, and 19% of these patients are virally suppressed 2 years from the 2020 treatment target in Cameroon [27].

New strategies to end the AIDS epidemic as a public health threat by 2030 are being instituted throughout most national HIV control programs [28]. Recent advances in the fast-track approach to HIV and AIDS in Cameroon has been the recommendation of offering to every client presenting to a clinic for any medical consultation to pass the HIV screening test and to allow as many people to know their HIV status [29]. In addition, the government of Cameroon through the Ministry of Public Health has instituted new directions by placing the systematic treatment of HIV under the strategy called test and treat (screening and treatment) [29]. This new strategy requires that any person screened and confirmed positive for HIV is directly placed on antiretroviral treatment. Proper retention in care and a high level of adherence are needed to sustain lower viral load counts and reduce chances of drug resistance that might result from treatment defaulting. More people will be accessing ART services as a result of enhanced HIV testing.

There is a high need to devise strategies that would lead to improved retention in care and sustained adherence to treatment.

In this light, the benefits of mobile phone SMS in improving and promoting health outcomes are warranted, particularly in this era of increased uptake and use of mobile phone devices. However, there is a paucity of economic data to support the use of mHealth behavioral interventions in low- and low-middle–income countries [30].

Improving retention in care and promoting adherence to treatments can play a key role in reducing the morbidity and mortality associated with HIV and tuberculosis diseases. The occurrence of drug-resistant strains and the waste of medication in health systems can be adequately managed. Findings generated from this trial may be generalizable to other chronic illnesses requiring lifelong treatments.

A major ethical concern is the harm that might be caused to participants due to the accidental disclosure of their disease status. This possibility shall be properly explained to the participant, even though our text messages shall neither disclose status nor make mention of medication but shall rather act as a reminder of health. Loss of privacy and confidentiality are not foreseeable problems in the study. The intervention shall be an addition to an already existing system in Cameroon where mobile operators deliver messages to their clients for business purposes. The text messages shall be delivered to the participants' mobile phones by the research team using phones with prepaid airtime.

The content of the SMS was developed following the construct of the health belief model of behavior change. Furthermore, the intervention shall focus on the health belief model. Collected data shall be used to test the efficacy of the SMS reminder as a cue to action. This study is timely, as it is based on this strategy to improve and promote ART and tuberculosis treatment adherence and retention in care in Cameroon. Furthermore, the study will enhance our understanding of the extent that mHealth intervention promotes healthy behaviors and support psychosocial well-being among patients receiving treatment for chronic diseases. The study shall also investigate the effect of tuberculosis coinfection on the health outcomes of HIV clients. Therefore, the study will contribute to an improved understanding of which type of text message frequency can be feasible when, why, and for whom.

Authors' Contributions

EAT and DSN conceived the study. EAT, DSN, NJCA, and TNN helped draft the manuscript. EAT, DSN, NJCA, and TNN designed the trial. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ART: antiretroviral therapy
CONSORT: Consolidated Standards of Reporting Trials
mHealth: mobile health
PIT: pill identification test
PRD: pharmacy refill data
VAS: visual analog scale

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Protocol

Effects of Alternative Offers of Screening Sigmoidoscopy and Colonoscopy on Utilization and Yield of Endoscopic Screening for Colorectal Neoplasms: Protocol of the DARIO Randomized Trial

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Abstract

Background: Flexible sigmoidoscopy and colonoscopy are recommended screening options for colorectal cancer (CRC). Despite colonoscopy being offered for CRC screening in Germany, the uptake of this offer has been very limited.

Objective: The objective of this study was to assess the potential for increasing use of endoscopic CRC screening and the detection of advanced colorectal neoplasms by offering the choice between use of flexible sigmoidoscopy and colonoscopy.

Methods: The DARIO study includes a cross-sectional study (part I), followed by a prospective 2-arm randomized controlled intervention trial (part II) with an associated biobank study (part III). Participation is possible in part I of the DARIO study only, parts I and II, or all 3 study parts. After obtaining informed consent from the municipalities, 12,000 people, aged 50-54 years, from the Rhine-Neckar region in Germany were randomly selected from residential lists of the responsible population registries and invited to complete a standardized questionnaire to investigate the nature, frequency, timing, and results of previous CRC screening and eventual diagnostic colonoscopies. In study part II participants from study part I with no colonoscopy in the preceding 5 years are randomized into 2 arms: arm A offering screening colonoscopy only, and arm B offering both options, either screening colonoscopy or screening sigmoidoscopy. The primary endpoint is the proportion of participants in whom colorectal neoplasms >0.5 cm are detected and removed at screening endoscopy. The secondary endpoints are the detection rate of any neoplasm and use of any endoscopic screening. Part III of the study will use samples from participants in study part II to construct a liquid and tissue biobank for the evaluation of less invasive methods of early detection of colon cancer and for the more detailed characterization of the detected neoplasms. Blood, urine, stool, and saliva samples are taken before the endoscopy. Tissue samples are obtained from the neoplasms removed during endoscopy.

Results: A total of 10,568 from 12,000 randomly selected women and men aged 50-54 years living in the Rhine-Neckar-Region of Germany have been invited for participation. The remaining 1432 (11.93%) could not be invited because they reached the age of 55 at the time of contact. Of those invited, 2785/10,568 (26.35%) participated in study part I; 53.60% (1493/2785) of these participants were female. Study parts II and III are ongoing.

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Conclusions: This study will answer the question if alternative offers of either screening sigmoidoscopy or screening colonoscopy will increase utilization and effectiveness of endoscopic CRC screening compared with an exclusive offer of screening colonoscopy. In addition, alternative noninvasive screening tests will be developed and validated.

Introduction

Background

Colorectal cancer (CRC) is the third most common cancer and the second most common cause of cancer deaths globally, responsible for more than 1.8 million cases and more than 800,000 deaths annually [1]. In Germany there are annually approximately 60,000 cases and 25,000 deaths as a result of CRC [2]. Slow progression of the cancer through the adenoma–carcinoma sequence opens up promising possibilities for prevention and early detection interventions [3].

The majority of CRC cases could be prevented by detection and removal of adenomas at screening sigmoidoscopy or colonoscopy [4]. Several countries provide an opportunistic screening programme including colonoscopy (Austria, Czech Republic, Greece, Iceland, Luxembourg, Portugal, Slovakia); in very few countries organized screening programs offer either colonoscopy (Germany, Poland) or sigmoidoscopy (England and Italy). The United States and South Korea offer both endoscopic screenings, reporting uptake of up to 60% [5]. Screening colonoscopy has the advantage that adenomas can be detected and removed in the entire colon and rectum but the procedure requires full bowel cleansing starting the day before colonoscopy. Screening sigmoidoscopy detects adenomas only in the distal colon and rectum (where the majority of CRCs occur), but is less invasive and less demanding regarding bowel preparation, with an enema immediately prior to the procedure being sufficient. Thus, adherence to the offer of screening sigmoidoscopy is expected to be higher than adherence to the offer of screening colonoscopy.

Severe complications during or after colonoscopy or sigmoidoscopy are very rare [6]. Besides, participants greatly benefit from the removal of advanced adenomas that would develop into CRC in about 30% of the carriers within the next 10 years [7,8]; participants also benefit from removal of nonadvanced adenomas, which are also targets of screening endoscopy with a somewhat lower CRC transition rate [8-10].

Several large-scale randomized trials have demonstrated a major reduction of CRC incidence and mortality by screening sigmoidoscopy [11-18]. Even larger effects are expected from screening colonoscopy, but first results from the only large-scale randomized controlled trial assessing this question will not be available before mid-2020. Evidence from epidemiological studies suggests that the majority of CRCs and CRC deaths could be prevented by detection and removal of adenomas by screening colonoscopy [15,19], with somewhat lower effects but better adherence to be expected from screening sigmoidoscopy [15,19-21]. Overall, low adherence is the major limiting factor for a more effective prevention of CRC incidence and mortality within the population. In Germany, screening colonoscopy (but not screening sigmoidoscopy) has been offered for women and men aged 55 and older since the end of 2002. However, only 20%-25% of those eligible have utilized this screening offer within the first 10 years [10].

Objectives

The DARIO (German title: "Darmkrebsprävention: Innovative Wege am Nationalen Centrum für Tumorerkrankungen [NCT]) study includes 3 study parts (Figure 1) and has 3 major objectives: part I of the study, an epidemiological cross-sectional study that assesses through a standardized questionnaire in a random sample of women and men aged 50-54 years type, frequency, date, and results of previous early detection examinations and of potential diagnostic colonoscopies for CRC.

Part II of the study, a randomized intervention study including eligible participants from part I, randomizes those into 2 arms: arm A, in which a free screening colonoscopy alone is offered, and arm B, in which one of the two endoscopic screening options is offered: a free screening colonoscopy or a free screening sigmoidoscopy. The main objective of part II is to assess if and by how much the complementary offer of the less invasive screening sigmoidoscopy will lead to a higher number of detected and removed neoplasms (>0.5 cm). Endoscopies are performed at the Interdisciplinary Endoscopy Center (IEZ) of the Heidelberg University Hospital according to common clinical practice. Tissue samples are obtained from the neoplasms removed during endoscopy and will be banked for diagnostics and research purposes at the NCT tissue bank.

Part III of the study builds up a liquid biobank from biosamples (blood, urine, stool, saliva) of study part II participants, with samples taken prior to endoscopy. The main objective of study part III is the evaluation of less invasive methods of CRC screening and further characterization of detected neoplasms and defining biomarkers or biomarker panels of different composition (such as proteins, metabolites, DNA, microRNA, methylation markers) obtained via different -omics platforms.

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Figure 1. DARIO study design.
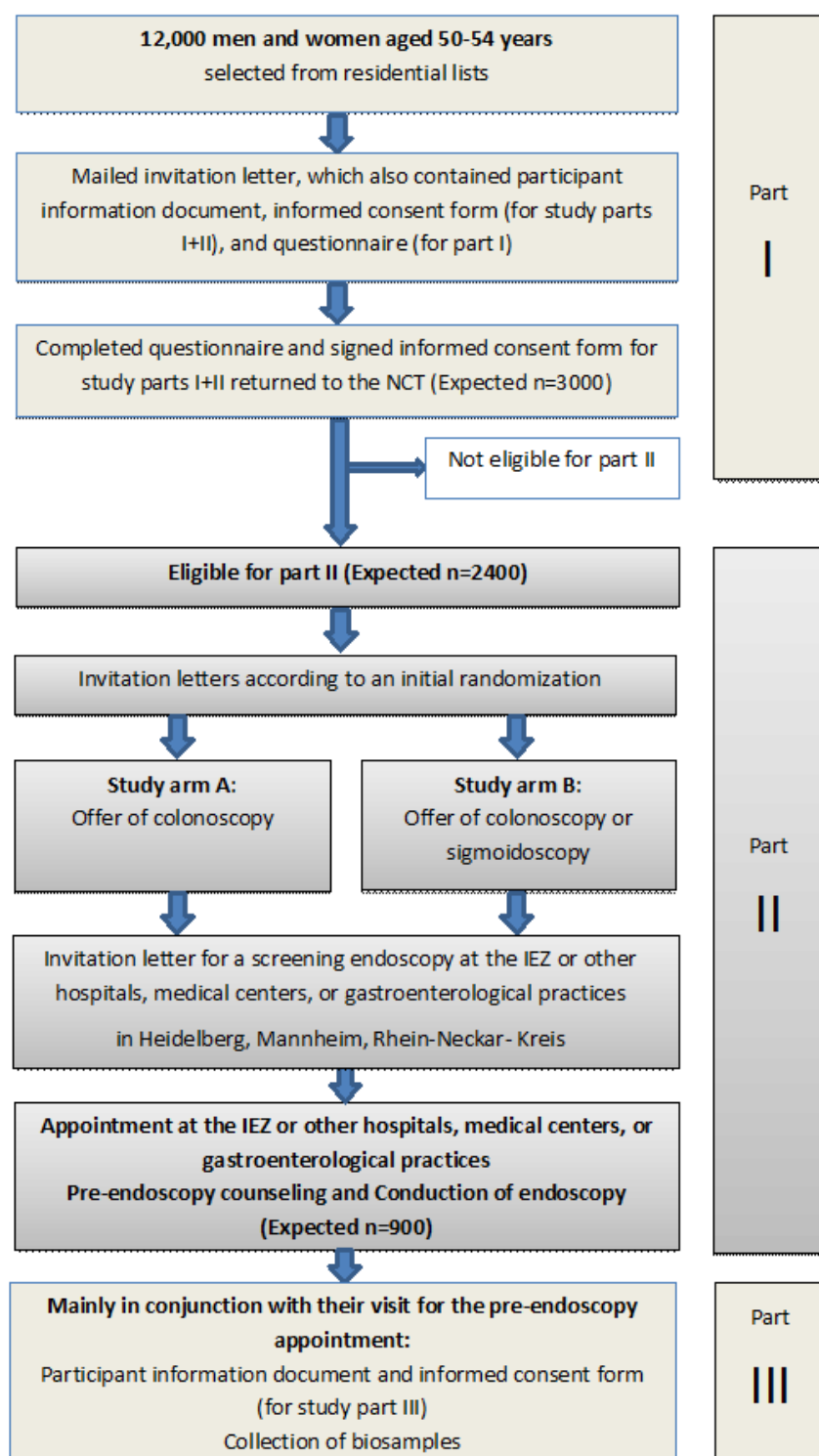
Methods

Study Design

The DARIO study is designed in 3 study parts: as a cross-sectional study (part I), followed by a prospective 2-arm randomized controlled intervention trial (part II) with an associated biobank study (part III) for biomarker evaluation as diagnostic tests of less invasive methods. The study design is

shown in Figure 1. The trial was registered during recruitment of the participants in Deutsches Register Klinischer Studien on September 30, 2019.

Study Part I: Cross-Sectional Screening for Previous Early Detection Examinations and Risk Factors

A total of 12,000 randomly selected potential participants aged 50-54 years living in the Rhine-Neckar region of Germany (main residence in Heidelberg, Mannheim, and Rhein-Neckar-Kreis,

as defined by community codes) received a participant information document for study parts I + II and a short questionnaire by letter, and were invited by the DARIO study center at the National Center for Tumor Diseases in Heidelberg, Germany to participate in the study. Persons willing to participate were asked to sign and return the informed consent form for parts I + II of the study (included in the letter, together with a prepaid return envelope) and the questionnaire to the DARIO study center. The questionnaire includes questions on previous early detection examinations as well as questions concerning familial risk factors, lifestyle, health behavior, and nutritional factors.

Eligibility for parts II and III of the study is contingent on absence of a number of exclusion criteria that are specifically asked for in the questionnaire of part I. Exclusion criteria for parts II and III of the study are a history of CRC, a colonoscopy in the previous 5 years, a history of familial adenomatous polyposis or Lynch syndrome, and a severe illness which makes it impossible for the potential participant to visit the IEZ at the University Hospital Heidelberg or collaborating medical centers or gastroenterological practices in the Rhine-Neckar region (Heidelberg, Mannheim, and Rhein-Neckar-Kreis).

Study Part II: Pre-Endoscopic Counseling and Endoscopic Screening in Study Arm A or B

Eligible participants are randomly allocated into either study arm A or B. Study arm A offers the participants a free screening colonoscopy, and in study arm B the eligible participants receive a letter, which offers the choice of either a free screening colonoscopy or a free screening sigmoidoscopy. The endoscopies take place at the IEZ or at other hospitals or medical centers or gastroenterological practices in the Rhine-Neckar region (Heidelberg, Mannheim, and Rhein-Neckar-Kreis).

To randomize the participants eligible for part II into arm A or arm B, a unique random number is generated for all 12,000 persons via a computer by a statistician with no involvement in the trial, before the persons are contacted in part I of the study, not knowing who will eventually participate in part I and who will be eligible for part II. Persons who agree to participate and who are eligible for part II are assigned into the respective study arm and a letter is sent to the participants inviting them to a pre-endoscopy counseling appointment at the NCT Study Center or at the IEZ. During pre-endoscopy consultation, the participants will receive routine patient information documents and, if they decide to have such an examination, they will sign the informed consent routinely used and required before endoscopy in clinical practice. Participants can be excluded from the study by the consulting physician due to underlying diseases or insufficient health status influencing endoscopy.

Screening colonoscopy and screening sigmoidoscopy are conducted at and under the responsibility of the performing center (hospitals, medical centers, or gastroenterological practices). Blinding of employees at the respective sites or at the study center is not feasible, because knowledge of endoscopy type(s) offered is a prerequisite for pre-endoscopy consultation and performing endoscopy. The study visit for the screening colonoscopy at the respective centers takes about 60 minutes for the screening colonoscopy and about 30 minutes for the screening sigmoidoscopy.

Study Part III: Biosample Collection and Set up of a "Prevention Biorepository" for Biomarker Analysis

In conjunction with their visit for pre-endoscopy consultation at the NCT or IEZ, study participants willing to undergo endoscopy are informed in detail about study part III for which they are invited to donate biological samples (36 mL of blood, and samples of stool, urine, and saliva) for the evaluation of noninvasive or minimally invasive early detection markers. Biosamples are delivered directly to the Laboratory of the Division of Preventive Oncology at the NCT, the DARIO study center, without any delay. The stool sample is taken by the participants at their homes, collected prior to initiation of the large bowel preparation for colonoscopy, stored cool according to the manual, and delivered to the respective endoscopy center on the day of endoscopy. The sample reaches the NCT Laboratory on the same day and is processed and stored immediately. Exceptions occur with a maximum delay of 3 days for arrival or processing (eg, over weekends). The samples are then stored at 4°C for further processing or frozen directly at –80°C if no processing is required. All samples are processed according to the state-of-the-art standard operating procedures of the NCT Liquid Biobank, within 2-4 hours after taking the samples or entry of the biomaterial at the study center for the analysis of biomarkers. The samples are stored in barcoded vials and either frozen at –80°C or stored in liquid nitrogen for long-term storage. They are documented in a laboratory information management system (STARLIMS). For part III of the study, patients are asked to sign a separate specific informed consent form and a transfer agreement form for provision of biological samples.

Data Collection and Documentation in the Coordinating Center

The unique participant number links biological samples, questionnaires, and endoscopy results. Information collected from endoscopy and histology reports is entered into a standardized study database by trained staff in the coordinating center at the NCT, using double data entry by 2 independent staff members. Data entries are checked through comparison of the corresponding data sets for inconsistencies and in case of differences in data sets, the data are validated by checking the original reports.

The information collected in the questionnaire in part I is documented by automated scanning of the questionnaires, optical verification of the scans by trained staff, and by applying comprehensive plausibility checks prior to statistical analysis. All collected information is stored at the coordinating center for at least 10 years after the end of the trial.

Data and Biosample Analysis

Statistical analyses will be conducted using basic and advanced statistical methods for clinical epidemiological studies, including the analysis of biomarker data. The samples in the biobank built up in this trial will be used for determining the diagnostic value of novel biomarkers for early detection of colorectal neoplasms using standard receiver operating characteristic analyses for

single markers and advanced biostatistics and bioinformatics tools for high-dimensional data obtained from -omics technologies.

The biospecimen will be used for identifying and evaluating biomarkers and biomarker signatures for cancer early detection and risk assessment. The most desirable highest scientific benefit from all biospecimen requires the determination of specific laboratory parameters and laboratory techniques according to the state of the art at the time of the analyses, which for most participants and most measurements will be years after recruitment. Examples of measurements anticipated at the time of conception of the DARIO study were measurements of defined metabolites in blood, stool, urine and saliva; circulating microRNA, especially in blood samples; single-nucleotide polymorphism analyses; next-generation sequencing; transcriptomics and application of several available and emerging -omics technologies, such as epigenomics, serolomics, proteomics, and stool metagenomics potentially related to the presence of early and advanced adenomas or colorectal carcinoma or both.

Long-term storage of the biosamples collected in this trial will enable timely validation of emerging promising early detection markers in the years to come.

Method Against Bias

Data on confounding factors such as education, smoking, nutrition and diet, alcohol consumption, family history of cancer will be collected through the questionnaire in study part I. The trial is randomized to account for confounding factors. Extraction of clinical data from colonoscopy and pathology reports is accomplished in a blinded manner to avoid information bias. Data extraction and data entry (where applicable) are performed by 2 independent reviewers. Discrepant coding is resolved according to standard operating procedures to achieve the maximum accuracy possible. In addition, all recruiters and participants receive detailed instructions to ensure uniform collection and handling of biosamples. Preanalysis conditions, including sample transportation, are also documented to control for potential variation. All laboratory analyses are performed in a blinded fashion with respect to both treatment given and clinical/colonoscopy data.

Sample Size Calculation

The current participation rate in the German screening colonoscopy program is 2%-3% per year among those eligible in the absence of personal invitations (performed as so-called opportunistic screening program). It has been repeatedly demonstrated (including own studies) that this participation rate can be at least doubled by personal invitation letters. Our estimates of recruitment numbers are rather conservative.

The sample size calculation is based on an anticipated participation rate of 25% (n=3000) in study part I out of 12,000 eligible participants and of 20% (n=2400) eligible participants for study part II, who are randomized into arm A or B (1200 participants in each arm).

In study arm A, 300/1200 participants (25.00%) are expected to undergo screening colonoscopy within 1 year, of whom 16.0%

(48/300) are expected to have colorectal adenomas >0.5 cm detected and removed [22].

In study arm B, 240/1200 (20.00%) are expected to undergo screening colonoscopy and another 360/1200 (30.00%) are expected to undergo screening sigmoidoscopy within 1 year.

With an expected detection rate of neoplasms >0.5 cm of 16% and 12% by screening colonoscopy and screening sigmoidoscopy, respectively, the expected number of participants who have neoplasms >0.5 cm detected and removed is 81 (38 in arm A + 43 in arm B) [22,23].

The power to detect a significantly different rate of detection and removal of neoplasms >0.5 cm between both arms of study part II (48/1200 in arm A and 81/1200 in arm B) is 85% (two-sided chi-square test at α=.05).

As much as 90.0% (810/900) of participants undergoing endoscopy are expected to also participate in study part III. Evaluation of biomarker performance will be conducted according to standard methods of clinical epidemiology, bioinformatics, and biostatistics. Logistic regression models will be applied for individual biomarkers to construct prediction algorithm, and .632+ bootstrap [24] will be applied to adjust for potential overestimation of diagnostic performance. Areas under the receiver operating characteristic curves and their 95% confidence intervals, and sensitivity (true-positive rate) of each individual biomarker at cutoffs yielding 80% and 90% specificities (true‐negative rate) will be calculated.

In order to derive multimarker algorithms for the prediction of the presence of CRC, least absolute shrinkage and selection operator logistic regression models will be applied to markers that remain significant after multiple testing. The least absolute shrinkage and selection operator regression adapted to obtain models with the best prediction accuracy will be combined with .632+ bootstrap to adjust for overfitting. Prediction algorithms will be derived. Joint performance of biomarkers with known CRC risk factors (such as age, sex, family history, smoking, alcohol consumption, and dietary factors, information on which will be obtained from questionnaires) for predicting presence of neoplasms will additionally be evaluated in multivariable models. Analyses will be performed with statistical software R language and environment (version 3.5.3; R core team).

Quality Assurance, Safety, and Benefit Risk Assessment

Ethical approval for the DARIO study was obtained from the Ethics Committee of the Medical Faculty of the University of Heidelberg (DARIO: S-686/2015). The study is registered at the German Registry for Clinical Studies (Deutsches Register Klinischer Studien, DRKS) with the DARIO-ID DRKS00018932 and at the StudyBox with the StudyBox Registry Number ST-D453 by OnkoZert of the German Cancer Aid (see Multimedia Appendix 1).

The screening endoscopies offered in the course of study part II are well-known routine procedures and established clinical practice [25]. They are recommended for CRC screening in the average risk population aged 50 or older by expert committees in multiple countries including Germany. Conduction of

endoscopies (including informed consent, preparation, safety and quality considerations, insurance) follows routine clinical practice. The only difference in this study from clinical practice is that screening endoscopies otherwise not covered by health insurance in this age group in Germany (50-54 years) during the time of recruitment are offered free of charge to participants in the respective arms of study part II.

Advantages of both procedures to discover and remove preadenomatous, adenomatous, and cancerous lesions in the bowel are well known, as are their possible side effects. Both methods are valued as secure and controllable, with less risks and side effects to be expected with sigmoidoscopy due to the less demanding bowel cleansing, the shorter duration of the procedure, the smaller endoscopic intervention area in the bowel, and the reduced need for anesthetics. With adequate preparation, severe complications during or after colonoscopy or sigmoidoscopy are very rare and advantages in view of the screening prevail for both methods. Participants benefit from removal of advanced adenomas that would often develop into CRC and from removal of nonadvanced adenomas, which are also targets of screening endoscopy with a somewhat lower CRC transition rate.

The IEZ at Heidelberg University Hospital and the other hospitals or medical centers or gastroenterological practices in the Rhine-Neckar region routinely perform the procedures applied in this study within the course of diagnosis and treatment of colorectal tumors and precursors, on the basis of defined and quality-assured, internationally accepted standards and guidelines, as well as on the basis of local guidelines and standards. Patient briefing is conducted and informed consent is obtained following the clinical guidelines and practice of the hospital, medical center, or gastroenterologist practice. Participants are informed by a qualified physician on the endoscopic procedure(s) according to randomization (arm A, colonoscopy only; arm B, colonoscopy and sigmoidoscopy) and the potential anesthesia. Chances and risks are explicitly commented on during this conversation and participants have time to ask questions and to think about their decision regarding use of the offer of endoscopy. There are no disadvantages in case of denial at any time point within the course of the study. Potential light and severe complications occurring during endoscopy or during blood draw can be treated immediately at the Heidelberg University Hospital or the clinics close to the other medical centers or gastroenterologist practices.

The quality-controlled preanalytics with cold chain transport, time to freeze documentation, and barcoded processing and asservation of the collected biological samples are assured at the Preventive Oncology liquid biobank laboratories and the NCT tissue bank.

Availability of Data and Materials

The future data set(s) supporting the conclusions of the trial will be made available upon reasonable request. Study materials, including study protocol, participant information documents, informed consents, questionnaire, the invitation letters to study part I and to study part II for arm A and for arm B as well as the letter of exclusion to study part II and the completed

CONSORT checklist are provided as Multimedia Appendices 2–12.

Ethics Approval and Consent to Participate

This study is conducted in accordance with the principles of the Declaration of Helsinki (of 1975, revised in 2000) and with the German laws/regulations. The study follows the good epidemiological practice guidelines and in the hospitals, medical centers, and practices the physician work according to good medical practice, a code of conduct and medical ethics for doctors.

Before the trial was initiated, the DARIO study protocol and any related document provided to the study participants were approved by the responsible Ethics Committee of the Medical Faculty of the University of Heidelberg (Federführende Ethikkommission) and the institutional Research Board (IRB or REB) (DARIO Study Number: S-686/2015). Before being admitted to the study, participants consent to participate after the nature, scope, and possible consequences of the study have been explained in understandable form (informed consent).

Data Protection

This study is conducted in accordance with the General Data Protection Regulation (EU) 2016/679, the Data Safety Federal Protection Act, and the Data Protection Act of Baden-Württemberg. Study center is the Division of Preventive Oncology at the NCT of the German Cancer Research Center (GCRC/DKFZ) in Heidelberg. Documentation of programs and implemented databases is supervised within the legal frame and the IT and data protection rules of the DKFZ. The pre-endoscopy consultation and the colonoscopies are performed under the responsibility and based on the standard interview template and operating procedures of the IEZ of the Heidelberg University Hospital.

Results

A total of 10,568 people from 12,000 randomly selected women and men aged 50-54 years living in the Rhine-Neckar-Region of Germany have been invited for participation of whom 22.99% (2430/10568) were at age 50, 22.99% (2430/10568) at age 51, 22.99% (2430/10568) at age 52, 15.99% (1690/10568) at age 53, and 15.00% (1585/10568) at age 54. Of those invited, 2785 (26.35%) participated in study part I, of which 53.60% (n=1493) were female. A total of 1432 (11.93%) people could not be invited because they reached the age of 55 at the time of contact and an additional pool of participants was not accessible at the time. Study parts II and III are ongoing. Of the 2781 study part I participants who completed the questionnaire, 1060 (38.12%) participants were screened by an endoscopy.

Discussion

A large proportion of CRCs can be avoided by screening. Screening colonoscopy (but not screening sigmoidoscopy) has been offered in the German health care system for men and women at the age of 55 and older since the end of 2002, but participation rates have remained low. With this trial we aim to assess if and to what extent use of endoscopic screening can

be increased by alternative offers of screening sigmoidoscopy and screening colonoscopy, and if and to what extent this increases detection rates of advanced colorectal neoplasms at the age between 50 and 54 years in the defined study population. Endoscopic screening at this age was so far not supported by the German health care system, and sigmoidoscopy is so far not offered for CRC screening at any age in Germany. The study is expected to create awareness among the population included in the study and their immediate family or friends who also get to know about the study and its purpose. The fact that people are invited to participate and get a cost-neutral colonoscopy or sigmoidoscopy may motivate people to undergo screening who would not have participated at all or at a later point in time. In addition, a biobank is set up that will allow development and validation of novel noninvasive or minimally invasive tests for risk assessment and confirming presence of colorectal neoplasms

(eg, blood, stool and urine tests). The biobank with the potential biomarker analyses will be a gold mine for early detection research.

Limitations of the study also need to be acknowledged. The study population is only representing a small but representative area within Germany, namely, the Rhine-Neckar-Region, including the cities Heidelberg and Mannheim. The study can only include a certain manageable number of participants, who are provided endoscopic offers in addition to the already existing screening offers. Sample size will limit possibilities of in-depth analyses by subgroups. Long-term end points, such as CRC incidence and mortality, cannot be evaluated.

Despite its limitations, the study is expected to make a major contribution to develop more effective CRC screening strategies.

Acknowledgments

Authors' Contributions

Conflicts of Interest

None declared.

Multimedia Appendix 1
Accreditation Certificate for the DARIO Study from the German Cancer Society.
[PDF File (Adobe PDF File), 244 KB - resprot_v9i8e17516_app1.pdf]

Multimedia Appendix 2
Study Protocol, DARIO (latest version).
[PDF File (Adobe PDF File), 955 KB - resprot_v9i8e17516_app2.pdf]

Multimedia Appendix 3
Participant Information, DARIO Part I+II (latest version).
[PDF File (Adobe PDF File), 290 KB - resprot_v9i8e17516_app3.pdf]

Multimedia Appendix 4

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Participant Information, DARIO Part III (latest version).

[PDF File (Adobe PDF File), 280 KB - resprot_v9i8e17516_app4.pdf]

Multimedia Appendix 5

Informed Consent, DARIO Part I+II (latest version).

[PDF File (Adobe PDF File), 268 KB - resprot_v9i8e17516_app5.pdf]

Multimedia Appendix 6

Informed Consent, DARIO Part III (latest version).

[PDF File (Adobe PDF File), 284 KB - resprot_v9i8e17516_app6.pdf]

Multimedia Appendix 7

DARIO Questionnaire.

[PDF File (Adobe PDF File), 532 KB - resprot_v9i8e17516_app7.pdf]

Multimedia Appendix 8

Invitation Letter, DARIO Study Part I.

[PDF File (Adobe PDF File), 303 KB - resprot_v9i8e17516_app8.pdf]

Multimedia Appendix 9

Invitation Letter, DARIO Study Part II A.

[PDF File (Adobe PDF File), 760 KB - resprot_v9i8e17516_app9.pdf]

Multimedia Appendix 10

Invitation Letter, DARIO Study Part II B.

[PDF File (Adobe PDF File), 761 KB - resprot_v9i8e17516_app10.pdf]

Multimedia Appendix 11

Exclusion Letter, DARIO Part II.

[PDF File (Adobe PDF File), 600 KB - resprot_v9i8e17516_app11.pdf]

Multimedia Appendix 12

CONSORT 2010 Checklist.

[PDF File (Adobe PDF File), 146 KB - resprot_v9i8e17516_app12.pdf]

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Abbreviations

CRC: colorectal cancer
NCT: Nationalen Centrum für Tumorerkrankungen

XSL•FO
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Protocol

A Novel HIV-1 RNA Testing Intervention to Detect Acute and Prevalent HIV Infection in Young Adults and Reduce HIV Transmission in Kenya: Protocol for a Randomized Controlled Trial

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Abstract

Background: Detection and management of acute HIV infection (AHI) is a clinical and public health priority, and HIV infections diagnosed among young adults aged 18 to 39 years are usually recent. Young adults with recent HIV acquisition frequently seek care for symptoms and could potentially be diagnosed through the health care system. Early recognition of HIV infection provides considerable individual and public health benefits, including linkage to treatment as prevention, access to risk reduction counseling and treatment, and notification of partners in need of HIV testing.

Objective: The Tambua Mapema Plus study aims to (1) test 1500 young adults (aged 18-39 years) identified by an AHI screening algorithm for acute and prevalent (ie, seropositive) HIV, linking all newly diagnosed HIV-infected patients to care and offering immediate treatment; (2) offer assisted HIV partner notification services to all patients with HIV, testing partners for acute and prevalent HIV infection and identifying local sexual networks; and (3) model the potential impact of these two interventions on the Kenyan HIV epidemic, estimating incremental costs per HIV infection averted, death averted, and disability-adjusted life year averted using data on study outcomes.

Methods: A modified stepped-wedge design is evaluating the yield of this HIV testing intervention at 4 public and 2 private health facilities in coastal Kenya before and after intervention delivery. The intervention uses point-of-care HIV-1 RNA testing combined with standard rapid antibody tests to diagnose AHI and prevalent HIV among young adults presenting for care, employs HIV partner notification services to identify linked acute and prevalent infections, and follows all newly diagnosed patients and their partners for 12 months to ascertain clinical outcomes, including linkage to care, antiretroviral therapy (ART) initiation and virologic suppression in HIV-infected patients, and pre-exposure prophylaxis uptake in uninfected individuals in discordant partnerships.

Results: Enrollment started in December 2017. As of April 2020, 1374 participants have been enrolled in the observation period and 1500 participants have been enrolled in the intervention period, with 13 new diagnoses (0.95%) in the observation period and 37 new diagnoses (2.47%), including 2 AHI diagnoses, in the intervention period. Analysis is ongoing and will include adjusted comparisons of the odds of the following outcomes in the observation and intervention periods: being tested for HIV infection, newly diagnosed with prevalent or acute HIV infection, linked to care, and starting ART by week 6 following HIV diagnosis. Participants newly diagnosed with acute or prevalent HIV infection in the intervention period are being followed for outcomes, including viral suppression by month 6 and month 12 following ART initiation and partner testing outcomes.

Conclusions: The Tambua Mapema Plus study will provide foundational data on the potential of this novel combination HIV prevention intervention to reduce ongoing HIV transmission in Kenya and other high-prevalence African settings.

Trial Registration: ClinicalTrials.gov NCT03508908; https://clinicaltrials.gov/ct2/show/NCT03508908

International Registered Report Identifier (IRRID): DERR1-10.2196/16198

KEYWORDS

diagnostic tests; HIV infection; viral burden; contact tracing; highly active antiretroviral therapy; pre-exposure prophylaxis

Introduction

While some patients with acute HIV infection (AHI) remain asymptomatic, most experience an acute illness approximately 2 weeks following infection, and the majority of these patients seek urgent care [1-5]. Common symptoms of AHI include fever, joint and muscle pains, headache, fatigue, and rash, while a minority of patients have a mononucleosis-like illness with fever, sore throat, and oral ulcers [6]. In coastal Kenya, 81% of female sex workers participating in a prospective cohort experienced symptoms with seroconversion and 44% were sick enough to prevent them from working [7]. In a nearby Kenyan cohort of adults at high risk for HIV-1 acquisition, 69% of those who seroconverted had sought care at the research clinic or elsewhere due to AHI symptoms [3]. Unfortunately, most individuals who seek care in the setting of HIV-1 acquisition have not yet developed antibodies and are missed by standard HIV rapid antibody tests [8,9].

The 2012 Kenyan AIDS Indicator Survey showed a steady increase in HIV prevalence with increasing age among adults, with HIV prevalence peaking in women aged 35 to 39 years and men aged 45 to 49 years [10]. Given these data, our research team posited that identifying young adults aged 18 to 39 with AHI would be a key opportunity to interrupt ongoing transmission. Due to very high viral loads and characteristics of the infecting viral strain, AHI is a period of heightened risk for secondary HIV-1 transmission [11-14]. The proportion of transmission attributed to AHI varies with epidemic stage and other local factors but has been estimated to range from 25% to 50% in studies using viral sequences. Unfortunately, no current HIV-1 prevention guidelines in sub-Saharan Africa recommend evaluation for AHI among young adult patients

seeking care who test negative on standard rapid antibody tests [15].

While guidance exists for persons with discordant rapid antibody test results (ie, repeat testing is recommended after 2 weeks) [16], the value of demographic factors, signs, and symptoms to target AHI testing in patients with negative serologic test results has been unclear. In a study using cohort data from 4 sites in Kenya, Malawi, and South Africa, 122 AHI visits (ie, visits in which HIV-1 RNA or p24 antigen were detected in a seronegative patient who subsequently converted) were compared to 45,961 uninfected patient visits. In generalized estimating equation (GEE) modeling including signs and symptoms, age group, sex, and site, younger age (18-29 years) and reported fever, fatigue, body pains, diarrhea, sore throat, and genital ulcer disease (GUD) were independent predictors of AHI [17]. An AHI risk score was created that assigned a model-based score to each predictor, then calculated an overall risk score for each participant; GUD received a score of 3, while all other predictors received a score of 1 [17]. The performance (ie, area under the curve) for this AHI risk score overall was 0.78, with site-specific area under the curve estimates ranging from 0.61 to 0.89 [17]. A risk score of 2 or higher would indicate HIV-1 RNA testing for 15%, 26%, 50%, and 5% of risk populations in Mombasa and Kilifi, Kenya; Lilongwe, Malawi; and Durban, South Africa, respectively [17]. Sensitivity was highest for the risk score in Kilifi and Lilongwe (90.0% in Kilifi and 92.9% in Lilongwe), where the AHI risk score improved AHI detection over the published algorithms from these two sites [18,19].

In our earlier pilot study of AHI detection in Kenya, entitled Tambua Mapema (Kiswahili for "discover early"), all patients aged 18 to 29 years who met the AHI risk score criteria described above and had negative or discordant rapid antibody

test results were tested using a p24 antigen assay, then underwent repeat rapid antibody testing for HIV infection 2 weeks after first presentation [20]. This pilot study (ClinicalTrials.gov NCT01876199) was conducted from April 2013 to July 2013 at a network of 5 health facilities and 5 pharmacies selected from the 26 health facilities and 26 pharmacies located in the study area, Mtwapa/Shanzu town (total population approximately 100,000) [20]. AHI was diagnosed in 5 of 506 patients with negative or discordant rapid antibody test results who met risk criteria and were completely evaluated, for an AHI prevalence of 1.0%. Of the 5 AHI cases, 4 were diagnosed among the 241 patients with a documented fever (prevalence 1.7%), versus 1 among the 265 nonfebrile patients (prevalence 0.4%; P=.15) [20].

Now that point-of-care (POC) RNA diagnostics designed for AHI detection are becoming available, real-time AHI diagnosis before the patient leaves the clinic is within reach [21,22]. Guidance on the potential impact of targeted HIV-1 RNA or p24 antigen testing programs on the HIV epidemic in sub-Saharan Africa is therefore needed. Use of a simple algorithm based on 7 features (aged 18-29 years, fever, fatigue, diarrhea, body pains, sore throat, and GUD) to target young adults for AHI testing could substantially reduce the number of symptomatic HIV-1–seronegative patients requiring HIV-1 RNA or p24 antigen testing, while still capturing most infections among persons who present for clinical care [17]. When paired with standard rapid HIV testing to diagnose prevalent HIV infection, such a testing intervention could greatly reduce transmission among young, sexually active adults.

The Tambua Mapema Plus study aims to use an AHI risk score to identify young (aged 18-39 years), previously HIV-negative or status-unknown adults presenting to health facilities for care to undergo an HIV testing intervention using POC HIV-1 RNA followed by rapid antibody testing to differentiate acute from prevalent infection. We hypothesize that targeted evaluation for AHI among young adults who have symptoms compatible with our AHI risk score will increase rates of case finding and linkage to care relative to standard provider-initiated testing and counseling (PITC), which has not been successful at targeting this group [15]. We also hypothesize that the use of World Health Organization–recommended assisted HIV partner notification services [23] will identify additional cases of previously undiagnosed HIV infection, including small outbreaks in local sexual networks, and that enhanced HIV partner notification services using HIV-1 RNA testing will identify more infected partners than standard HIV partner notification services using rapid antibody tests. Finally, we hypothesize that the identification of previously undiagnosed acute and prevalent HIV infections will lead to a significant reduction in new HIV infections in Kenya and will be cost-effective under a range of assumptions.

Methods

Study Overview

Tambua Mapema Plus is a proof-of-concept study to determine outcomes of our health facility–based HIV-1 RNA testing intervention to identify acute (ie, RNA positive, seronegative

or discordant rapid antibody test results) and prevalent (ie, RNA positive, seropositive) HIV infection compared with standard care. A related objective has been to conduct focus group discussions with up to 60 individuals who work in the 6 health facilities where the trial has taken place (up to 10 participants per facility) to obtain their views on HIV-1 RNA testing and the research carried out at the facility, including challenges to intervention scale-up.

Secondary objectives for all individuals newly diagnosed with HIV infection during the study include (1) linkage to care and immediate antiretroviral therapy (ART), (2) partner testing, (3) barriers and facilitators, and (4) impact and cost-effectiveness.

First, we will provide linkage to care and immediate ART to determine the feasibility, acceptability, and uptake of offering immediate linkage and ART to all newly diagnosed patients with HIV in the intervention period, comparing this approach to standard care.

Second, we will conduct partner testing to determine the feasibility, acceptability, and uptake of HIV partner notification services for partner identification and testing, comparing the enhanced HIV partner notification services and HIV-1 RNA testing in the intervention period to the passive referral followed by delayed HIV partner notification services with standard HIV testing in the observation period.

Third, to identify barriers and facilitators, we will conduct qualitative in-depth interviews with up to 60 newly diagnosed patients with prevalent HIV or AHI and seronegative partners in discordant relationships to gain insights into their HIV testing experience and subsequent intervention uptake, including barriers and facilitators to ART or pre-exposure prophylaxis (PrEP) uptake and adherence in these groups.

Fourth, we will model the potential impact and cost-effectiveness of the HIV-1 RNA testing, linkage, immediate treatment, and partner notification interventions on the Kenyan HIV epidemic in terms of incremental costs per HIV infection averted, death averted, and disability-adjusted life years (DALYs) averted, using data on standard care outcomes from the observation period and data on intervention outcomes from the intervention period.

Full details on the procedures for these secondary objectives are included in Multimedia Appendix 1.

This protocol was prepared in accordance with Standard Protocol Items: Recommendations for Interventional Trials guidelines and is registered with the National Institutes of Health Division of AIDS Protocol Registration Office (DAIDS-ES Document Number: 38181) and with ClinicalTrials.gov (NCT03508908). All consents and additional details not found in this summary protocol can be found in the full published protocol.

Study Design

A modified stepped-wedge design has been used to evaluate the yield of the HIV-1 RNA testing intervention at 4 public and 2 private health facilities in Kenya before (1375 patients) and after (1500 patients) intervention delivery. We chose a modified stepped-wedge trial design for the following reasons: (1) we

predicted that the intervention would do more good than harm and (2) for logistical reasons, it was not practical to deliver the intervention simultaneously to all participants. Rolling out the intervention in a staggered fashion ensured that there was adequate time for individual site preparation and staff training as well as oversight of study activities. This study has therefore been conducted in 2 phases at each site.

Observation Period

The first phase was an observation period, in which all testing and treatment was conducted per Kenyan Ministry of Health guidelines and primary care clinician judgment. Young adults aged 18 to 39 years seeking care at primary health care clinics who had never been diagnosed with HIV and had a risk score of 2 or higher were offered participation. HIV testing was only done if ordered by the primary care clinician and was carried out according to standard care in Kenya, which currently misses AHI cases. Research procedures in the observation period consisted of a computer-assisted self-interview (CASI)/computer-assisted personal interview (CAPI) at baseline for all participants. Participants found to be HIV negative and those not tested ended their participation at the baseline visit. Those diagnosed HIV positive had a follow-up home visit at 6 weeks. The 6-week visit included a second CASI/CAPI and an assessment of linkage to care and treatment and of partner notification. Those who had not yet notified partners at this time point were offered standard HIV partner notification services [23]. Partners of observation phase HIV-positive participants (ie, index patients with prevalent HIV infection) were offered referrals for risk reduction counseling and for HIV care, if infected.

Intervention Period

In the intervention period, two major interventions were evaluated: testing for acute and prevalent HIV infection (primary objective) and enhanced HIV partner notification services using our HIV-1 RNA testing intervention (secondary objective). For the HIV-1 RNA testing intervention, a blood sample was obtained and tested for AHI using the Xpert HIV Qual assay (Cepheid Inc), with testing conducted on-site at the health facility where the participant was recruited and enrolled. This assay has been found to be easy to use and feasible in a community-based facility with limited or no laboratory infrastructure [24]. For participants in whom HIV-1 RNA was detected, a laboratory technician conducted rapid antibody testing (currently Determine; Abbott Laboratories and First Response; Premier Medical Corp) in accordance with Kenyan HIV testing guidelines. Test results were provided to participants

in real time, with posttest counseling by research staff and detailed documentation of results.

As in the observation period, young adults aged 18 to 39 years seeking care at primary care clinics who had no history of HIV and who had a risk score of 2 or higher were offered enrollment into the intervention period. All intervention participants underwent the HIV testing intervention, which consisted of testing for HIV-1 RNA initially, followed (if positive) by 2 rapid antibody tests. Those who tested HIV negative ended participation at the baseline visit after the CASI/CAPI, as above. Those who tested HIV positive (either AHI or prevalent case) were offered enhanced HIV partner notification intervention and linkage to an ART cohort at Kenya Medical Research Institute (KEMRI) with 12 months of follow-up. Those who declined follow-up at KEMRI ended their participation at a 6-week home visit (as described above for the observation period). Those who tested HIV positive were also offered participation in qualitative interviews, which they could accept or decline without influencing other components of the study.

Partners of intervention phase participants with HIV (ie, index patients with newly diagnosed acute and prevalent HIV infection) were offered the HIV-1 RNA testing intervention (as described for participants in the intervention phase above) and enrollment into the KEMRI ART cohort or a PrEP cohort with 12 months of follow-up, depending on their test results. In the intervention period, partners newly diagnosed with HIV through the enhanced HIV partner notification intervention were also offered the enhanced HIV partner notification intervention to identify and test their partners. Identified partners of these individuals were offered the same options as partners of index patients diagnosed in the stepped-wedge trial.

Study Sites

Our HIV-1 RNA testing intervention network included both public and private health facilities in a large periurban area (population >100,000) in coastal Kenya (Figure 1). This area, known for its busy nightlife, sex work, and tourist industry, has been the site of a KEMRI HIV/sexually transmitted infection research clinic since 2005. We selected 6 health facilities (4 public, 2 private) for inclusion in this study due to their size, central location (within 20 kilometers of our KEMRI research clinic in Mtwapa), patient volume (>500 patients aged 18-39 years seen over 3 months), availability of HIV rapid antibody testing on-site, availability of a private room for consenting participants, and willingness to collaborate with the research team.

Figure 1. Map of Tambua Mapema Plus study sites.
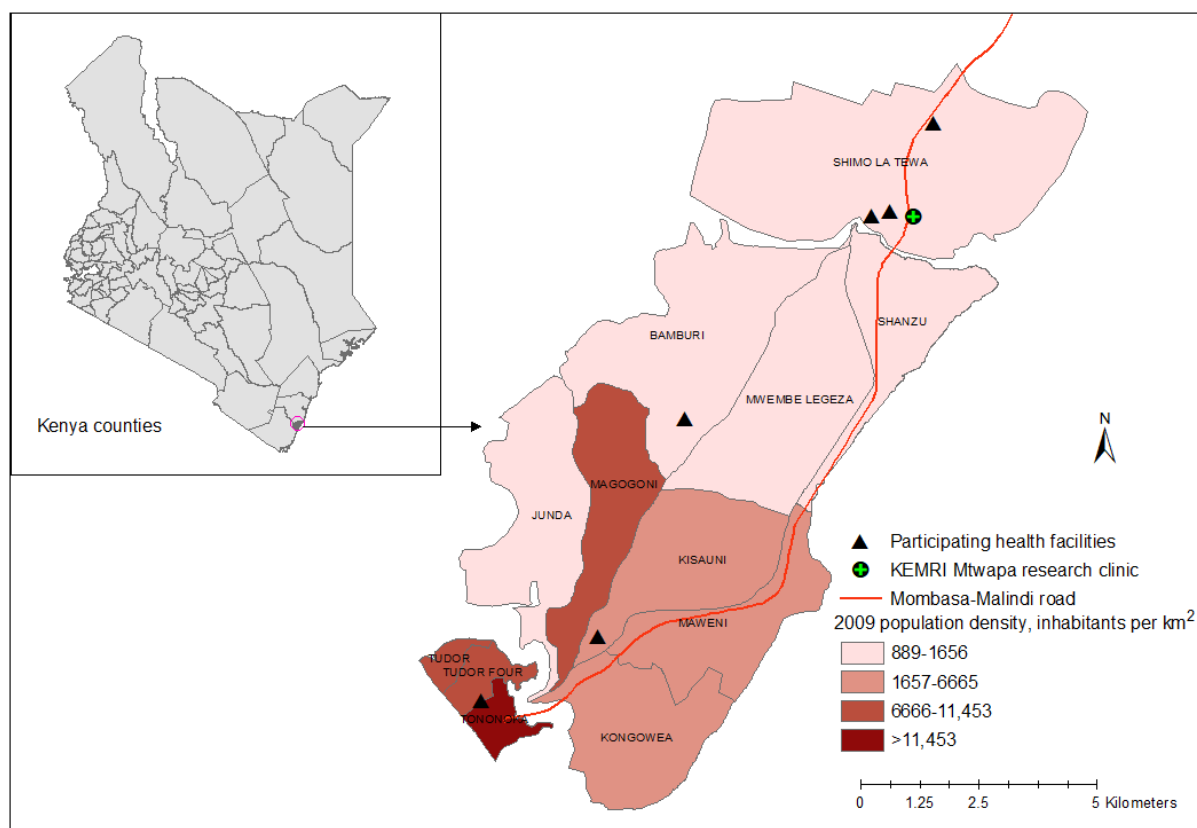
Randomization

Before study initiation, the 6 participating clinics were randomized into observation and intervention periods, as presented in Figure 2. Opening of the observational phase at each site was staggered in 3-month intervals so that no more than two sites would be in each phase at any given time. Each phase lasted 6 months per site, with the exception of the first site, which had only 3 months of observation to allow the study to proceed more efficiently.

Figure 2. Stepped-wedge design at 6 sites. I: intervention; O: observation.

Clinic	Month							
	0-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24
Site 1	O	I	I					
Site 2	O	O	I	I				
Site 3		O	O	I	I			
Site 4			O	O	I	I		
Site 5				O	O	I	I	
Site 6					O	O	I	I
Participants enrolled, n	250	375	500	500	500	375	250	125

Randomization was performed using a random number generator to assign each clinic to one of the 6 positions, with stratification by facility type (public vs private). Due to practical limitations, allocations were unblinded. We recruited 125 participants per clinic per 3-month time block, for 2875 total participants (1375 in the observation period and 1500 in the intervention period). By the end of the trial, each facility has undergone an observation period of 3 to 6 months and received the

intervention for 3 to 6 months. Thus, each health facility or cluster acts as its own control, with comparison of the patients enrolled during the observation period with those enrolled during the intervention period. Using this design, we can model the effect of time on the intervention, adjusting for temporal variations in HIV incidence [25,26].

Inclusion and Exclusion Criteria for the Stepped-Wedge Trial

Eligibility criteria for participation in the stepped-wedge trial included (1) aged 18 to 39 years; (2) not previously diagnosed with HIV infection; and (3) a score of 2 or higher on our risk score algorithm [17] used to identify persons at higher risk for AHI, with scoring as follows: aged 18 to 29 years (1 point), fever (1 point), fatigue (1 point), body pains (1 point), diarrhea (1 point), sore throat (1 point), and GUD (3 points).

Eligibility criteria for partners of newly diagnosed patients with prevalent or acute HIV included (1) aged 18 years or older and (2) not previously diagnosed with HIV infection. Patients not meeting inclusion criteria or those who were not willing or able to participate (eg, due to illness or time constraints, or at the discretion of the study clinician) were excluded. Individuals at high risk for intimate partner violence (IPV) were excluded from the enhanced HIV partner notification intervention but eligible for all other components of the study. While sex work and other high-risk sexual behaviors were not part of the eligibility criteria for the study, data on sexual risk behavior were collected from all eligible patients.

Inclusion Criteria for Staff Focus Group Discussions

Focus groups were held for up to 60 staff members at the 6 participating health facilities (up to 10 participants per facility). These individuals could work in any role but were required to have the following characteristics in order to participate: aged 18 years or older, planning to remain with the facility for the duration of trial implementation at that site, and willing to provide views on the detection of AHI and the research carried out at the facility, including challenges to intervention scale-up. Most participants were medical or clinical officers, nurses, laboratory technicians, or counselors.

Recruitment for the Stepped-Wedge Trial

Eligible participants were recruited from among young (aged 18-39 years) adults who presented to any of the 6 health facilities in our HIV testing network. At each facility, we aimed to enroll 2 to 4 participants per day, for a minimum of 10 and maximum

of 20 participants per week. Staffing schedules were developed in collaboration with each health facility, with a goal to ensure that recruitment targets were attained and that a range of time periods (eg, daytime, evening, weekend) were covered. While research staff were present at the facility, patients in the target age range were approached consecutively for study screening.

After obtaining verbal permission from the patient, facility clinicians or research staff present in the clinical room screened patients to determine eligibility and asked if they were willing to discuss participation with the research team after their consultation. The screening form (Multimedia Appendix 2) included a permission script to be read to potential participants and a space for research staff to initial that verbal consent for screening was provided. If a patient refused screening, only sex and estimated age were recorded; no identifying information was obtained during screening. All screening outcomes (ie, screening refused, screened out, screened in but refused participation, screened in and consented) were documented using the screening form. Facility clinicians then provided symptom-directed treatment to patients as per standard care and current Kenyan guidelines.

Upon completion of the consultation and before any HIV testing was conducted, patients who met eligibility criteria were approached by the research team and invited to participate in the study. Individuals recruited during the intervention period were shown a 2-minute, institutional review board–approved explainer video that presented the study rationale and overview in English or in Kiswahili [27]. Patients were then consented by research staff, who explained the purpose and design of the study, taking care to inform patients that participation was voluntary and would not influence their access to diagnostic testing or care.

Stepped-Wedge Trial and Procedures for Newly Diagnosed Participants

Figure 3 provides a flow diagram of procedures in the observation period and intervention period. A schedule of procedures for each period can be found in Multimedia Appendix 1, which also details procedures for all newly diagnosed participants in the intervention period, including 12-month follow-up in an ART cohort with periodic in-depth interviews, as well as enhanced HIV partner notification. Uninfected regular partners of newly diagnosed study participants were invited to 12-month follow-up in a PrEP cohort with periodic in-depth interviews.

Figure 3. Flow diagram of observation and intervention periods. ART: antiretroviral therapy; CAPI: computer-assisted personal interview; CASI: computer-assisted self-interview; HPN: HIV partner notification services; KEMRI: Kenya Medical Research Institute; PITC: provider-initiated testing and counseling; PrEP: pre-exposure prophylaxis.
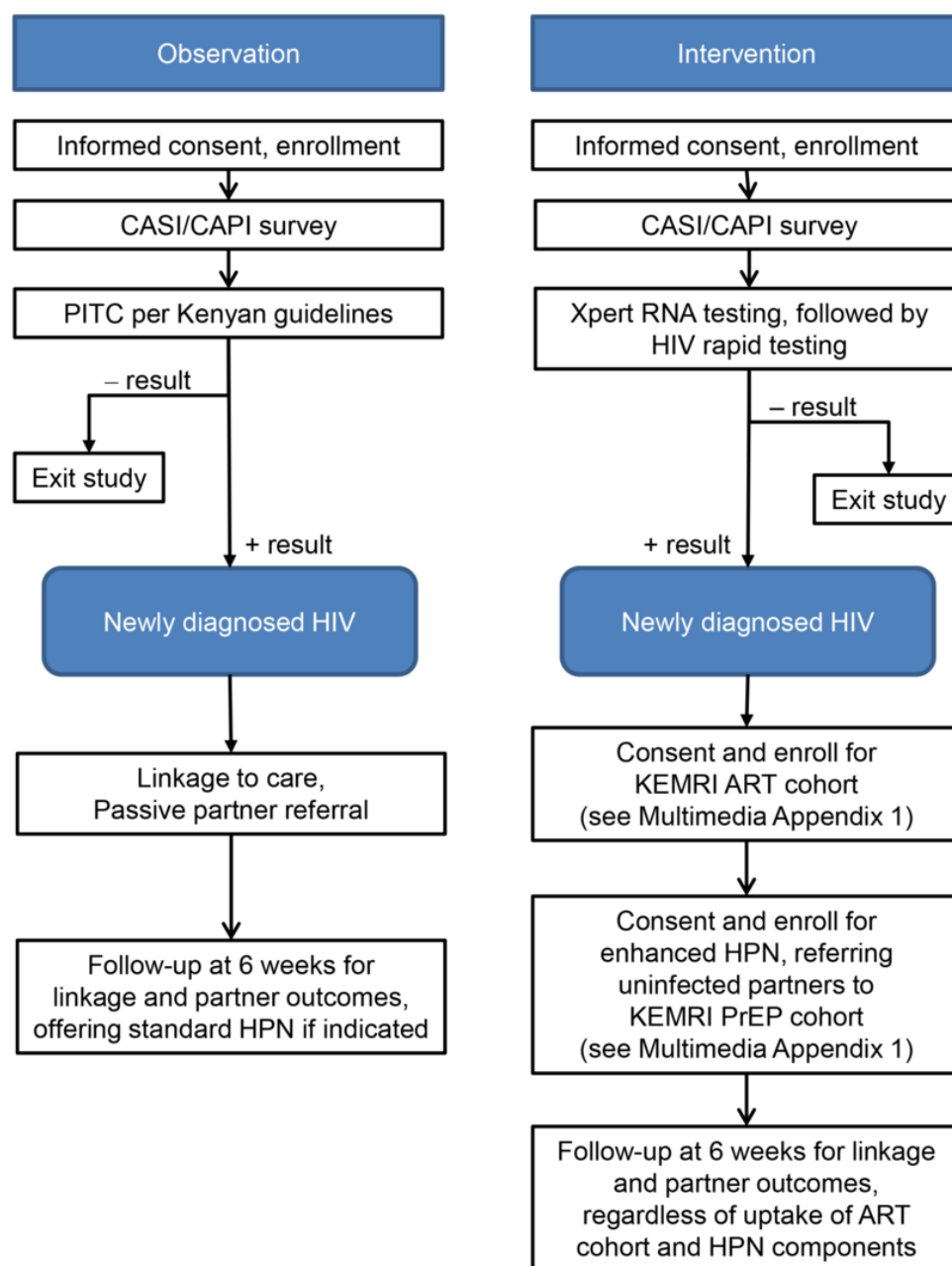
Observation Period: Enrollment Visit

Consenting patients took a brief CASI or CAPI (≤20 minutes) on a handheld tablet computer. This survey, included in Multimedia Appendix 3, captures demographic information, onset of illness, and data on sexual behavior, including partner numbers (with detailed questions on the 3 most recent partners), relational timing (ie, concurrent vs sequential), transactional sex, and same-sex behavior. After the CASI/CAPI, research staff answered any questions about the CASI/CAPI and offered counseling as needed, then helped participants who had a request form for PITC to find the laboratory. PITC results were recorded, and facility staff referred patients with a positive result to care, as per their standard practice. At the conclusion of their study visit, participants were asked about the last time they

tested for HIV, as well as costs they incurred for the health facility visit. All study participants who were newly diagnosed with HIV in the study were asked for contact details in order to arrange a 6-week follow-up visit. Research staff stressed the importance of linking to care, the availability of ART regardless of cluster of differentiation 4 cell count, and the need to inform partners that they should be tested.

Observation Period: 6-Week Follow-Up Visit

Individuals with a new diagnosis of HIV infection made in the observation period were visited in person or seen at the health facility from which they were recruited 6 weeks after diagnosis to repeat the CASI/CAPI and ascertain data on linkage to care, ART status, and partner notification outcomes. Linkage was verified by demonstration of a clinic registration card, and ART

status was confirmed by demonstration of a regimen card or the patient's pills. Partner notification outcomes were self-reported by the index patient. Participants who had not linked to care, started ART, or disclosed their HIV status were offered counseling and referrals at this time. At the conclusion of this data collection and counseling, these index patients were offered standard HIV partner notification services [23]. For those who accepted, standard rapid antibody testing was offered to all identified and successfully contacted partners.

Intervention Period: Enrollment Visit

After consent was obtained, research staff drew a 4-mL blood sample from participants for intervention HIV testing (ie, HIV-1 RNA followed by rapid tests, as described above). During wait time for this testing (up to 90 minutes), participants took the brief CASI/CAPI survey described above. After the CASI/CAPI, research staff answered any questions about the CASI/CAPI and offered counseling as needed, then helped patients with an order for lab tests other than an HIV test to find the facility laboratory. HIV test results were provided to participants in real time, with posttest counseling by KEMRI research staff; results were also shared with the facility clinician. At the conclusion of their study visit, participants were asked about the last time they tested for HIV, as well as costs they incurred for the health facility visit. All study participants who were diagnosed with acute or prevalent HIV infection by the KEMRI research team were asked for contact details in order to arrange a 6-week follow-up visit. Linkage to KEMRI ART cohort participation or care at a nonresearch facility of their choice was also offered at this time, and an IPV assessment previously used in Kenya [28] was conducted to determine eligibility for the enhanced HIV partner notification intervention.

Intervention Period: 6-Week Follow-Up Visit

Individuals with a new diagnosis of HIV infection made in the intervention period were visited in person or seen at the KEMRI research clinic 6 weeks after diagnosis to repeat the CASI/CAPI and ascertain data on linkage to care, ART status, and partner notification outcomes. Linkage was verified by demonstration of a clinic registration card, and ART status was confirmed by demonstration of a regimen card or the patient's pills. Partner notification outcomes were self-reported by the index patient. Of note, additional data were available on linkage, ART status, and partner notification outcomes for patients participating in the enhanced HIV partner notification intervention or the ART cohort. However, the 6-week follow-up visit served to document outcomes at the same time point in all trial participants, regardless of their uptake of other components of the Tambua Mapema Plus intervention package.

Views of Health Facility Staff

We held focus group discussions with up to 60 facility staff (10 in a single group at each participating facility) before and after the intervention was conducted. KEMRI research staff scheduled focus group discussions at facilities or at an off-site location, depending on facility and staff preferences. Before the intervention was delivered, facility staff members were asked about their general views on HIV testing, who is usually targeted for testing, and constraints to testing in their clinic. After these topics were addressed, participants were asked about the importance of early detection of HIV infection and the prevention of transmission through finding and testing partners of newly diagnosed individuals. After the intervention, we asked participants about the impact the Tambua Mapema Plus study had on the health facility in general and any challenges encountered during the study. We also asked their views about what factors might make it easier or more difficult to scale up a similar intervention in other health facilities in Kenya. Focus group discussions were led by a KEMRI research team member, with a second member present for note taking. When participants agreed to this, focus group discussions were tape-recorded. Multimedia Appendix 4 includes the topics that guides used for focus group discussions before and after the intervention.

Ethical Considerations

Risks of study participation consist mainly of social harms involving a breach of confidentiality. Especially with respect to the enhanced HIV partner intervention, IPV, or physical, sexual, or psychological harm by a current or former sexual partner, there is a potential risk at the initial health facility visit or at any time during cohort follow-up. The study team collects data on social harms, which are reported using a study-specific incident report form. In the event that a participant reports a social harm, every effort is made to provide appropriate care and counseling to the participant, either by the study team or through a referral as indicated. Research staff have been trained on counseling and the provision of referrals to counseling and social service support. While maintaining participant confidentiality, KEMRI may also engage their community representatives in exploring the social context surrounding instances of social harm in order to mitigate harm and minimize recurrences. Special monitoring on a weekly basis is undertaken for participants at moderate risk for IPV, and a protocol safety review team monitors for IPV. Stopping rules for the study will be activated if more than 3 episodes of physical IPV are reported at a single study site or more than 5 episodes are reported in the study overall.

This protocol was approved by the KEMRI Scientific and Ethics Review Unit (No. 3280), the University of Washington Human Subjects Division (STUDY00001808) and the Oxford Tropical Research Ethics Committee (Protocol 46-16). All participants provided written informed consent using a consent form specific to the relevant study component. Participants were reimbursed for study participation according to local norms in Kenya (KSh 350-500, or US $3.26-$4.68), depending on visit type and duration). A community advisory board provided study oversight, with input from local KEMRI community representatives at regular meetings.

Sample Size Considerations

The trial is powered for the stepped-wedge design. Based on our pilot work, we estimated that 50% to 60% of adults aged 18 to 39 years at the 6 participating facilities would be eligible for the study, and approximately 50% to 80% of these would accept study participation. Our preliminary data showed that approximately 2% of young adults in this age range were diagnosed with prevalent HIV-1 infection under standard care [15], while approximately 5% were newly diagnosed with acute

(1%) or prevalent (4%) HIV-1 infection when testing for both HIV-1 antigen and antibodies was routinely delivered [20]. If these estimates are correct, with 1375 participants in the observation period and 1500 participants in the intervention period and a type I error probability of 0.05, assuming a coefficient of variation (k) of 0.25, we will have more than 90% power to reject the null hypothesis that the HIV diagnosis rates for experimental and control subjects are equal [26]. This power is more than adequate for multivariable analysis related to the testing of this null hypothesis. Because facilities do not have the laboratory capacity to diagnose HIV before seroconversion

during the observation period, the base rate of AHI detection is 0, and power to detect AHI during the intervention period is greater than 90% even if AHI prevalence is well below 1%. Table 1 presents power for a range of coefficients of variation and acute and prevalent HIV prevalence in the intervention period, given our chosen sample size. Accounting for correlation within sites (ie, facilities participating in the randomized trial), precision for the estimated rate of AHI detection is within 0.54%, assuming a prevalence of 1% and k of 0.25; if AHI prevalence is 2%, precision will be within 0.81%.

Table 1. Power for evaluation of null hypothesis that HIV diagnosis rates are equal.

Diagnosed HIV prevalence, observation period	Diagnosed HIV prevalence, intervention period	k	Power
2.0%	5.0%	0.20	94.4%
2.0%	4.3%	0.20	82.2%
2.0%	5.0%	0.25	93.0%
2.0%	4.3%	0.25	80.0%
2.0%	5.0%	0.30	91.4%
2.0%	4.3%	0.30	77.3%
2.0%	5.0%	0.35	89.4%
2.0%	4.3%	0.35	74.6%

Data Analysis Plan

In general, P values of $P<.05$ will be considered significant; however, in analyses in which multiple null hypotheses are tested, P values will be adjusted using the Holm-Bonferroni method. Planned work to model the impact and cost-effectiveness of this HIV-1 RNA testing intervention is detailed in Multimedia Appendix 1.

HIV Testing Uptake and Diagnoses

We will compare the age and sex of individuals who accept versus refuse screening, using 2-tailed Student t and chi-square tests. In addition, we will tally reasons for refusal to participate among those eligible and compare eligible individuals who refuse versus consent to study enrollment, using chi-square or Fisher exact tests for categorical variables and Student t tests or Mann-Whitney U tests for continuous variables. Proportions of individuals who accept screening, are determined eligible, and enroll will be presented with exact binomial confidence limits. We will compare the proportion of patients with the following outcomes in the observation and intervention periods: (1) tested for HIV infection, (2) newly diagnosed with prevalent HIV infection (ie, HIV seropositive), and (3) newly diagnosed with AHI. Because we expect 0 AHI cases in the observation period, we will use a combined outcome (ie, newly diagnosed acute or prevalent HIV-1) to model the effect of the intervention so that models will converge. We will conduct analyses on the individual-level data, using log-binomial GEE models to account for clustering by health facility. We will use a small-sample variance correction to handle the small number of clusters [29]. Models will include indicator variables for calendar time period to control for trends in HIV incidence in the study area.

We will compare baseline characteristics between individuals in the observation and intervention groups, using chi-square or Fisher exact tests for categorical variables and Student t tests or Mann-Whitney U tests for continuous variables. Where imbalances are identified, we will control for these potential confounders in secondary analyses using GEE models, as above. We will also conduct exploratory analyses to identify predictors of the combined outcome (ie, newly diagnosed acute or prevalent HIV-1) in the intervention group, including age, sex, marital status, symptom or symptoms reported, sex of partners, number of partners, condom use, transactional sex work, and other risk behaviors. We will test for interactions between the intervention and other variables, such as sex, and will present stratified analyses if meaningful interaction is observed.

Views of Health Facility Staff

Audiorecordings of the focus group discussions will be transcribed verbatim; identifying information will be omitted from transcripts. Transcribed focus group discussions will be entered into NVivo (QSR International), and analysis will aim to identify and categorize knowledge, attitudes, and contextual factors associated with PITC in general and the HIV-1 RNA testing intervention evaluated specifically. Views related to HIV testing compared with other facility laboratory testing, such as testing for malaria, will be identified. Data analysis will be iterative and include open coding, axial coding, marginal remarks, comparisons, and memo writing. Themes will be analyzed and triangulated using a grounded theory framework.

Results

Study enrollment started in December 2017. As of April 2020, 1374 participants were enrolled in the observation period (1 participant was excluded due to a protocol violation) and 1500

participants were enrolled in the intervention period. During the observation period, 3368 of the 3382 patients approached (99.59%) accepted screening, of whom 1495 (44.39%) were eligible. Of the 1495 eligible patients, 1374 enrolled (91.91%). During the intervention period, 4889 of 4895 patients approached (99.88%) accepted screening, of whom 1818 (37.19%) were eligible. Of the 1818 eligible patients, 1500 enrolled (82.51%). There were 13 new HIV diagnoses (13/1374, 0.95% of those enrolled; 13/382, 3.4% of those tested) in the observation period and 37 new HIV diagnoses (37/1500, 2.47% of those enrolled and tested) in the intervention period. Of the 37 diagnoses in the intervention period, 2 were AHI diagnoses (5%). Linkage to care and ART by week 6 was successful for 9 of the 13 (69%) newly diagnosed patients in the observation period and for 33 of the 37 (89%) newly diagnosed patients in the intervention period. No IPV episodes related to study participation were reported by participants in either study period.

Analysis is ongoing and will include adjusted comparisons of the odds of being tested for HIV infection and of being newly diagnosed with prevalent or acute HIV infection by the HIV-1 RNA testing intervention, as well as adjusted comparisons of the odds of being linked to care and starting ART by week 6 following HIV diagnosis in the observation and intervention periods. Reporting will follow the recently published Consolidated Standards of Reporting Trials guidelines for stepped-wedge trials [30]. Qualitative analysis of staff focus groups will identify barriers and facilitators to facility-based HIV testing, views on the detection of AHI, and views on the HIV-1 RNA testing intervention carried out at the 6 health facilities, including challenges to intervention scale-up.

Follow-up in the ART and PrEP cohorts is ongoing and will end in March 2021. Additional analysis related to these cohorts will include evaluation of outcomes, including viral suppression by month 6 and month 12 following ART initiation, retention on and adherence to PrEP by month 6 and month 12 following PrEP initiation, and partner testing outcomes (ie, number of partners reported, successfully contacted, tested, newly diagnosed, and engaged in care with ART or PrEP as indicated). Qualitative analysis of participant interviews will identify barriers and facilitators to HIV testing uptake, HIV partner notification uptake, ART uptake and adherence, and PrEP uptake and adherence.

As cohort follow-up continues, modeling and cost-effectiveness analyses are planned, as detailed in Multimedia Appendix 1. Modeling outputs will include HIV infections averted, life years gained, DALYs averted, costs per HIV infection averted, costs per death averted, and costs per DALY averted. Impact and cost-effectiveness will be evaluated by comparing these outputs for standard care (observation period) to these outputs for the HIV-1 RNA testing intervention (intervention period).

Discussion

In this stepped-wedge trial of a novel HIV-1 testing intervention, acceptance of screening was high (>99% in both periods; 3368/3382, 99.59% in the observation period and 4889/4895, 99.88% in the intervention period), and enrollment rates among those eligible was only somewhat lower in the intervention

period (1500/1818, 82.51%), when HIV testing was performed for all patients, compared with the observation period (1374/1495, 91.91%), when decisions about HIV testing were left to the facility clinician. The proportion of participants newly diagnosed with HIV in the intervention period (37/1500, 2.47%) was higher than the proportion diagnosed in the observation period (13/1374, 0.95%), although it was lower than the proportion diagnosed among participants selected by providers for testing in the observation period (13/382, 3.4% of those who received PITC). There were 2 AHI cases diagnosed among the 37 total diagnoses in the intervention period, making up 5% of all cases diagnosed by the testing intervention. Linkage to care was high (33/37, 89%) in the intervention period, when intensive linkage to care procedures were in place, compared with linkage to care in the observation period (9/13, 69%), when standard referral was used. Data analysis that accounts for clustering within facilities is ongoing, and more detailed results will be presented by the end of 2020.

In the 2012 AIDS Indicator Survey, around the time this study was proposed, Kenya had an adult HIV prevalence of 5.6% [10], and most (53%) seropositive individuals were unaware of their status, presenting a major challenge for epidemic control [31]. Expanded testing efforts are critical in order to attain the Joint United Nations Programme on HIV/AIDS (UNAIDS) 90-90-90 targets, which stated that by 2020, 90% of all people living with HIV should know their HIV status, 90% of those who test positive should be provided therapy, and of those, 90% should achieve virologic suppression [32]. We believed that such outreach should take advantage of the care-seeking behavior of adults who acquire HIV-1 in sub-Saharan Africa. For example, in our study of 72 participants who acquired HIV-1 while participating in a prospective cohort in coastal Kenya, 54 (75%) reported fever and 50 (69%) had sought care for symptomatic illness, including 23 (32%) who sought care in a nonresearch setting [3]. Of note, 29 of the 72 (40%) patients received presumptive malaria treatment, suggesting that AHI is frequently misdiagnosed as malaria in Kenyan health facilities [3].

In the Tambua Mapema Plus study, we detected fewer AHI and prevalent HIV cases than predicted based on our earlier work. This may be a result of falling HIV incidence in Kenya, as the 2018 Kenya Population-based HIV Impact Assessment reported a decline in HIV incidence among adults aged 15 to 64 years from 0.5% in 2012 to 0.14% in 2018 [33]. Kenya has also made great progress on HIV testing; in its 2019 report, UNAIDS estimated that 89% of Kenyans of all ages who are living with HIV are aware of their status [34]. Of note, individuals known to have HIV infection were excluded from this study.

Detection and management of AHI has been called a "clinical and public health emergency" [14] and a "common occurrence overlooked" [35]. POC HIV-1 RNA testing is becoming more available in sub-Saharan Africa and has multiple clinical uses, including viral load monitoring, early infant diagnosis, and AHI detection [36]. Because the cost of HIV-1 RNA testing is considerable, detection of AHI in resource-limited countries should be targeted using algorithms that identify at-risk individuals [37]. The Tambua Mapema Plus study will provide foundational data on the potential of this novel combination

HIV prevention intervention to reduce ongoing HIV transmission in Kenya and other high-prevalence African settings through the detection of AHI and prevalent HIV infection among young adults aged 18 to 39 years presenting to health facilities with symptoms of acute infectious illness. If our novel intervention proves cost-effective and promising in terms of reducing HIV-1 transmission, we will use these data to design further research focusing on implementation of the intervention, including barriers and facilitators to its success. If the use of HIV-1 RNA testing should prove too costly, we can still analyze the impact of scaling up rapid tests, which were part of our novel testing intervention. PITC at health facilities contributes the majority of new HIV diagnoses in most contexts in sub-Saharan Africa [38], yet innovations in health facility–based HIV testing are urgently needed to increase testing rates. Recently, the use of oral self-testing has been shown to increase HIV testing in health facilities [39]. It is our hope that analysis of the Tambua Mapema Plus trial data and our planned modeling and cost-effectiveness analysis efforts will make an important contribution to the optimization of facility-based HIV testing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Detailed Procedures for Secondary Outcomes.
[DOCX File , 71 KB - resprot_v9i8e16198_app1.docx]

Multimedia Appendix 2
Tambua Mapema Plus Eligibility Form.
[DOCX File , 29 KB - resprot_v9i8e16198_app2.docx]

Multimedia Appendix 3
Computer-assisted self-interview/Computer-assisted personal interview.
[DOCX File , 48 KB - resprot_v9i8e16198_app3.docx]

Multimedia Appendix 4
Focus group topic guides.
[DOCX File , 52 KB - resprot_v9i8e16198_app4.docx]

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Abbreviations

AAS: African Academy of Sciences
AHI: acute HIV infection
ART: antiretroviral therapy
CAPI: computer-assisted personal interview
CASI: computer-assisted self-interview
DALY: disability-adjusted life year
DELTAS: Developing Excellence in Leadership, Training and Science
GEE: generalized estimating equation
GUD: genital ulcer disease
IPV: intimate partner violence
KEMRI: Kenya Medical Research Institute
NIAID: National Institute of Allergy and Infectious Diseases
PITC: provider-initiated testing and counseling
POC: point of care
PrEP: pre-exposure prophylaxis
UNAIDS: Joint United Nations Programme on HIV/AIDS

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Protocol

Effectiveness of Combining Organizational Alcohol Policy and Skills Training for Managers to Reduce Hazardous Alcohol Consumption in Swedish Workplaces: Study Protocol for a Cluster Randomized Study

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Abstract

Background: High alcohol consumption poses risks to individual health and society. Previous alcohol interventions have mainly focused on high-risk consumers or young adults in school-based settings. Since the majority of the adult population is in the workforce, the workplace can be considered a favorable arena for implementing interventions.

Objective: This protocol describes a project aimed at increasing knowledge of the effectiveness of combining the implementation of an organizational alcohol policy with skills training for managers as a workplace alcohol prevention program, by evaluating the intervention and exploring managers' perceptions of the intervention.

Methods: Organizations with at least 100 employees were invited to take part in the project. A total of 11 organizations (744 managers and 11,761 employees) were included in the project. Data are collected through self-administered online surveys at baseline, 12 months, and 24 months. The primary outcome is managers' inclination to initiate an early alcohol intervention (eg, by initiating a dialogue) when concern regarding employees' hazardous alcohol consumption arises. The secondary outcomes of interest are managers' and employees' organizational alcohol policy knowledge and changes in alcohol consumption, as measured using the Alcohol Use Disorder Identification Test (AUDIT) score. A linear mixed-model framework will be used to model variability on different levels. Primary analysis will follow an intention-to-treat approach. Additionally, managers' responses from semistructured interviews will be analyzed using thematic analysis to explore managers' experiences regarding the prevention program.

Results: This study is ongoing. The overall study start was on January 2018, and the study is planned to end in December 2020. Baseline and 12-month follow-up measurements have been collected.

Conclusions: This project is designed to evaluate the effectiveness of an alcohol prevention program regarding higher inclination to initiate early alcohol interventions after policy implementation and skills training among managers, compared to the usual practices in the workplace. The results from this study can contribute to increased knowledge about alcohol interventions and future prevention programs in the workplace.

Trial Registration: ISRCTN17250048; http://www.isrctn.com/ISRCTN17250048

International Registered Report Identifier (IRRID): DERR1-10.2196/17145

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Introduction

High alcohol consumption poses risks not only to individual health [1-3] but it may also lead to detrimental effects in the society [4,5]. In Sweden, although a decrease in alcohol consumption is observed among the younger population, older adults have shown the opposite trend over the past few decades [6,7]. For example, the Public Health Agency of Sweden reported that 13% of women and 20% of men (>16 years old) are classified as hazardous alcohol consumers [6].

The majority of existing interventions have been conducted in health care settings and social services, which often focus on high-risk individuals aiming at reducing their alcohol consumption [8,9]. However, since the majority of adults neither consume a harmful amount nor have an alcohol dependence, those with a low to moderate consumption are often overlooked [10]. Some of the adverse effects include increased rate of injuries [1] and economic losses (absenteeism and presenteeism) [11,12]. Given the costs stemming from high alcohol consumption, the workplace may be an appropriate setting for preventive strategies. However, previous studies often focused on young adults in school-based settings [13,14], and workplace-based prevention programs have solely been conducted outside of Sweden [5,15-17].

Considering that workers with high alcohol consumption are often identified at a later stage, such as after the occurrence of adverse effects, many workplace-based interventions employ brief intervention (BI) strategies aiming to reduce alcohol consumption. Some workplaces conduct BI with various methods, including motivational approaches and personalized feedback [18-20], which are often combined with alcohol screening. Moreover, some workplaces conduct alcohol screening or monitoring prior to or during employment. Although screening and monitoring can reduce harmful alcohol consumption, it only shows effectiveness in the short-term. Conversely, an organizational alcohol policy could be effective in the long-term, especially in workplaces with limited resources [16]. However, it may be counterproductive if not implemented properly.

From a public health perspective, a preventive strategy is a focal point of interest for many reasons. Based on Rose's Prevention Paradox theory — that the effects of a prevention program are greatest when it is targeted at the population at large rather than high-risk individuals [21] — the workplace can help reach hazardous consumers while reducing the risk of stigmatization. Many workplace alcohol preventive interventions aimed at reducing alcohol consumption target high-risk consumers by combining BI and screening, a combination that could be effective in some sectors [18,22]. Based on previous literature, some workplace sectors, such as construction, hospitality, and transport sectors, have an overrepresentation of high alcohol consumption [23]. Therefore, it is of interest to examine whether these sectors would benefit from an alcohol preventive intervention targeting the whole workplace. For instance, a recent study conducted in Australian manufacturing organizations investigated whether a multicomponent preventive intervention (organizational policy and skills development among managers) could effectively identify hazardous alcohol consumers at an early stage [17]. Even though Pidd et al [17] concluded that the program was not effective in reducing alcohol consumption, it raised awareness of the negative consequences of alcohol consumption, not only for individual's health but also for the workplace as a whole.

Given that the implementation of an organizational alcohol policy is recommended in Swedish workplaces [24], the combination in terms of improving managers' skills to identify hazardous alcohol consumption is still deficient. By collaborating with an organization that provides substance-related prevention services to workplaces (Alna), this project evaluates a multicomponent alcohol prevention program, which includes development of an organizational alcohol policy and skills training for managers. Specifically, the prevention program aims to contribute to knowledge about the potential effects of the combination of an organizational alcohol policy and managers' skills development in the workplace. In addition, we hypothesize that the prevention program will result in (1) managers reporting an increased inclination to initiate an early alcohol intervention when concern or suspicion of hazardous alcohol consumption arises; (2) an increase in employees' knowledge on organizational alcohol policy, guidelines, and support regarding hazardous alcohol consumption; (3) an increased number of early interventions (eg, initiate a dialogue) to help employees with hazardous consumption of alcohol and other substances; (4) more sustainable alcohol consumption both among managers and employees, as measured using the Alcohol Use Disorder Identification Test (AUDIT) score; (5) a reduction in the number of cases of hazardous alcohol consumption among managers and employees, as measured with the AUDIT score; and (6) increased confidence among managers in handling hazardous alcohol consumption in the workplace.

Methods

This project is a two-armed cluster randomized study with follow-up at two time points: 12 months and 24 months (Figure 1). The organizations are randomized to an intervention group or a control group. More detailed information on each trial arm can be found in the "Intervention" and "Control Group" sections, respectively.

Figure 1. Schematic overview of the study process, from recruitment of participants to follow-up endpoints of the cluster randomized study.
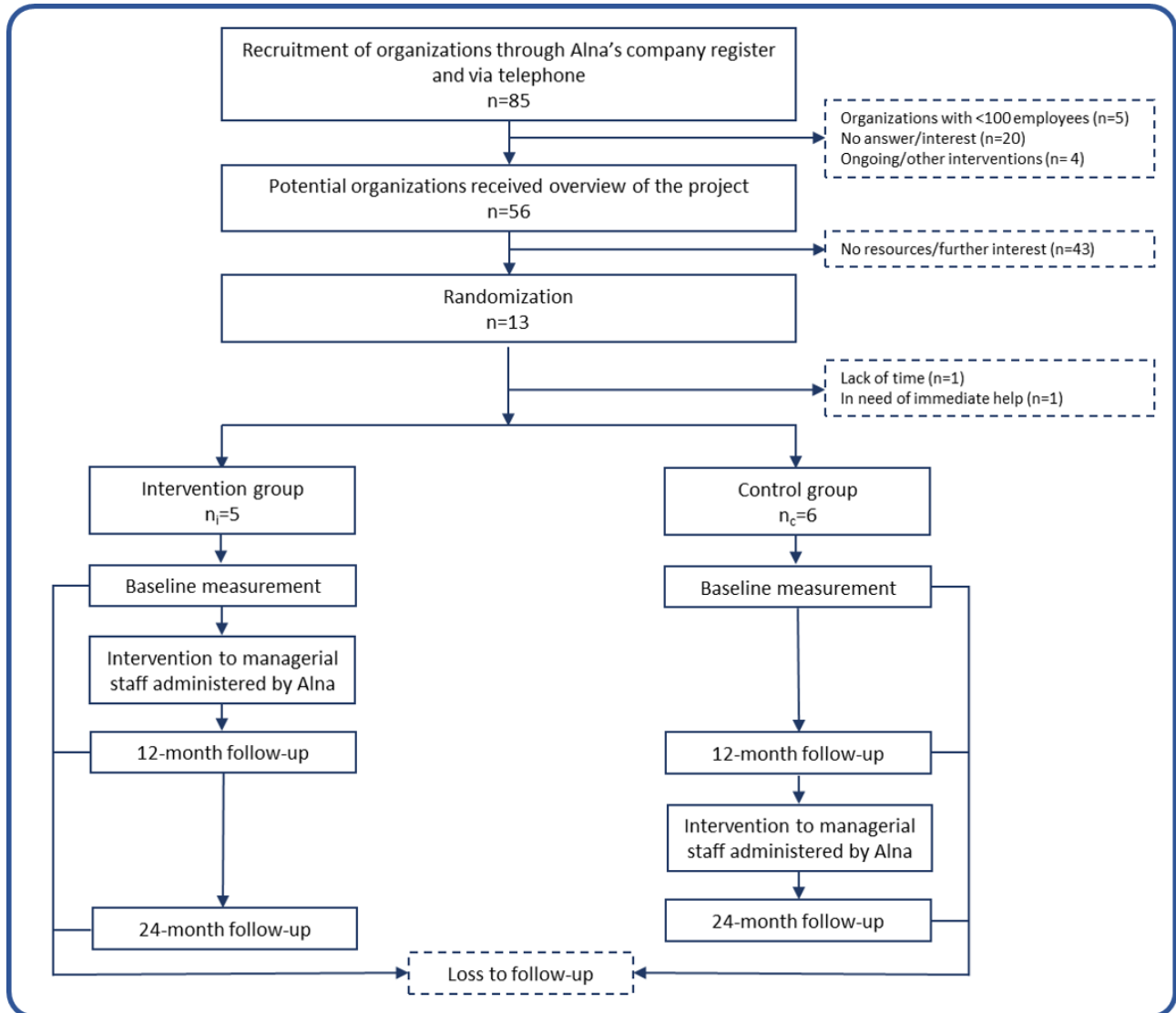
Study Population and Recruitment

This project consists of managers (n=744) and employees (n=11,761) from 11 organizations in Sweden. The manager group comprises all individual staff members with delegated staff liability, including supervisors, group leaders, and human resources personnel. All other individuals are classified as employees. Table 1 summarizes the organizational sectors, gender distribution, and age of all staff members in each recruited organization.

The organizations were recruited in two ways: partly by sending information about the study rationale to all organizations with a minimum of 100 employees registered in Alna's company register (2139 organizations) and partly by contacting representatives from some of the largest organizations in Sweden by telephone and inviting them to participate in the study. In accordance with previous research, the necessity for alcohol prevention programs is greater amongst certain sectors and consequently, the construction, hospitality, and transport sectors were prioritized during the recruitment process of this project [23].

Table 1. Overview of each organization's staff members.

ID	Sector	Number of staff members[a]	Female, n (%)	Age (years), mean
1	Brewery	153	49 (32.2)	41.1
2	Insurance	1628	707 (43.4)	37.6
3	Security	1963	538 (27.4)	38.9
4	Hospitality	521	314 (60.3)	36.8
5	Transportation	781	337 (43.1)	43.0
6	Nursing care	429	344 (80.2)	42.0
7	Security	5000[b]	N/A[c]	N/A[c]
8	Construction	1066	209 (19.6)	41.1
9	Hospitality	685	333 (48.6)	32.8
10	Transportation	164	15 (9.1)	44.0
11	Security	111	15 (13.5)	N/A[c]

[a]The number of staff members reflects the population of managers and employees at the time of recruitment.

[b]Number of individuals was approximated.

[c]N/A: not available because the information was not provided by the organization.

During the recruitment process, 13 organizations expressed their interest. An overview of the study, including information about its relevance, was sent to the recruited organizations. Two of the organizations were dissatisfied with the group allocation and dropped out.

Information about the study procedure was provided to the participants, both at the organizational and individual levels. In terms of individual-level consent, information about the study and a statement of consent provision were presented prior to the start of the survey. The consent statement informed the participants that commencing the survey was considered as consent to participate in the study. See Multimedia Appendix 1 for an English translation of the information presented at the beginning of the survey.

Randomization

In order to avoid contamination between the intervention and control groups, the organizations were randomized at the organizational level through block randomization. The organizations were matched based on type of sector (eg, hospitality sector) and size of organization in blocks of 2-4 organizations. Each block was allocated to either the intervention or control group by an online web service (random.org).

Blinding

Due to the nature of the study and assessment of the waitlist condition, it was not possible to blind either the researchers or the managers in each organization. However, the surveys are administered online without any involvement of the researchers. Hence, the survey is not subject to interpretation bias from the researchers.

Trial Arms

Intervention Group

Based on Alna's previous experience [25] and framework, the prevention program comprises two components: implementation of an organizational alcohol policy and skills development training.

The first component focuses on the implementation of an organizational alcohol policy. Alna is assisting managers in improving and implementing an organizational alcohol policy, where the policy is based on Alna's previous experiences. This includes examples of responsibility and an operational plan in which strategies, reasons for action, person responsible, timeframe, and required resources are included. The alcohol policy was developed together with human resources personnel and management on 3-4 occasions, each lasting for approximately 2 hours depending on the availability of the organization. In addition, the alcohol policy was tailored to each organization and aligned with their organizational values.

The second component of the program is skills development training, with the purpose of helping managers identify early signs of hazardous alcohol consumption and act upon behaviors that may lead to adverse effects for both employees and the organization. Managers attend 2 training workshops directed by Alna, which last for 3.5 hours per session. The workshops cover various topics regarding addiction, prevention, and dialogue about the hazardous use of alcohol. At the end of the second session, a "checklist for managers regarding alcohol use" is introduced (Textbox 1).

Textbox 1. Topics covered during the skills development workshops

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1. Types of alcohol use: differences between risk consumption, harmful consumption, and alcohol dependence

2. Prevalence: statistics on prevalence and trends over time regarding alcohol use and hazardous alcohol consumptioc in Sweden

3. Risk factors: risk and protective factors of hazardous alcohol consumption in the workplace

4. Initiating a dialogue: the importance of dialogue as a tool; preparation, conducting, and evaluation of a dialogue regarding potential problematic drinking

5. Signals: behaviors and signs indicating hazardous alcohol consumption

6. Workplace culture and policy: the role of workplace culture in contributing to or preventing hazardous alcohol consumption; benefits of implementing workplace policies

7. Roles and responsibilities: discussion of roles and responsibilities of the organization involving managers and employees

8. Use of an implementation checklist: participants go through an implementation checklist and its purpose

9. Dilemma: discussion about ambiguous cases

Control Group

Organizations in the control group are placed on a waitlist and continue their usual practices. The control group receives the same prevention program as the intervention group after the 12-month follow-up. Individuals in the control group respond to the survey parallel to individuals in the intervention group.

Data Collection

Data are collected through self-reported online questionnaires. The organizations have provided Alna with a list of emails and demographics of the staff. The surveys are distributed using email, SMS text messaging, or a general link. Participants with email addresses and phone numbers receive a unique link to the survey, which reduces the probability of the data being wrongly coded or disappearing. The participants who do not have or do not provide an email address or telephone number receive a general link to the survey via their workplace's internal website. In order to follow up with the participants with a general link, they are requested to create a code prior to the survey using their initials and the last four digits of their social security number. For example, a fictional person, Anna Carlsson with social security number 19520824-5982 would enter AC5982. This ensures that they are able to fill in the same code during the follow-ups without having to remember or store anything.

Two surveys were created: one for managers and one for employees. Both surveys include questions regarding demographics, knowledge of organizational alcohol policies, and alcohol habits measured using the AUDIT. The survey for managers also includes questions regarding managerial responsibility and experience and their inclination to initiate early alcohol interventions, such as initiating a dialogue with their employees. The AUDIT segment of the survey is based on the previously validated World Health Organization screening tools to assess alcohol consumption [26]. The surveys were piloted (n=20) upon completion of the online version of the survey, and appropriate modifications (reformulation of questions and design layout) were completed.

To increase the response rate, 3 reminders at 1-week intervals are sent to participants who provide incomplete answers to the survey.

Managers across the organizations were interviewed using semistructured interviews. Managers' experiences with the implementation processes and effects of the prevention program will be explored. In order to explore managers' perceptions of an alcohol prevention program, semistructured interviews were conducted with managers (n=61) in the intervention and control groups. The interviews were conducted after the first follow-up to avoid influence of the outcome measures on the follow-up survey. Participants that expressed interest in being interviewed during the time of the "intervention to the managerial staff administered by Alna" were contacted by telephone or email between September and November 2019. The interviews were conducted via telephone for approximately 40 minutes. The participants provided verbal consent, and the interviews were recorded and transcribed verbatim.

The interview questions and analysis aim to explore respondents' perceptions and experiences of (1) alcohol problem prevention in the workplace, (2) the educational part of the "intervention to the managerial staff administered by Alna," (3) difficulties as well as enabling factors associated with implementing an alcohol policy in the workplace, and (4) how to handle a situation in which an employee or co-worker appears to have an alcohol problems. The interview questions were constructed primarily by one of the authors, a psychologist with clinical experience working with addiction.

All interview questions were open-ended to invite managers' own thoughts and experiences; the aim is to cover their general understanding of phenomena as well as their personal experiences. Follow-up questions were asked in order to ameliorate comprehension of the respondents' experiences and thoughts, with the number of follow-up questions varying based on how detailed the respondents were in their descriptions. The transcripts will be analyzed qualitatively using thematic analysis. All personal details are coded to ensure anonymity.

Outcome Measures

The primary outcome of this project is managers' self-reported inclination to initiate early alcohol interventions, such as initiating dialogue with employees when suspicion or concern about hazardous alcohol consumption arises (outcome 1). This is measured using the following items: "To be able to initiate a dialogue about alcohol consumption with an employee, I want

to be sure that the person has a problem," "For an employee to receive help with their alcohol-related issues, the person has to first admit that they have a problem," and "If an employee has a problem that could be due to alcohol use, I feel confident in initiating a dialogue about it." A 5-point scale is used, ranging from 1 (strongly disagree) to 5 (strongly agree).

Survey items regarding employees' knowledge on organizational alcohol policy, guidelines, and available support (outcome 2) are measured using statements rated on a 5-point Likert scale, ranging from 1 (very poorly) to 5 (very well). Managers' actions to address employees' alcohol consumption is measured using 2 items with yes/no alternatives (outcome 3). The total AUDIT score is used to assess sustainable alcohol consumption (outcome 4) and number of cases of hazardous alcohol consumption (outcome 5) among managers and employees. To examine confidence among managers, questions regarding managers' self-perceived knowledge about hazardous alcohol consumption and the way to handle alcohol-related issues are used (outcome 6).

In addition, basic demographic questions, including gender, age, and highest level of education attained are utilized to examine the individual differences within and across organizations.

Statistical Analyses

The project inherits a hierarchical structure, which violates the assumption of independent samples required for analysis of variance. Therefore, a linear mixed-model framework will be conducted during the statistical analyses to model the variability on different levels (managers and employees) [27]. Each outcome corresponds to the questionnaire question (see Outcome Measures), and changes in the corresponding question from baseline to the follow-ups will be analyzed. Data management and all statistical analyses will be conducted using Stata Statistical Software v.14 (StataCorp, College Station, TX).

Qualitative Analysis

The interview transcripts will be analyzed using inductive thematic analysis, a method aimed at identifying recurring themes, concepts, or phenomena described by the participants [28]. In inductive analysis, no attempt will be made to fitting data into a pre-existing framework. The qualitative analysis will be conducted using the program Atlas.ti. Transcripts of extracted data are read and coded independently to be able to extract relevant data that may contribute to answering the research questions of the study. After the coding process, each dataset will be reread to ensure that nothing was overlooked. Codes and ideas will be discussed between the authors prior to categorizing extracts and creating themes.

Attrition

This study will use intention-to-treat analyses to retain information about the participants based on their group allocation and complete case analyses to be able to compare changes in outcome measures for managers and employees who adhere to the prevention program. We expect to be able to perform sensitivity analyses to examine differences between complete samples and respondent samples since organizations

are providing some demographic data about their employees. Imputation using maximum likelihood techniques may be applied to avoid distortion of the mean, variance, or covariance to other variables.

Sample Size

The data will be fitted using a repeated measures hierarchical linear model [29]. We aimed to recruit 10-14 organizations, with approximately 10,000-15,000 participants. Assuming there are no associations between hierarchical levels (ie, managers and employees), the power of this study is calculated based on the total number of participants, yielding a power >95%, given the small effect size (Cohen d <0.20) at 5% significance. In contrast, if all the variance in the study could be explained by the hierarchical level, the power of this study is calculated based on the number of levels, yielding approximately a 69% power given the small effect size with a significance level set at 5%. Presuming that the hierarchical levels explain only some of the variance, the current study design should be sufficient to achieve greater than the conventional norm of 80% power.

Results

This study is ongoing. Recruitment of organizations was completed between March and May 2017. The overall start was on January 2018 and is planned to end in December 2020. Baseline and 12-month follow-up measurements have been collected. This project was granted an ethical permit by the Ethical Review Board of Stockholm Region (dnr 2018/634-31/5) on April 12, 2018. In 2018, we recruited a total of 12,505 participants (744 managers and 11,761 employees). Basic scientific results of the project have been uploaded on the ISRCTN registry on April 7, 2020 (https://www.isrctn.com/ISRCTN17250048).

Discussion

This study is designed to evaluate the effectiveness of an alcohol prevention program in the workplace in Sweden. To our knowledge, it is the first study in Sweden targeting individuals in workplace settings. The strategies used to prevent harm to the individuals and organizations will help create evidence-based policies in the workplace. If the program is successful, it will act as a complementary method to a conservative approach to treating high-risk alcohol consumers in the workplace.

This prevention program targets the majority of the adult population instead of high-risk individuals, which is one of the key approaches in the public health field [21]. This study could potentially lead to managers being able to identify and feel more confident in initiating interventions before their employees develop drinking problems that could be hazardous to their health. The results produced in this study could possibly be of high value to other workplace settings that are often not considered to be vulnerable to high alcohol consumption, as suggested by previous literature and organizations included in this project [23].

This study has some limitations. One of its main concerns is the self-reported perception of outcome measures. This may lead to bias, as participants may provide answers that are socially

desirable. Considering that policy implementation in this study is specific to each organization, the generalization of such effects to other settings (different types of sectors) and populations (nonworking populations) may be difficult. Further, a low response rate is expected in some of the organizations, given that some participants will receive their questionnaires through a general link. The validity of the study may be negatively affected due to difficulties interpreting the results and comparing them across organizations. In addition, since this project implements and evaluates the prevention program, we are merely able to evaluate the combined effect of the prevention program. Therefore, the effect of one of the intervention components is unknown. Finally, considering that the prevention program is implemented at the organizational level and outcome assessments are conducted on individual level (ie, managerial and employee levels), we are unable to identify organizational factors that may influence the results of this project.

Ethics and Dissemination

Ethical Approval

The Ethical Review Board of Stockholm Region (dnr 2018/634-31/5) granted an ethical permit for this study.

Information and Informed Consent

An overview of the project's rationale was distributed at the organizational level, and a representative from each organization provided organizational level consent. With regard to individual-level consent, an information sheet was distributed by the representatives through the organization's internal website or newsletter. Moreover, each participant was presented with information about the study and a statement of consent provision at the start of the survey. Therefore, participants were considered to give their consent to participate in the study by starting the survey. Participants' data are handled according to the General Data Protection Regulation and Stockholm University's rules and guidelines. In addition, participants are able to decline or withdraw their participation in the study without giving any reason.

Dissemination of Results

The results of this study will be presented at conferences and published in peer-reviewed scientific journals.

Authors' Contributions

DLE drafted the first version of the manuscript. MW, PC, PW, and KS provided feedback and reviewed and revised the manuscript. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Consent form.
[PDF File (Adobe PDF File), 241 KB - resprot_v9i8e17145_app1.pdf]

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Abbreviations

AUDIT: Alcohol Use Disorder Identification Test
BI: brief intervention

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Protocol

The Effect of Improved Access to Family Planning on Postpartum Women: Protocol for a Randomized Controlled Trial

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Abstract

Background: The World Health Organization recommends that a woman waits at least 24 months after a live birth before getting pregnant again; however, an estimated 25% of birth intervals in low-income countries do not meet this recommendation for adequate birth spacing, and the unmet need for postpartum family planning (PPFP) services is high. Few randomized controlled trials have assessed the causal impact of access to PPFP services, and even fewer evaluations have investigated how such interventions may affect postpartum contraceptive use, birth spacing, and measures of health and well-being.

Objective: This protocol paper aims to describe a randomized controlled trial that is being conducted to identify the causal impact of an intervention to improve access to PPFP services on contraceptive use, pregnancy, and birth spacing in urban Malawi. The causal effect of the intervention will be determined by comparing outcomes for respondents who are randomly assigned to an intervention arm against outcomes for respondents who are randomly assigned to a control arm.

Methods: Married women aged 18-35 years who were either pregnant or had recently given birth were randomly assigned to either the intervention arm or control arm. Women assigned to the intervention arm received a package of services over a 2-year intervention period. Services included a brochure and up to 6 home visits from trained family planning counselors; free transportation to a high-quality family planning clinic; and financial reimbursement for family planning services, consultations, and referrals for services. Two follow-up surveys were conducted 1 and 2 years after the baseline survey.

Results: A total of 2143 women were randomly assigned to either the intervention arm (n=1026) or the control arm (n=1117). Data collection for the first follow-up survey began in August 2017 and was completed in February 2018. A total of 1773 women, or 82.73% of women who were eligible for follow-up, were successfully contacted and reinterviewed at the first follow-up. Data collection for the second follow-up survey began in August 2018 and was completed in February 2019. A total of 1669 women, or 77.88% of women who were eligible for follow-up, were successfully contacted and reinterviewed at the second follow-up. The analysis of the primary outcomes is ongoing and is expected to be completed in 2021.

Conclusions: The results of this trial seek to fill the current knowledge gaps in the effectiveness of family planning interventions on improving fertility and health outcomes. The findings also show that the benefits of improving access to family planning are likely to extend beyond the fertility and health domain by improving other measures of women's well-being.

Trial Registration: American Economics Association Registry Trial Number AEARCTR-0000697; https://www.socialscienceregistry.org/trials/697 Registry for International Development Impact Evaluations (RIDIE) Trial Number RIDIE-STUDY-ID-556784ed86956; https://ridie.3ieimpact.org/index.php?r=search/detailView&id=320

International Registered Report Identifier (IRRID):   DERR1-10.2196/16697

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Introduction

The Role of Family Planning

The World Health Organization (WHO) guidelines recommend that a woman wait at least 24 months after a live birth before getting pregnant again [1,2]. Poorly spaced births may contribute to higher rates of mortality for both mothers and infants [3,4]; however, an estimated 25% of birth intervals in low- and middle-income countries do not meet the WHO's 24-month recommended guideline for adequate birth spacing [5]. This gap between recommended spacing and realized spacing highlights the importance of postpartum family planning (PPFP), particularly in sub-Saharan Africa where the unmet need for PPFP is high. Given that the ideal family size is higher among women in sub-Saharan Africa than in other parts of the world, the demand for and use of family planning is driven more from a desire to space future births rather than to limit births. Nevertheless, an estimated 8 million women in sub-Saharan Africa have an unmet need for limiting future births [6]. The continuing high unmet need for and lack of access to PPFP highlights the need to mobilize efforts toward meeting the family planning and fertility goals of postpartum women. To this end, interventions that aim to influence the demand and supply of PPFP have become increasingly common in developing countries. These interventions have targeted key populations in a variety of ways, from education and awareness programs in schools to multicomponent, community-based campaigns [7,8].

Recently, the number of family planning interventions that have undergone more rigorous impact evaluation has increased to assess the effects of family planning on fertility, health behavior, and health outcomes. However, findings from community-level social programs such as the Maternal and Child Health–Family Planning Extensions project in Matlab, Bangladesh, and the Navrongo experiment in Ghana have also shown that contraceptive use declines considerably following the discontinuation of family planning services [9-12]. Although not all the studies focused on postpartum women, these results suggest that increased access to high-quality family planning services, particularly for new mothers, needs to be expanded beyond the neonatal clinic. To this end, few randomized controlled trials have been conducted to assess the causal impact of family planning in low-income countries, and even fewer impact evaluations have been conducted to determine the extent to which such family planning interventions may affect downstream health and development outcomes. To date, not many impact evaluations have sought to identify the effectiveness of family planning and reproductive health programs at the individual or household level; apart from the frequently cited Matlab quasi-experimental study and a recent field experiment by Ashraf et al [13], no randomized controlled trial, to the best of our knowledge, has attempted to causally identify the impact of family planning and birth spacing on both immediate and longer-term outcomes of health and well-being in sub-Saharan Africa.

Study Objectives

To address these gaps in the evidence, we conducted a randomized controlled trial to identify the causal impact of improved access to PPFP. The study population included married postpartum women aged 18 to 35 years in Lilongwe, Malawi. As part of the trial, each woman in the study was randomly assigned to either the treatment or control arm. A woman who was assigned to the intervention arm received a 2-year–long family planning intervention that was designed to reduce key barriers to access for postpartum women in urban Malawi [14,15]. The primary objective of this study is to evaluate the impact of the family planning intervention on contraceptive use, fertility, birth spacing, and other measures of maternal and child health and well-being in postpartum women who received the family planning intervention (the intervention arm) compared with women who did not receive the intervention (the control group). Primary outcomes include short-term outcomes related to modern contraceptive use and contraceptive method mix (the profile of the relative level of use of different contraceptive methods within our study sample) as well as intermediate outcomes related to fertility and birth spacing. Shorter-term secondary outcomes include changes in desired fertility, unmet need for family planning, and outcomes associated with maternal and child health, including safe pregnancy, birth height and weight, and nutritional status. Longer-term secondary outcomes include educational attainment (matriculation rates and years of schooling completed), labor market outcomes (employment status, female labor supply, and women's time use), and income. This study seeks to fill the current knowledge gaps on the effectiveness of family planning interventions by directly identifying the impact of an increase in access to family planning on fertility and health outcomes. A downstream objective of this study is to demonstrate that the benefits of improving access to family planning are likely to extend beyond the health domain by also improving well-being and contributing to the alleviation of poverty.

Methods

Study Approval

Human subject approvals for this study were obtained from the Harvard University Institutional Review Board (IRB; Protocol Number: IRB16-0421), the Malawi National Health Sciences Research Committee (NHSRC Approval Number: 16/7/1628), the Lilongwe District Council, the Malawi Police Service, and the Malawi Ministry of Health (MOH) to conduct the study. Memoranda of Understanding were established with our partner family planning clinic in Lilongwe, the Good Health Kauma Clinic.

Study Setting

Our study was conducted in urban Lilongwe, the capital of Malawi. Despite declining birth rates and improvements to maternal health care, the total fertility rate or the average number of births per woman has remained relatively high in Malawi.

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In 2017, the average total fertility rate in Malawi was 4.2 births per woman (with a slightly lower fertility rate in Lilongwe), which is below the average total fertility rate of 4.9 births per woman in sub-Saharan Africa, but almost twice the average total fertility rate of 2.7 births per woman in South Asia and more than twice the average total fertility rate of 2.2 births per woman in Latin America and the Caribbean [16,17]. In addition, estimates from the 2015-16 Malawi Demographics and Health Survey (MDHS) show that the contraceptive prevalence rate in Malawi was 45.2% among all women of reproductive age (15-49 years) and 59.2% among married women of reproductive age. These estimated contraceptive prevalence rates are a significant increase from the 32.6% and 46.1% prevalence rates for all women and married women, respectively, from the 2010 MDHS. Nevertheless, the unmet need for family planning has remained high, with an estimated 18.7% of women in Malawi reporting to have an unmet need for spacing or limiting births [17]. Injectable contraceptives were reported to be the most popular method in Malawi in 2010 and were used by 22.5% of women, followed by intrauterine devices (IUDs) and female sterilization at 9% and 8.3%, respectively [17]. The method mix of women has not changed significantly over time among married women in Malawi, as injectable contraceptives, IUDs, and female sterilization remain to be the most popular methods among married women and are used by 30%, 11.5%, and 10.9%, respectively [17].

When compared with antenatal care, the utilization of postpartum maternal health care services remains to be low in Malawi. Although 97.6% of pregnant women received antenatal care from a skilled professional between 2012 and 2017, 57.6% of new mothers did not receive any postnatal care within the immediate postpartum period (within 48 hours following birth)

[17]. Although a range of maternal health programs have attempted to combine PPFP with existing maternal health services, these programs continue to face difficulties in reaching significant portions of the population. Prior studies have shown that women in Malawi and in sub-Saharan Africa more generally face a range of barriers to accessing high-quality postpartum care, including (1) informational barriers (lack of awareness or knowledge of postpartum care options), (2) physical barriers (distance to care, long travel times to health facilities, high cost of transport, and poor access to effective transport options), and (3) barriers that impede effective service provision (long waiting times at clinics, user fees for services, lack of availability of services and supplies, and poorly trained service providers, among others) [18]. Additionally, women and children often receive postnatal care from different locations and through different providers, which often compels a woman to make the choice to seek care for her child at the expense of her own care [19]. These barriers to access are common to interventions that aim to increase access to and use of postpartum health care services, including PPFP, and are key barriers that we aimed to address when designing our intervention.

Study Sample and Inclusion Criteria

This study is a two-armed randomized controlled trial that was conducted with a sample of women of reproductive age from urban Lilongwe, Malawi. The study consists of a baseline survey, followed by the randomization of women into intervention and control arms and the implementation of the 2-year family planning intervention. Two follow-up surveys were conducted 1 and 2 years after the baseline survey. Figure 1 outlines the general framework of the complete field experiment.

Figure 1. Experimental framework and flowchart.
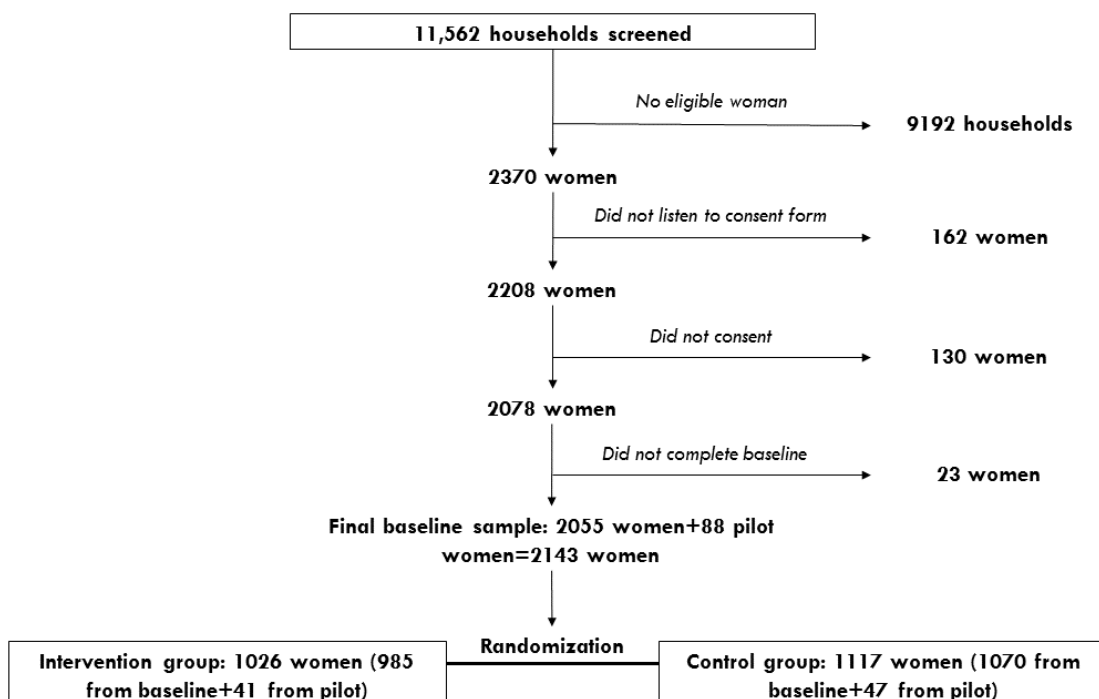
For the study, we recruited women who, at the time of the baseline survey, (1) were married, (2) were either currently pregnant or had given birth within 6 months from the time of the baseline screening, (3) were between the ages of 18 and 35 years, and (4) lived in the city of Lilongwe. Women who successfully met these criteria and consented to participate in the study were recruited. In addition, no 2 eligible women were enrolled from the same household. If multiple women from the same household were potentially eligible to be recruited based on the 4 inclusion criteria above, the youngest eligible woman from the household was chosen to participate—given that randomization was to be administered at the individual woman level, it was necessary for us to select only 1 eligible woman from a household to minimize any possible contamination across women in the intervention and control groups. We also ensured that eligible women who were selected for the study were sufficiently distant (at least five households apart) from each other, which also served to reduce any spillover effects between treated and control women who lived in the same neighborhood. Following the recruitment of women, 1 member from the recruited woman's household was identified and selected to respond to sections in the baseline and follow-up surveys that inquired about household expenditures, assets, and consumption. The household member selected for this part of the study was required to meet the following inclusion criteria: (1) he or she was >18 years old, (2) he or she was a resident of the same household from which the woman respondent described above was selected, and (3) he or she claimed to be knowledgeable about the household's financial status, consumption, and expenditure. The household member who successfully met these inclusion criteria and who consented to participate in this part of the study was recruited to participate. Finally, children in the household were recruited to complete an anthropometric module, including data collection of height, weight, and anemia status at baseline and again at the 2 follow-ups. The children who were selected from the household for this part of the study (1) were aged <6 years, (2) were identified as the biological or adopted children of the woman who was recruited for the main part of the study, and (3) resided in the same household as the eligible woman. Children who successfully met these inclusion criteria and whose mothers consented to them participating in this part of the study were recruited to participate.

Recruitment and Study Timeline

Using the most recent Demographic and Health Survey (DHS) and census maps of Lilongwe's enumeration areas and listings of households and neighborhoods, which were provided to us by the Malawi MOH; National Statistics Office (NSO); and our

implementation partner, Innovations for Poverty Action (IPA) Malawi, we employed a two-stage sample selection procedure that was based on the sampling strategy used by the DHS. In the first stage, we randomly selected areas in Lilongwe to be surveyed until we selected enough areas to contain at least 11,000 households in total. In the second stage, our surveyors proceeded door-to-door to screen households in each selected area for potentially eligible women. Surveyors continued to screen households until they identified at least 2000 women for the study in accordance with the inclusion criteria listed above, and these eligible women were recruited in accordance with the recruitment protocols outlined below. Surveyors used a recruitment script to verify eligibility and presented the eligible woman with a consent form to participate in the study. Written informed consent was obtained from all participating women before proceeding to administer the baseline survey. Multimedia Appendix 1 shows recruitment script and the consent form that were administered to the women respondents. Women who met the eligibility criteria and who consented to participate in the study were recruited into the study. On the basis of our knowledge of participation refusal rates and the estimated number of eligible women in Lilongwe, we estimated the need to screen an estimated 3000 households to obtain a desired sample size of at least 2000 women. We required a study sample of at least 2000 women to achieve sufficient power to measure our outcomes of interest; see our power calculations below. As women who were selected into the study would also be at least five households apart from each other, we would need to choose enough enumeration areas to have at least 11,000 households in total (2000×5=10,000 households among the women who make up our sample and who are at least five households apart, plus an additional 1000 households that were screened but where women either did not meet the eligibility criteria or refused to participate). Recruitment from the selected enumeration areas ceased once at least 2000 women were found who met the eligibility criteria, consented to participate in the study, and were administered the baseline survey.

The planned experiment spanned 42 months. Table 1 shows the study timeline. Before recruiting and conducting the study with the main study sample, a small sample of women was recruited as a means to pilot new survey instruments and intervention activities over the study period. All research activities, including recruitment, consent, study instrument administration, and intervention administration, were administered to the pilot sample using the same study protocols as those used for the main sample. For this reason, the final analytic data sets for the study consist of data from both the pilot and main samples.

Table 1. Study timeline.

Study activities	Months													
	1-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24	25-27	28-30	31-33	34-36	37-39	40-42
Prepare survey instrument; hire study staff and interventionists; obtain IRB[a], partner, and local approvals; identify and finalize sampling strategy	✓	✓	✓	—[b]	—	—	—	—	—	—	—	—	—	—
Training of local staff, lay interventionists, and enumerators	—	—	—	✓	—	—	—	—	—	—	—	—	—	—
Household screening and sample recruitment	—	—	—	✓	✓	—	—	—	—	—	—	—	—	—
Baseline survey administration, randomization, and intervention administration	—	—	—	—	✓	—	—	—	—	—	—	—	—	—
Intervention period	—	—	—	—	✓	✓	✓	✓	✓	✓	✓	✓	—	—
First-year follow-up and analysis	—	—	—	—	—	—	—	—	✓	—	—	—	—	—
Intervention study close-out, second-year follow-up, and analysis	—	—	—	—	—	—	—	—	—	—	—	—	✓	—
Final reports, publications, and dissemination	—	—	—	—	—	—	—	—	—	—	—	—	✓	✓

[a]IRB: Institutional Review Board.

[b]—: indicates the month in which that specific study activity is not taking place (eg, the preparation of the survey instruments only take place in the first 9 months and is completed by then).

Informed Consent and Participant Privacy

The process to obtain consent was consistent for all potential participants: women, financially knowledgeable members of the household, and children <6 years. Written consent to participate was obtained from all participants before administering each survey (baseline and annual follow-ups). Once participants agreed to join the study, a copy of the consent form script was read to them and they were given opportunities to ask questions and express concerns. Surveyors checked for comprehension throughout the consent process. This process was estimated to take between 5 and 10 min, although it took longer if a participant had many questions—refer to the consent documents in Multimedia Appendix 1 for details concerning the consent process. After completing the consent script, potential participants were encouraged to ask questions and asked if they would like to participate. If the participant wished to take further time to reflect, the surveyor and the participant determined the time and method of reconnecting. If the potential participant agreed to be a part of the study, consent was obtained and documented by obtaining the signatures of both the participant and the study staff member who conducted the consent discussion. Upon consenting, the surveyor then conducted the survey.

For follow-up surveys, verbal consent to participate was obtained over the phone from only those participants who were originally recruited at baseline but since either moved outside of Lilongwe or were unreachable in person after 3 contact attempts. The only respondents who were recontacted for the phone follow-up survey were those respondents who were simply lost to follow-up. Respondents who had previously indicated that they were no longer interested in participating in the study were not contacted.

Throughout the consent process, the surveyor clearly explained to the participant that even if she decided to participate and sign the consent form, she could decide at any time to end her participation. If the study participant was not literate, then a witness who did not work for the study signed the consent form. In the absence of witnesses, the participant could confirm their consent by placing a thumbprint on their consent form and a photo of the thumbprint was taken as a record of consent. Moreover, participants were encouraged to contact the researchers with any further questions during the informed consent discussion or any time during the study. Consent was obtained before any surveys were conducted. All participants were informed that their participation was completely voluntary and that they could choose not to participate in the study or to end their participation in the study at any time.

The recruitment scripts, consent forms, and survey instruments were translated from English into Chichewa by a certified translator.

With regard to consent during the administration of the intervention, women were informed that they could take part in any component of the interventions that was offered to them; they could take up and stop any or all components of the intervention at any time. For example, counselors asked for a woman's consent to participate in a counseling session each time they visited a woman's home.

All surveys and administration of the intervention were conducted in a private room. To maintain a respondent's privacy during an attempt to reach her by phone, the field enumerator conducting the call left no indication of the reason for the phone attempt (eg, voicemail, text message) on the respondent's phone should there be no response to a call. Any disruption or interruption during the interview, either in person or by phone, resulted in the postponement or termination of the interview.

Randomization

Following the baseline survey, women who consented to participate in the study were individually randomized into 1 of 2 experimental arms: an intervention arm or a control arm. The women were randomized to the intervention and control groups such that intervention assignment was balanced according to the following baseline characteristics: neighborhood or household cluster, distance to the nearest family planning clinic, number of living children, months since last live birth, current use of family planning, age of marriage, educational attainment, and household wealth. As part of the balancing process, strata by each combination of characteristic values were created and observations were assigned to their respective strata. Observations within each stratum were then individually randomized by the Principal Investigators in a 1:1 allocation to either the treatment or the control group using computer-generated randomization through STATA, version 13 (StataCorp). Block randomization was not used in this study. Following individual randomization, the IPA Malawi intervention team implemented the intervention to the participants who were randomized into the intervention arm.

The Intervention

Following randomization of women into the intervention and control arms, women assigned to the intervention arm were offered the following 3 intervention components over a 2-year period:

1. Transportation component: women were offered a free transportation service from their homes to our partner family planning clinic, the Good Health Kauma Clinic. The transportation service was provided by a driver who was hired and trained by our local implementation partner, IPA Malawi. Women received the driver's phone number and were instructed to contact the driver to transport them to the Good Health Kauma Clinic during the clinic's normal working hours, which are between 8 AM and 5 PM from Monday to Saturday. The driver maintained a daily schedule of the women who requested his services, and women were instructed to notify the driver at least one day before they wished to go to the clinic to make sure that the driver was able to transport them. The driver also provided 1 day's notice to the Good Health Kauma Clinic to inform them of how many women from the study could be expected to attend the clinic on the following day. The Good Health Kauma Clinic assured the project team that women in the intervention arm who come for services would not have to wait more than 1 hour before being examined by a medical professional. In addition, one of our female field managers from IPA Malawi accompanied the driver at all times. Although all women in the intervention arm were presented with pictures of the field team (and could therefore recognize our team members), the presence of another woman in the vehicle served to minimize potential stigma associated with a woman traveling alone in the company of another man.

2. Counseling component: women who were assigned to the intervention arm were also offered free, private family planning counseling sessions over the 2-year intervention period. The counseling sessions were provided by trained counselors and included a risk assessment for clinical methods and detailed information on methods switching; side effects associated with each method; and the benefits of contraception, birth spacing, and dual protection. Consultations were designed to promote informed choice by discussing common misperceptions surrounding family planning and the use of modern contraceptives. Women received a detailed information brochure on birth spacing and side effects and also received counseling on both modern and natural family planning methods, in Multimedia Appendix 2. Strategies on how to communicate family planning messages with partners and on how to increase partner awareness were conveyed during sessions. Counseling sessions were scheduled to last no more than 1 hour per session and were administered in a private room by a counselor who was trained to provide family planning and reproductive health services. Counselors were hired and trained by IPA Malawi. We enlisted the support of the Malawi Reproductive Health Directorate (RHD) and several international nongovernmental organizations who work on family planning, including Population Services International (PSI), Banja La Mtsogolo (BLM), the Family Planning Association of Malawi (FPAM), and FHI360, to help us develop training materials, brochures and flyers, and other counseling resources. We also collaborated with the Malawi RHD, BLM, and PSI to assist with the counselor training. Women in the intervention arm received a total of 6 counseling sessions, 1 comprehensive 90-min session just after administration of the baseline (within 1 month) and 5 shorter 45-min follow-up sessions that were spaced out over the 2-year intervention period. The first session introduced women to the range of available family planning methods and counseled women on side effects. In the first session, counselors also informed women in the intervention arm about the transport service (described above) and side effects management service (described below) that were available to them and provided women with the necessary information on how to access these services. Counselors also provided their phone numbers to women and were on call over the course of the study period to respond to any questions and concerns.

3. Financial reimbursement component: women who were assigned to the intervention arm were financially reimbursed for any out-of-pocket expenditures that they incurred for receiving family planning care at the Good Health Kauma Clinic. Costs that were reimbursed at the Good Health Kauma Clinic included costs related to the procurement of family planning medications and contraceptive methods, family planning consultation fees, lab test fees, and exam fees. The reimbursement allowance for each woman was 17,500 MKW (US $25.00) and could be redeemed by the woman over multiple visits at the Good Health Kauma Clinic over the 2-year intervention period. For every family planning service that the woman received, the cost of the service was deducted from her reimbursement allowance of 17,500 MKW.

In addition, women who were assigned to the intervention arm and who experienced any side effects because of contraceptive

use over the course of the 2-year intervention period received a series of services for the treatment of side effects. In the event that a woman in the intervention arm experienced a side effect or contraindication, she could contact a trained Obstetrician-Gynecologist at the Kamuzu College of Medicine in Lilongwe, via telephone, and would receive advice on how she can best seek care. The doctor would conduct a preliminary telephone consultation and would refer the woman over the phone to seek care at their nearest public clinic, public hospital, or the Good Health Kauma Clinic. All women in the intervention arm also received an *emergency package* during the first counseling visit from the counselor (see above). This *emergency package* consisted of (1) a transport voucher, equivalent to an estimated 6500 MWK (US $9.28) and (2) a mobile phone credit scratch card for the mobile provider of their choice, equivalent to 500 MWK (US $0.72). A template of the transport voucher is provided in Multimedia Appendix 3. This *emergency package* was given to all women in the intervention arm, regardless of whether they took up any intervention component or experienced a side effect. The counselor informed the woman that, in addition to the other side effects management services mentioned above, the woman could use the *emergency package* that she was given to cover (1) any phone airtime costs that she used to have a consultation with one of the doctors who are on call and (2) any emergency transport costs (taxi) she incurred to travel to a health facility where she can receive treatment for her contraceptive-related side effects. The transport voucher could be presented to any taxi driver in the city of Lilongwe and the taxi driver would, in turn, redeem the voucher at the IPA Malawi office in exchange for cash equivalent to the cost of the trip. The woman was asked to keep receipts of any costs she incurred at the health facility so that she could be reimbursed later. Costs for which the woman could be reimbursed included costs of medications and lab tests, costs of additional consultations at the health facility, and costs of switching or discontinuing methods. The maximum reimbursement amount that a woman was eligible to receive for the treatment of family planning-related side effects or contraindications is 35,000 MWK (US $50.00) over the 2-year intervention period. The reimbursement could be applied to cover the cost of treatment for side effects for all family planning methods used by the woman, regardless of where the method or treatment was procured. All reimbursements for incurred costs were distributed as closely as possible to the time that the reimbursable cost was incurred.

Following the randomization of women into the intervention and control arms, women who were assigned to the intervention arm were visited by the family planning counselor. During this initial visit, the counselor described all 3 intervention components, including their terms and conditions, to the woman. The counselor answered any questions that the woman may have had about the intervention and then asked for and confirmed the woman's consent to participate in the intervention using a Terms of Service document (available upon request). Each woman received a paper copy of the Terms of Service document. If the woman consented to participate, the counselor then administered the first counseling session. Women assigned to the intervention arm could withdraw their participation from any intervention activity at any time and could also rejoin at any time without any penalty over the 2-year intervention period.

Control Arm

Women who are assigned to the control arm received a package of publicly available literature and information on the benefits of family planning as well as information about their nearest family planning clinic. This information package was delivered to all women at the time of the baseline interview. Women in the control arm were only recontacted by the research team at follow-up.

Participant Compensation

All women who participated in the study received a small token of appreciation (3 bars of soap, a monetary equivalent of 500 MWK [US $0.66]) after completing each survey. Parents or guardians of children who participated in the anthropometric measurement portion of the study received a small bag of puffed rice cereal (a monetary equivalent of 100 MWK [US $0.13]) after completing each survey. To avoid coercion into participation, participants were not informed of these tokens until after the survey had been administered.

All women who participated in the phone follow-up survey received mobile phone credit in the amount of 500 MWK (US $0.66) by means of a mobile airtime transfer. To avoid coercion into participation, women were not informed of this airtime transfer until after the survey had been administered.

Primary Outcomes

At the designated 1-year and 2-year follow-up periods, the entire study sample of women was resurveyed to create a panel of individual women in which each woman and household would be observed over 3 time periods. In each follow-up round, we collected survey data on a range of primary outcomes of interest, which include (1) contraceptive use, including changes in contraceptive prevalence, changes in method mix, and adherence to methods (compliance and discontinuation) and (2) fertility and birth spacing outcomes, including pregnancy status, parity, and time since the last birth.

Secondary Outcomes

A range of secondary outcomes were collected in each survey wave, including (1) child anthropometric outcomes, including child height, weight, and anemia status for all children born after the start of the intervention; (2) sexual and marital well-being; (3) women's anthropometric outcomes, including height, weight, and anemia status; (4) women's and children's educational attainment, including time spent in school, type of school (public or private) attended, and the highest educational qualification achieved; (5) work, income, and women's employment, including women's time use (time spent on child care vs household and income-generating activities) and sources of household income; (6) household assets and wealth, including changes in asset ownership over time; and (7) expenditures, in particular changes in food expenditures and durable expenditures over time.

Outcomes were collected according to the schedule outlined in Table 2. All survey instruments (baseline and follow-up) and intervention-monitoring tools to track participants and

intervention uptake over the course of the study are available   upon request.

Table 2. Outcome measures and instruments.

Outcomes and instruments	Baseline	Follow-up, year 1	Follow-up, year 2
Attitude and knowledge of family planning	✓[a]	✓	✓
Contraceptive use	✓	✓	✓
Pregnancy and fertility outcomes	✓	✓	✓
Child anthropometry (height, weight, and anemia)	—[b]	✓	✓
Women's anthropometry (height, weight, and anemia)	✓	✓	✓
Educational attainment	✓	✓	✓
Formal and informal employment	✓	✓	✓
Women's time use (primary and secondary activities)	✓	✓	✓
Household income and expenditure	✓	✓	✓
Household assets	✓	✓	✓
Baseline survey	✓	—	—
Year 1 follow-up survey	—	✓	—
Year 2 follow-up survey	—	—	✓

[a]✓: indicates that data on that outcome were collected in the indicated survey wave.

[b]–: indicates that data on that outcome were not collected in the indicated survey wave.

Survey Instruments and Monitoring Tools

A paper version of the baseline survey instrument, which served as a template for all follow-up surveys, is provided in Multimedia Appendix 1. Before administering the survey, we explained the purpose of the study to respondents and asked for their consent using the study consent forms. Baseline surveys, anthropometric measurements, and related study activities (eg, discussion of anthropometric and anemia test results) were administered in a private room in the woman's place of residence and lasted approximately two hours overall (75 min for administering the child anthropometry and woman questionnaire to the woman and her children aged <6 years and 45 min for administering the household questionnaire to the financially knowledgeable respondent). Short breaks of 5 to 10 min were given to the respondents at the end of each section, and additional breaks were taken at the request of the participant and at other scheduled times (eg, mealtime, picking children up from school, etc) as needed. Surveys were conducted in Chichewa, the local language, and followed the format of the survey questionnaire, which were electronically programmed into Android tablets. To successfully track our participants over time, we collected identifiable data, including names and contact information for each of the survey respondents (the woman, her children aged <6 years, and the financially knowledgeable member of the household), the names and background characteristics of other household members, the household address, contact phone numbers and emails, and GPS coordinates of the household. For the purpose of minimizing loss to follow-up, we took photographs of the household and of the survey respondents, and we asked respondents to provide the names and contact information of 2 contacts who did not live in the household and who could be contacted if the respondents could not be directly located in the follow-up

period. To protect participant privacy and ensure confidentiality, all identifiable data are appropriately stored and secured in accordance with the data security measures described in the sections below.

The 1-year and 2-year follow-up surveys were administered in person to all women who continued to live in urban Lilongwe and who could be contacted within 3 contact attempts by the local field team. For women who either moved out of urban Lilongwe or who were unreachable after 3 contact attempts, the field team attempted to contact them by phone up to a maximum of 3 attempts; women who were reachable by phone within these 3 attempts were asked to participate in a short phone follow-up survey. To maintain a respondent's privacy during an attempt to reach her by phone, the field enumerator conducting the call left no indication of the reason for the phone attempt (eg, voicemail, text message) on the respondent's phone if there was no response to a call. To ensure that the respondent's participation remained private, the field enumerator only continued with the phone call once she received assurance from the woman that she was able to speak on the phone without being overheard or interrupted. Any disruption or interruption during the phone call resulted in postponement or termination of the call. The phone follow-up survey instrument took no more than 20 min overall, and was an abbreviated version of the main in-person follow-up survey instrument. The aim of the phone survey was to maximize survey follow-up rates by attempting to include women who were physically unreachable. The only respondents who were recontacted for the phone follow-up survey were those respondents who were simply lost to follow-up. Respondents who had previously indicated that they were no longer interested in participating in the study were contacted.

The phone follow-up survey instrument consisted of abbreviated modules from the main in-person follow-up survey instrument. Before administering the phone survey, we explained clearly the purpose of the follow-up to respondents and asked for their consent to participate in the survey verbally over the phone. Following receipt of consent, we ensured confidentiality and privacy of responses by asking the respondent to find a private room or space where their responses could not be overheard by others. We proceeded with the phone survey only after having received confirmation from the respondent that her responses could not be overheard.

Analysis Plan

Analysis of quantitative study data will be conducted using STATA and R (the R Project), where appropriate. A descriptive analysis will be performed for all variables, and unadjusted comparisons between experimental arms will be conducted. Descriptive statistics will be performed, including frequencies, means, and standard deviations. In addition, chi-square tests and one-tailed t tests will be used to examine associations in the data. A P value <.05 will be considered statistically significant for all statistical tests that are conducted. Given our hypotheses of the impact of our intervention on our key outcomes, one-sided hypotheses tests will be conducted for all our main analyses. Continuous variables will be tested for normality and nonnormal values will be categorized or transformed appropriately.

Our main econometric specifications will estimate the intent-to-treat (ITT) effect of our family planning intervention on fertility and other outcomes by directly regressing our outcomes of interest on a binary variable indicating receipt of the intervention. The main econometric specification for estimating the ITT effect of our family planning intervention is defined as follows:

where Y_{it} is the outcome variable of interest for woman i in the period $t=0,1,2$ for baseline, 1-year follow-up, and 2-year follow-up, respectively; T_{it} is an indicator of assignment to the treatment arm; X_{it} is a vector of individual-level covariates that are controlled for in the analysis; $_i$ is the individual-specific fixed effect; Y_{i0} is the baseline level of the outcome; and ε_{it} is the error term. Here, the outcome variables of interest include immediate, intermediate, and long-term outcomes mentioned in the previous sections.

We will conduct several subgroup analyses to examine how the family planning intervention effects vary across particular subpopulations. Subgroups of interest include pregnant women, new mothers, women who have previously used family planning, women who expressed a desire to space or limit births at baseline, poorer women, and women with low educational attainment. In addition, we will estimate heterogeneous treatment effects for girls, older children, and high-parity households.

Sample Size and Power Calculations

The sample size of this study was powered to primarily identify the effect of using family planning on fertility; however, we will also examine the effects of the intervention on other maternal and child health outcomes of interest, in addition to key social and economic measures of well-being. On the basis of the preliminary power calculations for our primary outcomes of interest, a total of 2000 women were needed to be enrolled in the study. Of the women who were enrolled, the family planning intervention, baseline survey, and 2 follow-up surveys were administered to 1000 women (the treatment group), whereas a basic family planning information package, the baseline survey, and 2 follow-up surveys were administered to the other 1000 women (the control group).

Our target baseline sample consists of 2000 women who met the eligibility criteria and who consented to participate in the study. Previous research studies in Accra, Ghana, have found that 32% of initially screened women either did not meet the eligibility criteria or refused to participate [20-22]. Therefore, to meet our target sample size of 2000, we would need to screen 3000 households if we conservatively assumed a combined ineligibility or refusal rate of 32% from the screening. Of the 2000 women who were to be recruited into the study at baseline following the initial screening process, 1000 women were to be randomly assigned to the intervention arm and the remaining 1000 women were to be randomly assigned to the control arm. On the basis of prior study findings from Zambia [13], we expected an attrition rate of 27% in the sample over a 2-year study period, which would leave us with an attrition-adjusted sample size of 730 women in each treatment arm, or 1460 women overall, at the end of the 2-year study period.

Given this attrition-adjusted sample size, we have powered our study to detect effects in 2 key outcomes, namely changes in contraceptive prevalence and fertility, the latter measured by the number of births per woman.

Contraceptive Prevalence

Using modern contraceptive prevalence estimates for Lilongwe from the 2010 Malawi DHS, we expect a modern contraceptive prevalence rate of 19.5% among women aged 18 to 35 years who are either currently pregnant or who are up to 6 months postpartum at baseline. To infer a potential effect size for our intervention, we look to evidence from (1) the Navrongo study in Ghana, which found that a family planning intervention with a comprehensive outreach and contraceptive delivery component increased contraceptive use by 6 to 8 percentage points over a 4-year study period and (2) the Matlab study in Bangladesh, which found far larger effects of contraceptive uptake among women in the intervention areas over a longer study period [9,23]. Our power calculations show that we will have 90% power to detect a 6.5 percentage point increase in the modern contraceptive prevalence rate in the intervention arm, from 19.5% to 26%, assuming that we will have an attrition-adjusted sample of 1460 women (730 women in each arm) at the end line.

Table 3 presents the levels of power 1-ß that will be achieved for various minimum effect sizes for modern contraceptive

prevalence use (ie, the difference in the modern contraceptive prevalence rate between the intervention and control arms at end line), assuming a baseline contraceptive prevalence rate of

19.5 percentage points in both intervention and control arms and a fixed end-line sample size of 1460 women (730 in each arm).

Table 3. Power calculations—contraceptive prevalence rate.

Control CPR[a], n (%)	Intervention CPR, n (%)	Significance level, α	Control sample size	Intervention sample size	Power
142 (19.5)	190 (26)	.05	730	730	0.90
142 (19.5)	183 (25)	.05	730	730	0.79
142 (19.5)	175 (24)	.05	730	730	0.65
142 (19.5)	168 (23)	.05	730	730	0.47

[a]CPR: contraceptive prevalence rate.

Fertility (Number of Children Per Woman)

Similarly, we use fertility estimates for Lilongwe from the 2010 Malawi DHS and assume a baseline fertility rate of 4.5 births per woman in the sample at baseline. To infer a potential effect size, we again look to evidence from the Navrongo and Matlab studies, both of which found a total reduction of 1 birth per woman (equivalent to a 15% decrease in their respective baseline fertility) among women in their respective intervention arms over their respective study periods [9,23]. In recognizing that both the Matlab and Navrongo studies were larger-scale, cluster-randomized designs with longer follow-up periods, we estimate that we will only be able to observe differences of 0.5 births. Our power calculations show that we will have 99% power to detect a 0.5 birth per woman decrease, equivalent to a 12% decrease in fertility, in the intervention arm from 4.5 children per woman to 4.0 children per woman, assuming an

attrition-adjusted sample of 1460 women (730 women in each arm) by end line.

Table 4 presents the levels of power 1-ß that will be achieved for various minimum effect sizes for fertility (ie, the difference in the average number of children per woman between the intervention and control arms at end line), assuming a baseline fertility of 4.5 children per woman in both intervention and control arms, a standard deviation of 2 children per woman for both arms, and a fixed end-line sample size of 1460 women (730 in each arm).

Finally, robustness checks (5% and 10% sample truncations and coarsening of independent variables) and falsification tests, which include placebo regression, simulation, and resampling methods, will be conducted to ascertain the strength and significance of our estimates. We will also conduct attrition-adjusted analyses to assess the extent of differential loss-to-follow-up outcomes.

Table 4. Power calculations—fertility.

Control fertility, number of children per woman	Intervention fertility, number of children per woman	Significance level, α	Control sample size	Intervention sample size	Power
4.5	3.5	.05	730	730	1
4.5	4.0	.05	730	730	0.99
4.5	4.2	.05	730	730	0.89
4.5	4.3	.05	730	730	0.61

Dissemination Plan

For this study, we have partnered with Dimagi, a privately held social enterprise based in Cambridge, Massachusetts, and will use Dimagi's CommCare open-source software suite to develop our electronic survey instruments, supervise survey enumerators and field staff activities, collect and manage respondent data, and monitor data quality. In addition to supporting our study from their Cambridge headquarters, a Dimagi field engineer will provide on-site technical support and train local field staff and survey enumerators to use the CommCare software for administering the baseline survey. We have also formed a partnership with IPA Malawi, a US-based nonprofit research organization with operations in 42 different countries. IPA Malawi has provided extensive technical and research assistance in health and development to many governmental and nongovernmental organizations in Malawi, including the MOH

and the World Bank. We worked with the IPA Malawi management team and a hired team of surveyors, field managers, intervention staff (family planning counselors and driver), and other support staff to conduct the fieldwork. IPA Malawi's primary role in the study was to conduct the local field research activities, including (1) hiring, training, and management of the local field staff; (2) data collection, monitoring, and evaluation; (3) implementation of the intervention; and (4) assisting the investigators with the dissemination of results in Malawi. Finally, we worked closely with the MOH and RHD on dissemination activities for this study and regularly met with representatives from the MOH and RHD to share results and to facilitate collaboration on the study.

Aggregate summary statistics and final peer-reviewed publications will be shared with participants, key partners (IPA Malawi, Dimagi, Good Health Kauma Clinic), the Malawi

MOH, the Malawi RHD, and the Malawi NSO. Individual survey responses of other participants will not be shared among the participants verbally, by recording, or in writing. Each interviewee's responses will remain confidential as per the terms of their consent to study participation.

We will produce the output in peer-reviewed journals, working papers, and policy briefs that are accessible to academics, policy makers, and practitioners and contribute to the policy change in this area. Aggregate results and final publications will be disseminated to the community and local institutions where the research is conducted. The research team will also present intervention findings at local and national venues, including annual meetings of professional organizations, community gatherings, and meetings with local service providers. Our work will also be effectively disseminated to practitioners through local partnerships as well as through the RHD and MOH. We have worked with these organizations during the study design phase to ensure that the interventions are appropriate for the country setting. Upon completion of the intervention, we will know the midterm and long-term effects of the interventions, and our local partners can use this information to expand or tailor their services to help women achieve their family planning goals within the specific country context. We will also share our descriptive and analytical findings with members of the community who are engaged in advocacy efforts.

Our dissemination efforts are engrained in our interventions from the outset. We tailored our information packs and counseling materials for women in Malawi based on knowledge gained from preliminary studies of the family planning environment. This dissemination of information as part of the intervention will help us learn how to disseminate the results of our research to the women in the communities we are working in.

Data Confidentiality

All identifiable data collected from surveys (both baseline and follow-up) and from the intervention were administered in an electronic computer-assisted personal interview format using the Dimagi CommCare survey management system. Electronic survey data were collected by interviewers on Android-based tablets, and data were securely transferred onto a CommCare-supported secure cloud server. The CommCare cloud server was Health Insurance Portability and Accountability Act–compliant and met all the necessary security requirements for storing identifiable data. A technical overview of the CommCare system and an electronic version of the CommCare Terms of Use or End User License Agreement can be found on the web [24,25].

All data uploaded to the CommCare server were encrypted and password protected in accordance with the approved data storage regulations. For each collected data case, all personal identifiable data were separated from the other nonidentifiable data. Identified data were only accessed for the purpose of revisiting the households at the 1- and 2-year follow-up periods. Only deidentified data sets will remain available for analysis purposes after the end of the study. All confidential identifiable data were secured by trained study personnel upon collection. Identifiable hardcopy data, including signed consent forms, were stored in

locked cabinets in access-limited rooms at the IPA Malawi office.

With specific regard to the dissemination of identifiable data, policies were put in place to limit data dissemination beyond the immediate research team (comprising the principal investigator and coinvestigators and the project managers). Team members received training on the proper handling and storage of such data, and all staff members of the study were required to sign a data confidentiality agreement. Data sharing of deidentified data between the principal investigators and authorized research staff was conducted in person. Deidentified data are transmitted from Malawi to the Harvard T. H. Chan School of Public Health (HSPH) via secure file transfer (through the Harvard system). All hardcopy data and electronic data are retained for 7 years after study closure, after which they will be destroyed (shredding hardcopies and permanently deleting all electronic files). Following the completion of the analysis, data will be stored on the HSPH network and will be deleted from all the hard drives of all the authors.

Data Safety and Monitoring

The study principal investigator, DC, has assumed overall responsibility for the safety, monitoring, and review of the data. DC and MK have been present during the rollout of the baseline survey, intervention, and follow-up surveys. The local project manager at IPA Malawi; the local coinvestigator, Bagrey Ngwira; and the principal investigator, DC, have reviewed any adverse events. This information has been provided to the IRB at Harvard University and the Malawi NHSRC ethics committee in Lilongwe. Unanticipated adverse events were immediately reported by the local field team to both the Harvard IRB and the NHSRC in writing within 5 business days. We did not anticipate that there would be any research-related injuries. Nevertheless, IPA Malawi field staff (surveyors, field managers, and interventionists) were trained in first aid and project managers at IPA Malawi were on call via mobile phone during the entire duration of the study.

Regulatory Compliance

MK, Bagrey Ngwira, and the IPA Malawi project manager are the immediate supervisors of study staff in the field (research assistants). In addition, the local team and the Boston-based team have been in regular contact via email in the interim to discuss the progress of the study protocol procedures. DC and MK traveled regularly to Malawi over the course of the study period, particularly during the data collection phases to monitor field activities. All regulatory documentation will be maintained for 7 years after IRB study closure.

Authorship Eligibility Guidelines

A publication committee consisting of Dr DC, the overall principal investigator, and Dr MK has been established to address and decide on all matters related to access to project data and publications using such data. All guidelines for data access and publications are outlined in the publication committee Terms of Reference document (available upon request).

Availability of Data and Materials

Following our own use and analysis of the data and publication of the main findings that have been identified as part of the study preanalysis plan (a minimum period of 1 year from the end of the study), we hope to open access to deidentified baseline and follow-up survey data at no cost to authorized users. Only deidentified data will be available for download through a secure website, through which authorized users can download deidentified survey data files for legitimate academic research. To access the data, prospective users must first register on the secure website and must then create a new research project request. The request must include a project title and a description of the analysis that the user proposes to perform with the data. The requested data should only be used for research or study purposes. To request the same data for another purpose, a new research project request needs to be submitted. Requests for data access will then be reviewed by the principal investigator, who can then grant or deny access to the user. All publications that users produce from the data set must appropriately acknowledge the data source and project from which the data were collected. Once downloaded, the data sets must not be passed on to other researchers without the written consent of the principal investigator. All reports and publications based on the requested data must be sent via email to the principal investigator in a PDF file or as a printed hardcopy. See the Publications Committee's Terms of Reference document (available upon request).

Results

Recruitment, Study Sample, and Randomization

Field activities for the baseline survey began with field staff hires, training, and piloting of the survey instrument in July and continued through August 2016. During the 5-month baseline survey period, 11,562 households were approached and women in these households were screened based on the eligibility criteria. On the basis of the eligibility screening, 2370 women (20.5%) in these households were eligible to participate in the study. Of these 2370 women, 2208 women (93.1%) agreed to go through the consent form with the enumerator, and 2078 women (94.1%) of the 2208 women who agreed to go through the consent form consented to participate and were subsequently enrolled in the study. This consenting sample of 2078 women constituted 87.7% of the eligible sample. Of these 2078 women, 2055 women (98.8%) completed the baseline survey and were eligible to be randomized into the intervention or control groups. From this baseline sample, 985 women were randomly assigned to the intervention group whereas the remaining 1070 women were randomly assigned to the control group. In addition to the 2055 women who were selected for the main study, 88 women were interviewed as part of a preliminary pilot study to test the feasibility of the survey instruments and implementation of the intervention. As part of the intervention rollout, these 88 respondents were also randomized into the treatment (n=41) and control (n=47) groups. The final analytic sample for the baseline survey comprised 2143 eligible women, of whom 1026 women were randomized into the treatment group and 1117 women were randomized into the control group. The experimental framework is presented in Figure 1.

Intervention Activities

Rollout of the multicomponent family planning intervention to women assigned to the intervention group began shortly after the launch of the baseline survey in September 2016. Six family planning counselors (registered nurses and midwives with previous counseling experience in family planning) were identified in mid-September 2016 and were trained through October 2016 to administer 6 counseling sessions in women's homes over a 2-year intervention period. Counseling of clients in the intervention group began in November 2016 and concluded in March 2018, at which time counselors may have completed up to 6 visits with each client.

In addition to hiring 6 counselors, the study management team hired and trained a licensed taxi driver in October 2016 to assist with the implementation of the transportation component of the intervention. In October 2016, the management team also identified an obstetrician at the Kamuzu College of Medicine to be the *medical doctor on call*. The obstetrician was asked to be responsible for (1) answering any calls from clients, (2) providing any support or consultation services over the phone, to the best of his ability, and (3) referring any clients who may be experiencing health concerns, particularly those related to their use of family planning, to the management team for follow-up.

Counseling activities with women in the intervention group concluded in March 2018; however, other intervention activities (providing transportation to women to visit the Kauma Clinic for services, providing financial reimbursements to women for any family planning services that they obtain) continued until February 2019.

Follow-Up Surveys

Two follow-up surveys were conducted 1 and 2 years after the baseline survey. Field activities for the Year 1 follow-up survey (wave 2) began with field staff hires, training, and piloting of the follow-up survey instrument in July 2017 and continued through August 2017. Official data collection for the baseline survey began in August 2017, and the last respondents were interviewed at the end of February 2018. During the 6-month Year 1 follow-up survey period, a total of 2092 women (which includes the full sample of 2055 women from the main study and an additional 88 women who were interviewed at baseline as part of the pilot phase of the study, but did not include the 51 women who withdrew from the study before start of the Year 1 follow-up survey) were selected for follow-up at their homes. A total of 1773 women, or 82.73% of women who were eligible for follow-up, were successfully contacted and reinterviewed at follow-up. Analyses of the 319 women who were lost to follow-up for this survey were conducted.

Field activities for the Year 2 follow-up survey (wave 3) began with field staff hires, training, and piloting of the follow-up survey instrument in July 2018 and continued through August 2018. Official data collection for the survey began in August 2018, and the last respondents were interviewed at the end of February 2019. During the 6-month Year 2 follow-up survey period, a total of 2090 women, which includes the full sample of 2055 women from the main study and an additional 88

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women from the pilot sample but excludes 51 women who were withdrawn from the study before the start of the Year 2 follow-up survey and 2 women who had died from causes unrelated to the study, were selected for follow-up at their homes. A total of 1669 women, or 77.88% of women who were eligible for follow-up, were successfully contacted and reinterviewed at follow-up. Analyses of the 421 women who were lost to follow-up are being conducted.

Analysis

All study-related field activities for the Year 2 follow-up survey concluded in March 2019. Cleaning and analysis of the baseline, Year 1, and Year 2 data is ongoing and will continue through 2021. A complete cleaned survey wave includes the following: a recoded and indexed data set, a data codebook, a recode map and variable list, a final survey questionnaire, a final report and user manual for the survey wave, and data analysis files and templates. Analyses of the primary outcomes are ongoing and are expected to be completed by 2021.

Discussion

Study Progress

We conducted a randomized controlled trial to identify the causal impact of improved access to PPFP among 2143 married postpartum women from urban Malawi. Women who were assigned to the treatment arm (n=1026) received a 2-year–long multicomponent family planning intervention that consisted of (1) a brochure and up to 6 home visits from trained family planning counselors, (2) free transportation to a high-quality family planning clinic, and (3) financial reimbursement for family planning services, consultations, and referrals for services. Two follow-up surveys were conducted 1 and 2 years after the baseline survey with 1773 and 1669 women, respectively. Through this randomized controlled trial, we aimed to investigate the extent to which improvements in access to family planning have effects on first-stage outcomes (contraceptive use, method mix, and adoption of long-acting methods, among others) as well as key intermediate and longer-term outcomes (short birth intervals, likelihood of pregnancy at 2 years, and downstream measures of well-being) of interest.

Although there is growing evidence to support the potential effectiveness of improved access to PPFP services on contraceptive use and method mix within the first year after birth, a recent review of PPFP interventions in low- and middle-income countries found that there is little to no evidence of the impact of such interventions on longer-term measures of contraceptive continuation, birth spacing, or pregnancy risk beyond the first postpartum year [1]. As a result, little is known about the role of PPFP on the continuation of contraceptive use and on birth spacing. In conducting this trial, we aim to provide the first causal estimate of the impact of PPFP on birth spacing and risk of subsequent pregnancy in sub-Saharan Africa, and perhaps globally.

Our PPFP intervention was designed to address the key barriers that women in urban Malawi face when seeking and accessing reproductive health services. When considering family planning within the larger context of maternal and reproductive health, we identified both barriers to access that are particular to family planning care-seeking behavior and utilization in addition to more common barriers to access (eg, geographic barriers, financial accessibility constraints, etc) [26]. Fear of contraceptive-related side effects has been identified as one of the most commonly cited barriers to family planning utilization and continuation, and is consequently a key contributing factor to unmet need for family planning, particularly in Malawi, where hormonal methods of contraception such as injectable contraceptives (Depo-Provera) are the most widely used [14,15,27]. In recognizing the role of contraceptive-related side effects on uptake and continuation, we included family planning counseling sessions that specifically focus on informing women in the treatment group about side effects and aimed at addressing myths and misperceptions around contraception. In addition, we provided women in the intervention arm with access to free over-the-phone consultations with a doctor, a service that women may utilize in the event that they may experience contraceptive-related side effects.

Our key outcomes are measured using a range of validated metrics and instruments. The baseline survey instrument consists of modules from the household and women's questionnaires from the Malawi DHS, which is a nationally representative survey that includes information on marriage, fertility, family planning, reproductive health, and child health [2] and modules on employment, household expenditures, and time use from the World Bank's Living Standards Measurement Study and the Institute of Statistical, Social and Economic Research Ghana Time Use and Health Study. By adapting these instruments for our study, we will also be able to compare our findings across a range of nationally representative data sources. When assessing the impact of our intervention, it will be important for us to reconcile our findings with previous evidence, particularly from the Matlab and Navrongo studies, where much of the evidence of family planning programs is generated. By the same token, we have also gathered costing data to speak to the cost-effectiveness of our intervention relative to other similar PPFP and reproductive health programs that have been implemented and evaluated.

Conclusions

There is an increasing emphasis by policy makers and practitioners on evidence-based policy for family planning and reproductive health. Practitioners require a strong evidence base of what works in family planning to decide which interventions are most likely to achieve the desired outcomes. Given the many competing needs for funds in developing countries, high-quality evidence that demonstrates the benefits and effectiveness of family planning is required if policy makers are to justify the provision of family planning services. Through this study, we seek to fill the current knowledge gaps on the effectiveness of family planning interventions by directly identifying the impact of an increase in access to family planning on fertility and health outcomes in a sub-Saharan African context, where rigorous experimental evidence is scarce. Service providers and policy makers will be able to use the findings from our study to improve the availability of and access to reproductive health services in Malawi as well as in other similar settings.

Related Articles

At present, no other publication containing the results of this study has been published or submitted to any journal.

Authors' Contributions

All authors contributed equally to the design and development of the study and to the production of the study protocol. MK contributed to various sections and drafted the manuscript. MK and DC contributed to the development or revision of study instruments, power calculations, sampling, implementation plans, and plans for data analysis. All authors have read and approved the manuscript for publication.

Conflicts of Interest

External funding for the study was provided through two grants by the William and Flora Hewlett Foundation, Menlo Park, California, United States. The funder had no role in the design and implementation of this study and will have no role in the data analyses, interpretation of results, or in the dissemination of findings. In addition, the study protocol did not undergo peer review by the funding body. Finally, the investigators declare that no competing interests exist.

Multimedia Appendix 1
Survey instrument, recruitment script, and consent form.
[PDF File (Adobe PDF File), 1072 KB - resprot_v9i8e16697_app1.pdf]

Multimedia Appendix 2
Family planning brochure.
[PDF File (Adobe PDF File), 276 KB - resprot_v9i8e16697_app2.pdf]

Multimedia Appendix 3
Transport voucher.
[PDF File (Adobe PDF File), 73 KB - resprot_v9i8e16697_app3.pdf]

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Abbreviations

BLM: Banja La Mtsogolo
DHS: Demographic and Health Survey
HSPH: Harvard T. H. Chan School of Public Health
IPA: Innovations for Poverty Action
IRB: Institutional Review Board
ITT: intent-to-treat
IUD: intrauterine device
MDHS: Malawi Demographic and Health Survey
MOH: Ministry of Health
NHSRC: National Health Sciences Research Committee
NSO: National Statistics Office
PPFP: postpartum family planning
PSI: Population Services International
RHD: Reproductive Health Directorate
WHO: World Health Organization

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Protocol

Specialized Nutritious Food Combined With Cash Transfers and Social and Behavior Change Communication to Prevent Stunting Among Children Aged 6 to 23 Months in Pakistan: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: In Pakistan, the prevalence of stunting in children younger than 5 years has remained above global critical levels over the past two decades, with the stunting rate being 40.2% in 2018. Children living in rural areas and in the poorest households suffer the most from stunting across the country—43.2% in rural areas and 51.4% in the lowest wealth quintile. As a continuing public health concern, it is essential that stunting prevention is a national priority in order to ensure human capital development, especially among the poorest households.

Objective: The primary objective of this study is to determine the effect of a medium quantity of a lipid-based nutrient supplement (LNS) combined with unconditional cash transfers and social and behavior change communication (SBCC) on reduction of stunting in children aged 6 to 23 months.

Methods: A 5-arm cluster randomized controlled trial will be conducted in the district of Rahim Yar Khan in Punjab, Pakistan. The intervention packages will be (1) cash only, (2) cash with LNS, (3) cash with SBCC, and (4) cash with SBCC and LNS. The control arm will receive routine standard of care. We will enroll children at 6 months of age and follow up on a monthly basis up to 24 months of age. A total of 2000 children, 400 in each arm, will be enrolled to detect a 20% reduction in the prevalence of stunting among children aged 24 months. Length, weight, food intake, compliance to interventions, morbidities, and other relevant data will be collected at enrollment and on a monthly basis over the period of 18 months. The process evaluation will assess acceptability of the interventions and potential barriers to implementation through focus group discussions and in-depth interviews with the target population and relevant stakeholders. Furthermore, a cost analysis will be conducted to assess the cost-effectiveness of each intervention package.

Results: The study protocol was approved by the Ethics Review Committee of Aga Khan University in Pakistan on January 4, 2017. Data collection began in May 2017 and was completed in July 2019. Data analyses are yet to be completed. This study will explore the effectiveness of intervention packages comprised of cash transfers from Benazir Income Support Programme with

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or without additional LNS and SBCC in preventing childhood stunting. We expect the results to be published in peer-reviewed journals by autumn of 2020.

Conclusions: The findings of this trial will provide robust evidence as to which intervention packages can have significant effects on linear growth of children and design effective intervention packages to prevent stunting in children aged 6 to 23 months.

Trial Registration: ClinicalTrials.gov NCT03299218; https://clinicaltrials.gov/ct2/show/NCT03299218

International Registered Report Identifier (IRRID):   DERR1-10.2196/19001

Introduction

Child stunting remains a major barrier to human capital development worldwide. In 2018, a total of 149 million, or 22%, of children younger than 5 years worldwide were found to be stunted [1]. South Asia has 57.9 million stunted children younger than 5 years, one of the highest burdens of stunting across regions [2].

In Pakistan, the prevalence of stunting in children younger than 5 years has remained above global critical levels over the last two decades, with the stunting rate being 40.2% in 2018. Children living in rural areas and in the poorest households suffer the most from stunting across the country—43.2% in rural areas and 51.4% in the lowest wealth quintile [3].

Stunting has underlying factors that expand beyond nutrition, health, and agriculture to include poverty and social vulnerability. Social protection is increasingly recognized globally as a strategic tool to improve maternal and child nutrition outcomes due to its ability to alleviate poverty and social vulnerability. In particular, cash transfers have become increasingly popular as an effective, efficient, and welcome means for welfare improvement of low-income households in many low- and middle-income countries (LMICs) [4-6]. Cash transfers may be in the form of unconditional cash transfers (UCTs) or conditional cash transfers, which are provided on the condition that recipient households must carry out certain actions (such as uptake of health, education, or nutrition services) [7].

A conditional cash transfers study from Mexico reported a significant positive impact on child growth, with an increase of 16% in the mean child growth per year (1 cm per year), and a positive effect on the consumption of vitamins and minerals among beneficiary households [8]. A review on the impact of conditional cash transfers in LMICs concluded that cash transfers had a positive impact on nutritional status [9]. Estimates of cash transfer programs in Africa indicated a positive effect on anthropometric status [10-12].

Evidence shows that people can change their behaviors to improve nutrition outcomes when provided with financial support to afford nutritious foods [13]. Through the Maternal and Child Cash Transfers for Improved Nutrition program in Myanmar, pregnant women in targeted villages were provided with monthly cash transfers of K 15,000 (US $10.50) and social and behavioral change communication (SBCC) until their child was aged 2 years [14,15]. The cash transfer aimed to support women's ability to afford nutritious food for themselves and their children. A recent impact evaluation study of the program revealed that cash transfers combined with SBCC reduced stunting by 4 percentage points and wasting by 3 percentage points compared with only cash transfers. However, with the limited size of the cash transfers (US $10-15 per month) and the large affordability gap experienced in the poorest 20% to 30% of households, in-kind nutritional supplementation is essential in order to prioritize improving nutrition for the most vulnerable, pregnant and lactating women (PLW) and children younger than 2 years [14,15].

Lipid-based nutrient supplements (LNS) were developed for the treatment of moderate acute malnutrition and prevention of undernutrition among children aged 6 to 59 months. [16]. Many intervention studies showed contrasted effects on the incidence of wasting and stunting and on mean change in weight for height, weight gain, height for age, and height gain, with some experiments demonstrating positive results and others indicating no impact [17-25]. The variations in outcomes of these studies might be due to differences across studies, such as targeting of children of various age groups and nutritional statuses, use of different types and quantities of supplements, different study designs, and implementation in different contexts.

Punjab, where half of the population of Pakistan lives, has one of the highest burdens of stunting (36.4%). Nearly 47% of the children from the poorest households in the province are stunted. Based on provincial statistics, the highest rate of stunting and poverty can be seen in Southern Punjab, especially in the district of Rahim Yar Khan, where more than 20% of the people live in extreme poverty and 2 out of 5 children younger than 5 years are stunted. Among the poorest 20% of households, 1 out of 2 children younger than 5 years are stunted in the district of Rahim Yar Khan in Punjab [3].

The Aga Khan University (AKU) will conduct a cluster randomized controlled trial in the district of Rahim Yar Khan in collaboration with the Integrated Reproductive Maternal Newborn, Child Health & Nutrition Program and the Benazir Income Support Programme (BISP). The intervention packages include LNS, UCTs, and SBCC, targeting the current BISP beneficiary households (poorest 20% of households) of the district. The World Food Programme provided the funds.

The primary objective of this study is to determine the effect of the unconditional cash transfer program alone and combined

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with behavior change communication, specialized nutritious food supplementation, or both on reduction in the prevalence of stunting among children aged 24 months. Secondary objectives include reduction in the prevalence of wasting and underweight, improvement in the micronutrient status and infant and young child feeding practices, and evaluation of the cost-effectiveness of different packages for reduction of stunting among children aged 24 months.

Methods

Study Setting

The study will be conducted in the district Rahim Yar Khan in Punjab, Pakistan. The district is located in the southern part of Punjab province, with an area of 11,880 square kilometers. The district is administratively subdivided into 4 tehsils and 122 union councils and has a population of 4.8 million (79% living in rural areas). According to the 2018 Multiple Indicators Cluster Survey conducted in Punjab, the literacy rate is 43.1% among women and 58.1% among men aged 15 to 49 years in Rahim Yar Khan [26]. Within the district, 13.1% of the population has

access to improved sources of drinking water (piped water), 75.6% have access to improved sanitation, and 90.6% have access to electricity. As a predominately agrarian district, only 7.8% and 56.2% of households own agriculture land and livestock, respectively. Furthermore, infant mortality (56 infant deaths per 1000 live births) and under-5 mortality (66 child deaths per 1000 live births) are similar to the provincial (60 infant deaths per 1000 live births and 69 child deaths per 1000 live births) and national averages (62 infant deaths per 1000 live births and 74 child deaths per 1000 live births) [26].

Interventions

A combination of preventative interventions will be implemented to address stunting among children aged 6 to 23 months from BISP beneficiary households. The interventions will consist of locally produced LNS for children aged 6 to 23 months, a UCT delivered through BISP for households with children aged 6 to 23 months, and SBCC focused on health, nutrition, and hygiene delivered through lady health workers (LHWs) (Textbox 1). The nutritional value of the LNS is shown in Table 1. The control group will receive routine public health services available within the area.

Textbox 1. Intervention packages.

Unconditional cash transfers

A total of Rs 5000 (US $32) on a quarterly basis will be transferred by the Benazir Income Support Programme throughout the study period. Participants will be able to collect their cash transfers from automated teller machines in the form of direct cash after biometric verification.

Lipid-based nutrient supplement – medium quantity

A locally produced lipid-based nutrient supplement (called Wawamum) will be provided to children aged 6 to 23 months by the study team. Wawamum is made with heat-treated (roasted) chickpeas, vegetable oils, dry skim milk, sugar, vitamins, minerals, emulsifier, and antioxidants (Table 1). A daily ration of 50 grams of Wawamum (1 sachet) will be provided to cover the recommended daily allowance of most micronutrients and 260 kilocalories of energy (about a quarter of daily energy requirements). Each recruited child will receive Wawamum for a duration of 18 months from 6 months to 24 months of age.

Social and behavior change communication (SBCC)

SBCC messages will be delivered by the lady health workers from the existing public health system during their routine monthly house-to-house visits and in community sessions on a quarterly basis with the help of a specialized picture booklet. Lady health workers will receive 2 days of intensive SBCC training before the initiation of the study enrollment and a 1-day refresher training annually, with special emphasis on communication skills, introduction of complementary feeding, and dietary diversity. All enrolled mothers will receive 18 individual house-to-house visits and 6 community sessions. Other household and community members will also be encouraged to participate in the sessions.

Table 1. Nutritional values of lipid-based nutrient supplement—medium quantity.

Nutritional values (per 50 g/1 serving)	Minimum	Maximum
Energy, kcal	255	280
Protein, g	5.5	8
Fat, g	13	18
ω-3 fatty acids, g	0.15	0.9
ω-6 fatty acid, g	1.3	3.1
Retinol (Vitamin A), µg	275	575
Thiamin (Vitamin B_1), mg	0.5	—[a]
Riboflavin (Vitamin B_2), mg	1.05	—
Niacin (Vitamin B_3), mg	6.5	—
Pantothenic Acid (Vitamin B_5), mg	2	—
Pyridoxine (Vitamin B_6), mg	0.9	—
Biotin (Vitamin B_7), µg	30	—
Folate (Vitamin B_9), µg, DFE[b]	165	—
Cyanocobalamin (Vitamin B_{12}), µg	1	—
Ascorbate (Vitamin C), mg	30	—
Cholecalciferol (Vitamin D), µg	7.5	10
Tocopherol Acetate (Vitamin E), mg, ATE[c]	8	—
Phytonadione (Vitamin K), µg	13.5	—
Calcium, mg	268	375
Copper, mg	0.7	1.0
Iodine, µg	50	70
Iron, mg	5	7
Magnesium, mg	75	113
Manganese, mg	0.6	1.2
Phosphorus, mg	225	375
Potassium, mg	450	700
Selenium, µg	10	20
Sodium, mg	—	135
Zinc, mg	5.5	7

[a]Not available.

[b]DFE: dietary folate equivalents.

[c]ATE: α-tocopherol equivalents.

Study Design

A 5-arm cluster randomized controlled trial will be conducted to examine the effectiveness and cost-effectiveness of UCT, LNS, SBCC, and their combinations to prevent stunting in children aged 6 to 23 months living in BISP beneficiary households. The 5 study arms will be (1) control group, which will receive routine government health services; (2) BISP cash transfers; (3) BISP cash transfers and SBCC; (4) BISP cash transfers and LNS; and (5) BISP cash transfers, LNS, and SBCC (Figure 1).

Figure 1. CONSORT flow diagram of the study. BISP: Benazir Income Support Programme; CONSORT: Consolidated Standards of Reporting Trials; LNS: lipid-based nutrient supplement; SBCC: social and behavior change communication.
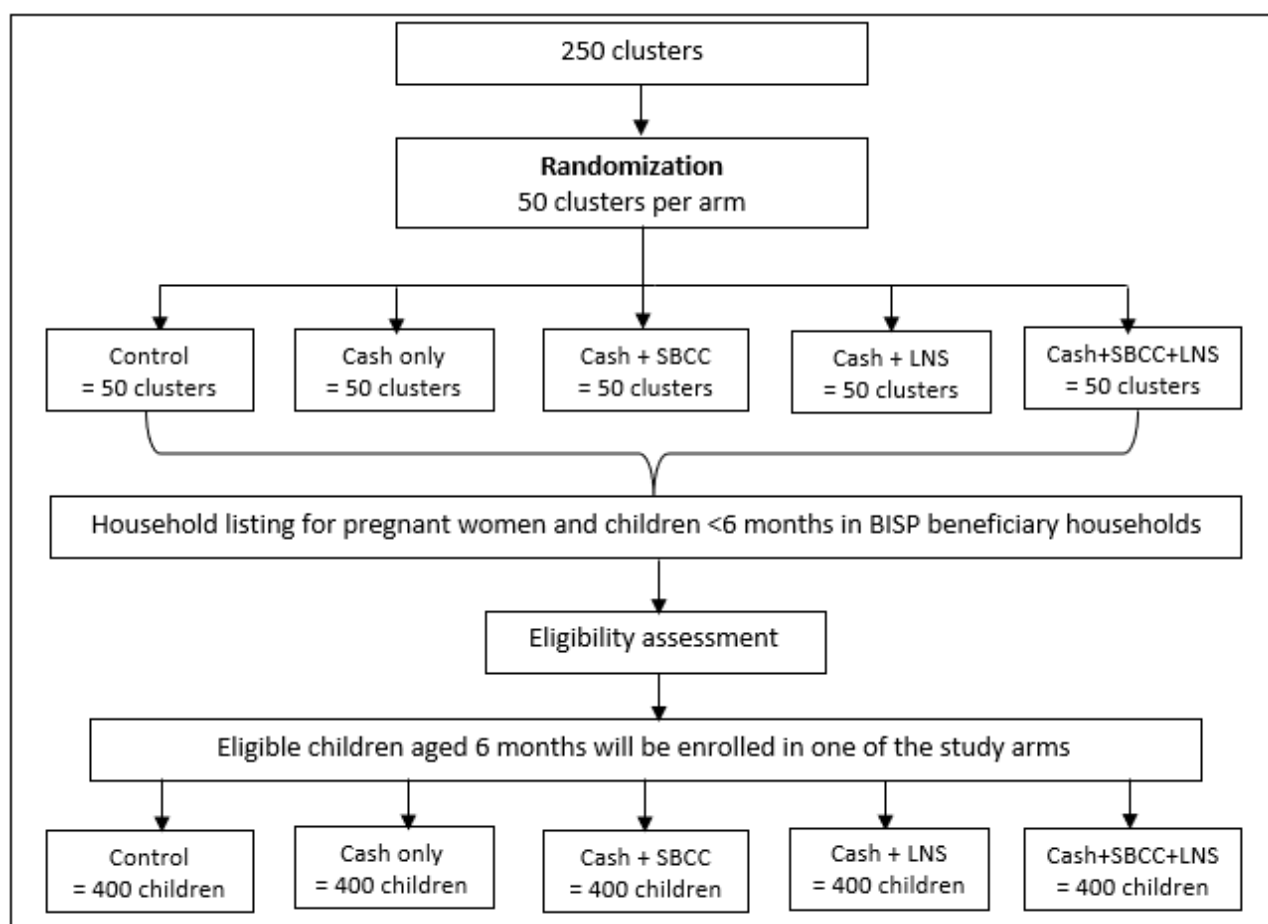
Furthermore, a formative research study will be conducted to design the SBCC package based on social cognitive theory and principles of social marketing using concepts from an integrated behavioral model. The implementation of the SBCC package will foster eating practices following the World Health Organization recommendation for PLW, adequate infant and young child feeding (IYCF) practices, use of LNS, and water, sanitation, and hygiene (WASH). A process evaluation will be conducted every 6 months to assess and identify bottlenecks, opportunities, and operational factors affecting the implementation. A cost analysis will also be conducted to assess the cost-effectiveness of each intervention.

Ethics Approval and Consent to Participate

The Ethics Review Committee of Aga Khan University has granted approval for the proposed study (No. 4572-Ped-ERC-16). The National Bioethics Committee of Pakistan has granted approval for the study to be conducted on human participants (No. NBC-238). The trial is registered on Clinicaltrials.gov (NCT03299218). Written informed consent will be obtained from all study participants prior to enrollment in the study.

Sample Size

A sample size was calculated to detect a 20% reduction in the prevalence of stunting among children aged 24 months, with 45% as the baseline prevalence of stunting among children aged

6 to 23 months [27]. The unit of randomization was the LHW's catchment area, while the catchment area of 2 LHWs was considered one cluster. A sample size of 8 children per cluster was estimated with a statistical significance of P=.05, power of 0.80, and intracluster correlation of 0.0001. Each study arm has 50 clusters, from which 400 children aged 6 months will be enrolled in the study. A total of 2000 children will be enrolled in the study. The sample size was calculated using PASS software (version 11; NCSS LLC) [28].

BISP beneficiary households are defined as households with a poverty score of less than 16.17, based on indicators such as household size, housing structure, type of toilet facilities, education, child status, household assets, agricultural landholding, and livestock ownership. Children with severe acute malnutrition or chronic illness will not be enrolled and will be referred for treatment to the nearest public health facility.

For the formative research study and process evaluation, qualitative data will be collected through 80 in-depth interviews with key informants and 30 focus group discussions with mothers, fathers, mothers-in-law, and LHWs. Direct observations will also be conducted at household level to observe feeding practices and at community level to observe delivery of counseling sessions by LHWs every 6 months and at endline.

Randomization

The unit of randomization will be catchment area of LHW. The randomization and allocation of study arms will be done by the data management unit (DMU) at AKU in Karachi, Pakistan using secondary data from BISP and the Punjab Health Department from the district Rahim Yar Khan. A total of 250 clusters, 50 in each study arm, will be randomized to the 4 interventions and 1 control arm.

Eligibility Criteria

To be included in the study, households will have to meet 4 eligibility criteria: (1) BISP beneficiary for intervention arms and BISP poverty score between 16.18 and 20.00 for control arm; (2) living in the catchment area of LHW; (3) have at least one child aged 6 months at the time of inclusion; and (4) willing and able to provide written informed consent or thumbprint for the study.

Data Collection

A total of 6 data collection teams will be hired locally from the district of Rahim Yar Khan for the study. Only women can collect data from mothers and their anthropometric measurements in the study area due to local cultural restrictions. Therefore, each team will consist of 2 female data collectors to interact with mothers and 1 male team leader to coordinate with fathers and male community members. The data collection teams will receive a 5-day hands-on training on study objectives, methods, data collection tools, techniques, anthropometric measurements, hemoglobin testing, and ethical issues. All questionnaires will be pretested in the field and changes will be incorporated accordingly before the actual data collection. A 1-day field test will be carried out before initiating field work. As part of the training, all field staff will be trained on anthropometric measurements with additional days for team measurers to continue to refine their skills. The training will include both in-class explanations and exercises with field practice. The training program will also include practice for weighing and measuring children.

Two trained staff will measure anthropometric measurements. The first measurer will measure and record each anthropometric measurement without revealing the values obtained to the second measurer. The second measurer will then independently repeat the same measurements. Each measurer will record their own values independently with no knowledge of the values recorded by the other measurer. After collecting the data, the 2 measurers will compare their measurements to ensure that the differences between their measurements fall within the standard maximum allowed differences (7 mm for length and 50 g for weight). Any pair of measurements that fall outside the maximum allowed differences will be repeated by both measurers and will be entered on the recording sheet. If this second pair of measurement values again exceeds the standard limits for that measurement, the measurers will repeat the measurement for a third and final time.

A structured questionnaire will be used to collect data on sociodemographic characteristics, parents' and children's anthropometric measurements, IYCF practices, immunization status, child morbidity, WASH, access and uptake of health services, exposure to other interventions, household food consumption, hunger scale, and household coping strategies at enrollment. The monthly follow-up questionnaire will be used to collect data on anthropometry (length and weight), compliance to intervention, morbidity, mortality, care-seeking patterns, and IYCF practices. Blood samples will be collected at 24 months of age for anemia and biochemical assessment.

Compliance data will be obtained by mother's recall and comparing the number of used and unused sachets during each follow-up visit. Children's weight will be assessed using a calibrated balance that allows double weighing (mother and child) and an automatic deduction of the mother's weight to obtain the child's weight. The scale (Seca GmbH) that will be used will have an accuracy of 50 g. Children's length will be measured using a length measuring board (Seca GmbH) with an accuracy of 0.1 cm. Hemoglobin levels will be tested using HemoCue Hb 301 (HemoCue AB) analyzers.

A subset of households (5%) will be revisited for the purpose of data quality control and quality assurance. The entire process of data collection will be carried out on handheld tablets and will be supervised by team leaders and study managers, who will review data entry for errors and inconsistencies. The data will be stored in the MySQL Workbench (Oracle Corp) database at the DMU.

Data Analysis

The primary independent variable will be the study arm, modeled as a 5-level categorical variable, with the control arm as the reference group. The primary outcome will be the prevalence of stunting, while wasting and underweight prevalence will be the secondary outcomes. Stunting will be defined as length-for-age z score (LAZ) less than –2 SD, wasting as weight-for-length z score (WLZ) less than –2 SD, and underweight as weight-for-age z score (WAZ) less than –2 SD. The primary outcomes will be measured at 6, 12, 18, and 24 months. Total number of monthly measurements with stunting, wasting, and underweight will be calculated by counting the number of times the child has a score less than –2 SD from WLZ, LAZ, or WAZ at a monthly measurement throughout the study period.

Since the study will be geographically clustered, prior to modeling, baseline characteristics will be compared by analyzing differences in means and proportions among the study arms using cluster-adjusted chi-square tests for proportions and analysis of variance for continuous variables. The adjusted analysis will account for the effect of baseline covariates found to differ across arms. A wealth quintile will be calculated using principal component analysis with data on household assets and characteristics.

For stunting, wasting, and underweight at individual time points (6, 12, 18, and 24 months), cluster-adjusted generalized linear models will be used with log link function to assess the risk ratios for each arm compared with control group. Negative binomial models will be built to examine incidence rate ratios for the total number of monthly measurements showing wasting, stunting, and underweight events. Gaps in measurement visits, and thus varying total number of months in which children were

measured, will be controlled for using an offset of the natural log of the total number of months in which the child will be measured. All models will be checked for multicollinearity using variance inflation factors with cutoffs of ≥10 and assessed for influential outliers using leverage plots. All analyses will be performed with Stata statistical software (version 16; StataCorp). A cost-effectiveness analysis will also be conducted to quantify the net costs of the interventions and assess the costs per disability-adjusted life year saved.

Results

The study protocol was approved by the Ethics Review Committee of Aga Khan University in Pakistan on January 4, 2017. Data collection began in May 2017 and was completed in July 2019. Data analyses are yet to be completed. This study will explore the effectiveness of intervention packages comprised of cash transfers from BISP with or without additional SNF, SBCC, or both in preventing childhood stunting. We expect the results to be published in peer-reviewed journals by autumn of 2020.

Discussion

Overview

The 2013 Lancet series on maternal and child nutrition estimated that a third of all child deaths attributed to malnutrition can be reduced by scaling up the provision of folic acid, multiple micronutrients, calcium, vitamin A, and balanced energy protein supplementation, along with adequate infant and child feeding practices for PLW and children in the most malnourished countries across the world [29]. To further capitalize on this, nutrition-sensitive actions are critical to eliminate undernutrition, as these actions address the lack of food security, adequate

caregiving resources, access to health services, and a safe and hygienic environment, the key underlying determinants of maternal and child malnutrition [15]. Social protection programs are key, as they are inherently nutrition sensitive by targeting families at risk of malnutrition.

With the rising interest in and reach of social protection, there has been a rapid increase in countries with functional conditional cash transfer programs—64 countries in 2013 versus 2 in 1997. Similarly, an increased interest in the use of cash-based programs in vulnerable settings to prevent malnutrition has occurred, especially among governments [15].

There is considerable evidence on nutrition-sensitive interventions delivered through social protection programs addressing malnutrition in developing countries. These studies have mainly been conducted in Latin America and Africa, where institutional capacities within the health and food systems differ. In addition, local conditions and environmental differences make it difficult to generalize the results to South Asia [15].

The findings from this study will also improve understanding of which combination of interventions (ie, cash transfers, SBCC, and LNS) can create a greater impact on the reduction in the prevalence of stunting among children aged 6 to 23 months in a vulnerable setting. Furthermore, the findings from the cost-effectiveness analysis will improve understanding of which combination of interventions provides greater value to achieve the ideal nutrition objectives.

Dissemination

The findings of this trial will be disseminated in a peer-reviewed journal to the governmental, academic, and policy-making communities, as well as to the wider public, and presented at relevant national and international conferences.

Authors' Contributions

SBS is principal investigator, hypothesized the study design, and approved the final version of the manuscript. ACG and SdP were involved in finalization of the study design. GNK, SK, AAU, and AM contributed to writing initial drafts of the manuscript. SA, MAH, SdP, NA, PRdC, and MH reviewed the manuscript. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AKU: Aga Khan University
BISP: Benazir Income Support Programme
DMU: data management unit
IYCF: infant and young child feeding
LAZ: length-for-age z score
LHW: lady health worker
LMIC: low- and middle-income country
LNS: lipid-based nutrient supplement
PLW: pregnant and lactating women
SBCC: social and behavior change communication
UCT: unconditional cash transfer
WASH: water, sanitation, and hygiene
WAZ: weight-for-age z score
WLZ: weight-for-length z score

Protocol

Fluid Administration in Emergency Room Limited by Lung Ultrasound in Patients with Sepsis: Protocol for a Prospective Phase II Multicenter Randomized Controlled Trial

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Abstract

Background: Sepsis remains a major health challenge with high mortality. Adequate volume administration is fundamental for a successful outcome. However, individual fluid needs differ between patients due to varying degrees of systemic vasodilation, circulatory flow maldistribution, and increased vascular permeability. The current fluid resuscitation practice has been questioned. Fluid overload is associated with higher mortality in sepsis. A sign of fluid overload is extravascular lung water, seen as B lines in lung ultrasound. B lines correlate inversely with oxygenation (measured by a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen ie, PaO2/FiO2). Thus, B lines seen by bedside ultrasound may have a role in guiding fluid therapy.

Objective: We aim to evaluate if fluid administration guided by lung ultrasound in patients with sepsis in emergency departments will lead to better oxygenation and patient outcomes than those in the standard therapy.

Methods: A phase II, multicenter, randomized, open-label, parallel-group, superiority trial will be performed. Patients will be recruited at emergency departments of the participating centers. A total of 340 patients will be randomly allocated to the intervention or standard-of-care group (30mL/kg). The intervention group will receive ultrasound-guided intravenous fluid until 3 B lines appear. The primary outcome will be oxygenation (measured as PaO2/FiO2 ratio) at 48 hours after starting intravenous fluid administration. Secondary outcomes will be patients' outcome parameters, including oxygenation after 15 mL/kg fluid at 6, 12, 24, and 48 hours; sepsis progress through Sequential Organ Failure Assessment (SOFA) scores; pulmonary edema evaluation; and 30-day mortality.

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Results: The trial will be conducted in accordance with the Declaration of Helsinki. Institutional review board approval will be sought after the participating sites are selected. The protocol will be registered once the institutional review board approval is granted. The trial duration is expected to be 1.5-2.5 years. The study is planned to be performed from 2021 to 2022, with enrollment starting in 2021. First results are expected in 2022. Informed written consent will be obtained before the patient's enrollment in the study. An interim analysis and data monitoring will ensure the patient safety. The results will be published in a peer-reviewed journal and discussed at international conferences.

Conclusions: This is a protocol for a randomized control trial that aims to evaluate the role of bedside ultrasound in guiding fluid therapy in patients with sepsis via B lines evaluation.

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Introduction

Sepsis is a significant cause of in-hospital mortality [1]. Prompt and adequate intravenous (IV) fluid therapy is essential in the treatment of sepsis and to reduce sepsis mortality [2,3]. Especially, immediate initial resuscitation in an emergency department can impact patients' outcomes [4-6]. In 2001, fluid resuscitation with the volume of 30 mL/kg, as early-goal directed-therapy, was added to the standard therapy for sepsis in the emergency department [7]. However, later studies on the Protocolized Care for Early Septic Shock (ProCESS), Australasian Resuscitation in Sepsis Evaluation (ARISE), and Protocolised Management in Sepsis (ProMISe) debated this initial fluid amount. These studies suggested that the fixed amount approach is not appropriate and beneficial for all patients and can be even harmful [8-11]. Even the 2016 definitions of sepsis and septic shock (Sepsis-3) failed to redefine this amount [12-14].

Studies suggest that only 50% of patients with sepsis respond positively to increased fluid administration [15] since the mechanism of circulatory compromise in sepsis is not related to actual hypovolemia. Therefore, excessive volumes are considered harmful and can cause myocardial dysfunction, pulmonary congestion, and decreased cardiac output [16].

Techniques like passive leg raising and inferior vena cava monitoring are useful to identify additional fluid responsiveness in patients [17-19]. However, these tests are cumbersome and time-consuming, especially in the busy emergency department setting [20]. Reliability of passive leg raising test is limited for spontaneously breathing patients or with intra-abdominal hypertension. The test may also be inconvenient in case of pain [18,19,21]. Hence, there is a need for additional means to guide fluid therapy in patients with sepsis.

There is evidence that bedside lung ultrasound can guide the fluid therapy. Positive net fluid balance correlates with extravascular lung water (EVLW) and is associated with higher mortality in patients with sepsis [5]. EVLW detection by the Fluid Administration Limited by Lung Sonography (FALLS)-protocol can be used to monitor acute circulatory failure based on the presence of B lines [22,23]. B lines are related to the thickening of interlobular septa, which is a pathological ultrasound sign [22,24,25]. Additionally, lung ultrasound is used to detect pulmonary edema with a sensitivity and specificity of 97% and 95%, respectively [22,25].

Observational studies suggest that the number of B lines correlates with the amount of EVLW. There is an inverse correlation between the number of B lines and oxygenation measured as the ratio of the partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) [26]. The PaO_2/FiO_2 ratio is an integral part of the Sequential Organ Failure Assessment (SOFA) score, a score to assess and diagnose sepsis severity [14,27,28]. Elevated SOFA scores are associated with higher mortality in patients with sepsis [29]. However, lung ultrasound for guiding individualized fluid treatment in sepsis has never been tested in a randomized controlled setting.

We propose to limit the initial fluid volume in the treatment of patients with sepsis in the emergency department by detecting EVLW with lung ultrasound. This approach could enable physicians to better assess and meet individual fluid needs of patients with sepsis. This proposal may also lead to an improved therapy regimen for initial sepsis treatment that avoids administration of excess fluid volume, in turn, limits the consequent damage and decreases mortality in this high-risk group.

Therefore, we plan a randomized controlled trial with the primary objective to assess if fluid administration guided by bedside lung ultrasound can lead to an improved oxygenation (PaO_2/FiO_2) 48 hours after fluid administration than that in the current standard of care fluid administration in adult patients with sepsis in the emergency department.

Secondary objectives are to determine whether fluid administration guided by bedside lung ultrasound positively impacts the course of treatment after 15 mL/kg fluid at 0, 6, 12, 24, and 48 hours. These objectives will be evaluated by PaO_2/FiO_2 ratio, pulmonary outcomes (pulmonary edema, acute respiratory distress syndrome, or the need for invasive mechanical ventilation), the severity of sepsis (SOFA score), kidney function (mean creatinine level), the volume of administered fluid, and 30-day mortality.

Methods

Study Design

The trial (protocol version 1.1, April 2020; preprint version 1.0, April 2019 [30]) will be conducted as a prospective phase II multicenter, open-label with blinded endpoint assessment, parallel-group, randomized controlled trial. Study design will follow the Population, Intervention, Control, Outcome, and Time (PICOT) format (Multimedia Appendices 1 and 2). SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials)- and CONSORT (Consolidated Standards of Reporting Trials)-compliant flow diagram is shown Figure 1.

Multimedia Appendices 2 and 3 respectively present SPIRIT-compliant flow diagram and checklist, respectively.

The schedule of enrollment, interventions and assessments is shown in Table 1.

Figure 1. SPIRIT- and CONSORT-compliant flow diagram of study design. ED: emergency department; FiO2: fraction of inspired oxygen; GCS: Glasgow Coma Scale; IV: intravenous; PaO2: partial pressure of arterial oxygen; qSOFA: quick Sequential Organ Failure Assessment; SOFA: Sequential Organ Failure Assessment; US: ultrasound.
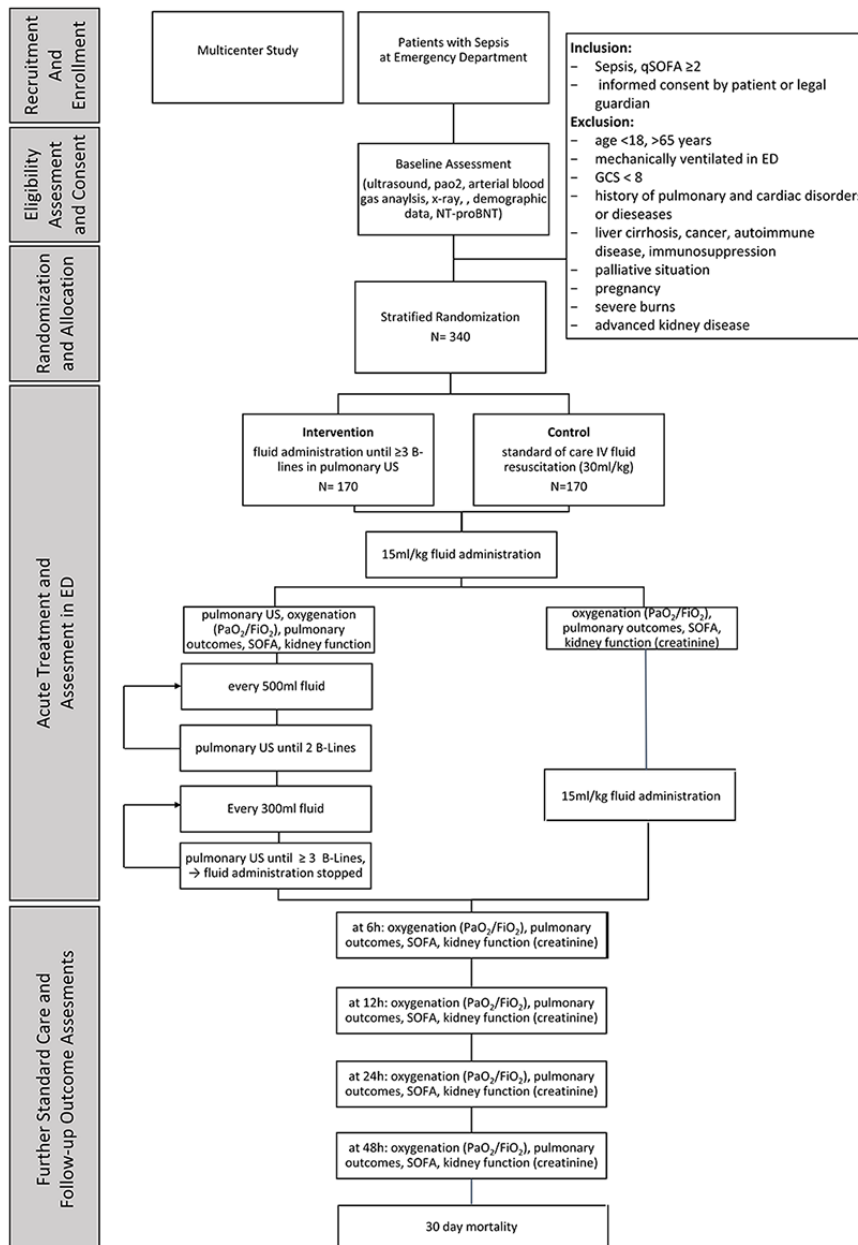
Table 1. SPIRIT-compliant schedule of enrollment, interventions and assessments.

Study schedule sections	Study period							
	Enrollment	Allocation	Post-allocation					Prognosis
Time points	T1[a]	0 h	6 h	12 h	24 h	48 h	In-between	30 d
Enrollment								
Eligibility screening	X							
Informed consent	X							
Registration form	X							
Baseline assessment (clinical features): sepsis with a qSOFA[b] score≥2; low systolic blood pressure≤100 mmHg; respiratory rate≥22 breaths per minute; altered mentation with Glasgow coma scale score<15		X						
Baseline assessment (laboratory parameters): ultrasound; PaO_2/FiO_2; arterial blood gas analysis; x-ray, NT-proBNP		X						
Allocation		X						
Interventions								
Intervention arm (fluid administration - 15mL/kg and ultrasound)		X	X	X	X	X		
Placebo (standard-of-care - 30mL/kg)		X	X	X	X	X		
Assessments								
Primary (PaO_2/FiO_2)[c]		X	X	X	X	X		
Secondary: PaO_2/FiO_2/Pulmonary outcome/SOFA[d] score/creatinine/volume		X	X	X	X	X		
Prognosis (30-day mortality)								X
Documentation (amount of fluid)			X	X	X	X	X	

[a]T1: timepoint 1 before baseline; unknown units of time.

[b]qSOFA: quick Sequential Organ Failure Assessment.

[c]PaO_2/FiO_2: partial pressure of arterial oxygen/ fraction of inspired oxygen.

[d]SOFA: Sequential Organ Failure Assessment.

Study Setting and Study Center Requirements

The study will be conducted as a multicenter study. Centers will be chosen and listed in the trial registration. Inclusion criteria will be as follows: patients with sepsis admission rate≥1000 patients/year; emergency department with necessary resources; personal and technical equipment (chest x-ray, point-of-care ultrasound devices, and access to blood analysis); intensive care unit (ICU); 24-hour availability of trained physicians; and academic hospital with an institutional review board conforming with the main center's institutional review board). The participating centers will follow standardized written protocols for the evaluation and acute treatment of patients with suspected sepsis or septic shock.

To guarantee compliance with the protocol and application of the same technique, physicians responsible for ultrasound will participate in a practical workshop for lung ultrasound conducted by physicians from the main study center. These participant physicians must demonstrate their competency in lung ultrasounds (through 20 or more scans that will be validated by a main center radiologist or a point-of-care ultrasound–certified emergency department physician).

The physicians responsible for the treatment will have experience in the treatment of patients with sepsis following the hospital's standardized protocols and Sepsis-3 guidelines. Investigators following up on patients will be either physicians or trained nurses.

Adherence to the study requirements and standardized protocol will be ensured at the participating sites with periodic quality monitoring and training of the associated staff.

Further roles and details will be mentioned in the protocol registered after acquiring funding, ethical approval, and selecting participating centers [31].

Recruitment and Adherence

Patients with suspected sepsis, that is, patients with a quick Sequential Organ Failure Assessment (qSOFA) score≥2 at the participating centers will be screened based on routine diagnostics and eligibility criteria and would consent to participate in the study. A low dropout rate is expected, due to short intervention time and fewer and brief follow-up periods. Nonetheless, participants will be informed about their right to withdraw from the study; and in the case of dropouts or withdrawal, the reasons will be documented. To achieve a sample size of 340 patients, a recruitment time of around 12-18 months is needed based on annually admission rate of 1000

patients and an expected recruitment rate of 5%-10% (50/1000-100/1000) per center. Multimedia Appendix 2 depicts the template for an attrition diagram [32]).

To ensure adherence, a standardized protocol and a checklist for the intervention will be provided to the participating centers and followed for each participant by the study investigators. The study investigators will document the patient's further treatment and monitor the treating department staff, to ensure that the protocol and necessary variables are documented. Patients or relatives will be reminded at the time of discharge from the hospital that they will be contacted for a follow-up.

Eligibility Criteria

The eligibility criteria for patient recruitment is shown in Textbox 1.

Textbox 1. Inclusion and exclusion criteria for patient recruitment.

Inclusion Criteria:

- Admitted into the emergency department.

- Age 18-65 years.

- Sepsis with a quick Sequential Organ Failure Assessment (qSOFA) score≥2 [3,14,28,33]

- Consent by the patient or legal guardian.

Exclusion Criteria:

- Mechanical ventilation at screening.

- Unconsciousness when admitted to emergency department (with Glasgow Coma Scale score<8)

- Preexisting pulmonary pathology as assessed by clinical symptoms or radiographic evidence in chest x-ray or by pulmonary bedside ultrasound (>2 B lines, a comet-tail artifact)

- History of pulmonary disorders (chronic obstructive pulmonary disease, asthma, parenchymal lung disease, or edema) or procedures.

- Preexisting cardiac pathology, disease, or dysfunction (ejection fraction<50, New York Health Association class>2) lung, or cardiac surgical procedures.

- History of liver cirrhosis, cancer, autoimmune disease, or immunosuppression.

- Patients under palliative care and patients facing imminent and inevitable death in the next 30 days due to causes other than sepsis

- Severe burns.

- Advanced kidney disease (chronic kidney disease stage 4 or above)

- Unstable medical conditions (eg, uncontrolled diabetes, uncompensated cardiac issues, heart failure, or chronic obstructive pulmonary disease).

- Pregnancy

- With other reasons or diseases needing a restricted fluid administration

Randomization and Blinding

Randomization will be web-based across centers using simple randomization stratified for patient's age and center, with 1:1 allocation. The sequence will be confidential and will be managed by a researcher independent of patient treatment. The treating physician will use the web-based randomization service—Viedoc (PCG Solutions AB). To increase the internal validity, possible confounders, such as pulmonary disorders, mechanical ventilation affecting imaging findings and bias results, kidney disease, and pre-existing cardiac disorders will be excluded by strictly implementing the eligibility criteria (Figure 1, Textbox 1, and Multimedia Appendix 2).

Patients and physicians will be unblinded to avoid endangering the patient's health and life in the situation of an emergency. However other study investigators collecting data, drawing blood samples for the analysis of PaO_2/FiO_2 and other parameters, and documenting, entering, or analyzing data will be blinded. Allocation concealment will be maintained until all data is collected and analyzed for the blinded personnel. The treating physician and patients will be instructed not to disclose information to the independent assessor and the data analyst. All breaches of blinding will need to be reported and documented.

Intervention

Trained physicians will perform lung ultrasound following the Bedside Lung Ultrasound in Emergency (BLUE) protocol technique [34]—an ultrasound protocol to identify points at the thoracic cage of patients using both hands of the investigator (Figure 2)—to identify pulmonary edema by the appearance of B lines [26].

Panel A shows a patient with sepsis admitted to the emergency department. Patient will be surveyed for eligibility and will accordingly receive either fluid limited by lung ultrasound or 30 mL/kg (ie, the control group). Ultrasound will be performed as per the BLUE protocol. Panel B shows how to identify points on the thoracic cage of a patient through morphological examination using both hands: little finger of the upper hand is just below the clavicle, fingertips at middle line, and the lower hand below the upper hand. The upper BLUE-point is at the middle of the upper hand, and the lower BLUE-point is at the middle of the lower palm, creating 4 points in both hemithoraxes. At these points (1-4, as shown in panel C), ultrasound will be conducted and fluid will be given until 3 B lines appear in the ultrasound. BLUE protocol defines B lines as those vertical and echogenic narrow-based lines that widen progressively as they pass to the other end of the image [25,34].

A phased array (1-5 MHz) transducer will be used. The images will be acquired while the patient is in a supine position, saved, and coded for further quality control and assessing inter-rater reliability. A baseline lung-ultrasound scan to assess the extent of B lines (Figure 2) will be performed. Subsequently, the resuscitation target in the intervention arm will be determined or limited by lung ultrasound as follows (Figure 1). Repeated ultrasound scan will be performed after the initial 15 mL/kg IV fluid bolus in the intervention arm and then after every 500 mL of fluid administration. If 2 B lines appear, scans will be performed after every additional 300 mL of fluid in the intervention arm. When 3 or more B lines are present bilaterally in more than 2 areas, further fluid administration will be stopped. Therefore, fluid resuscitation target for the intervention group is to administer volume until the appearance of 3 B lines (Figure1). If a further hemodynamic compromise is detected in the intervention arm following IV fluid discontinuation, vasopressors will be started or continued as per the Sepsis-3 guidelines (Figure 1).

The control arm will be assessed by a baseline lung ultrasound to document the absence of B lines and will then receive at least 30 mL/kg fluids as per the Sepsis-3 guidelines. After the initial bolus, the type and rate of IV fluid administration will be left to the discretion of the treating physician and the local emergency departments' protocols. All concomitant care and interventions are permitted during the trial.

Figure 2. Bedside Lung Ultrasound in Emergency (BLUE) protocol.
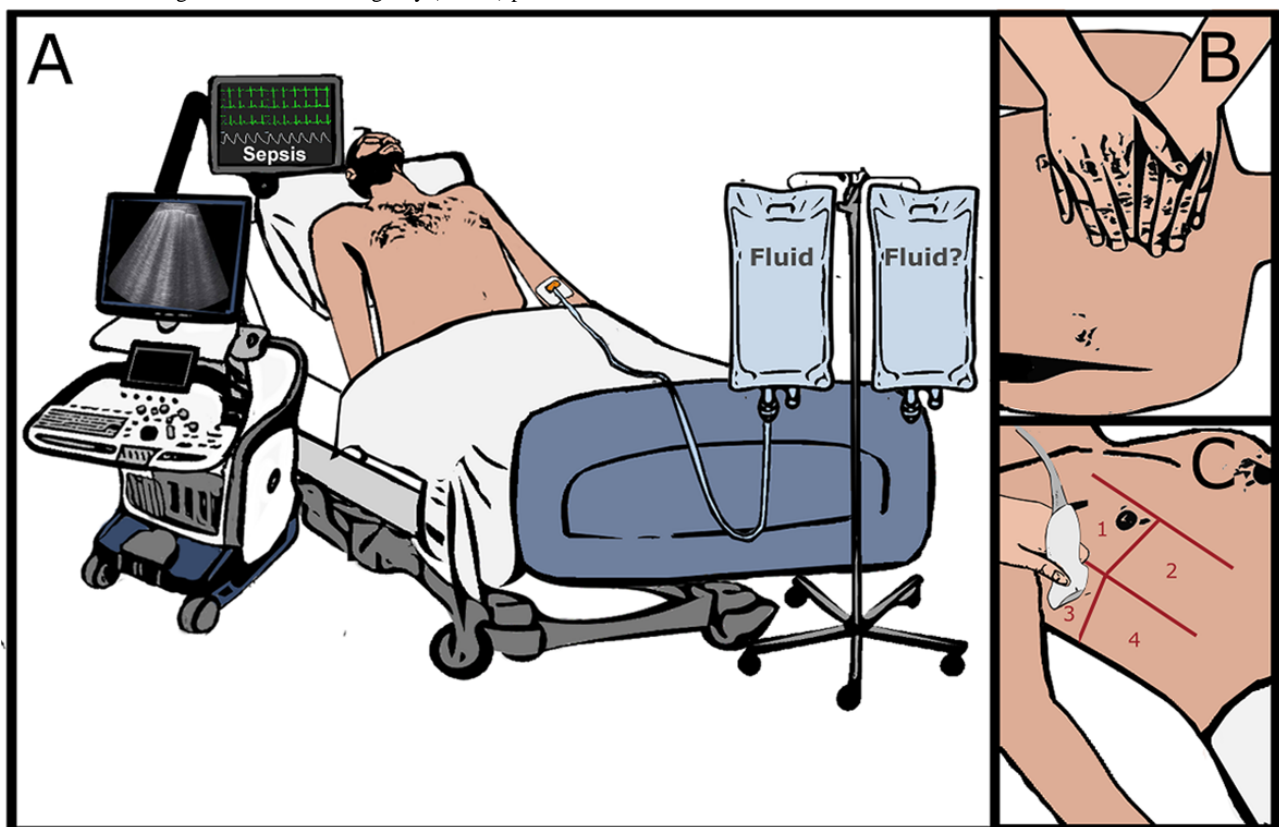
Outcomes

The primary outcome is the oxygenation (measured as mean PaO_2/FiO_2) at 48 hours after IV fluid administration. We expect a higher mean of PaO_2/FiO_2 in the intervention arm, which will be considered beneficial. A lower PaO_2/FiO_2 ratio is a sign of oxygenation compromise, which can occur with excessive fluid administration and increased EVLW. We will use PaO_2/FiO_2 ratio because it is a reliable and commonly used index of

oxygenation that is easy to obtain and clinically significant as a predictor for mortality in patients with sepsis [26,35]. Arterial blood samples will be obtained for PaO_2 measurement. FiO_2 will be estimated based on widely accepted approximated values for those patients not mechanically ventilated [36].

The secondary outcomes will be assessed at time points of 0, 6, 12, 24, and 48 hours and after 15mL/kg of fluid administration, and also at 30 days. We will then evaluate (1) means of PaO_2/FiO_2 ratio between groups at these time points, (2) the incidence of pulmonary outcomes (pulmonary edema, acute respiratory distress syndrome, or need for invasive mechanical ventilation), (3) mean SOFA score, (4) mean creatinine level (in milligram per deciliter), (5) mean amount of volume of administered fluid, and (6) proportion frequency of 30-day mortality. Additionally, the type of IV fluid will be documented (Table 1).

Pulmonary outcomes (namely, pulmonary edema) will be confirmed by physicians based on symptoms and signs (eg, shortness of breath after fluid resuscitation and crackles), laboratory parameters (raised NT-proBNP, adjusted for age [37]), and x-ray findings suggestive of pulmonary edema.

The outcomes will be measured and documented in data collection forms by a nurse from the participating center. These forms will be made available in the protocol. Reliability and validity of laboratory tests at different participating centers will be made available in the protocol.

Ethical Considerations

The protocol, templates, consent forms, and other requested documents (local language and English versions) will be reviewed and approved by the institutional review board/ethical committee at each participating site for the scientific content and regulatory compliance. Any modifications to the protocol will require a formal amendment and approval by the concerned institutional review board/ethical committee, notification to other research centers, and information update of trial registration [31].

Research investigators and physicians will have an informed discussion about the study details with conscious patients and provide printed information. The study investigator will use clinical judgment to discern between patients competent and incompetent to make a decision regarding their participation. Research investigators will obtain written consent from patients willing to participate in the study and will take the responsibility to protect those patients and follow ethical standards. Since it is likely that these patients might be ill or incompetent of taking decision at the time of giving consent. In such a case, the patient and their legal representative will receive an explanation about study details. They will be asked to provide an informed consent after expressing an understanding of the study procedures. When the patient is incapable of making a decision and there is no legal representative, the patient's next of kin will be asked (either in-person or by phone) to provide a no-objection form based on his or her understanding of the patient's wishes. If a no-objection form is provided, the patient will be included in the trial procedure since the intervention and assessment do not involve additional invasive or risky procedures. These patients will be retrospectively consented for their data to be included in the study as is the practice in other protocols [38]. Without a consent/no-objection form, the patient will be excluded from our study and will receive the usual care. We will reconsider the informed consent procedure repeatedly during the study in order to respect patients' rights to withdraw from the study at any time. Strict data monitoring guidelines will be followed (Multimedia Appendix 4 Data Monitoring).

Sample Size Justification

The sample size considerations were based on the PaO_2/FiO_2 differences between groups obtained from comparable prospective studies [26,39,40], where EVLW indices were used as a predictor for mortality. A PaO_2/FiO_2 ratio difference (delta) of 48 mm Hg was detected between the groups of survivors (mean 150, SD 81) and nonsurvivors (mean 198, SD78). Based on these studies, a delta of 25 mm Hg between the groups was considered clinically meaningful and feasible for our study. Interim analysis for safety reasons will be performed after 50% (170/ 340) of patient recruitment. An independent blinded statistician would perform the interim analysis and report to the data safety monitoring committee, as only safety is the monitored outcome no alpha level modification is needed (Multimedia Appendix 4 Interim analysis and safety).

The sample size was calculated (α=.05; ß=.80) with a potential dropout rate of 5% (17/340), resulting in n=170 patients per arm in a total of N=340 patients (Figure 1).

Statistical Analysis

The primary outcome will be PaO_2/FiO_2, a continuous variable. Mean (SD) will be reported after testing for normality, and then will be analyzed via *t* test. For secondary outcomes, a repeated measure ANOVA and *t* test will be used for analysis of continuous data. Categorical data will be reported using proportions and will be analyzed using chi-square test.

All analysis will be conducted according to the principle of intention-to-treat, and multiple imputation technique will be used to account for missing data. A subgroup analysis will be performed based on randomization of age, site, and severity of sepsis. An intention-to-treat analysis approach will be used in this study (Multimedia Appendix 4 Missing Data).

Limitations and Contingency Planning

Our study might lead to promising results but is not without limitations. The use of surrogate markers can be seen as a limitation. Using a surrogate marker to ensure study feasibility is universal in phase 2 trials. We will plan to study hard clinical outcomes in the following phase III trial. The chosen surrogate variable of PaO_2/FiO_2 ratio is a central component of the SOFA score [27,41]. Higher SOFA scores are associated with higher mortality [29]. Lower PaO_2/FiO_2 ratio is associated with adverse outcomes in patients with sepsis [41]. Additionally, the SOFA score will be assessed to evaluate changes in the patient's status over time since it is a core component of Sepsis-3 guidelines [14,28] and has predictive value [42]. It represents a valuable additional surrogate variable. These surrogate variables will be supplemented by other variables essential for evaluating the progress of sepsis.

We have strict inclusion and exclusion criteria in order to enhance the detectability of differences between groups and show the efficacy of the intervention if present. However, this may limit the external validity of our results and slow down the recruitment process. (Multimedia Appendix 4 Contingency Planning).

Ultrasound is an operator-dependent intervention. To standardize the ultrasound technique and interpretation, trained physicians who prove competent will perform the ultrasound. Kappa statistics will be used to assess inter-rater reliability.

Results

The study funding and ethical approval are being acquired, and the participating centers are being selected. The protocol will be registered with the intended registry name "Fluid administration in Emergency Room limited by Lung Ultrasound (FERLU) in patients with sepsis [31]: a phase II multicenter randomized controlled trial." The protocol will follow the SPIRIT checklist (Multimedia Appendix 3) [43] and include all items from the World Health Organization Trial Registration Data Set. Details of sponsorship, complete protocol, and model consent forms will be provided. Changes will be regularly updated. The study is planned to be performed from 2021 to 2022, with enrollment starting in 2021. First results are expected in 2022. Based on the results of this study, independent recommendations will be made for potential further clinical trials and their designs. The results will be disseminated at international meetings in the fields of emergency medicine and intensive care and published in a peer-reviewed journal. The study will follow the authorship criteria of the International Committee of Medical Journal Editors for all publications.

Discussion

The protocol and subsequent results can be the basis for an improved and individualized therapy regimen for initial sepsis treatment, which avoids damage resulting from excess fluid. It will be a further step toward new guidelines on tailored therapy approach for fluid administration in the management of sepsis.

Sepsis is one of the main reasons for ICU admissions, and 6%-30% of all ICU patients are assumed to suffer from sepsis [44]. The disease is associated with a high mortality and a considerable cost burden [45-47]. The adequate initial volume application is essential in the initial resuscitation of sepsis [8-11], and it affects patients' outcome and mortality risk [4-6]. There is a need for individualized fluid resuscitation of patients with sepsis and septic shock at emergency departments [8-11]. Therefore, there is a need for reliable, fast, and easily applicable screening tools and protocols to individualize the fluid amount for every patient. This approach could be also embedded as a telemedicine expert consultation to save resources [48]. Lung ultrasound following the FALLS-protocol could be a feasible and aiding approach [22,24].

Lung ultrasound as per the FALLS-protocol is not well validated yet. Therefore, our proposed trial, as a first randomized clinical trial, will lay the ground for developing and validating the bedside lung ultrasound protocol for detecting EVLW as a tool guiding early treatment in the emergency department and help to validate the FALLS-protocol usage in emergency departments.

In this phase II multicenter parallel-group superiority trial, we will guide the fluids using bedside lung ultrasound in patients with sepsis evaluated by B lines as a marker for EVLW. Based on previous literature, it is hypothesized that patients receiving individually-adapted fluid therapy limited by lung ultrasound have better oxygenation leading to a better outcome and lower risk of mortality. With positive results, the study would proceed to a phase III with more liberal inclusion and exclusion criteria mimicking a real-life scenario. FERLU trial will lead to a deeper understanding of the fluid response in sepsis. The results of this study could help to decrease the mortality in this high-risk group of patients with sepsis by providing physicians an additional tool applicable in the emergency.

Authors' Contributions

Order of the authors was determined based on contribution and followed authorship criteria of the International Committee of Medical Journal Editors. JRC developed the idea. JRC, SS, MFHM, and NMM developed the preliminary study design for the protocol. SS, JRC, MFHM, and AVC are in contact with potentially participating centers and organizing the execution of the study. NMM, JRC, SS, and MFHM organized and overlooked the writing and revising process. JRC, SS, MFHM, NMM, and HIZ wrote major parts of the manuscript. NMM designed the figures. DAMH was mainly involved in developing the blinding, randomization methods, and contingency planning. JLB was mainly involved in determining outcome and intervention. AVC

was involved in the introduction and JSS was involved in the ethical considerations. Every author contributed with ideas, writing, and revision and accepted the final versions.

Conflicts of Interest

None declared.

Multimedia Appendix 1
FERLU research question in PICOT format.
[PNG File , 47 KB - resprot_v9i8e15997_app1.PNG]

Multimedia Appendix 2
Template for an attrition diagram.
[PNG File , 265 KB - resprot_v9i8e15997_app2.PNG]

Multimedia Appendix 3
SPIRIT-compliant checklist for the FERLU trial.
[PDF File (Adobe PDF File), 120 KB - resprot_v9i8e15997_app3.pdf]

Multimedia Appendix 4
Supplemental information.
[DOCX File , 22 KB - resprot_v9i8e15997_app4.docx]

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Abbreviations

ARISE: Australasian Resuscitation in Sepsis Evaluation
BLUE: Bedside Lung Ultrasound in Emergency
CONSORT: Consolidated Standards of Reporting Trials
EVLW: extra vascular lung water
FALLS: Fluid Administration Limited by Lung Sonography
FERLU: Fluid administration in Emergency Room limited by Lung Ultrasound FiO2: fraction of inspired oxygen
ICU: intensive care unit
IV: intravenous
PaO2: partial pressure of arterial oxygen
PICOT: Population, Intervention, Control, Outcome, and Time
ProCESS: Protocolized Care for Early Septic Shock
ProMISe: Protocolised Management in Sepsis
qSOFA: quick Sequential Organ Failure Assessment
SOFA: Sequential Organ Failure Assessment
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Comparing the Keyto App and Device with Weight Watchers' WW App for Weight Loss: Protocol for a Randomized Trial

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Abstract

Background: Obesity and being overweight are major contributing factors for many diseases. Calorie restricted diets often fail to result in sustained long-term weight loss. Very low–carbohydrate, high-fat ketogenic diets have been suggested to have superior metabolic and weight loss effects. Keyto is a low-cost, highly scalable mobile health (mHealth) app paired with a noninvasive biofeedback tool aimed at facilitating weight loss through a personalized healthy and predominantly plant- and fish-based ketogenic diet.

Objective: This protocol describes a randomized trial comparing the efficacy of the Keyto mHealth app and device intervention to that of Weight Watchers' WW app in individuals who are overweight or obese. The primary outcome is weight loss after 12 weeks. Secondary and exploratory outcomes, including metabolic and cardiovascular risk factors, will be assessed at 12, 24, and 48 weeks.

Methods: A total of 144 participants will be recruited and randomized to either the Keyto program or Weight Watchers program. Study participants will be guided through the study via video conference or phone calls and will undergo a fasting blood analysis performed by a third-party diagnostic lab at weeks 0 and 12 to assess metabolic and cardiovascular risk markers. All participants will be asked to weigh themselves daily on a study-provided Bluetooth-enabled scale. Participants randomized to the Keyto arm will also be asked to measure their breath acetone levels, a measure of ketosis, with the Keyto device 3 times per day.

Results: Recruitment started in December 2019. Rolling recruitment is expected to be completed by July 2020. Data collection and analysis of the primary intervention phase is expected to be completed in October 2020. The 24- and 48-week follow-ups are expected to be completed in January 2021 and July 2021, respectively.

Conclusions: This trial will provide high-quality evidence regarding the efficacy of the Keyto weight loss program in individuals who are overweight and obese in a free-living condition. This study also fills a gap by examining the impact of a ketogenic diet emphasizing plant- and fish-based fats on blood lipid profile and cardiovascular disease risk.

Trial Registration: ClinicalTrials.gov NCT04165707; https://clinicaltrials.gov/ct2/show/NCT04165707.

International Registered Report Identifier (IRRID): DERR1-10.2196/19053

KEYWORDS

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Introduction

Obesity is a major risk factor for a variety of diseases, including type 2 diabetes, cardiovascular diseases, musculoskeletal disorders, and some cancers [1]. It is estimated that over 40% of adults worldwide attempt weight loss diets each year [2]. Unfortunately, conventional calorie restriction diets often fail to produce long-term weight loss [3]. Therefore, novel dieting techniques must be explored in order to successfully treat obesity and lower disease risk.

Although many different dietary approaches can lead to weight loss [4], increasing evidence suggests that a very low–carbohydrate ketogenic diet may have superior metabolic and weight loss effects [5-10]. On a ketogenic diet, when carbohydrate intake is kept very low (<50 g/day), high rates of lipolysis increase delivery of free fatty acids to the liver, which converts them into ketone bodies (β-hydroxybutyrate, acetoacetate, and acetone) that the brain and body can use as an alternative fuel source. Accumulating evidence suggests that ketones mediate reduced feelings of hunger when individuals follow a ketogenic diet [11,12], which could help facilitate sustained weight loss. A ketogenic or low-carbohydrate diet may also be beneficial because it can potentially increase energy expenditure during weight loss maintenance [13]. When compared to other dietary approaches, the ketogenic diet also provides a unique opportunity to follow and track a biomarker in the form of ketone levels that may provide useful and actionable information.

The effectiveness of any diet is limited by an individual's ability to adhere. Adherence to a diet requires considerable cognitive and self-regulatory resources daily at every meal or eating opportunity. Meta-analytic evidence suggests that self-regulatory behavior change strategies, such as self-monitoring, play a crucial role in increasing adherence to diet and healthy behaviors [14,15]. Very low-carbohydrate ketogenic diets can be particularly challenging to adhere to because of the complexity of understanding the carbohydrate content of consumed food and whether consuming certain foods will promote or limit ketosis [16,17]. However, the current approaches to self-monitoring ketogenic diets (eg, through finger stick blood monitors, urine ketone strips, or food logs) are typically expensive, painful, inconvenient, or inaccurate. There is emerging technology that can lower the burden of self-monitoring by measuring breath acetone to provide individuals embarking on a ketogenic diet with immediate ketone-specific self-monitoring that could help optimize adherence and success [18].

Keyto (Keyto Inc) is a scalable comprehensive weight loss program that combines resources (eg, recipes, searchable database, menus, meal plans, social support) delivered from a mobile health (mHealth) app with information from an accompanying breath acetone sensor to help individuals learn about and monitor whether they are in ketosis. Because a ketogenic diet is very low in carbohydrates but high in fat, there is some concern as to the impacts of such a predominantly high-(saturated) fat diet on cardiovascular health [19]. Keyto helps to guide users toward more heart-healthy plant- and fish-based fat sources to achieve ketosis. Thus, the goal of the Keyto program is to facilitate weight loss through a personalized healthy and ketogenic diet. As of January 2020, Keyto has delivered over 30,000 Keyto breath acetone analyzers to customers with reported anecdotal success, but robust evidence is required to evaluate the efficacy of this low-cost, scalable weight loss intervention. The purpose of this research is to conduct a pragmatic randomized trial to test the efficacy of the Keyto biofeedback and app intervention compared to Weight Watchers' WW (Weight Watchers International Inc) diet app. The WW app was chosen as the active comparator as it is a widely accepted dietary approach with robust evidence for its effects on weight loss and cardiovascular health [20]. The hypotheses and exploratory research questions can be found in Table 1.

Table 1. Overview of study hypotheses and research questions.

Measures	Outcomes	Timeframe	Hypothesis or question
Primary outcome			
Bodyweight scale	Change in body mass (in kilograms)	12 weeks	Those in the Keyto intervention arm will achieve greater weight loss at 12 weeks than those in the Weight Watchers arm.
Secondary outcome			
Bodyweight scale			
	Change in body mass (in kilograms)	24 and 48 weeks	Those in the Keyto intervention arm will achieve greater weight loss at 24 and 48 weeks than those in the Weight Watchers arm.
	Change in body mass (in kilograms)	Daily weight measured during the first 12 weeks	What are the patterns of body mass change during the first 12 weeks between the 2 study groups?
Automated self-administered 24-hour dietary recall			
	Carbohydrate intake in 24-hour period (in grams)	12, 24, and 48 weeks	Those in the Keyto intervention arm will report lower carbohydrate intake at 12, 24, and 48 weeks.
	Total fat, saturated fat, polyunsaturated fat, monounsaturated fat intake in 24-hour period (in grams)	12, 24, and 48 weeks	Does the Keyto intervention or WW app intervention influence fat intake from baseline to 12, 24, and 48 weeks?
	Total energy intake in 24-hour period (in kilocalories)	12, 24, and 48 weeks	We will examine changes from baseline to 12, 24, and 48 weeks in total energy intake in the Keyto and Weight Watchers groups.
Venous blood sample	HbA$_1$c[a], fasting glucose, fasting insulin, fasting high-sensitivity C-reactive protein, fasting HOMA-IR[b], fasting total cholesterol, fasting HDL[c] cholesterol, fasting lipoprotein fractions, fasting lipoprotein (a), fasting triglycerides, fasting non-HDL cholesterol	12 and 48 weeks	We will examine changes from baseline to 12 and 48 weeks in metabolic and cardiovascular risk blood biomarkers in the Keyto and Weight Watchers groups.
Exploratory outcome			
Venous blood sample	Fasting albumin, fasting globulin, fasting total bilirubin, fasting alkaline phosphatase, fasting aspartate aminotransferase, fasting alanine aminotransferase	12 and 48 weeks	We will explore changes from baseline to 12 and 48 weeks in blood biochemistry in the Keyto and Weight Watchers group.
Manipulation checks			
Questionnaires			
	Food attitude survey	12, 24, and 48 weeks	We will examine all baseline questionnaires as potential covariates. We will also examine differences in questionnaire measures between the 2 groups at 12, 24, and 48 weeks.
	Cravings, mood, and energy	Weekly	
	Self-reported dietary adherence	Weekly	
	Pittsburgh Sleep Quality Index	12, 24, and 48 weeks	

[a]HbA$_1$c: hemoglobin A$_1$c.

[b]HOMA-IR: homeostasis model assessment of insulin resistance.

[c]HDL: high-density lipoprotein.

Methods

Overview of Protocol

This study is a 2-arm pragmatic randomized clinical trial. Participants will be randomized to one of 2 weight loss conditions: Keyto or Weight Watchers. The primary endpoint will be weight loss at 12 weeks. There will be key secondary endpoints measured at 12 weeks, and weight loss will also be measured at 24 and 48 weeks. Participants will be asked to use the intervention materials for the arm to which they were

randomized in their weight loss efforts (ie, Keyto self-monitoring device and app or WW app [21]) throughout the 12-, 24-, and 48-week durations of the primary and secondary phases of this trial. The study has been approved by the corresponding author's university clinical research ethics board. External peer-reviewed funding was secured from Mitacs, a not-for-profit agency that facilitates academic research collaboration with industry partners.

Participants and Eligibility

We will recruit 144 adults living in the state of California to participate in the study. Please see Table 2 for a list of eligibility criteria. Because of the coronavirus disease 2019 (COVID-19) pandemic, we have also included COVID-19-specific eligibility criteria in Table 2, which were informed by World Health Organization classifications for symptom severity [22]. Eligibility criteria were established to control for extraneous factors and to maintain a relatively homogeneous sample in this trial. For example, participation was constrained to adults who are overweight or obese and without comorbidities to control for potential differential metabolic impacts of a ketogenic on older adults (who would be more likely to have comorbidities or medications) or those with class 3 obesity [23] who might have more complex conditions.

Recruitment, Screening, Randomization, Enrollment

Participants will be recruited through Facebook advertisements, poster advertisements placed in public spaces (eg, universities, libraries, coffee shops), and emails to the existing Keyto email list. Informed consent will be obtained digitally via Qualtrics (Qualtrics LLC). Following informed consent, participants will schedule a video conference or phone call with a member of the study team who will answer any questions participants may have, clarify the procedures of the study, and schedule a baseline blood test. After collection of the baseline blood sample, participants will be emailed the online baseline questionnaire. Participants will then be randomized by a researcher logging into a password-protected study website and mailed the study materials for their condition. All 144 participants will be randomized at 1:1 ratio to the Keyto (n=72) or Weight Watchers (n=72) trial arms using a variable permuted block sizes, stratifying for sex (male, female) and age (18-40 years, 41-64 years). The randomization website and schedule will be created and maintained by a third party (Centre for Health Evaluation and Outcomes Science, St. Paul's Hospital, Vancouver, Canada). Participants will be provided with a US $100 gift card to an online store of their choice upon completion of the 48-week follow-up surveys.

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Table 2. Trial inclusion and exclusion criteria.

Criteria
Inclusion
Aged 18-64 years
Living in the state of California
BMI 27-43 kg/m^2
Must speak, read, and comprehend English
Must have a valid email address and phone number
Willingness to a follow an evidence-based very low carbohydrate diet or calorie-restricted diet that have been demonstrated for weight loss
Must have a kitchen and be willing to cook
Willingness to reduce (net) carbohydrate intake to less than 30 g/day
Willingness to restrict intake of added sugar, bread, grain, rice, pasta, sweets, most fruits, pastries, and other carbohydrates
Willingness to comply with a strict diet for 12 months
Interest in losing weight
(COVID-19[a] specific criteria) If you have been diagnosed with COVID-19, you may be eligible if:
Do not currently have COVID-19 related symptoms
Your last symptoms were more than 4 weeks ago
You experienced uncomplicated or mild COVID-19 symptoms
You were not hospitalized because of your symptoms
Exclusion
HIV or immunocompromised
Current or past cancer diagnosis
Pregnant, breastfeeding, or planned pregnancy in next 12 months
Beginning or ending hormonal contraception in next 12 months
Current diagnosis of diabetes
History of heart attack or stent
Currently taking glucose-lowering drugs, statins, or oral steroids
History of gastric bypass surgery or any other weight-loss surgery
History of anorexia or bulimia
History of mental illness
Current smoker or smoked cigarettes within past 12 months
Currently eating fewer than 50 g carbohydrates per day
Currently following ketogenic diet or have strictly adhered to a ketogenic diet for greater than 3 weeks in the past 6 months
Lost or gained more than 5% body weight in past 6 months
Currently using Weight Watchers or have strictly adhered to the WW app for greater than 3 weeks in the past 6 months
(COVID-19 specific criteria) If you have been diagnosed with COVID-19, you may be ineligible if:
You have had moderate to severe COVID-19 associated disease
You have been hospitalized by COVID-19

[a]COVID-19: coronavirus 2019 disease.

Interventions

Keyto App and Device

Those randomized to the Keyto arm will be asked to download the Keyto app from an app store. They will receive a unique email username and password provided by the study team to log in. Participants will be guided through connecting their iHealth scale and the Keyto app and given a brief overview of its features, with the remainder of the intervention will be delivered entirely via the app. The app contains resource

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information about what to eat and what not to eat in order to achieve nutritional ketosis and ample resources. The app also contains a social support function. For the trial, all Keyto participants will be placed into a moderated support group of 4 to 6 participants per group. Keyto's registered dietician and executive medical director will be added to each group to answer questions about Keyto and starting a ketogenic diet. The identities of each user will be kept anonymous and users will be encouraged to refrain from using their names in this forum. Based on the premium version of the Keyto app, a phone or video conference call with the registered dietician will be available in the second week of the program. The app also includes tips and resources about how to succeed potential side effects or pitfalls. There is access to a short podcast offered 3 times per week discussing various aspects of the program including strategies and pitfalls.

The Keyto app uses its Key Eats nutrition plan as a heart-healthy ketogenic diet that emphasizes fish and plant-based fats, moderate protein and nonstarchy vegetables and is compatible with a vegetarian or mixed-diet lifestyle. The app reinforces users to avoid foods with refined carbohydrates like pasta, bread, pizza, or sweets and replacing those with foods high in healthy fats such as avocados, nuts, fatty fish (such as salmon), and olive oil.

The Key Eats Code is a searchable database of almost all foods that rates each using a red, yellow, or green code to indicate whether to eat it *ad libitum*, cautiously, or not at all. The Key Eats Code database was created based on nutritional information gathered from the United States Department of agriculture food database to categorize foods based on the amount of net carbohydrates. Foods labeled as green indicate participants can eat as much as they want; they are very low in carbohydrates and higher in fats. Foods labeled red should be avoided; these are typically high-carbohydrate and high sugar foods like pasta, potatoes, or candy. A yellow label means *think before you eat*. These foods can be eaten occasionally in moderation. There is a *Heart First* badge to indicate foods that are rich in monounsaturated and omega-3 polyunsaturated fats and low in saturated fats. Participants in this trial will be encouraged to eat foods with this badge. There is additionally a *Power Food* badge indicating a food that is especially high in healthy fats and promotes ketosis. For the trial, participants are told to aim to prioritize foods that fall in the green and heart-first category. While conventional ketogenic diets prioritize increased fat intake regardless of source, Keyto emphasizes plant and fish-based fats that are generally lower in saturated fatty acids and higher in unsaturated fatty acids. Research has shown that substituting saturated fats with unsaturated fats can improve cardiovascular disease risk markers [24,25].

Participants will be asked to measure their breath acetone concentrations with the Keyto sensor 3 times daily (immediately after waking up in the morning, before lunch, and before dinner). For this, the participants will be asked to exhale into the hand-held device, which is paired with the participant's phone. Participants will be able to drink alcohol in moderation but will be instructed to avoid blowing into the Keyto sensor after having an alcoholic beverage.

Weight Watchers' WW app

Those randomized to the Weight Watchers group will be given a unique link to download an app that includes information, resources, and food diary functions for the Weight Watchers diet. They will also receive a unique email and password, provided by the study team, to log in. The research team will pay for the WW app subscription, so there is no cost for participants randomized to the Weight Watchers group. Participants will be guided through connecting the iHealth scale and the WW app and given a brief overview of its features, with the remainder of the intervention will be delivered entirely via the app. Users will get information as to what to eat and what not to eat according to the Weight Watchers diet and points system [21].

The WW app takes a science-backed approach to weight loss that does not involve counting calories or macronutrients. Rather, all foods are assigned a point value. Certain foods are assigned a low number (eg, foods low in calories and fat, like lentils) and others are assigned a high number (eg, foods high in calories and fat, such as pizza). At the start of the program, participants will enter their current and goal weight for the next 12 weeks and complete a baseline assessment to determine current eating habits. Based on this information, participants will be assigned to one of 3 groups within the WW app (green, blue, or purple). Group assignment will determine the number of points allotted for the participant to eat in a day, as well as the number of weekly flex points that can be used if a participant goes over their allotted daily points. The app also contains approximately 100 to 300 zero-point foods (depending on the Weight Watchers group). These are low-calorie foods that participants can eat as much of and do not take any points away from daily or weekly allotted points. Participants record their dietary intake through the app, and the app automatically tracks their point intake and provides feedback to help users stay within their allotted point limit.

The WW app has similar support features as those of Keyto, such as live 24/7 dietary coaching and weight loss groups that participants can join for social support. Additionally, both apps offer recipes and meal plans to improve user experience and aid in dietary adherence. Both apps offer a food search option to allow users to determine if any food fits well into their eating plan.

Measures

Participants will be asked to respond to survey measures at the 4 outcome time points: baseline and at 12, 24, and 48 weeks from start of the program. Daily and weekly questionnaires and app data will be used as manipulation checks of adherence and intervention fidelity, which are described below.

Outcome Measures

Body Mass

Participants will be asked to weigh themselves each morning using the Bluetooth weight scale (iHealth Lina H2). Weight measurements will be automatically uploaded to the iHealth cloud that can be accessed by the research team. Body mass measured at baseline, the initial measurement made at the start

of the study, and follow-up time points (12, 24, and 48 weeks) will be calculated as the mean of measures taken across the week. A measure of daily adherence to self-weighing will also be examined as the total proportion of days that a participant records their weight.

Venous Blood Sample

Participants will be sent to a third-party blood clinic (Quest Diagnostics), to provide a ≥12 hour fasting blood sample obtained by venipuncture from an antecubital vein in the seated position. Blood samples will be obtained at baseline and 12 weeks, with an optional blood sample obtained at 48 weeks. See Table 1 for a complete of list of blood measures including hemoglobin A_1c, blood glucose, insulin sensitivity, and fasting lipids.

24-Hour Dietary Recall

Participants will complete the Automated Self-Administered 24-Hour Dietary Recall [26] to determine caloric intake and macronutrient composition. Participants will be asked to report all caloric intake within the past 24 hours at baseline and at 12, 24, and 48 weeks. This retrospective questionnaire allows for extraction of detailed information regarding specific nutrients and food groups (eg, carbohydrate intake, consumption of saturated fat). The Automated Self-Administered 24-Hour Dietary Recall has demonstrated high consistency with interviewer assessed 24-hour diet (r=0.80) [27] and with 4-day food records [28].

Sleep Quality

The Pittsburgh Sleep Quality Index [29] is a validated measure used to assess sleep schedules and sleep quality. The questionnaire assesses quality of sleep from the previous month by measuring the following components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. An overall score will be calculated by totaling these component scores whereby lower scores denote a higher sleep quality. Sleep quality will be assessed at baseline and at 12, 24, and 48 weeks.

Demographics

Participant characteristics, including sex, race or ethnicity, education level, occupation, income, marital status, and number of dependents will be collected at baseline via online survey.

Manipulation Checks

App Data

We will extract app usage data, food logs, breath acetone levels (for the Keyto group only), and weight.

Food Attitudes Survey

Participants will complete the Food Attitudes Survey [30], a short, 9-item survey to assess their thoughts and feelings toward food. Participants will be asked, "On a 5-point scale, answer how these comments reflect your thoughts and feelings toward food," where scores range from 1 (not at all like me) to 5 (exactly like me). An example stem item reads, "It is difficult for me to leave food on my plate." Attitudes will be measured at baseline and at 12, 24, and 48 weeks.

Cravings, Mood, And Energy

This 12-item questionnaire asks participants about the impact of their dietary intervention on aspects of their cravings, mood, and energy in order to determine possible barriers to diet adherence. Participants will be asked, "How does the following impact your ability to stick with your diet?" An example craving response includes, "Having delicious foods in front of you and you can't resist." An example mood response includes, "Having a really hard or stressful day." An example of an energy response includes, "You become too hungry and can't continue to resist eating." Responses are rated on a 4-point scale ranging from 1 (not at all) to 4 (every day). As these are manipulation checks and to not overburden participants, 3 of the 12 items will be randomly asked per week. By the primary endpoint at 12 weeks, each participant will have answered each of the 12 questions 3 times. This measure was developed for this study in consultation with a health psychologist and registered dietician.

Diet Adherence

Diet adherence will be assessed using 2 questions relating to adherence with the diet participants were randomized to. Participants will be asked, "To what extent do you believe you were able to stick to the diet as part of this study in the past week?" on a 5-point scale ranging from 0 (not at all) to 4 (completely). There will be an open-ended response option for participants to provide an explanation if they wish. Second, participants will be asked, "How often did you monitor and track your food intake on average each day in the past week?" on a 4-point scale ranging from 0 times per day to 3 or more times per day. Participants will be asked about their diet adherence at the end of every week throughout the 48-week trial period.

Physical Activity

The Godin Leisure-Time Exercise Questionnaire [31] is a validated and commonly used self-report measure of physical activity. Participants will be asked to report the number of 30-minute bouts of light, moderate, and vigorous physical activity they engaged in over the past week. The Godin Leisure-Time Exercise Questionnaire will be assessed at 12 and 48 weeks.

Sample Size Calculation

There are no known studies with protocol design as we describe. Thus, the amount of weight loss expected with a hands-off self-monitoring ketogenic mHealth application is not known. Thus, we determined sample size in order to detect a clinically meaningful 5% difference in weight loss, assuming a mean body mass of 100 kg with a standard deviation of 15 kg [32]. A 5% weight loss corresponds to a small-to-moderate effect size (Cohen d=0.33, f=0.165). Using G*Power software (version 3.1.9.3) a total sample size of 124 is required to detect a between groups effect with 80% power and α=.05 with 2 groups and 2 time points (primary outcome at 12 weeks) assuming a correlation among repeated measures of r=0.75. In order to preserve power and account for 15% loss to follow-up, we will aim to recruit 144 participants (ie, n=72 per group).

Planned Analysis

A statistician independent of the research team will analyze the data. Data will be analyzed on an intention-to-treat basis. Descriptive statistics (mean, SD, and frequency) will be calculated. Univariate and multivariate statistical assumptions will be examined and managed according to recommendations by Tabachnick and Fidell [33]. Mixed linear effects models will be used to assess between-group differences across time. All primary and secondary study outcomes will be analyzed similarly. Follow-up mean comparisons and Cohen d effect sizes will used to examine differences between individual time study points. Two rounds of analyses will occur: the primary outcome (body mass) and key secondary outcomes (blood variables, surveys, app data) will be assessed at the 12 weeks and follow-up exploratory analyses will be performed after 24 and 48 weeks. An additional exploratory mixed effects model using all daily body mass measures during the first 12 weeks will examine whether the patterns of body mass change differ between the 2 study groups.

Potential Risks and Mitigation

The potential risks of this research are minimal and relate to following a low-carbohydrate diet. As with many dietary changes, the switch to a low-carbohydrate diet can sometimes lead to headaches, nausea, or low energy. The Keyto program uses a modified ketogenic or low-carbohydrate high-fat diet which derives 70% of calories from fat. At the beginning of low-carbohydrate high-fat diets, some participants may experience transient adverse side effects including headache, light-headedness, achiness, and muscle cramps [34]. These side effects are sometimes referred to as the "keto flu [35]," appear to be related to changes in electrolytes and diuresis and can be mitigated by broth or bouillon supplementation and adequate sodium intake. The intensity of these symptoms is expected to decline as the study progresses and participants become adapted to a ketogenic diet. Possible long-term adverse side effects of ketogenic diets in adults who are overweight and obese, but otherwise healthy, are currently unknown.

Results

The study was registered at ClinicalTrials.gov (NCT04165707). Recruitment opened December 1, 2019. The first participants began the app-based diet plan to which they were allocated on January 6, 2020. As of April 2020, there were 49 participants enrolled in the study. We expect rolling recruitment to be completed by July 2020, and the primary intervention phase to be completed 12 weeks later (October 2020), with 2 exploratory follow-up time points at 24 weeks (January 2021) and 48 weeks (July 2021).

Discussion

Any diet is only as effective as adherence to it. Low-carbohydrate diets can be complex and challenging to adhere to [9,36], and very low–carbohydrate ketogenic diets may be even more challenging as they require greater dietary restriction to promote ketosis and sustain weight loss. Low-carbohydrate and ketogenic diets have been shown to be efficacious at promoting weight loss in structured settings [9,11,37], but maintaining them in free-living conditions may be challenging. This paper outlines the protocol for a randomized trial testing the efficacy of the Keyto breath sensor and app intervention against the WW app in promoting weight loss for 12 weeks. The Keyto intervention is delivered entirely through an app and lowers the burden of self-monitoring required to promote weight loss when following a ketogenic diet by providing an easy means of tracking ketosis using a handheld breath acetone monitor. For this reason, Keyto may be particularly effective at promoting weight loss in free-living conditions.

One potential challenge that may be encountered during the conduct of this trial is strong preferences for one of the diet conditions. Participants with strong diet preferences that are not randomized to their preferred diet may be less motivated to adhere to their allocated condition, which may influence outcomes. In real-world settings, individuals would simply choose the diet plan that they want. However, the design of a randomized trial precludes this possibility. To alleviate this potential confounder, we established eligibility criteria requiring participants to be open to both types of diets. This may constrain the generalizability of our findings to those who are most motivated. However, it is viewed as less of a confounding factor given that both interventions are mHealth products that must be purchased, so users in real-world settings would need to be motivated in order to consider either weight loss app. Furthermore, a randomized efficacy trial with strict eligibility criteria is necessary and appropriate for the stage of research [38]. The findings are generalizable to those meeting the eligibility criteria (eg, motivated adults with overweight or obesity and without comorbidity) and may not be generalizable to the entire population.

This trial will provide evidence comparing weight loss outcomes between a handheld breath ketone monitor and ketogenic diet app (Keyto) and an established caloric restriction–based weight loss app or program (Weight Watchers). The Keyto intervention may help with adherence to a ketogenic diet through direct biofeedback and personalization thereby helping to promote maintained weight loss equivalent or superior to the gold-standard weight loss app. This would provide evidence for breath ketone monitoring as an adjunct to ketogenic diets for adults with obesity who are trying to lose weight.

Research examining changes in metabolic health outcomes following ketogenic diet have typically found a differential impact on blood lipids, with potentially favorable increases in high-density lipoprotein concentrations and decreases in triglycerides observed concomitantly with a potentially unfavorable increase in low-density lipoprotein levels [19]. The heart-healthy approach used by Keyto is novel and is designed to increase consumption of plant- and fish-based foods that are higher in monounsaturated and omega-3 polyunsaturated fatty acids in order protect against an increase in low-density lipoprotein cholesterol. Exploratory blood measures will help to determine whether the heart-healthy ketogenic dietary approach results in changes in blood lipid profile (including low-density lipoprotein particle size distribution) that are favorable for cardiovascular health.

It is important to examine different strategies to combat obesity given its prevalence and adverse impacts. A ketogenic diet may be an effective strategy for weight loss; however, its success depends on adherence, and adherence to a ketogenic diet can be challenging. Furthermore, there are concerns about the potential detrimental cardiovascular effects of the high-fat intake that is promoted in ketogenic diets. This trial will provide high-quality evidence regarding whether Keyto's version of the ketogenic diet promotes weight loss without detrimental effects on the blood lipid profile.

Conflicts of Interest

JPL is chief scientific officer for the Institute for Personalized Therapeutic Nutrition, a not-for-profit organization promoting a food-first approach to treating and preventing chronic disease. JPL holds shares in Metabolic Insights Inc, a for-profit company developing a saliva insulin monitor. EJW is an equity holder at Keyto and Virta Health. DAL is employed as a consultant for Keyto. All other authors have no conflicts to declare.

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       10.1037/hea0000161] [Medline: 25642841]

Abbreviations

mHealth: mobile health

XSL•FO
RenderX

Protocol

Tailored Medication Adherence Incentives Using mHealth for Children With High-Risk Asthma (TAICAM): Protocol for a Randomized Controlled Trial

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Abstract

Background: Poor adherence to inhaled corticosteroid medications for children with high-risk asthma is both well documented and poorly understood. It has a disproportionate prevalence and impact on children of minority demographics in urban settings. Financial incentives have been shown to be a compelling method to engage those in a high-risk asthma population, but whether adherence can be maintained by offering financial incentives and how these incentives can be used to sustain high adherence are unknown.

Objective: The aim of this study is to determine the marginal effects of a financial incentive–based intervention on inhaled corticosteroid adherence, health care system use, and costs.

Methods: Participants include children aged 5 to 12 years who have had either at least two hospitalizations or one hospitalization and one emergency department visit for asthma in the year prior to their enrollment (and their caregivers). Participants are given an electronic inhaler sensor in order to track their medication use over a period of 7 months. After a 1-month period of observation, participants are randomized to 1 of 3 arms for a 3-month period. Participants in arm 1 receive daily text message reminders, feedback, and gain–framed, nominal financial incentives; participants in arm 2 receive daily text message reminders and feedback only, and participants in arm 3 receive no reminders, feedback, or incentives. All participants are subsequently observed for an additional 3-month period with no reminders, feedback, or incentives to assess whether any sustained effects are apparent.

Results: Study enrollment began in September 2019 with a target sample size of N=125 children. As of June 2020, 61 children have been enrolled. Data collection is estimated to be completed in June 2022, and analyses will be completed by June 2023.

Conclusions: This study will provide data that will help to determine whether a financial incentive–based mobile health intervention for promoting inhaled corticosteroid use can be effective in patients with high-risk asthma over longer periods.

Trial Registration: Clinicaltrial.gov NCT03907410; https://clinicaltrials.gov/ct2/show/NCT03907410

International Registered Report Identifier (IRRID): DERR1-10.2196/16711

Introduction

Poor adherence to asthma control medication is well documented yet poorly understood. Despite compelling evidence demonstrating improved disease control and fewer exacerbations with regular use of inhaled corticosteroids, adherence to prescribed inhaled corticosteroid regimens in childhood asthma has been found to be 50% of prescribed doses [1]. In minority populations living in urban settings that suffer higher rates of morbidity and mortality from asthma, adherence estimates are even lower, ranging from 11% to 37% [2-5].

Improving asthma control medication adherence, particularly in high-risk populations, remains a challenge. Previous interventions [6,7] to improve medication adherence have demonstrated effects that are modest, at best. As a result, opportunities for innovation in adherence interventions exist. Technology-enhanced reminders have demonstrated robust inhaled corticosteroid adherence improvements in countries outside of the United States [8-10]. Adult interventions consisting of financial and social incentives drawn from behavioral economics have demonstrated an effect on medication adherence and smoking cessation [11,12]. Few studies, however, have attempted to leverage mobile health technology (mHealth) and incentive design to improve medication adherence in children with high-risk asthma.

Two critical challenges have limited the efficacy of existing adherence interventions—lack of knowledge (of what it takes to engage high-risk children and their caregivers) and lack of enduring change (behavior change that lasts beyond the active intervention phase). Recent studies [13,14] have begun to identify intervention components that tend to demonstrate greater efficacy in engaging minority demographic groups and that lead to sustained changes in behavior (or habit formation). We recently conducted a pilot study [15] to investigate the effect of daily reminders and feedback supplemented with nominal financial incentives on inhaled corticosteroid adherence (US $1 per day of adherence for up to 30 days). The pilot study included families of children aged 5 to 11 years who had been hospitalized 3 times in the year prior to enrollment as a result of asthma. The proportion of participants who were approached

for consent and enrolled was high (69%), and mean adherence during the intervention month (80%) was robust; however, adherence dropped to 33% after incentives, reminders, and feedback ceased [15]. These findings revealed that financial incentives were a compelling method to engage this high-risk asthma population in regular inhaled corticosteroid use; however, whether adherence can be maintained and how it can be sustained in pediatric populations is still unknown.

In this study, the intervention used in the pilot was automated by implementing the study on a behavioral research platform. This randomized controlled trial was designed to assess inhaled corticosteroid adherence trajectories in children who are at high risk for hospitalization from asthma, to identify potential mechanisms of adherence, and to assess the perceived efficacy and acceptability of the intervention among children and caregivers. The primary objective of this study is to determine the marginal effects of a financial incentive–based intervention for inhaled corticosteroid adherence on monthly adherence in children of minority demographics living in urban settings.

Methods

Study Design

A 3-armed randomized controlled trial has been designed to assess the effects of different financial incentive strategies on asthma control medication adherence on a sample of children; the target population consists of children of minority demographics in urban settings with high-risk asthma. Participants are randomized to 1 of 3 experimental conditions: financial incentives, adherence reminders, and feedback (arm 1); adherence reminders and feedback without incentives (arm 2); or electronic monitoring only (arm 3). To provide an objective measure of medication use over time, upon study enrollment, research staff place electronic sensors [16] on the inhalers of participating children. These sensors have been validated and used in previous studies [17,18]. Within the study, three discrete phases span a 7-month period: a run-in phase lasting 1 month, an experiment phase lasting 3 months, and an observation phase lasting another 3 months (Figure 1). Subsequently, over a 6-month period, there is a passive follow-up phase where adherence data are not actively tracked.

Figure 1. Overall study design, arm assignment, and timeline.
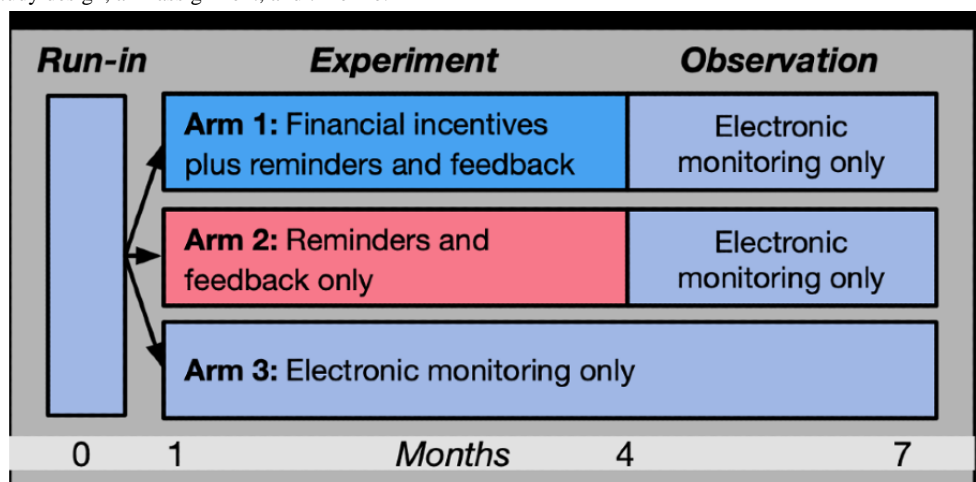
Study Setting

The study is being conducted at a large mid-Atlantic pediatric health system in the US that includes 31 primary care centers and an academic children's hospital. Eligible participants are identified through review of daily inpatient and emergency department census reports and population health management reports in the electronic health record system.

Inclusion and Exclusion Criteria

Children from 5 to 12 years of age (and their parent or legal guardian) who have been prescribed an inhaled corticosteroid or combination inhaled corticosteroid/long-acting beta-agonist for daily use, who have had either at least two hospitalizations or at least one hospitalization and one emergency department visit for asthma in the preceding year, whose parent or legal guardian have access to a smartphone, whose parents or legal guardians give permission (informed consent), and if appropriate, who give their assent are eligible for participation.

Participation from the study will be precluded if the mobile app is not compatible with the parent or guardian's smartphone, their inhaler is not compatible with the electronic sensor, they have a major developmental delay or disability, they have comorbid chronic diagnoses that influences their asthma management (ie, cystic fibrosis, bronchopulmonary dysplasia, or cyanotic heart disease), their family has active Department of Human Services involvement, their family is non-English speaking, or if recruitment for participation would be against medical advice (if factors such as clinical instability or other extenuating circumstances that may influence the informed consent process are present).

Eligible children and their caregivers are recruited during an asthma-related hospital admission or emergency department visit, whenever possible, or in the month following discharge from one of these events if the study team is unable to reach the family during the hospital visit. In the latter circumstance, the study team contacts eligible participants by phone, and if the caregiver expresses interest, the study team approaches the caregiver and child for informed consent and assent at a follow-up visit or a scheduled study visit, whichever is more convenient for the caregiver. Parental or guardian permission (informed consent) and, if applicable, child assent are obtained prior to any study-related procedures being performed. Participants are enrolled through consecutive sampling until the target sample size is reached.

Outcome Measures

The primary outcome is adherence to prescribed inhaled corticosteroid regimen during the experiment phase (months 1 to 3). Adherence is characterized as the monthly mean of daily observed-to-prescribed inhaled corticosteroid dose proportion which has an upper limit of 1; this prevents doses taken above the prescribed limit—either during flare ups or as an attempt to achieve further incentives—from influencing interval adherence measurements. Observed actuations will be quantified using Bluetooth-enabled electronic sensors (Propeller Health [16]) that attach to the inhalers. To properly track medication use from inhaler actuation, the sensors must be synced to the smartphone.

Secondary outcomes include monthly adherence to prescribed inhaled corticosteroid regimen during the observation phase (months 4 to 6), parent- and child-reported asthma control, asthma-specific health care system use and cost, and adherence trajectories. Asthma control is measured using the child Asthma Control Test [19]. Health care system use is assessed, primarily, using electronic health record data and, secondarily, from caregiver reports of visits that may have occurred outside of the institution's health care system. Emergency department visits and hospitalizations are characterized as asthma-specific using existing, validated asthma registry definitions that include asthma visit diagnoses (ICD-9 493.XX or ICD-10 J45.XX), medication orders, and asthma pathway order set activation. Costs are estimated using average insurance payments for asthma emergency department visits and hospitalizations, in addition to the costs of the intervention components (ie, sensor, incentive, and research staff costs).

To model inhaled corticosteroid adherence over time, adherence trajectories will be constructed for the combined experiment–observation period for each participant using group-based trajectory modeling. This modeling approach accounts for changes in behavior over time and allows for identification of several distinct developmental progressions without imposing statistical assumptions of normality [20,21].

Additionally, data will be collected from semistructured interviews conducted at the end of the experiment phase in a randomly selected subset of participants. The interviews are designed to provide in-depth insight into the experiences of the child and their family with respect to intervention components, in particular, perceived influence or lack of influence of the incentives on inhaled corticosteroid adherence behavior. In addition, we will explore other factors that the children and caregivers perceive to influence daily inhaled corticosteroid adherence. Interview prompts include the perceived impact of the intervention components (financial incentives, adherence reminders, adherence feedback, study app, electronic monitoring), component design factors (duration of incentive exposure, duration and frequency of reminders and feedback, child and caregiver engagement strategies, and potential alternative incentive strategies), and nonintervention factors (medication access, perceived medication efficacy, and family and social circumstances).

Potential Mediators

At study visits, to assess how intervention strategy impacts adherence trajectory, the following will be measured: (1) parent self-efficacy using the Parent Asthma Management Self-Efficacy scale, (2) parent and child asthma medication responsibility measured using the Asthma Responsibility Questionnaire, and (3) habit formation measured using the Habit Strength Index adapted for asthma controller use [22-24].

Study Platform and Devices

Way to Health is a web-based intervention platform [25]. For this study, the Way to Health platform automates randomization, text message delivery, and summary of longitudinal adherence data. Text messages include reminders to administer the inhaled corticosteroid inhaler and to resync the sensor with the

smartphone; reminders are sent once a week. Parents receive weekly summaries regarding medication adherence, how much money their child has earned for using their medication, and tips and encouragement for the upcoming week.

The electronic monitoring sensor records the date, time, and number of inhaler actuations. The sensor is used in conjunction with an app (compatible with iPhone and Android-based phones), which receives the medication use data from the sensor through Bluetooth. The application programming interface has been integrated with the Way to Health research platform for the purpose of this study. In order to ensure that inhaled corticosteroid use data are relayed to platform in a timely fashion, participants are instructed to ensure that their smartphone's Bluetooth is on and that the Propeller app is opened at least once weekly, as transmission of sensor data is dependent upon these steps.

Intervention

Study visits are described in Figure 2. The first study visit consists of a 30-minute survey administered on the Way to Health platform. At the initial enrollment visit, study staff demonstrate to participants how to attach and properly sync the sensor to their inhaler and smartphone. The run-in phase begins on the day of enrollment.

During the 1-month run-in phase, all participants have access to the electronic inhaled corticosteroid use monitoring app. Inhaled corticosteroid use is tracked using the electronic sensor that remains affixed to their inhaler throughout the 7-month study period. During the run-in phase, participants are sent 4 text messages, each designed to elicit a response from the caregiver about either the study technology or the study itself. Participants for whom any inhaler use data are transmitted to the study platform within the first 2 weeks of the run-in phase AND who reply to 1 or more of the 4 text messages are randomly assigned into 1 of the 3 arms at the end of the run-in phase. Assignments are computer-generated through the Way to Health platform and are determined using a block randomization allocation sequence. The subsequent 2 weeks of the run-in phase are designed to provide baseline adherence data. Participants for whom no medication-use data are received or who do not respond to any of the text messages in the first 2 weeks are considered nonresponders and are deemed to no longer be participating in the study.

Participants are randomly allocated to arm 1 (financial incentives, adherence reminders, and feedback), arm 2 (adherence reminders and feedback without incentives) or arm 3 (electronic monitoring only) in a 2:1:2 scheme, without stratification by participant or enrollment characteristics. The financial incentives in arm 1 consist of 3 months of gain-framed, fixed-ratio incentives for each inhaled corticosteroid actuation (ie, US $0.25 per puff for children on 4 daily inhaled corticosteroid doses or $0.50 per puff for children on 2 daily doses) to a maximum of $1 per day. In arms 1 and 2, study participants receive automated daily text messages and automated weekly feedback summarizing their adherence performance through the platform.

At the end of the first month of the experiment phase, families are contacted by study staff to complete a survey that reassesses disease control, medication supply, and intentions and behaviors with regard to inhaled corticosteroid use (study visit 2). At the end of the experiment interval, families are contacted again by study staff to complete a survey (study visit 3). Participants are also randomly assigned to complete a semistructured interview for study visit 3. At this point, all reminders, feedback, and incentives cease, but daily inhaled corticosteroid use electronic monitoring continues through the observation phase (the remaining 3 months) for all arms to assess sustained effects. Surveys are complete at study visit 4 (in the final month of the study) and at the fifth and final visit at a 1-year follow-up which assesses asthma control and health care use outside of the institution's health care system.

For participants receiving adherence incentives in the experiment phase, the accrued sum at the end of each 30-day interval (maximum $30) is added to a debit card that is provided to the child upon enrollment. In the experiment phase, children randomized to arms 2 and 3 who have any inhaled corticosteroid actuations recorded in each study month receive a $10 disbursement at the end of each month of the experiment phase (months 1 to 3). Children in all 3 study arms receive a $10 disbursement per month during the observation phase (months 4 to 6) in which any adherence data are transmitted to the platform. This compensation is not contingent upon the participant's inhaled corticosteroid adherence. Separate study visit compensation ($20) is provided to the caregiver after enrollment and at each study visit.

After completion of the observation phase, participants enter into a follow-up period. After an additional 6 months of follow-up, participants complete a final study survey. The study team also assesses electronic health records for emergency department and hospital use for asthma over the study time period.

Figure 2. Flow diagram of the study. cACT: child Asthma Control Test.
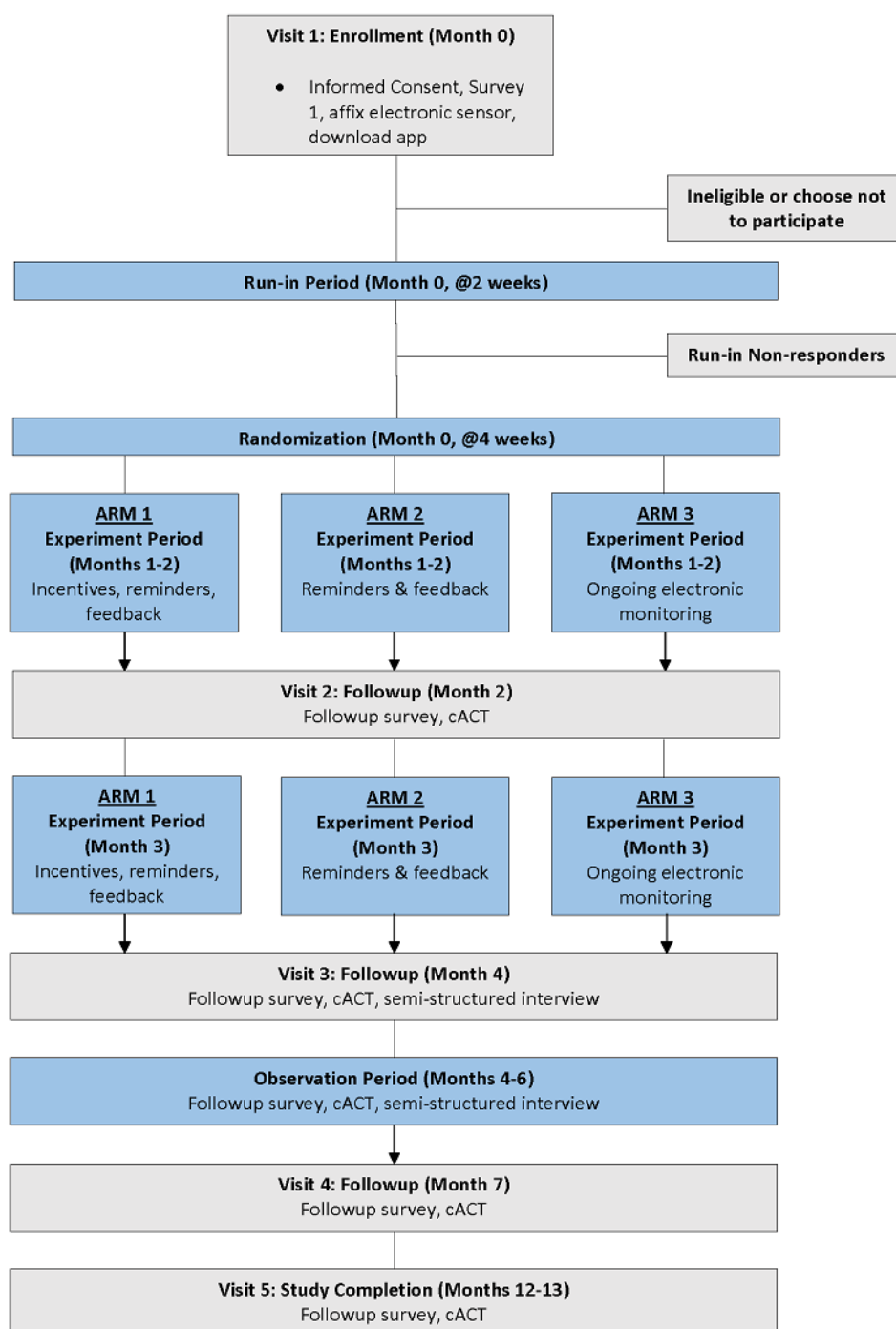
Data Analysis

Baseline and demographic characteristics will be summarized as mean and standard deviation for continuous variables (ie, age) and as percentages for categorical variables (ie, gender). Study arm demographic, clinical, and past health care use variables will be compared using analysis of variance and *t* tests (or the nonparametric equivalent) for continuous variables as

well as chi-square tests (or Fisher exact tests) for categorical variables.

To adjust for within-subject correlations due to repeated measures for the primary and secondary adherence outcomes, we will use generalized estimating equations that model main effects by trial arm, time (in months), and arm-by-month interactions to allow for differing inhaled corticosteroid adherence over time between arms. The dependent variable will be the mean daily observed-to-prescribed inhaled corticosteroid

actuation proportion for each month. Mean daily adherence proportions are capped at 1 as previously described. All statistical tests will be 2-tailed, and a *P* value<.05 will be considered statistically significant.

We will use group-based trajectory modeling (PROC TRAJ) in SAS statistical software (SAS Institute) to construct adherence trajectories for the combined experiment and observation phases for each participant. Participants with similar daily adherence trajectories are grouped by similar longitudinal trends and the model output is probabilistic assignment of individuals to one of several adherence trajectory group models [20,21]. We will compare the models and number of groups to identify which best fit the data based on lowest Bayesian information criterion and group percentages that are sufficiently large (ie, greater than 5% of the population). A bivariate multinomial or ordered logistic regression model will be used to estimate odds ratios for the covariates and for baseline data on trajectory group membership. For the ordered logistic regression, the Brant test will be performed to check the proportional odds assumption. Variables that are not marginally predictive (*P*>.2) of any trajectory group in the bivariate analysis will be excluded from the subsequent multivariable analysis. A multivariable multinomial regression model of trajectory of all marginally significant covariates, first including baseline data, then including study arms, and finally including our 3 hypothesized mediators, will be performed [7]. Mediation analysis will be conducted with variables associated with both study arm and trajectory membership. Covariance matrices will be generated and regression estimates will be standardized to obtain an overall mediated effect of each potential mechanism variable on each of the 3 study arms. The percentage of the total effect of the study arm that is mediated by the potential mediator will be calculated using standard beta estimates [8].

For the cost offset analysis, the total medical costs will be estimated for the 12 months following study enrollment, accounting for asthma-related emergency department visits and hospitalization, as well as for expenses incurred for incentives, sensors, and the use of the Way to Health automated platform. We will estimate potential savings in medical costs, or cost offset, by calculating the difference in average total medical cost and study-related expenses for each study arm.

Semistructured interviews will be conducted with at least two trained interviewers and will be conducted in person or by phone. Audio recordings of the interviews will be transcribed by a transcription agency service and deidentified. Transcripts will then be uploaded to NVivo (version 12; QSR International LLC) for coding and analysis. At least two trained coders will use inductive theory building and the constant comparative method to identify data patterns [9,10] As themes and patterns emerge, we will search for negative cases within the data to refine our analysis [11] and create an initial set of codes that will be applied openly to a set of transcripts. Codes will be revised through an iterative process by constant comparison within a set of transcripts. A final codebook will be established and applied to all transcripts. Interrater reliability will be assessed on at least 20 percent of the transcripts to establish consistency and the coders will meet regularly throughout the process to reach a consensus on major discrepancies in coding.

Sample Size and Power

Analysis of pilot data [15] demonstrated a 48% difference in inhaled corticosteroid adherence when comparing a time interval with financial incentives to a time period without incentives similar to the schema proposed in this study. Using a conservative estimate of detecting a 30% difference in average adherence between arm 1 (treatment arm with financial incentives corresponding to 65% adherence) and arm 3 (control arm corresponding to 35% adherence), 40 patients are required for each of these arms in the experiment phase to ensure a power of 80% at a significance level of α=.05. Estimating a 20% loss to follow-up, we aim to enroll 50 participants each in arms 1 and 3 and 25 participants in arm 2 for a total sample size of 125 participants to achieve sufficient power. This study is not powered to detect differences in relation to arm 2 (treatment arm with no financial incentives) because of insufficient existing data to estimate power, as well as practical considerations such as the number of potentially eligible patients. Rather, arm 2 will provide preliminary estimates of marginal effects of the intervention components and effect sizes on use outcomes to power a future multicenter study.

Results

This study was approved by the Children's Hospital of Philadelphia institutional review board and is registered (Clinicaltrial.gov NCT03907410; https://clinicaltrials.gov/ct2/show/NCT03907410). Study enrollment began in September 2019. As of June 2020, 61 children have been enrolled. The intervention and follow-up phases are ongoing. Data collection is estimated to be completed in June 2022, and analyses will be completed by June 2023.

Discussion

This study will evaluate the efficacy (using monthly inhaled corticosteroid adherence) of implementing gain-framed, nominal financial incentives, text message reminders, and weekly feedback in a cohort of children with multiple asthma exacerbations in the preceding year. While our previous work [15] demonstrated the feasibility and acceptability of financial incentives to encourage inhaled corticosteroid use among a high-risk asthma population, this study will assess the efficacy of such an approach. The study will also assess trajectories of inhaled corticosteroid adherence in the six months following the mHealth intervention to see if and how inhaled corticosteroid adherence varies between the study arms.

This study has several limitations. Participants who are adherent may still experience asthma morbidity since morbidity can be influenced by factors other than medication adherence, such as environmental exposures. This intervention will occur in the context of standard asthma care provided within our health care system; thus, children and families may be referred to a community health worker home visiting program, housing initiatives, and other programs that address social and environmental determinants of health based upon predetermined eligibility criteria. Because this study design is randomized, these exposures should not vary by study arm. Additionally, because children from 5 to 12 years of age cannot be expected

to have personal smartphones to receive medication reminders, feedback, and monetary rewards, this study relies on the caregiver to relay reminders and feedback to their children. Our pilot intervention data demonstrated that most children regularly engaged with their caregiver's smartphone, inquiring about adherence performance and incentive accrual over a 1-month period [15]. A third limitation is the challenge of implementing a technology-based intervention for high-risk families. This includes lower prevalence of home internet service, limited monthly data on cellular contracts, and the possibility that parents' cell phone numbers may change throughout the course of the study, making it difficult to contact study participants. Additionally, some caregivers and their children will not always be in the same location and this could limit their ability to relay the reminder messages to their children. To address these limitations, we limit the frequency of adherence feedback (weekly reminders) to compensate for intermittent data uploads, and we obtain multiple telephone numbers and alternate contacts in the event that caregivers cannot be reached. Also, since having a compatible smartphone is part of the inclusion criteria, there is the potential for selection bias based on smartphone ownership. Notably, however, smartphone ownership is nearly ubiquitous, mitigating this concern [26,27]. Lastly, there may be differential attrition and data loss by study arm. Since only 1 of the 3 study arms receives financial incentives, there is a possibility that the other arms could have a higher attrition rate; however, this limitation is addressed by compensating participants in arms 2 and 3 based solely on receipt of monthly data, regardless of their adherence percentage.

Acknowledgments

Conflicts of Interest

None declared.

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Abbreviations

ICD-9: International Classification of Diseases, Ninth Revision
ICD-10: International Statistical Classification of Diseases, Tenth Revision
mHealth: mobile health technology

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Protocol

Promoting Physical Activity With Self-Tracking and Mobile-Based Coaching for Cardiac Surgery Patients During the Discharge–Rehabilitation Gap: Protocol for a Randomized Controlled Trial

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Abstract

Background: Home-based cardiac rehabilitations (CRs) with digital technologies have been researched and implemented to replace, augment, and complement traditional center-based CR in recent years with considerable success. One problem that technology-enhanced home-based CR can potentially address is the gap between cardiac interventions and formal CR programs. In the Netherlands and some other countries (eg, Australia), patients after cardiac interventions stay at home for 3-4 weeks without much support from their physicians, and often engage in very little physical activity (PA). A home-based exercise program enabled by digital technologies may help patients to better prepare for the later center-based CR programs, potentially increasing the uptake rate of those programs.

Objective: In a randomized controlled trial (RCT), we will evaluate the effectiveness of a home-based walking exercise program enhanced by self-tracking and mobile-based coaching (treatment condition), comparing it with a version of the same program without these technologies (control condition). The added value of the digital technologies is justified if patients in the treatment group walk more steps on average (primary outcome) and show better physical fitness in a bicycle ergometer test and higher self-efficacy toward PA (secondary outcomes).

Methods: Based on a power analysis, we will recruit 100 cardiac patients and assign them evenly to the 2 parallel groups. Eligible patients are those who are scheduled in the postanesthesia care unit, know the Dutch language, have basic literacy of using smartphones, and are without medical conditions that may increase risks associated with PA. In a face-to-face meeting with a nurse practitioner, all patients are prescribed a 3-week exercise program at home (2 walking exercises per day with increasing duration), based on national and international guidelines and tailored to their physical conditions after cardiac intervention. Their physical activities (daily steps) will be measured by the Axivity AX3 accelerometer worn at hip position. Patients in the treatment group will also be supported by a Neo Health One self-tracking device and a mobile platform called Heart Angel, through which they are monitored and coached by their nurses. After the study, all patients will perform a bicycle ergometer test and return the devices within 1 week. In addition, 5 questionnaires will be sent to the patients by emails to assess their self-efficacy toward PA and other psychological states for exploratory analyses (at discharge, at the end of each monitoring week, and 1 week after the study). To minimize bias, the randomization procedure will be performed after introducing the exercise program, so the nurse practitioners are blind to the experimental conditions until that point.

Results: The study protocol has been approved by the Medical Research Ethics Committees United on February 26, 2018 (NL 62142.100.17/R17.51). By the end of 2018, we completed a small pilot study with 8 patients and the results based on interviews

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and app usage data suggest that a larger clinical trial with the targeted population is feasible. We expect to complete the RCT by the end of 2021, and statistical analyses will follow.

Conclusions: Results of the RCT will help us to test the hypothesized benefits of self-tracking and mobile-based coaching for cardiac patients in home-based exercise programs during the discharge–rehabilitation gap. If the results are positive, cost-effectiveness analysis will be performed based on the insights of the study to inform the translation of the technology-enhanced program to clinical practice. We also note limitations of the trial in the discussion.

Trial Registration: Registered at Netherlands Trial Register NL8040; https://www.trialregister.nl/trial/8040

International Registered Report Identifier (IRRID): PRR1-10.2196/16737

Introduction

Cardiac rehabilitation (CR) is an evidence-based and widely recommended strategy for the secondary prevention of cardiovascular diseases. Recent reviews have shown that CR is efficacious and cost-effective not only for reducing mortality by up to 26%, but also for preventing hospital re-admissions and improving quality of life [1-4]. In the Netherlands, after cardiac intervention, such as coronary artery bypass graft surgery, it is a standard practice to refer patients to participate in outpatient rehabilitation programs for 6-12 weeks, where group-based trainings of physical activity (PA), nutrition, and other lifestyle aspects are applied [5]. However, despite the proven benefits and the enforced practice, a general challenge for CR worldwide is the low rate of participation and completion by patients [5-8]. According to a Dutch cohort study [5], although patients after cardiac surgeries had the highest uptake rate among all cardiac patients, the number was just above 50%.

A particular challenge in the Netherlands is that there is usually a gap of 3-4 weeks between the discharge after cardiac surgery and the start of the formal CR, during which patients stay at home without much guidance on what they can do to improve their fitness. The same issue has also been reported in Australia [6]. The lack of guidance, combined with their low levels of self-efficacy for PA after surgery [9] and sometimes their preceding sedentary lifestyle, results in postsurgery PA levels that are below the level needed for optimal recovery [10]. Therefore, there is clearly a missed opportunity in this gap, which could be used to better prepare patients for the formal CR programs and even to increase the uptake rate of the programs. Moreover, because people are generally more susceptible to behavior change right after disruptive life events (eg, a cardiac surgery) [11], training patients at home for regular PA may also foster a long-term active lifestyle. To realize this opportunity, a home-based solution for supporting PA is needed.

In recent years, home-based CR has been gradually accepted as an alternative to the more traditional center-based CR. Evidence has been accumulated that home-based CR programs are often as effective as center-based CR programs [12-15], and they may incur lower costs [16,17] (but see [18]). A practical barrier for traditional CR is also eliminated as patients can stay at home and contact doctors or trainers through information and communication technologies (ICTs) only when necessary.

Although long-term effects of home-based CR on PA and fitness are still in question [16], for our goal of preparing patients for the formal CR, a home-based approach is well suited in theory. However, most of the studies on applying ICTs in CR have focused on either replacing traditional CR with home-based CR [16,19] or augmenting ongoing center-based CR with new technologies [20,21], but much less on complementing the existing CR practice. One recent study examined the potential benefits of an internet- and mobile-based intervention on the maintenance of PA after regular CR, but the high attrition rate in the randomized controlled trial (RCT) prevented the authors from drawing clear conclusions [22]. More relevant to our research question, an ongoing RCT was designed to evaluate the use of SMS text messaging to support patients in the transition period after acute coronary events and before the start of CR [6]. More research is clearly needed to understand whether home-based interventions with ICTs before or after center-based CR are beneficial to patients.

Designing a cost-effective home-based PA intervention also raises the question of what intervention components are essential for an intervention to be efficacious. One component emphasized and utilized in almost all CR programs is personalized guidance from physicians based on patient monitoring [16], which can be implemented through several different communication modalities, including face-to-face meetings [23], phone calls [16], SMS text messages [24], and chat sessions using websites or mobile apps [19]. From a theoretical perspective, physician guidance plays multiple roles, such as goal setting, social persuasion, and emotional support, and it can even be more important for patients who have low cognitive capacities, or low self-efficacy toward PA after surgery [9,10]. Regardless of which modality to use, any physician guidance will increase workloads for health care professionals, so its benefits and costs are ought to be carefully weighted.

Another promising component is the self-monitoring of behavior and health status by patients themselves, usually supported by mobile and wearable self-tracking devices. Psychological theories generally consider self-monitoring as an important mechanism in self-regulation [25], and meta-analyses have demonstrated the effectiveness of self-monitoring as a behavior change technique [26]. Several RCTs examined the applications of self-tracking technologies in related clinical settings [27-29]. In one trial after myocardial infarction [27], patients who were

required to record their weight, PA levels, blood pressure, and heart rate during a standard CR program reported higher self-efficacy toward PA and also exercised more than their peers in the control group 1 year later. In another trial [28], the use of pedometer alone led to higher levels of PA that were maintained 6 weeks and 6 months after a CR program. Finally, in [29], patients who wore an electronic step tracker and followed a home-based CR program showed similar levels of physical improvements to those who followed a center-based CR program.

In this study, we compare the effectiveness of 2 home-based PA programs that fill the gap between discharge and formal CR for patients after cardiac surgery, one with the support of digital technologies and one without this support. In the technology-enhanced group (intervention group), patients use a wristband to track their steps and communicate with physicians through a mobile app for 3 weeks. In the control group, patients are only told to follow a specific PA program at discharge, but do not receive any additional support while at home. Both trial conditions can be considered as clear improvements over the usual care, but they may differ greatly in their effectiveness and costs. We hypothesize that the use of self-tracking and

mobile-based coaching will lead to higher PA levels and potentially also bring physical and psychological benefits at the end of the program, which would provide a rationale to implement these technologies into clinical practice. At the same time, costs associated with the technology-enhanced program can be estimated and used in cost-effectiveness analysis in the future.

Methods

Design

The study (registered at Netherlands Trial Register NL8040) will have a parallel-group randomized experimental design with an allocation ratio of 1:1. Participants will be randomized to the intervention or the control group during the introduction meeting at the date of discharge (Figure 1). Variables regarding participants' psychological states (eg, self-efficacy toward PA) will be measured repeatedly over the weeks during the experiment (see the "Outcomes" section for details). The protocol conforms to the SPIRIT 2013 statement [30] and is described according to the CONSORT-EHEALTH checklist [31] (Multimedia Appendix 1).

Figure 1. Design of the randomized controlled trial.
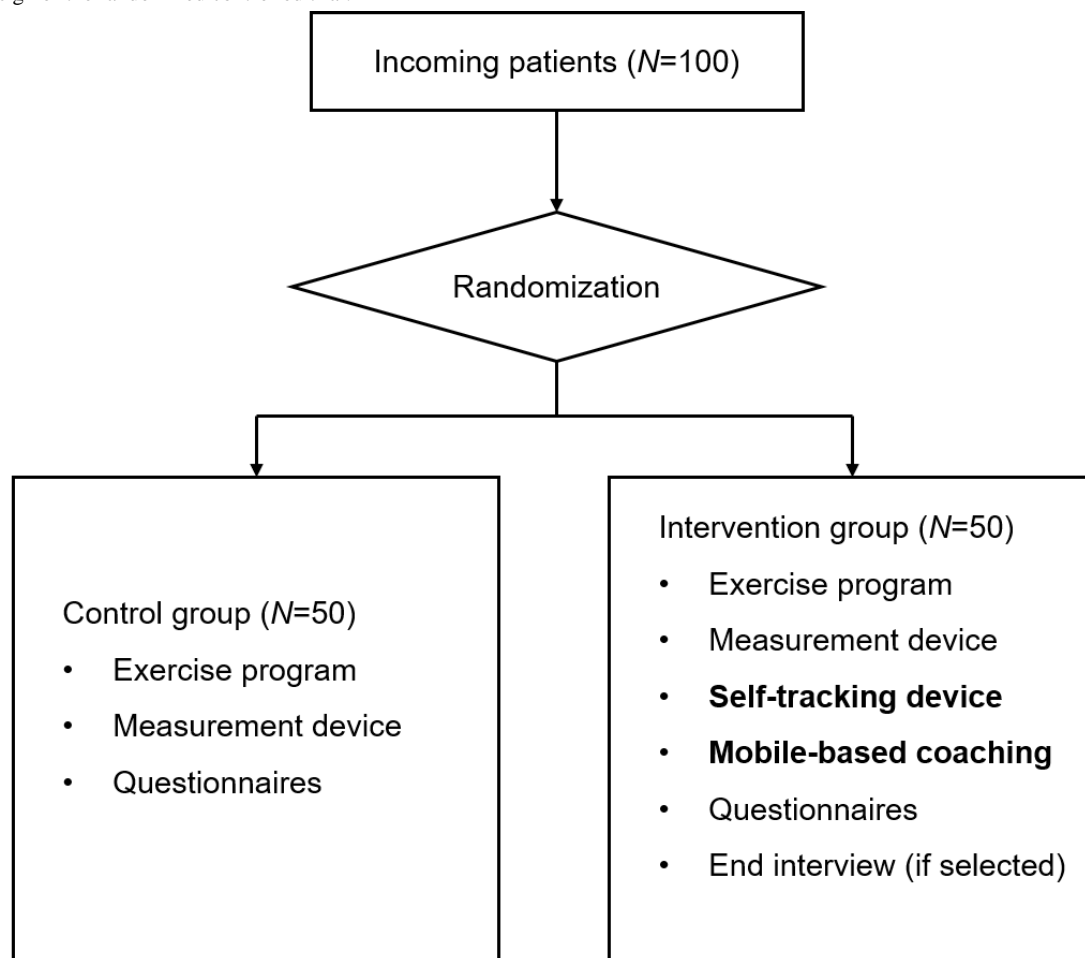
Eligibility and Recruitment

Patients who are expected to undertake a cardiac intervention at Catharina Ziekenhuis Eindhoven (CZE) and to follow a conventional CR program at least four weeks after discharge

are eligible for this study. Eligible patients should also be scheduled as postanesthesia care unit patients, who are at relatively low risk and are expected to recover smoothly. Definition of postanesthesia care unit patients is

well-operationalized in preoperative workup. Other inclusion criteria are (1) the patients are in possession of an Android or an iOS device (eg, a smartphone or a tablet), and have sufficient level of digital literary to use the device (eg, regular previous uses of emails and mobile apps); and (2) they understand the Dutch language. Patients are excluded if they are immobile, have a history of stroke with remaining dysfunction, or have serious complications, including stroke, severe myocardial infarction with echocardiography-confirmed myocardial function loss, or a serious infection that requires prolonged hospital stay and intravenous antibiotics.

Patient are always screened at the outpatient clinic at least three weeks before the operation. During the screening, information concerning the study are provided and the patient is given enough time (at least one week) to read the information and to ask questions. Signing the informed consent takes place during the admission 1 or 2 days before the operation.

Sample Size Calculation

We used a minimum effect size of interest approach to calculate the sample size needed to detect a statistically significant difference between the intervention group and the control group in terms of the primary outcome (average daily steps over 3 weeks). In an internal discussion between researchers, physicians, and CR experts at CZE, a 2000-step daily difference was proposed to be the minimum effect size of interest, and a 3000-step within-group standard deviation was assumed based on [32]. These assumptions amount to a moderate to strong effect size in terms of Cohen d of 0.67, which is justifiable given the large differences between the two conditions in terms of costs. Based on a simulation study in the R statistical programming environment [33], 100 participants (50 in each group) are required to have a 90% power to detect the effect at a significance level of .05. Because we will also have day-level data for steps over 3 weeks, multilevel regression models can also be used for examining the differences in PA between the two groups, which should have much higher power due to the large number of observations (ie, data collected over 21 days

by 100 patients). Details of the simulation-based power analysis (and the R code) can be found in Multimedia Appendix 2.

Interventions

The Daily Exercise Program

The daily walking exercise program was designed based on both Dutch and European PA guidelines for the prevention of cardiovascular diseases and its rehabilitation [34,35], and also in compliance with expert opinions from physiotherapists at CZE. The program consists of 2 walking exercises and 1 overall goal for the amount of PA per day, with increasing intensity over the duration of the trial. The restricted durations of each walking exercise session are between 5 and 15 minutes for the first week, 10 and 20 minutes for the second week, and 15 and 25 minutes in the third week. The exact duration in each week will be decided by the patients and their physician together in the introduction meeting, adapted to the physical conditions of the patients after surgery (see Figure 2 for an example). Patients are also told to continue the same walking exercise after the 3-week study as long as the exercise plan does not conflict with their formal CR program.

One feature of the program is that patients will be encouraged to execute the 2 daily walking exercises at the same time and in the same context throughout the weeks. According to psychological theories of habit [36], performing the exercise in this way facilitates the formation of a strong exercise habit through the repetition of the behavior in the same environment. Based on the idea of implementation intention [37], patients will be asked to decide the time and context themselves according to their existing daily routines, and to imagine themselves performing the walking exercises in that context for 1 minute. This feature was used not only to prevent patients from omitting the exercise, but also to potentially promote a habit of exercising after the trial. The daily exercise program will be introduced to the intervention and the control group indifferently, and a booklet of the planned program will be distributed to all patients.

Figure 2. An example of a personalized rehabilitation plan for a patient.
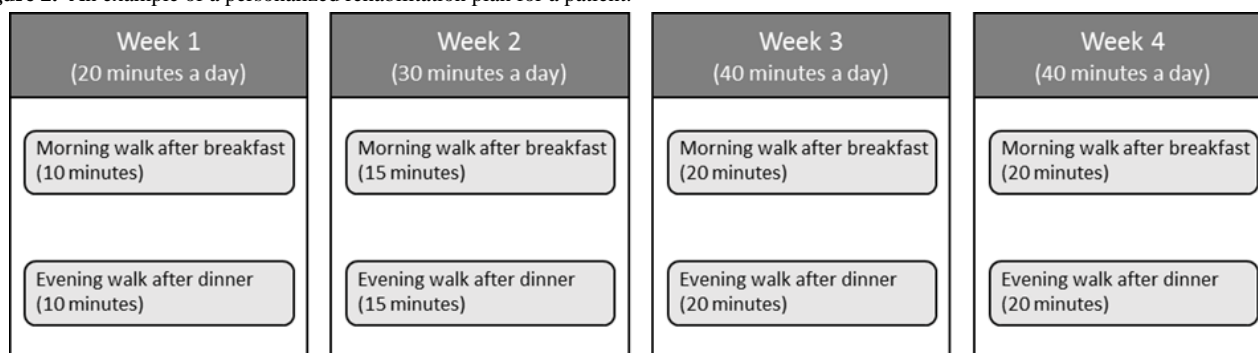
The Self-Tracking Device

Patients in the intervention group will receive a Neo Health One wristband (Figure 3), which is a commercial and CE-marked self-tracking device with build-in accelerometers. Patients are instructed to wear these bands as much as possible during the

day. They can review at any time the number of steps they walked on a specific day and the step data are also synchronized to the mobile-based coaching app used in the trial. Patients in the intervention group will be instructed to wear the device as a wristband on their nondominant side.

Figure 3. The Neo Health One wristband as the self-tracking device in the study.

The Mobile-Based Coaching App

Patients in the intervention group will also be monitored and coached by nurse practitioners through an e-coaching app called Heart Angel, which is a customized version of the commercial Virtuagym platform [38]. We decided to use this particular app because (1) the platform meets our needs for e-coaching and is free; (2) a customized version tailored to the context of CR was made available; and (3) the platform works seamlessly with the Neo Health One self-tracking device. The nurse practitioners work at the same cardiac surgery department at CZE and are known by the patients during their stays at the hospital, and they receive a 1-day training to use the platform provided by the researchers. The patients will use a mobile version of the Heart Angel app, while the nurse practitioners will use an associated web platform for coaching.

The Heart Angel app serves the following functions. First, the daily walking exercise program is saved and shown in the app, so the patients can always open it to review their goals and plans (Figure 4B). Second, data from the self-tracking device are transmitted to the app, so both patients and their coaches (the nurse practitioners) can monitor their PA performance using the app (Figure 4C). Third, the mobile app sends daily notifications in the morning to remind the patients of their planned daily step goals, and whenever a goal is reached, they receive achievement badges from the app. Fourth, when there is a need to contact their coach, the patients can send messages through the mobile app (Figure 4D). Conversely, the nurse practitioners are asked to closely monitor their patients' compliance and performance, and to coach them whenever needed through the app, for example, to check for problems if a patient is not exercising sufficiently according to the plan, or to compliment a patient who is doing well. As the above functionalities are prototypical for e-coaching platforms in general, our RCT is meant to be an evaluation of the general functionalities of e-coaching rather than the Heart Angel app per se.

Figure 4. Screenshots of the Heart Angle mobile coaching app. (A) Homepage of the app showing the navigations to different functions. (B) Recorded walking exercise plan in the app in a calendar view. (C) Progress page showing the step data from the Neo Health One band. (D) An example of chatting between a patient and a coach.
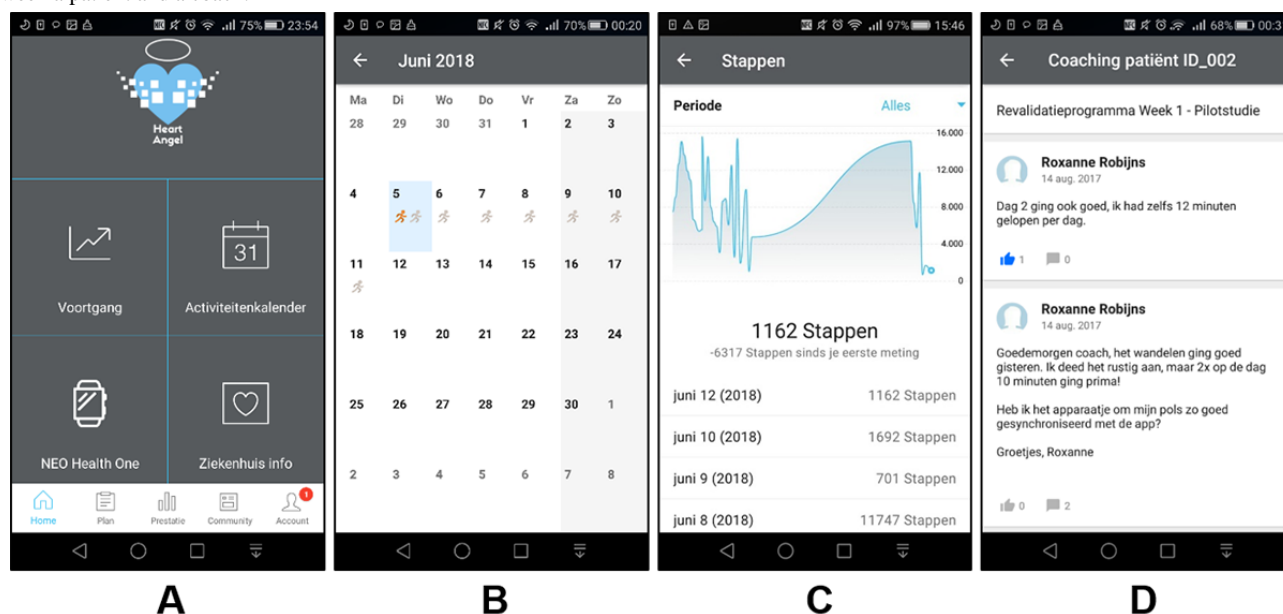
Primary and Secondary Outcomes

The primary outcome is the amount of daily physical activities by the patients, operationalized as the average daily steps over the 3 weeks. The steps are measured by the Axivity AX3 tracker, which is a CE-marked 3-axis logging accelerometer developed by the Open Movement organization at Newcastle University (Figure 5). The device is intended to be used in research on activity recognition, motion measurement, medical research, and movement science. It has been used previously in a large-scale clinical trial in UK [39] and validated for measuring PA in older adults [40]. Patients in both intervention and control group will be asked to wear the device as a clip on their cloths at their hip on the nondominant side (eg, a belt clip). The device has a long battery life (around 1 month) and large internal memory (1-month's data with a sampling frequency of 50 Hz), so the patients do not have to worry about charging the device or offloading the data. Unlike the self-tracking device (the Neo Health One), this measurement device only records data but provides no feedback about steps to the patients.

In addition to the primary outcome, 2 secondary outcomes are used to test whether the behavioral-level increase of daily PA levels would bring patients benefits at physical and psychological levels for their preparations for the formal CR program. To measure physical fitness, a bicycle ergometer test will be held for each patient at the Cardiac Function Department as their usual clinical practice within 1 week after the 3-week trial. The research team will not be involved in the administration of the test, but 3 parameters of interest, namely, peak oxygen uptake (peak VO_2), maximal workload, and maximum heart rate (HR_{max}), will be provided to us. Previous studies have shown positive effects of walking trainings on physical fitness [41-43]. However, because of the short duration and moderate intensity of our exercise program, we do not strongly predict significant effects given the sample size.

Psychologically, we will examine whether patients in the intervention group report higher level of self-efficacy toward PA compared with the control group at the end of the third week. The rationale is that patients in the intervention group receive more guidance, social and emotional supports, and their ability to walk more steps may also increase perceived efficacy [44]. Based on a theory-based recommendation in [45], a scale for measuring self-efficacy in our context was developed specifically for this study and will be included in the 5 questionnaires sent to the patients (Multimedia Appendix 2).

Figure 5. The Axivity AX3 accelerometer as the measurement device.
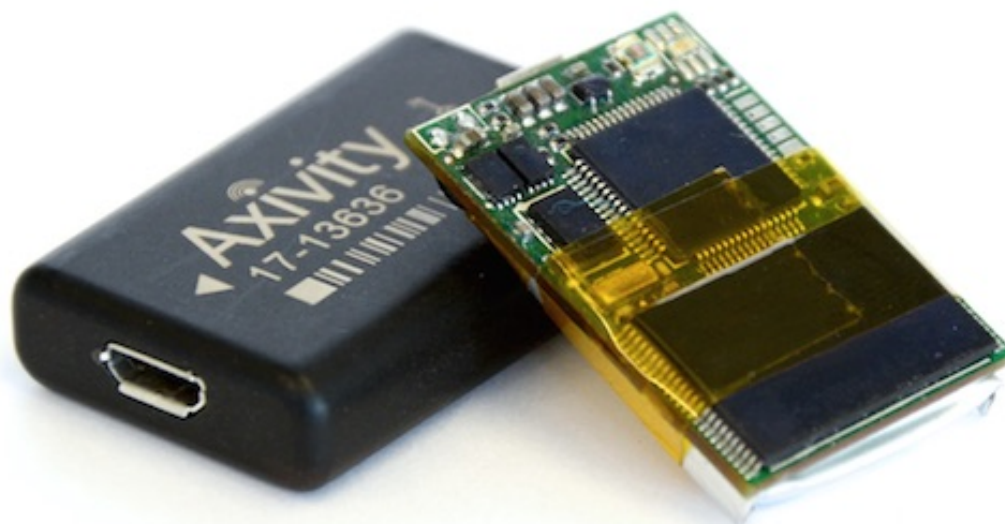
Additional Measurements for Exploratory Analyses

Besides primary and secondary outcomes and demographic and clinical data collected as part of the usual care, we will also collect app usage data and additional self-report measures for exploratory analyses. App usage data can provide preliminary insights into the role of specific features of the app in its overall effectiveness by correlating outcome variables with usage metrics, including login frequency, frequency of monitoring one's step data (Figure 4C), coaching message frequency, and coaching message content.

Additional self-report measures are used to assess patients' baseline PA levels before their cardiac events and to examine the dynamics of their psychological states over the weeks between the intervention and the control group. A complete list of the self-report measures in English can be found in Multimedia Appendix 2. All questions will be translated into Dutch for the trial.

Physical Activity Levels Before Cardiac Events

Patients' regular PA levels before their cardiac events will be measured using the validated International Physical Activity Questionnaire [46], available in Dutch.

Trait Self-Control

Trait self-control has been shown to relate positively to a variety of health outcomes [47,48] and to people's abilities to form healthy lifestyle habits [49]. However, the role of self-control in CR following cardiac intervention has not been examined. We will use the 10-item Brief Trait Self-Control Scale [50].

Attitude Toward the Daily Walking Exercise

Attitude refers to the subjective evaluation of a behavior object as positive or negative [51], and it is one of the most studied and important determinants of behavior change [52]. We will explore how patients' attitude toward PA changes over time and whether self-tracking and mobile-based coaching lead to more positive attitude. Attitude is measured using seven 7-point semantic differential scales, for example, *good–bad*, *beneficial–harmful*, *pleasant–unpleasant*.

Habit Strength of the Daily Walking Exercise

As a patient repeats the daily walking exercise in a stable daily environment, the behavior will potentially become habitual and more likely to be maintained outside the context of the study [36]. We are interested in the dynamics of this habit formation [53] and how the intervention and control groups would differ in this regard. The validated 4-item Self-Report Behavioral Automaticity Index will be used [54].

Randomization and Blinding

Patients will be allocated to the intervention or control group through a computerized randomization procedure during the introduction meeting. Specifically, the procedure takes place after the introduction of the general study information and the

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daily walking exercise program, and before the tutorials about how to use the (condition-dependent) technologies. The timing of the randomization is designed to blind the experimenter (a nurse practitioner) to treatment allocation until the daily walking exercise program is fully introduced, in order to minimize potential biases in guiding and motivating the patients. As with most electronic health (eHealth) trials, patients in our trial are not blinded to their conditions. Assessors of the bicycle ergometer test will be blinded to the research purposes as well as treatment allocation.

Patient Timeline

Patient timeline in this RCT is illustrated in Figure 6. During the preoperative screening in the outpatient clinic, patients are informed about the study and are given 1-2 weeks to make their participation decisions. If they agree to participate, a consent form is signed a few days before the surgery. After the surgery and the 3-5-day monitoring at the hospital, an introduction meeting with a nurse practitioner is held at discharge. In this

meeting, the study goals and procedure are introduced first, and then the daily walking exercise program is explained and details are planned together with the patients. After the randomized group allocation, according to the assigned group, patients are handed the devices and are guided through the installation, registration, and use of the devices and the mobile app. After returning home, patients are expected to follow the exercise program at home for 3 weeks, before they are referred to the conventional CR program. Right after discharge and at the end of each study week, a questionnaire is sent to the patients by email to measure the variables of interest discussed above. After the 3-week trial, a bicycle ergometer test is scheduled to take place at the hospital within 1 week, where patients also return the devices. A final questionnaire is sent 1 week after the study to measure the same set of variables to explore the prolonged effects of the exercise program on patients' psychological states. Eight patients from the intervention group will be randomly selected for an additional interview about their experience with the devices and the mobile app.

Figure 6. Patient timeline in this randomized controlled trial.
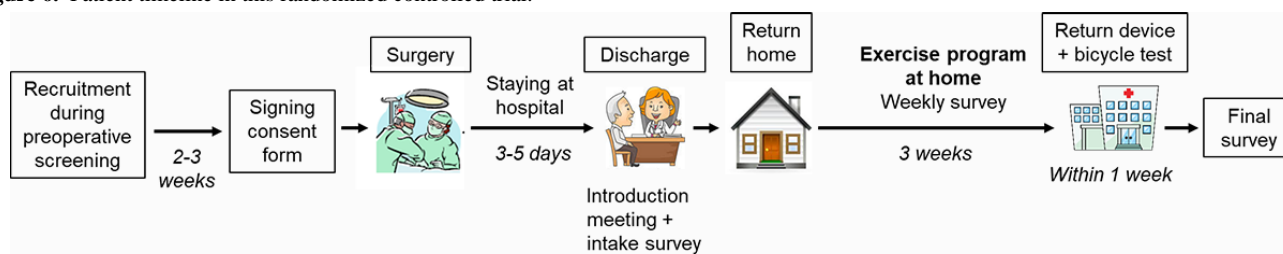
Feasibility Study

To access the feasibility of the RCT (eg, whether patients after surgery can handle the devices), we conducted a small-scale trial with 8 patients in 2018. These patients followed the procedure for the intervention group in the RCT, except that the trial duration was only 1 week. Feasibility was assessed based on the usage data of the devices and the mobile app, a questionnaire that measures relevant psychological variables, and an interview (face-to-face or by phone call).

Statistical Analysis

For the outcome variables of interest, that is, average daily steps, overall compliance rate, and physical fitness measured in the bicycle ergometer test (peak VO_2, maximal workload, HR_{max}), the following 2-step procedure will be used. In the first step, independent sample t tests (unpaired) will be used to compare the outcome variables between the two study conditions. Second, when potential confounding variables are identified post hoc, they will be added to multiple regression models to control for their influences. For step data at the day level, multilevel models will be built to test the same hypotheses, with patient ID as the grouping variable [55]. We will use the conventional α level of .05 to judge for statistical significance, and more importantly to use the estimated effect sizes in order to judge the clinical significance of the effects.

Data Management and Ethics

The provider of the Heart Angel platform, Virtuagym, has a data management and privacy policy that is in accordance with

the General Data Protection Regulation under the law of the European Union (GDPR) and Dutch laws for data protection. Because of the sensitive nature of the patient study, several additional measures will be taken to protect patients' privacy. These include the following: (1) private chat groups will be created to only allow each patient to communicate with his/her coach but no others in a secured environment. (2) Questionnaire data will be stored on a local server, and no names or email addresses but only participant IDs will be used to identify questionnaire data. The participant IDs will not be used for the Axivity AX3 nor for the Neo Health One devices, in order to prevent risks of data breach in cases where the devices are lost. When these devices are returned, data will be removed from the devices and saved on a secured local computer at CZE. After the study, all data on the server of Heart Angel will be deleted, including patients' user accounts, and only anonymous and aggregated data will be archived for research purposes.

Considering the low risk of this RCT, we have been granted an exemption from insurance by the Medical Research Ethics Committees United (MEC-U) according to Article 7, paragraph 6, of the Medical Scientific Research Act with People (WMO). The study protocol (including the feasibility trial) was formally approved by the MEC-U on February 26, 2018 (NL 62142.100.17/R17.51; see Multimedia Appendices 3 and 4), and by the local ethical committee at CZE in May 2018.

Results

Relevant Results From the Feasibility Study

Results from the feasibility study strongly suggest that the planned RCT is feasible. First of all, from both interviews and objective data measured by the self-tracking device (see Figure 7 for all patients' daily steps over the study week), it was evident that patients perceived the walking exercise very positively and they were able to almost always perform the exercise according to the plan. They also considered the exercise to be useful and pleasant to do, and did not experience any physical or mental problems with the exercise. A few patients even mentioned that they would like the durations of the exercise to be longer, and this proposition will be supported in the RCT with the increasing duration of the exercise over the 3 weeks.

Figure 7. Number of steps walked for each patient throughout the 7-day feasibility study.
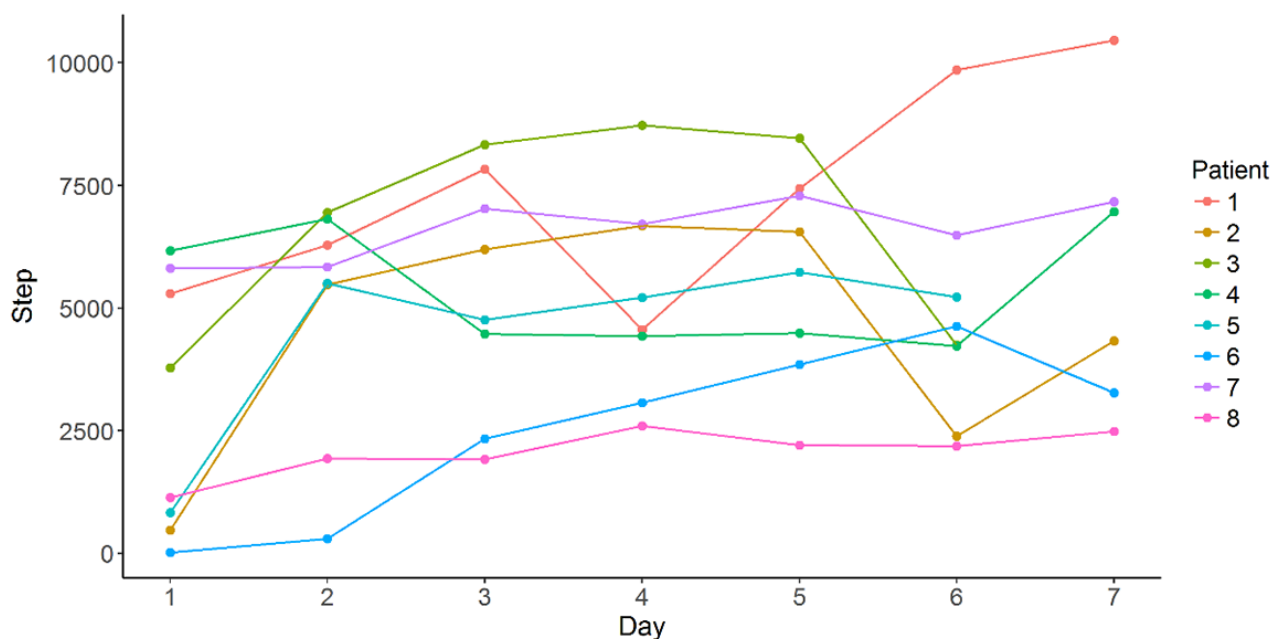
Second, during the interviews, patients indicated that they had no trouble wearing both the Axivity AX3 and the Neo Health One devices. Sensor data from both devices suggest that the compliance rates of wearing the devices were close to 100% (54/56 days [96%] from 8 patients). When the patients went to sleep, they usually put the devices near their beds so that they will not forget wearing them in the next morning. Most patients found it convenient to wear one of the devices on the wrist and the other one as a clip on their belts or trousers. This observation and the fact that Axivity AX3 as a measurement device is more valid at lower limb positions [40] informed our decisions for the devices' wearing positions in the protocol. In addition, all patients were able to fill out the questionnaire upon receiving emails.

Finally, usage data from the Heart Angel app showed that patients and coaches (the nurse practitioners) were able to use the app for chatting. Figure 8 shows the number of messages sent to and from the patients. We did find that some patients sent the messages to the wrong places—instead of sending directly to the coaches, the messages were posted to their public profile in the app. We will take this into account and explain the messaging function more clearly to the patients in the RCT.

Figure 8. Number of messages sent to and from the patients.
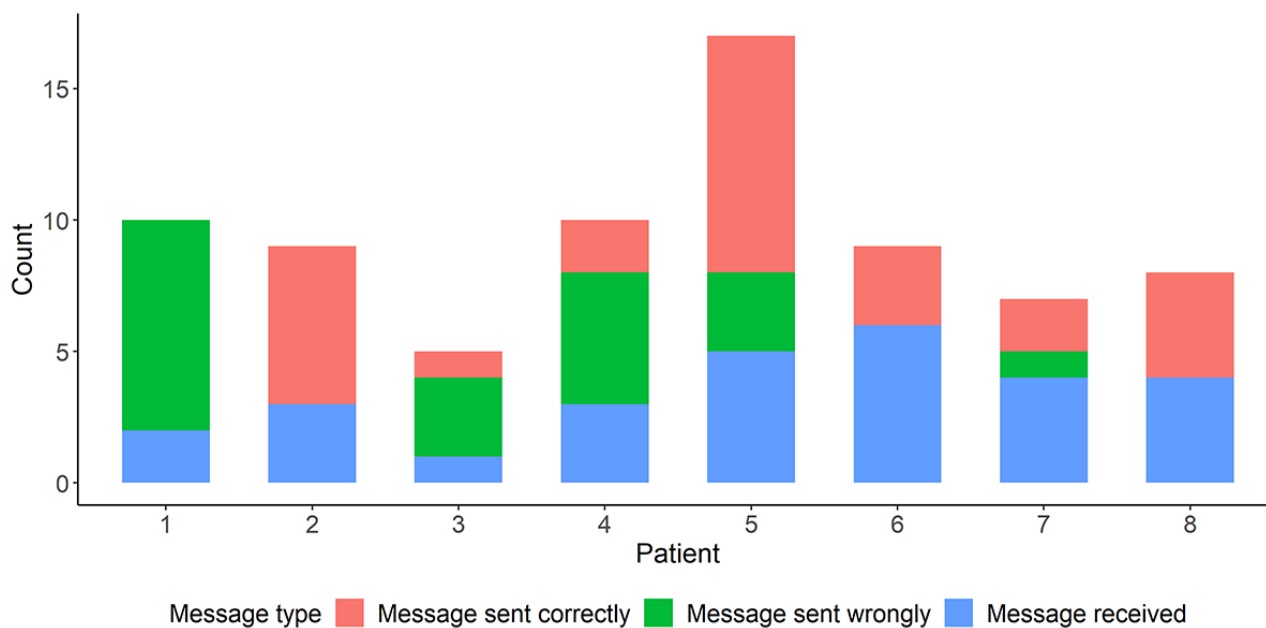
Expected Results for the Main RCT

We are planning to enroll the first patients in September 2020 and the RCT is expected to be completed by the end of 2021. After the completion, statistical analyses will be conducted based on the planned method reported in this protocol to determine if the two groups differ in the primary and secondary outcomes, in addition to the psychological variables under study.

Discussion

We designed this RCT to evaluate the potential value of digital technologies—self-tracking and mobile-based coaching—in a home-based exercise program that fills the gap between surgery discharge and conventional CR programs. If our main hypothesis is confirmed (ie, patients in the intervention group would exercise more and become physically and psychologically better prepared for the formal CR than patients in the control group at the end of the trial), the study will provide a rationale to use self-tracking and mobile-based coaching in the home-based program. The technologies are also relatively cheap as, for example, the Heart Angel platform is free for users and a self-tracking device similar to Neo Health One could cost less than €20 (approximately US $22.5). Although a cost-effectiveness analysis is beyond the scope of this protocol, the results of the trial should provide good estimates about the benefits of the technologies and insights about the required workloads from nurse practitioners. If the hypothesis is not confirmed, the results may imply that giving patients a more structured exercise program in combination with an implementation intention procedure is sufficient to support them during the gap period without technologies.

One apparent limitation of the study is that the 2 home-based CR conditions are not directly compared with the usual care. Although ideally adding such a baseline condition is useful, given practical constrains (eg, time, financial resources) our design can be justified. Both previously published research [9] and expert opinions from local physicians suggest that under the current practice, patients are clearly not supported enough and they do not exercise enough during the gap period. Thus, compared with this *straw man* condition, the condition with the low-tech exercise program is a more meaningful baseline for evaluating the technologies, because it requires minimum effort to improve the usual care. Another limitation is that our experimental design does not allow us to disentangle the beneficial effects of self-tracking and e-coaching. For example, it might be that self-tracking is the main active component of the intervention, so the costs associated with human coaching can be saved. While future research is needed to accurately separate the effects, the planned exploratory analyses on app usage data may provide preliminary answers. A third limitation relates to potential reactivity to the measurement device in the control group. Although the Axivity AX3 device does not support self-monitoring, merely wearing the device may increase patients' awareness of their PA levels and motivate to perform more activities [56-59]. This limitation does not invalidate the testing of the differences between the trial conditions, but caution should be exercised when generalizing the results of the control group to the low-tech solution in practice. Despite the limitations, our study should provide valuable data for bridging the discharge–rehabilitation gap in the current CR practice and more generally contribute to the growing literature on enhancing traditional center-based CR with digital technologies [6,21].

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-EHEALTH checklist.
[PDF File (Adobe PDF File), 2328 KB - resprot_v9i8e16737_app1.pdf]

Multimedia Appendix 2
Self-report measures.
[DOCX File , 18 KB - resprot_v9i8e16737_app2.docx]

Multimedia Appendix 3
Initial review and comments by MEC-U.
[PDF File (Adobe PDF File), 547 KB - resprot_v9i8e16737_app3.pdf]

Multimedia Appendix 4
Second review and acceptance by MEC-U.
[PDF File (Adobe PDF File), 538 KB - resprot_v9i8e16737_app4.pdf]

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Abbreviations

CR: cardiac rehabilitation
CZE: Catharina Ziekenhuis Eindhoven
GDPR: General Data Protection Regulation under the law of the European Union
HR$_{max}$: maximum heart rate
ICT: information and communication technology
MEC-U: Medical Research Ethics Committees United
PA: physical activity
Peak VO$_2$: peak oxygen uptake
RCT: randomized controlled trial

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<u>Protocol</u>

Assessing a WeChat-Based Integrative Family Intervention (WIFI) for Schizophrenia: Protocol for a Stepped-Wedge Cluster Randomized Trial

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Abstract

Background: Schizophrenia is a persistent and debilitating mental illness, and its prognosis depends largely on supportive care and systematic treatment. In developing countries like China, families constitute the major caregiving force for schizophrenia and are faced with many challenges, such as lack of knowledge, skills, and resources. The approach to support family caregiving in an accessible, affordable, feasible, and cost-effective way remains unclear. The wide-spread use of WeChat provides a promising and cost-effective medium for support.

Objective: We aim to present a protocol for assessing a WeChat-based integrative family intervention (WIFI) to support family caregiving for schizophrenia.

Methods: We will develop a WIFI program that includes the following three core components: (1) psychoeducation (WeChat official account), (2) peer support (WeChat chat group), and (3) professional support (WeChat video chat). A rigorous stepped-wedge cluster randomized trial will be used to evaluate the implementation, effectiveness, and cost of the WIFI program. The WIFI program will be implemented in 12 communities affiliated with Changsha Psychiatric Hospital through the free medicine delivery process in the 686 Program. The 12 communities will be randomized to one of four fixed sequences every 2 months during an 8-month intervention period in four clusters of three communities each. Outcomes will be assessed for both family caregivers and people with schizophrenia. Family caregivers will be assessed for their knowledge and skills about caregiving, social support, coping, perceived stigma, caregiver burden, family functioning, positive feelings, and psychological distress. People with schizophrenia will be assessed for their symptoms, functioning, quality of life, recovery, and rehospitalization. Cost data, such as intervention costs, health care utilization costs, and costs associated with lost productivity, will be collected. Moreover, we will collect process data, including fidelity and quality of program implementation, as well as user attitude data. Treatment effects will be estimated using generalized linear maximum likelihood mixed modeling with clusters as a random effect and time as a fixed effect. Cost-effectiveness analysis will be performed from the societal perspective using incremental cost-effectiveness ratios. Qualitative analysis will use the grounded theory approach and immersion-crystallization process.

Results: The study was funded in August 2018 and approved by the institutional review board on January 15, 2019. Preliminary baseline data collection was conducted in May 2019 and completed in September 2019. The WIFI program is expected to start in September 2020.

Conclusions: This is the first study to assess a WeChat-based mHealth intervention to support family caregiving for schizophrenia in China. The innovative study will contribute to the development of a more cost-effective and evidence-based family management

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model in the community for people with schizophrenia, and the approach could potentially be integrated into national policy and adapted for use in other populations.

Introduction

Schizophrenia and Family Caregiving

Globally, schizophrenia is a debilitating persistent psychiatric disorder affecting over 21 million people [1,2], and there is a 60% increase in premature deaths among people living with schizophrenia compared with the general population [3]. The most recent global burden of disease study in 2016 showed that schizophrenia contributes 13.4 million years of life lived with disability to the burden of disease globally [2]. The prognosis of schizophrenia depends largely on integrated mental health and social care services in community-based settings, which has been listed by the World Health Organization (WHO) as one of the four major objectives in its Mental Health Action Plan 2013-2020 [3]. Among the multiple initiatives proposed by the WHO [3], strengthening the active involvement and support of family caregivers in caring for people living with schizophrenia stands out as the most sustainable and cost-effective solution for addressing the worldwide treatment gap in resource-poor settings. Recent years have seen a global shift in the responsibility of care from the hospital setting to families [4], such that the economic value of informal family caregiving now greatly exceeds spending through formal health care systems. Recently, the Chinese government recognized the value of family caregiving by instituting the Reward Policy (described below) to support family caregivers financially [5]; however, this policy is an exception globally [6].

The Reward Policy and Challenges

In China, there are over 7.16 million people living with schizophrenia [7], and over 90% of them live with and depend on their families for care [8]. Family caregiving often requires a range of support that extends across physical, psychological, emotional, social, and financial domains [9]. The essential roles of family caregivers in the care of schizophrenia have been increasingly recognized in China's mental health policy. In 2016, the Chinese government instituted a Reward Policy to encourage family involvement in the care of people with serious mental illness. According to the Reward Policy, a monthly subsidy equal to the local poverty line allowance (currently at least RMB 200 or US $28.6) is paid to each family based on good management and care of the family member with serious mental illness, including schizophrenia [5,10].

Three years after its implementation, the Reward Policy has helped alleviate the financial burden for caregiving families. However, family caregivers are still faced with other challenges during the process of caregiving, such as insufficient knowledge and skills in providing appropriate care to people living with schizophrenia, social isolation due to stigma, stress from caregiving, family conflict on task-sharing, and lack of self-care due to overwhelming caregiving responsibilities [4,11,12]. As a result, family caregivers experience a considerable level of burden that not only detrimentally impacts their own health and well-being, but also leads to poor prognosis in people living with schizophrenia owing to impaired quality of care. These challenges have stimulated a focus beyond simply identifying caregiver burden to also developing effective family interventions to reduce this burden and improve care [13].

Family Intervention Programs

To date, several family intervention programs have been developed and tested, with the following three elements identified as most promising and feasible: (1) psychoeducation for families to increase knowledge about schizophrenia and strengthen related caregiving skills; (2) peer-support for both family caregivers and people living with schizophrenia where they can share experiences and feelings, exchange information, and provide mutual emotional support; and (3) professional support to family caregivers that troubleshoots specific problems and provides private targeted guidance to address specific needs [13-18]. Thus far, integrative application of all three intervention components has been limited in China owing to their low accessibility and high cost, and evidence on their combined use and effectiveness to support family caregivers and people living with schizophrenia is lacking. An innovative, affordable, and cost-effective platform that integrates all three of these intervention components thus represents a pressing need in the scientific literature and for the national health care policy.

WeChat Use in China

WeChat is the most common social media platform in China, with over 1 billion monthly active users of all ages [19]. About 93% of urban users log into WeChat every day [20]. WeChat features diverse platforms, such as moments, chat group, and WeChat official account (WOA), and boasts of multiple powerful functions including voice and text messaging, voice and video calls, photo sharing, payment, and games. Owing to its wide range of platforms and functions, WeChat has been dubbed China's "app for everything" and has been characterized as "4A" (anybody, anytime, anywhere, and anything) [21,22]. The seamless integration of WeChat into every aspect of human life makes it a promising and cost-effective medium for health intervention delivery. A growing number of WeChat-based health intervention programs have been developed for patients with various health conditions, with robust evidence showing their acceptability, feasibility, and efficacy [23-27]. Specifically, WeChat-based health interventions have been found to cost

less, improve treatment adherence, have fewer complications, increase rates of follow-up, require less intervention time, and improve patient satisfaction [23-27]. Thus, we hypothesize that a WeChat-based Integrative Family Intervention (WIFI) program that includes the three elements noted above (psychoeducation, peer support, and professional support) will be an accessible and cost-effective approach to improve the outcomes of both people living with schizophrenia and family caregivers.

Theoretical Framework for the Proposed Study

The theoretical mechanisms underlying the proposed study are psychoeducation, peer support, and professional support (Figure 1). There is empirical evidence that each of these mechanisms promotes the expected outcomes examined. Psychoeducation is central to the proposed study because it directly increases knowledge about schizophrenia and caregiving and indirectly works through the actions of peers and professionals in the provision of support. More specifically, there is considerable evidence that psychoeducation has been widely employed with caregivers and with people living with schizophrenia to yield a range of positive effects. For example, with caregivers, psychoeducation has been shown to increase knowledge and skills [28], improve social support [29] and coping [30,31], improve family functioning [32], decrease stigma [28] as well as family burden [33-35], promote positive feelings and decrease emotional distress [34-36], and reduce the cost of care [37]. Furthermore, for people living with schizophrenia, psychoeducation has been shown to decrease symptoms, improve functioning, enhance quality of life, increase recovery, decrease hospitalizations, and reduce health care costs [15,38-40]. Importantly, psychoeducation also yields positive effects for caregivers and people living with schizophrenia when delivered through peer support and professional support [18,41-43].

Figure 1. Theoretical framework of the proposed study. PLS: people living with schizophrenia.
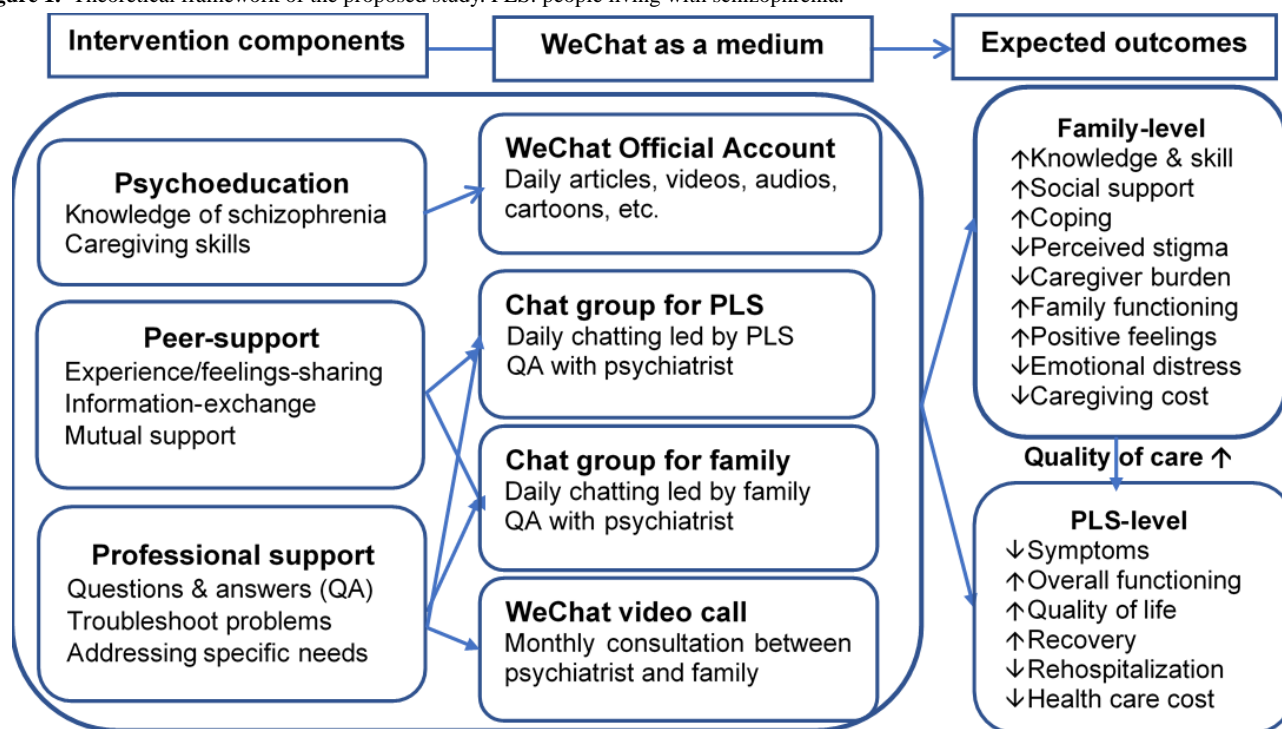
Consistent with the literature, three components are included in the WIFI program to provide education and support to families (psychoeducation, peer support, and professional support) (Figure 1). WeChat will provide access for caregivers and people living with schizophrenia to each of these intervention components. Psychoeducation and support will increase knowledge and skills, as well as social support (peer and professional) and coping to reduce perceived stigma and caregiver burden. In addition, these components are expected to enhance family functioning and positive feelings, such that emotional distress will be reduced. Finally, these effects are hypothesized to reduce caregiving costs. For people living with schizophrenia, these components are expected to enhance the overall quality of care in the community, which is hypothesized to reduce symptoms in people living with schizophrenia and enhance functioning, increase quality of life and recovery, and decrease rehospitalization, thus reducing overall health care costs.

This paper describes the protocol of a study designed to assess the impact of a WIFI program fully aligned with the Reward Policy for families caring for people living with schizophrenia compared with the Reward Policy alone. The specific aims are as follows: (1) compare the effects of the WIFI program plus the Reward Policy with the Reward Policy alone on caregiving and the health outcomes of family caregivers and people living with schizophrenia, such as knowledge and skills, social support and coping, burden, family functioning, positive feelings, and psychological distress of caregivers, as well as symptoms, functioning, and recovery of people living with schizophrenia; (2) compare the total cost of the WIFI program plus the Reward Policy with the Reward Policy alone, including the program itself, health care utilization of people living with schizophrenia and family caregivers, and production loss of family caregivers;

and (3) conduct a process evaluation of the WIFI program to assess fidelity and quality of program implementation, as well as user attitudes toward the program. To simultaneously assess intervention effectiveness and implementation strategies using mixed methods in "real-life" health care settings, we used a stepped-wedge cluster randomized trial (SWCRT) design [44].

Methods

Setting

The study will be conducted at Changsha Psychiatric Hospital (also named The Ninth Hospital of Changsha). Established in 1952 and affiliated to Changsha Civil Affairs Bureau, Changsha Psychiatric Hospital has the responsibility of prevention, treatment, and rehabilitation for all residents with mental illnesses in Changsha City. The hospital not only provides out-patient and in-patient health care, but also extends its services to community-based mental health care for its 12 affiliated communities, including the "686 Program" and Reward Policy implementation. The "686 Program" is China's largest demonstration project in mental health service aimed at integrating hospital and community services for serious mental illnesses, with the following services provided mainly through community health workers: patient registration and initial assessment, free medication and regular follow-up in the community, management of community emergencies, and free emergency hospitalization [45-47]. In Changsha Psychiatric Hospital, a medical team involving three psychiatrists and four nurses is responsible for the "686 Program," and the members circulate around the 12 communities each month to delivery free medicines to over 1000 registered clients who they know very well after long-term visits. The Reward Policy is a newly issued policy to encourage family care of people with serious mental illness, with RMB 200 (US $28.6) per month currently offered to each family registered under the 686 Program by Changsha Psychiatric Hospital.

Design

This study uses a pragmatic stepped-wedge design [44] to evaluate both the effectiveness and implementation strategy of the WIFI program. The CONSORT checklist is presented in Multimedia Appendix 1, and the SPIRIT checklist is presented in Multimedia Appendix 2. We will conduct a multicenter prospective controlled trial, using a stepped-wedge design, comparing the WIFI program integrated into the Reward Policy (intervention group) and the Reward Policy alone (control group) in family caregiving among people living with schizophrenia.

In a SWCRT, all clusters are randomly and sequentially crossed over from control to intervention over a number of time periods [48]. All clusters serve as a control group at the beginning of the study and end up in the intervention group at the end of the study. Compared with traditional randomized controlled trials and parallel cluster studies, a SWCRT enjoys unique ethical benefits since all clusters will ultimately receive the assumingly beneficial intervention at the end of the study [49]. In addition, a SWCRT enables analyses of any temporal effects of the intervention since each cluster acts as its own control and also allows for estimation of both between- and within-cluster effects of the intervention owing to repeated measurements [49]. As a result, a SWCRT design achieves greater statistical power with smaller sample sizes and is more cost-effective than parallel group designs.

In the proposed study, a WIFI program will be implemented sequentially across an 8-month intervention period in the 12 communities by Changsha Psychiatric Hospital. A total of 20 families will be recruited from each community, leading to a total sample of 240 families. Allocation will be determined by an external statistician using a computer-generated random number sequence. Each number will be secretly and securely stored in a sealed envelope by the external statistician until the intervention starts. The first author (YY) will generate the allocation sequence, the medical team will work on enrolling participants, and the second author (TXL) will assign participants to interventions. The 12 communities will be randomized into four groups according to geographic distance and number of people living with schizophrenia to reduce the risk of contamination and group size inequality. After allocation, each group will be randomized to one of four fixed sequences every 2 months during an 8-month intervention period (Table 1 and Figure 2). All communities will receive the usual financial benefit of the Reward Policy as the control condition before the intervention, and then, successively and in random order, will cross over to the WIFI program at 2-month intervals until the study ends.

Figure 2. Flowchart for participant recruitment and allocation. C: community; F: family.
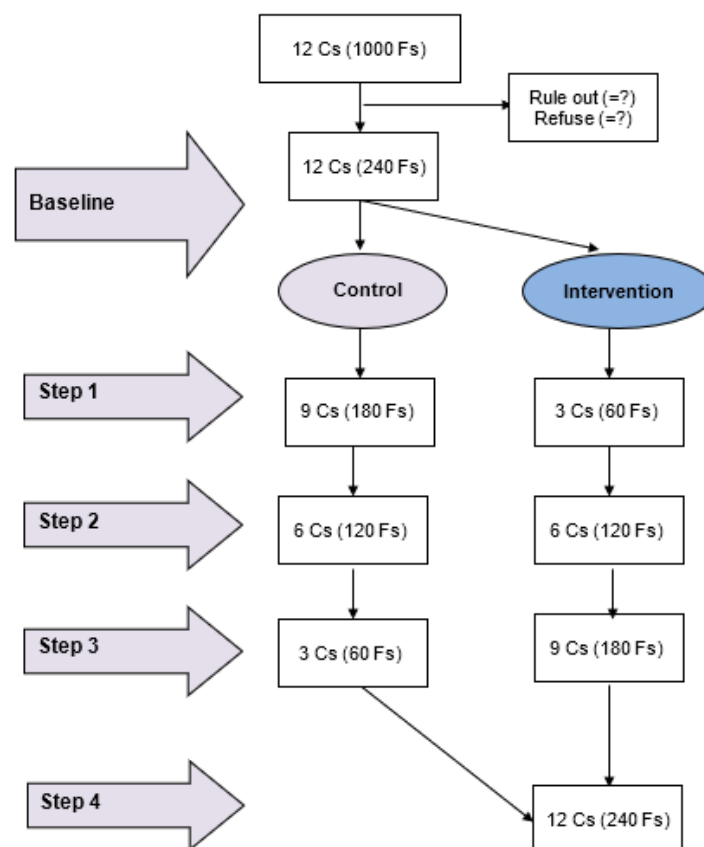
Table 1. Design of the four-stage stepped-wedge cluster randomized trial.

Cluster community (CM) group[a]	Assessment[b]				
	Baseline (M$_{1-2}$)[c]	Step 1 (M$_{3-4}$)	Step 2 (M$_{5-6}$)	Step 3 (M$_{7-8}$)	Step 4 (M$_{9-10}$)
CM$_{1-3}$	C[d]	WIFI[e]	WIFI	WIFI	WIFI
CM$_{4-6}$	C	C	WIFI	WIFI	WIFI
CM$_{7-9}$	C	C	C	WIFI	WIFI
CM$_{10-12}$	C	C	C	C	WIFI

[a]Number of clusters=12; number of groups=4; number of clusters per group=3.

[b]Step length=2 months; number of participants per step=20.

[c]M: month.

[d]C: control (Reward Policy alone).

[e]WIFI: WeChat-based Integrative Family Intervention.

Participants and Recruitment

Recruitment is estimated to start in September 2020. The study aims at recruiting 240 families of people living with schizophrenia from 12 communities affiliated to Changsha Psychiatric Hospital through the "686 Program." Within each community, 20 eligible people living with schizophrenia will be randomly selected from the registry name list by a statistician, leading to a sampling frame of 240 families of people living with schizophrenia. Each family will be approached and invited to participate in the study during the monthly medicine delivery by the medical team from Changsha Psychiatric Hospital. We do not require both a person living with schizophrenia and a family caregiver to be recruited into the study at the same time. The entire family may benefit from the intervention as long as there is one member from the family participating. The medical team has been providing mental health services, including free antipsychotic medicine delivery, in the communities for a long time and thus knows very well about each family having a person living with schizophrenia, which greatly facilitates participant recruitment and retention. Detailed information about the research will be provided both orally and in written format to interested families by the medical team. All families will be

fully informed of the study risks and benefits, and their right to drop out of the study at any time ([Multimedia Appendix 3](#)). Families agreeing to participate in the study will be invited to scan a WeChat barcode of the research program, so that they can be allocated to receive the intervention in the future. Our research team will include three psychiatrists who will complete clinical assessments of symptoms and functioning of the people living with schizophrenia through WeChat video chat. In addition, 10 postgraduate students will assist people living with schizophrenia and their caregivers to complete online questionnaires through WeChat. The research team will receive extensive training for both the intervention and evaluation to ensure quality and consistency.

Participants of the study will include both people living with schizophrenia and their family members. The inclusion criteria for participating people living with schizophrenia are as follows: (1) registration in the "686 Program;" 2) fulfilling the Chinese Classification of Mental Disorders-3 (CCMD-3) or the International Classification of Diseases-10 (ICD-10) criteria for schizophrenia; (3) age 18 years or older; (4) living with at least one family member; and (5) ability to use a smartphone and WeChat to read and communicate. The inclusion criteria for participating family members are as follows: (1) registration in the Reward Policy and receiving a subsidy for family care; (2) living with a person having schizophrenia for at least the past 2 years; (3) age 18 years or older; 4) involvement with caregiving activities of people living with schizophrenia; (5) ability to use a smartphone and WeChat to read and communicate; and (6) at least one family member having a smartphone with the WeChat app installed.

Blinding

People living with schizophrenia, family caregivers, medical team members, and researchers cannot be blinded to the allocated treatment. The program team conducting the intervention will not be involved in assessing any of the outcomes. The data analyses by researchers will be blinded.

Intervention

Participants in the control group will receive the usual financial benefits of the Reward Policy and receive payments from Changsha Psychiatric Hospital. However, they will not have access to the WIFI program since they cannot scan the WeChat barcode for the research.

Participants in the intervention group will receive the usual financial benefits of the Reward Policy as well as the WIFI program that will include the following three key components: psychoeducation through WOA publications, peer-support through a WeChat chat group, and professional support through WeChat private chat and video calls ([Table 2](#)).

Table 2. Content of the WeChat-based integrative family intervention program.

Component	Format	Frequency	Leader	Possible content/topics
Psychoeducation	WeChat official account publications	Weekly	Psychiatrists and researchers	What is schizophrenia? What causes schizophrenia? How is schizophrenia treated? What can be done to promote recovery in schizophrenia? What are the early signs of relapse? What support do families need? How can feelings of stigma be addressed?
Peer support	WeChat chat group of people living with schizophrenia	Daily	People living with schizophrenia volunteers	Introduce self and tell your story; identify a specific problem encountered to discuss with the group; discuss skills and techniques used to cope with challenging situations; share feelings and resources; organize offline activities for support and stress reduction, such as hiking, dinner, and group meetings.
Peer support	WeChat chat group of caregivers	Daily	Caregiver volunteers	Introduce self and tell your story; identify a specific problem encountered to discuss with the group; discuss skills and techniques used to cope with challenging situations; share feelings and resources; organize offline activities for support and stress reduction, such as hiking, dinner, and group meetings.
Professional support	Private WeChat chat and video call	Monthly	Psychiatrists	Evaluate symptoms and function in people living with schizophrenia; update on medication and treatment; troubleshoot specific problems; provide consultation, guidance, assistance, etc.

Contamination

Since randomization is performed at the community level, using the stepped-wedge design, the risk of contamination between the control and intervention groups is very low. Moreover, since the intervention is delivered through WeChat and each participant scans the special WeChat barcode of the research program to obtain access to the WIFI program, it is unlikely that participants in the control group will receive the intervention during the control stage. Even if participants in the control group learn about the WeChat account of the research program, they will not be able to add it because the research team will recognize each participant and decline any request from the

control group until receiving the allotted sequence to join the intervention. Thus, intervention contamination will be avoided.

Outcomes

Effect Measures

The effect of the intervention will be assessed at the individual level for both family caregivers and people living with schizophrenia.

For family caregivers, the outcomes will include knowledge and skills about caregiving (Knowledge and Skill of Caregiving for Schizophrenia, self-developed), social support (Multidimensional Scale of Perceived Social Support) [50], coping (Simplified Coping Style Questionnaire) [51], perceived stigma (Perceived Devaluation and Discrimination Scale) [52], caregiver burden (Zarit Burden Interview [ZBI]) [53], family functioning (Family Adaptation, Partnership, Growth, Affection and Resolve Index scale) [54,55], positive feelings (Caregiving Rewarding Feelings) [56], perceived stress (Perceived Stress Scale) [57], depression (Patient Health Questionnaire-9 [PHQ-9]) [58], and anxiety (Generalized Anxiety Disorder Scale-7 [GAD-7]) [59].

For people living with schizophrenia, the outcomes will include clinical symptoms (Brief Psychiatric Rating Scale [BPRS]) [60] and overall functioning (Global Assessment of Functioning [GAF]) [61], which will both be rated by psychiatrists. Other outcomes will include self-reported quality of life (World Health Organization Quality of Life Brief Scale) [62], recovery (Recovery Assessment Scale [RAS]) [63], rehospitalization, depression (PHQ-9) [58], and anxiety (GAD-7) [59].

Potential Confounding Factors

At baseline, we will also collect information about potential confounding factors by adjusting for the following: (1) sociodemographic data, such as age, gender, education, and occupation; (2) clinical data, such as diagnosis type of schizophrenia, length of illness, and length of caregiving; and (3) WeChat use intensity as assessed by the WeChat Use Intensity Questionnaire [64,65].

Cost Measures

Costs will be measured from a societal perspective and consist of at least the following three levels: (1) costs of the intervention, (2) health care utilization costs, and (3) costs associated with lost productivity. All of the costs will be converted to that for the year 2019 using consumer price indices.

The intervention costs pertain to implementation and operation of the WIFI program. A bottom-up approach will be used to assess the intervention costs, which may include but are not limited to (1) training of psychiatrists, researchers, and other project team members and (2) the WeChat intervention (WOA fee, administrator time, consultation fee of the psychiatrists, etc).

The health care utilization costs pertain to medical care for both people living with schizophrenia and family caregivers. A monthly cost diary will be used to retrospectively track medical expenses incurred by people living with schizophrenia and family caregivers, which may include but are not limited to (1)

visits to health care professionals in primary or secondary care; (2) hospitalization; (3) visits to alternative medicine therapists; (4) medication; and (5) other nonmedical expenses associated with medical care, such as transportation, food, and lodging. Health care utilization costs will be estimated by China guideline prices that are supplemented by population-based estimates in the literature.

The costs associated with productivity loss will be assessed at both the people living with schizophrenia and caregiver levels. For both people living with schizophrenia and caregivers, costs include absenteeism due to sick leave, which will be assessed by monthly sick leave calendars. The human capital approach will be used to calculate the costs of losses to production due to sickness or caregiving (net number of days on leave during follow-up multiplied by the daily wage of the worker if employed or an equivalent value if unemployed).

Process Measures

A process evaluation will be conducted to evaluate the implementation process of the intervention to understand potential factors related to implementation that may be associated with observed outcomes. The evaluation includes fidelity and quality of WIFI implementation, as well as users' attitudes toward the program, which will be evaluated separately for people living with schizophrenia, their family members, and psychiatrists. After completion of the intervention in each randomized community, both quantitative and qualitative process data will be collected from survey samples of people living with schizophrenia and family members to assess their awareness of and responsiveness to the WIFI program.

Quantitative data will be directly collected through the WeChat backstage management system and include information about families' use of and engagement with the WIFI program. For psychoeducation data, we will collect information on views, downloads, and shares of WOA publications. For peer-support data, we will collect information on chatting topics, number of messages sent, and active users of the WeChat chat group through chat records. For professional support, we will collect information on help-seeking behaviors of families, number of consultations, problems addressed by psychiatrists, etc.

Qualitative information will be collected through online one-to-one video interviews using the video chat function of WeChat. The technology acceptance model will be used to explore perceived usefulness and perceived ease of use of the WIFI program among people living with schizophrenia, family members, and psychiatrists at the end of the intervention [66-69]. People living with schizophrenia and family members will be asked about their feelings and experiences with the WIFI program, such as attitudes, beliefs, and feedback about the program. Psychiatrists will be asked about their exposure to and experiences with each element of the WIFI program in order to find both facilitators and barriers of program implementation at the provider level. All this information will help the research team gain insights into the feasibility and replicability of the program.

Data Collection and Management

Data are collected from people living with schizophrenia, their family members, and psychiatrists at baseline (months 1-2) and at 4, 6, 8, and 10 months. A pilot study with face-to-face interviews was recently completed with 400 families of people living with schizophrenia prior to the formal WIFI program to test all measures and collect baseline data. For this data collection, all participants will be invited through WeChat to complete questionnaires through an online survey known as Sojump [70]. Sojump provides a series of services including questionnaire design and distribution, data collection, and analysis. In addition, all qualitative information (on process measures) will be collected by online one-to-one interviews through WeChat video chat. Each family will be reimbursed with money for participation each time, which will depend on the completion of their relevant questionnaires (about 20 minutes for the people living with schizophrenia and 45 minutes for the caregivers). The reimbursement will increase by 25% for each successive assessment to reflect participants' ongoing study commitment. Specifically, participants will receive RMB 35 (US $5) for the baseline measurement, followed by RMB 44 (US $6.25), RMB 55 (US $7.81), RMB 69 (US $9.77), and RMB 86 (US $12.21) for the subsequent assessments. A family will be reimbursed with a total of RMB 289 (about US $41) for completion of all five assessments. Payment will be sent directly to one designated family member through the WeChat money transfer function. The double entry method will be adopted to input data, with the range for data values preset to avoid any wrong input. All data will be safely stored on a disk and managed by a special data specialist. Table 3 provides an overview of all outcome measures and assessment instruments that will be used in this trial.

Table 3. Assessment of study outcomes.

Outcome measures	Assessment				
	M_{1-2}[a]	M_{3-4}	M_{5-6}	M_{7-8}	M_{9-10}
Caregivers					
Knowledge and skill (Knowledge and Skill of Caregiving for Schizophrenia)	Yes	Yes	Yes	Yes	Yes
Social support (Multidimensional Scale of Perceived Social Support)	Yes	Yes	Yes	Yes	Yes
Coping (Simplified Coping Style Questionnaire)	Yes	Yes	Yes	Yes	Yes
Perceived stigma (Perceived Devaluation and Discrimination Scale)	Yes	Yes	Yes	Yes	Yes
Caregiver burden (Zarit Burden Interview)	Yes	Yes	Yes	Yes	Yes
Family functioning (Family Adaptation, Partnership, Growth, Affection and Resolve Index scale)	Yes	Yes	Yes	Yes	Yes
Positive feelings (Caregiving Rewarding Feelings)	Yes	Yes	Yes	Yes	Yes
Perceived stress (Perceived Stress Scale)	Yes	Yes	Yes	Yes	Yes
Depression (Patient Health Questionnaire-9)	Yes	Yes	Yes	Yes	Yes
Anxiety (Generalized Anxiety Disorder Scale-7)	Yes	Yes	Yes	Yes	Yes
People living with schizophrenia					
Symptoms (Brief Psychiatric Rating Scale)	Yes	Yes	Yes	Yes	Yes
Functioning (Global Assessment of Functioning)	Yes	Yes	Yes	Yes	Yes
Quality of life (World Health Organization Quality of Life Brief Scale)	Yes	Yes	Yes	Yes	Yes
Recovery (Recovery Assessment Scale)	Yes	Yes	Yes	Yes	Yes
Rehospitalization	Yes	Yes	Yes	Yes	Yes
Depression (Patient Health Questionnaire-9)	Yes	Yes	Yes	Yes	Yes
Anxiety (Generalized Anxiety Disorder Scale-7)	Yes	Yes	Yes	Yes	Yes
Potential confounding factors					
Social demographic variables	Yes	No	No	No	No
Clinical variables	Yes	No	No	No	No
WeChat use intensity (WeChat Use Intensity Questionnaire)	Yes	No	No	No	No
Cost					
WIFI program (bottom-up approach)	Yes	Yes	Yes	Yes	Yes
Health care utilization (cost dairy)	Yes	Yes	Yes	Yes	Yes
Productivity loss (sick leave calendar)	Yes	Yes	Yes	Yes	Yes
Process					
Fidelity (quantitative)	No	No	No	No	Yes
Quality (quantitative)	No	No	No	No	Yes
Attitudes (qualitative)	No	No	No	No	Yes

[a]M: month.

Statistical Analysis

We will use mixed-methods analysis for both qualitative and quantitative data collected during each step of the WIFI program. For qualitative data, a grounded theory approach [71] and immersion-crystallization process [72] will be used to assess process implementation and gain deep insights into the feasibility and replicability of the WIFI program. For quantitative data, descriptive analysis will be conducted to describe the characteristics of the participants during the control and intervention periods. Continuous variables will be described by mean (SD) or median (IQR) depending on the shape of the distribution. Categorical variables will be described by number and percentage in each category. For two-group comparisons, the Student t test or nonparametric test will be conducted for continuous variables, while the chi-square test or Fisher exact test will be conducted for categorical variables. Multiple imputations will be adopted to deal with missing values.

Treatment effects (WIFI vs control) will be estimated using generalized linear maximum modeling with clusters as a random

effect and time as a fixed effect. All of the available measurements (2, 4, 6, 8, and 10 months) will be used, with the baseline values of each outcome as a covariate. This analysis will take into account the within-cluster and between-cluster correlations, as well as any evolution of the intervention effect over time. Statistical analyses will be performed at the individual level and according to the intention-to-treat principle, which will be compared to per-protocol analyses. Additionally, extra costs of the WIFI program will be evaluated.

Power Analyses

To illustrate the power for analyses of both caregivers and people living with schizophrenia, we can use a baseline ZBI score of 45 for caregivers and a baseline GAF score of 42 for people living with schizophrenia based on previous studies as well as a baseline study conducted by the research team with caregivers and people living with schizophrenia in Hunan province. For a SWCRT with 12 communities over five time periods or steps (baseline and four intervention steps), assuming an intracluster correlation of 0.05, 90% power at a 5% significance level, and 20% dropout ratio, a sample size of 235 is needed to detect a clinically important decrease in caregiver burden as assessed by a decrease in the ZBI score from a baseline of 45 to 30 [50]. Similarly, for people living with schizophrenia, a sample size of 210 is needed to observe an increase in the GAF score from a baseline of 42 to 52, assuming α=.05, β=.15, and 20% attrition. Based on the above calculations, we decided on a sample size of 20 families per community (240 families in total), which will be sufficient to detect expected improvements in both caregiver burden and functioning of people living with schizophrenia.

Cost-Effectiveness Analyses

A cost-effectiveness analysis will be performed from the societal perspective according to the intention-to-treat approach, with missing data imputed using multiple imputations [73]. CIs (95%) will be obtained by bias corrected and accelerated bootstrapping. The incremental cost effectiveness ratios will be calculated by dividing the differences in mean total costs between both groups by the difference in mean effects between both groups (eg, ZBI score of caregivers and BPRS and GAF scores of people living with schizophrenia). The incremental cost utility ratio will be calculated by dividing the incremental costs by the difference in the quality-adjusted life years assessed with the EuroQoL five-dimensional instrument (EQ-5D) between both treatment groups. These ratios will be graphically presented in a cost-effectiveness plane [74].

Data Monitoring and Evaluation

In order to ensure the smooth progress of the intervention and protect participants' welfare, a data monitoring committee (DMC) will be established. The DMC will involve administrative staff from both the hospital and its 12 affiliated community health centers, who are independent from the sponsor and have no competing interests. The main responsibility is to monitor the study progress and deal with any adverse event during the study process, which will be reported by the medical team to the principal investigator (YY) and then to the DMC. Every month, the DMC will hold a study meeting to summarize study progress, troubleshoot problems, and deal with any adverse events during the study. The DMC also has the right to terminate the intervention when it deems that the intervention is a large risk to participants.

Ethical Consideration

The study protocol was reviewed and approved by the Institutional Review Board (IRB) of Xiangya School of Public Health Central South University (approval number: XYGW-2019-029). All procedures are in accordance with the Declaration of Helsinki. The WIFI program has been registered as a clinical trial (NCT04393896). Any modifications (eg, changes to eligibility criteria, outcomes, and analyses) to the study protocol will be reported to relevant parties (eg, investigators, IRB, trial participants, trial registries, journals, and regulators) immediately. The medical team will approach participants to fully inform them of the study aims and contents and acquire written informed consent from them before recruitment. The medical team will recommend the WIFI program to all people living with schizophrenia and their family members who come for free medicines, without any biased selection based on personal preference. Participation or refusal will not affect medicine acquisition and subsequent medical or nursing care. In order to protect participant confidentiality, personal information of participants will be collected only once during baseline data collection and then deidentified with newly generated numbers (instead of name, age, etc) after the trial. The deidentified data will only be shared or reported aggregately instead of individually. All data will be securely and secretly stored on a disk and managed by a special data specialist. Only the principal investigator and the research team will have access to the final trail data sets.

Knowledge Dissemination

Trial results will be communicated to participants, health care professionals, the public, and other relevant groups through papers published in peer-reviewed journals (four to six international and two to four national), a PhD thesis, a master's thesis, presentation at one national and one international conference, lectures targeted at people living with schizophrenia and family members in psychiatric hospitals, posters and pamphlets in community health centers, and popular science articles on WOA. Authorship will follow the ICMJE recommendation for authorship based on the criteria of substantial contributions to the conception or design of the work; acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; and final approval of the version to be published. The full protocol, participant-level data set, and statistical code are available from the first author (YY) and corresponding author (SYX) on reasonable request.

Results

The study was funded in August 2018 and was approved by the IRB on January 15, 2019. Preliminary baseline data collection was conducted in May 2019 and completed in September 2019. The WIFI program is expected to start in September 2020.

Discussion

Using a SWCRT design, the proposed study will develop a WIFI program fully aligned with the Reward Policy and test its effectiveness. Expected results will include the following: (1) significant improvement in outcomes for both people living with schizophrenia and their family members owing to WIFI program participation; (2) stronger impact for WIFI combined with the Reward Policy than the Reward Policy alone; and (3) development of a cost-effective replicable family management model for schizophrenia that can be integrated into the current national Reward Policy.

The study has some unique advantages and innovations. First, the WIFI program recruits the whole family of people living with schizophrenia as the intervention target, which may produce more far-reaching positive effects than interventions targeted at people living with schizophrenia alone or caregivers alone. In Asian countries like China, family cohesion and harmony are the core of the family-oriented culture. Interventions targeted at the family not only directly improve the well-being of each member, but also improve the family dynamic, which, in turn, will promote each member's well-being. Second, the WIFI program is based on the most widely used social media platform in China (WeChat), which is accessible, affordable, feasible, and cost-effective. Compared with traditional on-site interventions, the WeChat-based intervention provides both synchronous and asynchronous communication that can serve a broad range of respondents who would otherwise not be recruited owing to time restraints and geographical constraints. Third, the WIFI program provides the most comprehensive intervention by integrating all three key components of family intervention that have been internationally recognized (psychoeducation, peer support, and private/professional support). Each component has its unique effect in improving the health outcome of people living with schizophrenia and their family members, and the components compensate each other to maximize the benefits to the family. Fourth, the stepped-wedge design has ethical advantages by ensuring all participants receive the intervention, as well as statistical advantages by generating more sound and robust scientific evidence than a traditional randomized cluster trial. Fifth, the WIFI program involves a medical team with both clinical psychiatrists and psychiatric nurses who work as both intervention implementers and data collectors. The medical team has a long close relationship with the community and is well accepted by people living with schizophrenia and their families, which can greatly increase the participant recruitment rate. In addition, the medical team knows about each person living with schizophrenia and can make more accurate assessments regarding the symptoms and functions of people living with schizophrenia, which can further increase the reliability and validity of the WIFI program.

One concern about this study is the potential attrition of participating people living with schizophrenia and their family members, which is very common in longitudinal intervention studies, especially those involving online interventions. Since all participants are recruited through the monthly medicine delivery process of the "686 Program" that has been running successfully for many years and the people living with schizophrenia are known to the medical team, we believe this stable and long-term community connection will increase program retention and reduce study attrition. Moreover, the use of the most widely accepted social media platform in China, WeChat, which is embedded in many aspects of daily life, is likely to reduce program and study attrition. Nevertheless, we account for attrition by estimating a 20% attrition rate in our study sample. In addition, the reimbursements for participants will increase by 25% for each successive assessment through the conclusion of the study to reflect participants' ongoing commitment.

Another concern is the potential risk of privacy violation with the use of the WeChat platform as a means to deliver the intervention, especially the peer-support group through the WeChat group chat. It is likely that some personal information and chat records of participants may be disclosed intentionally or unintentionally by other participants. For each peer-support WeChat group, we will appoint a research team member to monitor participant interactions and flag privacy issues that emerge for group members. Regarding information and data collected through WeChat, we will store the data in an encrypted file managed by a member of the research team.

In conclusion, this innovative study will contribute to the development of a more cost-effective and evidence-based family management model in the community for people living with schizophrenia. The proposed study is among the first to develop and test a WeChat-based mHealth intervention to support family caregiving for schizophrenia in China. If found to be effective, the intervention could potentially be integrated into the current national policy to support family caregiving. The intervention could also be adapted for use in other populations having a persistent and disabling condition.

Authors' Contributions

All authors have made substantial contributions to the study conception and design, data collection and analysis, and development and editing of the manuscript. The principal investigator YY led the initial study design, while JKT and SYX substantially revised and updated the research question and study design prior to initiating the project. YY was responsible for obtaining ethics approval and acquiring financial support. YY, TXL, SJX, and YLL provided essential input on executing the research in partnership with Changsha Psychiatric Hospital and its 12 affiliated communities. YY, JKT, and SYX developed the WeChat-based Integrative Family Intervention program. XX, MY, and XPG developed detailed evaluation methods based on the original research plan. YY, TXL, YLL, and SJX assisted with methodology and statistical analytic planning for the quantitative part, while XX, MY, and XPG contributed to methodology and statistical analytic planning for the qualitative part. YY drafted the publication with contributions from all authors. All authors are contributing to the conduct of the study and have read and approved the final manuscript for publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT checklist.
[DOCX File , 28 KB - resprot_v9i8e18538_app1.docx]

Multimedia Appendix 2
SPIRIT checklist.
[DOC File , 139 KB - resprot_v9i8e18538_app2.doc]

Multimedia Appendix 3
Informed consent form.
[DOCX File , 21 KB - resprot_v9i8e18538_app3.docx]

Multimedia Appendix 4
Funding letter.
[PDF File (Adobe PDF File), 100 KB - resprot_v9i8e18538_app4.pdf]

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Abbreviations

BPRS: Brief Psychiatric Rating Scale
CCMD-3: Chinese Classification of Mental Disorders-3
DMC: data monitoring committee
EQ-5D: EuroQoL five-dimensional instrument
GAD-7: Generalized Anxiety Disorder Scale-7
GAF: Global Assessment of Functioning
ICD-10: International Classification of Diseases-10
IRB: Institutional Review Board
PHQ-9: Patient Health Questionnaire-9
RAS: Recovery Assessment Scale
SWCRT: stepped-wedge cluster randomized trial
WHO: World Health Organization
WIFI: WeChat-based Integrative Family Intervention
WOA: WeChat official account
ZBI: Zarit Burden Interview

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Protocol

Development and Evaluation of an HIV-Testing Intervention for Primary Care: Protocol for a Mixed Methods Study

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Abstract

Background: Late diagnosis of HIV fosters HIV transmission and may lead to hidden HIV epidemics. In Belgium, mathematical modeling indicates a high prevalence of undiagnosed HIV infections among men who have sex with men of non-Belgian origin and among sub-Saharan African migrants. Promotion of HIV testing facilitates early diagnosis, but diagnostic opportunities are missed in primary care.

Objective: The intervention study aims to enhance provider-initiated HIV testing by GPs. This protocol presents the conceptual development, implementation, and evaluation of an HIV-testing intervention for Flemish general practitioners (GPs).

Methods: A mixed methods evaluation design is used. Guided by a simplified intervention mapping approach, an evidence-based intervention was developed in collaboration, guided by an interdisciplinary advisory board. The intervention consisted of an evidence-based tool (ie, "HIV-testing advice for primary care") to support GPs in provider-initiated HIV testing. A modified stepped-wedge design compare two different intervention levels: (1) online dissemination of the HIV-testing advice and (2) dissemination with additional group-level training. Both conditions were compared against a control condition with no intervention. The effect of the intervention was measured using Poisson regression for national surveillance data. The primary outcome was the number of HIV diagnoses made by GPs. Secondary outcomes were HIV diagnoses among groups at risk for undiagnosed HIV, distribution of new diagnoses by CD4 cell count, number of HIV tests prescribed by GPs, and rate of new diagnoses by tests. To evaluate the intervention's implementation, the GPs' fidelity to the intervention and the intervention's feasibility and acceptability by GPs were assessed through (web-based) surveys and in-depth telephone interviews.

Results: The study was funded in 2016 and ethically approved in January 2017. The implementation of the intervention started in January 2017 and ended in December 2018. Data was completed in October 2019 and was the starting point for the ongoing data analysis. The results are expected to be published in the second half of 2020.

Conclusions: Results of the intervention study will provide useful information on the intervention's effectiveness among Flemish GPs and can inform further development of official testing guidelines. Limitations of this real-life intervention approach are potential spill-over effects, delay in access to surveillance data, and little detailed information on HIV-testing practices among GPs.

Trial Registration: ClinicalTrials.gov NCT04056156; https://clinicaltrials.gov/ct2/show/NCT04056156

International Registered Report Identifier (IRRID): DERR1-10.2196/16486

Introduction

HIV-positive individuals who are unaware of their status have a higher risk of transmitting HIV [1], potentially fueling a hidden HIV epidemic. HIV testing is a crucial step in HIV prevention continuum facilitating timely HIV diagnosis [2]. However, in 2017, about half of the HIV patients newly diagnosed in countries that belong to the European Union/European Economic Area with a known CD4 cell count were diagnosed late (CD4 cell count<350 cells/mm^3); 28% were diagnosed at an advanced stage (CD4 cell count<200 cells/mm^3) [3]. In Belgium, two key populations are most affected: men who have sex with men (MSM) and sub-Saharan African Migrants (SAMs) [4]. More than a third of new Belgian HIV cases were diagnosed late in 2017, ranging from 27% among MSM to 50% among SAMs.

The *HIV European Research on Mathematical Modeling and Experimentation of HIV Testing in Hidden Communities* (HERMETIC) project applies a mathematical model for routine HIV-surveillance data to calculate the size and proportion of these undiagnosed HIV-infected populations. Modeling results obtained using a back-calculation method [5] for Belgium indicate that almost 2818 people living with HIV remained undiagnosed in 2015, corresponding to a prevalence rate of 4.1 undiagnosed persons per 10,000 [6]. The most affected populations were non-Belgian MSM (almost 264 undiagnosed persons per 10,000), SAMs with a higher proportion among women (about 173 per 10,000) than among men (about 93 per 10,000), and Belgian MSM (about 55 per 10,000) [6]. While Belgian HIV-testing rates are relatively high and cost-effective with 1.25 new HIV diagnoses per 1000 tests [4,7], these estimates of undiagnosed HIV infections indicate that current HIV-testing strategies fail to reach all people at risk of infection in a timely manner.

General practitioners (GPs) are well placed to facilitate early HIV diagnoses; their long-term and holistic relationships with patients provide opportunities for HIV testing, as they are the first entry point to health care [8-10]. However, many diagnostic opportunities are missed in primary care [11-13]. A recent systematic review showed the following GP-specific barriers and facilitators: lack of time, fear to disturb the consultation process, language barriers, lack of culture-sensitive sexual counseling skills, and concerns about pretest discussion or result management [11]. GP-specific training and practical tools to support HIV testing were found to facilitate HIV testing in primary care. Earlier research mentions similar barriers among Belgian GPs [14]. A recent analysis on Belgian surveillance data has shown that Belgian GPs predominantly diagnose MSM, whereas SAMs are more often diagnosed by specialists [15]. The fact that about half of all HIV tests conducted in Belgium in 2017 were prescribed by GPs [4] and that complementary community-based testing initiatives are in place [16,17] indicates the potential to increase the HIV-testing offer in primary care.

To identify solutions to these barriers and reduce the hidden HIV epidemic in Belgium, we developed an HIV-testing intervention for primary care by adopting a simplified intervention mapping approach [18,19] (Figure 1). This approach was chosen to ensure appropriateness and future sustainability, as it promotes the use of theory and evidence, as well as the inclusion of stakeholders [18]. Collaborative participation [20] was ensured through an advisory board consisting of 22 experts including GPs, representatives of GP umbrella organizations, policy makers, HIV care specialists, public health specialists, prevention specialists, and lab specialists. The advisory board has been consulted at all stages of the research, providing inputs to content and strategic decisions.

In the preparatory phase, a detailed contextual analysis of the problem within the local Flemish context was conducted (see step 1 in Figure 1). The aforementioned modeling results [6] were triangulated with multiple data sources [21], such as behavioral surveys and an expert meeting for validation and to gain further in-depth insight. The results of a mixed research synthesis on HIV testing in European general practices [11] provided additional guidance. The advisory board selected two evidence-based HIV-testing strategies to be further elaborated for this intervention: provider-initiated testing of key populations and indicator condition–based testing. A participatory, formative research with 122 GPs using group discussions was conducted to obtain their inputs on the acceptability and feasibility of these strategies [22]. While the two proposed testing strategies were generally accepted by the participants, deficits in knowledge about relevant HIV epidemiology and skills to propose testing became apparent. GPs emphasized on the lack of official policy guidelines to support them in provider-initiated HIV testing.

On the basis of the results of the preparatory phase, it was decided in collaboration with the advisory board that the intervention should integrate the two assessed HIV-testing strategies into one intervention consisting of a GP-specific HIV-testing tool for providing information and an accompanying group-level training that practically supports GPs in performing provider-initiated HIV testing. Here, we present the HERMETIC study protocol for the intervention's content development, and the practical strategies for implementation and evaluation in Flanders, Belgium (steps 2, 3, 4, 5, and 6 in Figure 1).

Figure 1. Developing an HIV-testing intervention for Flemish GPs. A stepwise approach to intervention development 19.
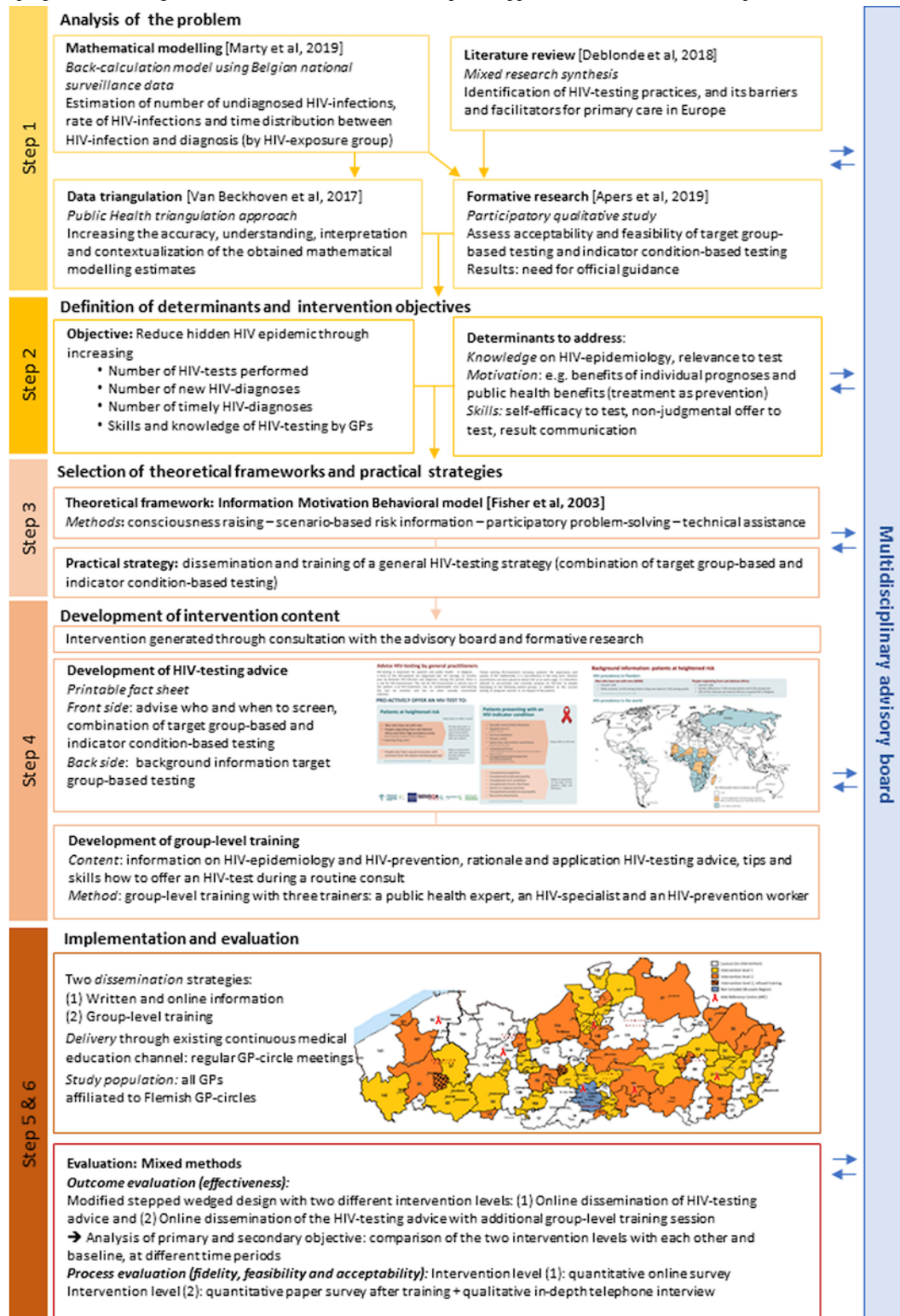
Methods

Figure 2 shows a schedule of the enrollment, intervention, and evaluation of the HIV-testing intervention.

Figure 2. Schedule of enrolment, allocation, intervention, and evaluation of the HIV-testing intervention.

| | | Enrollment | Allocation | STUDY PERIOD | | | | | |
| | | | | Intervention period | | | | Evaluation | |
Timeline		2016	12/2016	01/2017	03/2017	09/2017	12/2017	2018	2019
ENROLLMENT	Eligibility screen	X							
	Randomization and allocation of GP circles		X						
INTERVENTIONS	[Control]			●——————————————————●					
	[Intervention level 1]				●————————————————●				
	[Intervention level 2]					●——————————●			
ASSESSMENTS	[Primary outcome: intervention effectivity]								X
	[Secondary outcomes intervention effectivity]								X
	[Secondary outcomes intervention fidelity, feasibility, acceptability]							X	

Objectives and Outcomes

The objective of the study is to evaluate the effectiveness of two different intervention levels (dissemination of the information tool and group-level training) against a control condition. This will be assessed by the following primary and secondary outcomes:

1. Primary outcome measure is the number of HIV diagnoses made by the GPs. We will evaluate the change in the number of new HIV diagnoses made by GPs by comparing the data from 2016, which serve as baseline data, to data from 2017 and 2018.
2. Secondary outcome measures are HIV diagnoses among groups identified to be more likely undiagnosed, distribution of new diagnoses by CD4 cell count (to assess changes in late HIV diagnoses), the overall number of HIV tests prescribed by GPs, and the rate of new diagnoses by the number of HIV tests performed.

To evaluate the intervention's implementation, GPs' fidelity to the intervention and its perceived feasibility and acceptability by GPs are assessed using mixed methods (see "Methods" section).

Study Population

The study aims to enroll all Flemish GPs who are affiliated to a *"GP circle" (ie, huisartsenkring or HAK)*. The *HAK* is the local focal point for GPs and policy makers to implement health policy in primary care, and provides continuous medical education [23]. HAKs are subsidized by the Flemish government and are organized by geographical zones. In 2016, 8163 GPs were active in Flanders [24]. Among them, 6211 (76.1%) are affiliated to one of the 86 HAKs (Zorg en Gezondheid, personal communication via email, September 2016). The choice of enrolling only GPs affiliated to a HAK is a pragmatic one: GPs can be easily accessed through HAKs, and the geographical aspect provides an opportunity for nonindividual comparison. No data are available to describe GPs who are not affiliated to HAKs, but they are assumed to be mainly working in nonprimary care contexts such as specialist centers for educational health care (Zorg en Gezondheid, personal communication via email, September 2016).

Intervention Content and Practical Strategies

The findings of HIV knowledge gaps and testing skills as determinants among GPs during the formative research [22] led

to the selection of the empirically widely tested *information-motivation-behavioral skills model* [25] as a theoretical base for the intervention's content, practical strategies, and implementation (see steps 2 and 3 in Figure 1). To meet GPs' demand for official guidelines, the intervention should include dissemination of an HIV-testing advice and a group-level training (step 4 in Figure 1).

HIV-Testing Advice

User-friendly advice combining the two selected HIV-testing strategies was created (see Figures 3 and 4). Informed by the expressed needs of GPs during the formative research, it guides them in proactively testing patients at heightened risk of HIV

acquisition and patients presenting with an HIV-indicator condition and gives a time indication of how often an HIV test should be performed. National epidemiological information and the HERMETIC modeling results have defined the key target groups that an HIV test should be offered to. The extensive 64 HIV-indicator conditions formulated in the HIV Indicator Diseases Across Europe Study [7] were reduced to 14 conditions often diagnosed in primary care, as indicated by the formative research results and in collaboration with the AB [22]. The advice also provides country-specific information on HIV prevalence as an additional rationale as to why targeting patients at heightened risk due to migration from high endemic regions is recommended.

Figure 3. Advice HIV-testing by GPs (front side).

Figure 4. Advice HIV-testing by GPs (back side).
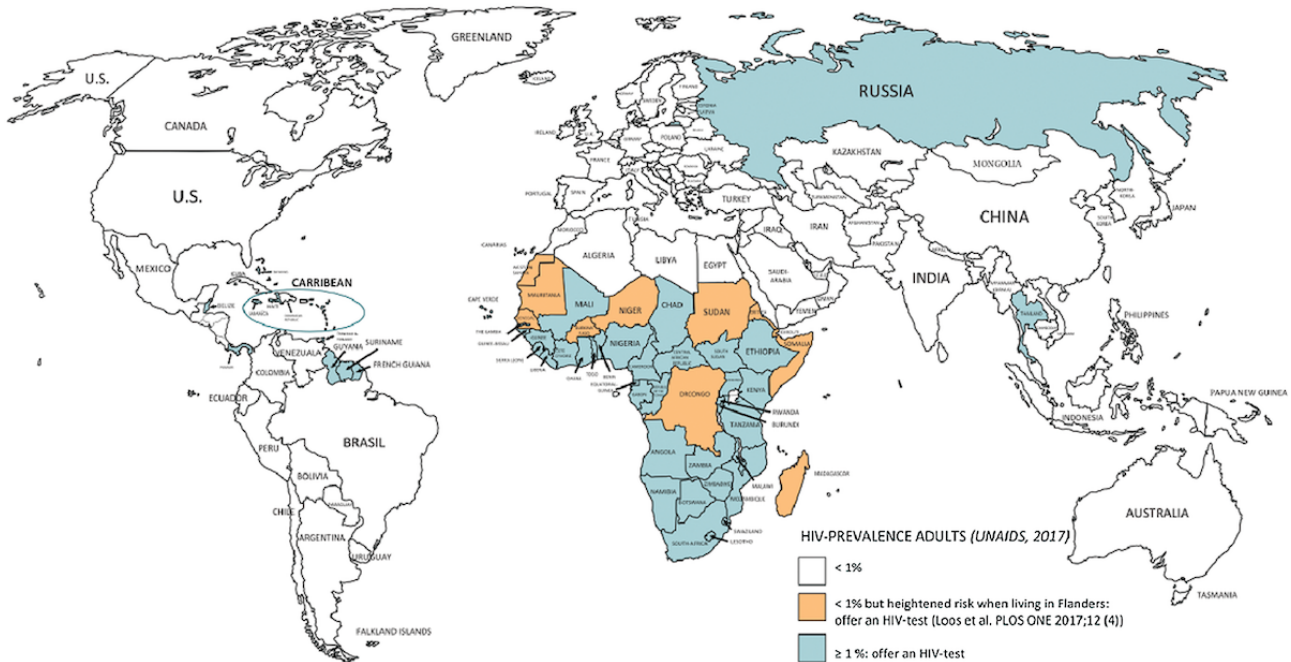
Group-Level Training

GPs expressed their preference for a face-to-face training as an intervention delivery channel [22]. To increase GPs' motivation and skills on HIV testing, we designed a group-level training for 1.5-2 hours, consisting of three main parts, each led by trainers with different types of expertise. The introduction given by a public health expert discusses current HIV epidemiology, advantages of early diagnosis, missed opportunities in primary care, current HIV-prevention approaches and GPs' role in these, and common misconceptions about HIV risk. The second part presents the HIV-testing advice in detail. An HIV specialist provides specific medical information (ie, on the indicator conditions). The third part given by an HIV-prevention worker focuses on the use of the advice including aspects of patient-provider interaction and communication skills. In the latter part, specific tips and reference to hands-on tools were given to overcome the barriers related to the specific target groups (such as using the visual online support tool Zanzu [26] to reduce language- or culture-related barriers).

Intervention Implementation

Two intervention levels were established, differing in terms of degree of information delivered and delivery channels. For the latter, the existing GP channels were selected: the website of the GP umbrella organization [27] and HAK networks. At the third level, the control condition, GPs receive no intervention, that is, they are not actively targeted according to the current standard practice.

Intervention Level 1: Online Dissemination of the HIV-Testing Advice

GPs included at the first level receive the HIV-testing advice through an email by their HAK coordinator, which contains an information message with the printer-friendly version of the HIV-testing advice attached (see Figures 3 and 4). The message also provides a link to the website of the Flemish umbrella organization for GPs, where the tool is available for download for all Flemish GPs. A reminder is sent out to all participants after 13 months.

Intervention Level 2: Online Dissemination of the HIV-Testing Advice with Additional Group-Level Training Session

At the second intervention level, GPs first receive intervention condition 1 and then the face-to-face group-level training session. These sessions are organized as part of regular continuous medical education provided by HAKs at their usual venues and are organized a few months after receiving intervention level 1. A reminder of the advice is sent out 13 months after the initiation of intervention level 1.

Study Duration

Study duration including intervention development is from January 2017 to December 2019. Intervention implementation and evaluation take place in the framework of the HERMETIC study; implementation started in December 2017 and evaluation results will be available in December 2019 (see steps 5 and 6 in Figure 1).

Study Design

This mixed methods study adopts a modified stepped-wedge design. The classical stepped-wedge cluster design involves a random and sequential crossover of clusters from control to intervention until all clusters are exposed. It includes an initial period in which no clusters are exposed to the intervention [28]. We adopted a modified version: the two different intervention levels are added stepwise, while a control condition is retained until the end of the study period. Participants of both intervention levels serve as their own (historical) controls receiving no intervention during approximately 2 months, then all the participants receive the HIV-testing advice online. Those assigned to the first intervention level remain at this level until the end of the project. Participants assigned to the second intervention level are offered the additional group-level training after 7 months. The rationale for this adaptation is twofold: (1) to compare the effects at all intervention levels among each other over time and (2) to assess feasibility (ie, resource and time restrictions).

The process of information distribution is monitored: confirmation is obtained through short phone interviews with GP-circle coordinators to verify if the emails were sent to individual GPs and to allow for timely assessment of problems and reasons for noncompliance with the procedure.

Randomization Strategy

Intervention groups are identifiable in HIV-surveillance data using the administrative code referring to geographical zones defined by the National Institute of Statistics (ie, NIS code). HAKs that correspond to the same NIS code have been merged, regrouping 86 HAKs into 76 clusters. Each cluster is randomly allocated by the study team to one of the three intervention conditions using block sampling. Block sampling took the variability of the different target populations at risk for HIV in the intervention groups into consideration: each block consists of three clusters with approximately the same number of SAMs in the respective NIS-code areas. The main reason for this approach is that the intervention is assumed to generate the largest effect among SAMs, given their low testing rates in primary care. Since SAMs are unevenly distributed over Flanders with the largest communities living in central cities [29], block randomization assures that the expected effect is equally distributed across the three intervention levels. This approach results in 25 clusters being assigned to intervention level 1 or 2, and 26 clusters assigned to the control condition.

Intervention Evaluation

A mixed methods evaluation approach is applied throughout the intervention implementation (see "Objectives and Outcomes" section and steps 5 and 6 in Figure 1). An outcome evaluation assesses the intervention's effectiveness and changes in GPs' targeting behavior in HIV testing using routine surveillance data on new HIV diagnoses and HIV tests performed in Flanders. Changes in the number of new HIV diagnoses made by GPs, changes in the number of diagnoses among groups at high risk for undiagnosed HIV and at different stages of HIV infection, and changes in the number of HIV tests performed by GPs and in the rate of diagnoses by tests will be assessed.

Process evaluation assesses several implementation aspects: GP's fidelity to the intervention in addition to the intervention's feasibility and acceptability. In intervention level 1, this will be evaluated through an online survey sent out together with an email reminder. The survey is accessible for 2 months. In intervention level 2, GPs attending the group-level trainings are registered to calculate the actual attendance rate. Sociodemographic characteristics of the trained GPs and their evaluation of the training, perceived feasibility, and acceptability of the advise are assessed by means of a structured questionnaire.

A qualitative component collects in-depth and contextual insights on perceived fidelity to the intervention, feasibility, and acceptability of the group-level intervention. It serves to understand first-hand experiences with real-life implementation, for instance, if the intervention can be implemented as designed, and aims to better understand the intervention mechanisms. Data are collected among purposively selected, trained GPs for individual telephone interviews after 5-6 months. To guide this selection, potential "rich cases" among HAKs are identified considering specific indicators assessed through the questionnaire: appreciation of group-level training, anticipated feasibility and acceptability of the advice, and impact on knowledge and skills. HAKs with the lowest, middle, and highest median scores for each of the indicators are identified, and 10% of the trained GPs per HAK are randomly selected and invited to an interview. If GPs refuse, the reason for refusal is noted and another GP from the same HAK is invited until data saturation is obtained. No postprocess evaluation from patients is planned, as previous research has shown that proactively offering an HIV test is well accepted by patients [14].

Data Collection

For outcome evaluation, the following routine surveillance data are used:

- *National Health Insurance (Rijksinstituut voor Ziekte en Invaliditeitsverzekering [RIZIV]) data on the number of HIV tests conducted:* HIV tests are reimbursed by the Belgian National Institute for Sickness and Invalidity Insurance. Data on the number of HIV tests performed, the type of the physician requesting the test, and his/her geographical locations are available in the RIZIV database. The organization in charge of the HIV surveillance in Belgium (Sciensano, ie, the National Public Health Institute) receives extracted data on HIV tests prescribed by GPs, which will be aggregated according to the different clusters and intervention levels as identified by the NIS codes.

- *Laboratory data on new HIV diagnoses:* Seven national AIDS Reference Laboratories (ARL) perform HIV-confirmation tests on samples found to be reactive in screening tests in clinical laboratories. Yearly, each ARL reports data on all newly diagnosed HIV cases including sociodemographic, clinical, and limited behavioral characteristics (eg, transmission group). Sciensano links this information to the type of physician who initially prescribed the HIV test (collected through the physician's registration number at the national social assurance system,

ie, "RIZIV number"), the cluster number, and the intervention level (using the NIS codes of HAKs).

For process evaluation, data on perceived fidelity to the intervention, feasibility, and acceptability for intervention level 1 (information only) are collected through an online survey, located at the server of SoSciSurvey [30]. For intervention level 2, data are collected through a quantitative evaluation questionnaire immediately filled in on paper after the group-level training session. Data on experienced feasibility and acceptability are collected through recorded telephone interviews. In each of these data collected, limited sociodemographic characteristics of the participants are gathered, for example, age, gender, and years of experience.

Data Extraction and Management

For outcome evaluation, HIV-surveillance data will be transferred through technical interfaces with encrypted data to Sciensano by Healthdata, the agency responsible for data captation and secure data transfer. Data will be checked and duplicated records will be removed. Sciensano will provide the aggregated data of both HIV tests and HIV diagnoses to the researchers for further analysis.

For process evaluation, data from the online survey are collected anonymously and extracted through a downloadable Excel Database. Interview recordings will be transcribed verbatim. Pseudonymized data are managed and archived by the Institute of Tropical Medicine in locked and secured (digital) locations that are only accessible by the researchers.

Data Analysis and Statistical Methods

Using the stepped-wedge design, the distribution of results across unexposed observation periods is compared with that across the exposed observation periods. To determine the intervention's effectiveness, primary and secondary outcomes at the three levels are compared against each other at three different time periods, that is, baseline and before March 2017, from March to August 2017, and from August 2017 to December 2018 (data available in late 2019).

Poisson regression is used to estimate the relative change in outcome variables. This change is explored through several alternative models, comparing the intervention group to the control group or to each other over time. In addition, we are investigating the differences in the ability to diagnose groups that are at high risk for acquiring HIV (MSM, SAMs, people who inject drugs, and others) and timely diagnosis (represented by CD4-cell count in three categories: less than 200 cells/mm^3, 200-350 cells/mm^3, and above 350 cells/mm^3) across time periods and interventions.

To quantify the level of uncertainty associated with the estimates, Poisson regression models will be fitted to the data using Bayesian modeling under weakly informative priors. For each parameter, we will report the 90% central credible interval from the marginal posterior distribution.

Within the process evaluation, survey data are analyzed descriptively to compare groups with different intervention exposures in terms of self-perceived effects of the intervention levels such as gains in knowledge, self-efficacy to test, and future intention to use the intervention tools.

Qualitative data collected through telephone interviews are analyzed inductively. Using NVivo 8 (QSR International), a data-driven codebook will be established according to the principles of thematic analysis [31].

Availability of Data and Materials

Datasets used and/or analyzed during the study are available from the corresponding author on request.

Ethics and Dissemination

Informed Consent

Strict attention to maintain confidentiality is paid at every stage of data collection, analysis, and storage. Data extraction measures will be put in place to ensure that individual HIV patients cannot be identified (grouping of diagnosis as per HAK, analysis every 2 months). HIV-testing and diagnosis data will be managed through the legal entities in charge of the HIV/AIDS surveillance system (Royal Decree of October 8, 1996) authorized by the Belgian Privacy Commission.

To ensure transparency, GPs receive the HIV-testing advice, with an accompanying email that explains that the dissemination of the advice is part of the study monitoring the intervention's effects through routine data collection. During the training sessions, GPs are informed of the same. The structured questionnaire for GPs contains an introductory statement with information stating that filling in the questionnaire is considered as providing informed consent.

Oral informed consent is obtained before the telephone interview from the participants, who agree to interviewed, in addition to their permission to audio-record the interview.

Dissemination

Results of the study will be disseminated at scientific conferences targeting GPs and HIV experts and through articles in GP-specific media and international peer-reviewed journals.

Ethical Approval

This study has been approved by the Institutional Review Board of the Institute of Tropical Medicine, Antwerp (approval number: 1228/18; dated January 6, 2017). The study is carried out according to the principles stated in the Declaration of Helsinki and according to established international scientific standards.

Consent to Participate

Not applicable for study effectiveness: analysis of HIV-testing and HIV-diagnosis data is managed through the legal entities in charge of the HIV/AIDS surveillance system (Royal Decree of October 8, 1996), authorized by the Belgian Privacy Commission. For transparency, GPs receive an accompanying email together with the HIV-testing advice, which explains that the dissemination of the advice is part of the study monitoring the intervention's effects through routine data collection. During the training sessions, GPs are informed of the same.

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With regard to the evaluation of the study's feasibility, acceptability, and GPs' fidelity to the advice, the structured questionnaire for GPs participating in the evaluation contains an introductory statement with information stating that filling in the questionnaire is considered as providing informed consent. Similarly, oral informed consent is obtained before the telephone interview from the participants, who agree to be interviewed, as well as their permission to audio-record the interview.

Results

The study was funded in 2016 and was ethically approved in January 2017 (see Multimedia Appendix 1). The intervention implementation started in January 2017 and ended in December 2018. Data was completed in October 2019 and was the starting point for the ongoing data analysis. The results are expected to be published in the second half of 2020. The intervention study described in this protocol has been funded through the framework of the European HIV-ERA JTC 2014 (see Multimedia Appendix 2) and the Belgian Funding Agency IWT 140922. The Institute of Tropical Medicine is the study sponsor.

Discussion

This study will deliver useful information on the implementation and effectiveness of an intervention to promote HIV testing among GPs in Flanders. The participatory intervention development strategy allows for a high degree of tailoring of the intervention to the needs of primary care providers. This should lead to a sustainable intervention [32] with high intervention effectiveness [33]. Systematically collected experiences on disseminating and adopting the HIV-testing advice can inform further development of national HIV-testing policies, sexual health strategies, and GPs' respective roles in these. Yet, this approach of a real-life intervention trial has its limitations: spill-over effects among intervention levels may occur, as GPs not included in the respective intervention condition may download the advice from the GP umbrella organization's website or may attend training events of a neighboring HAK. The influence of other initiatives to promote HIV testing cannot be excluded, for example, media messages on HIV testing or HIV prevention. Information on the background of GPs not affiliated to a GP circle is lacking and may cause a selection bias.

The use of surveillance data for analysis, however, provides an opportunity to evaluate a real-life intervention including all Flemish GPs. The formative research indicated this as the most feasible data collection method, enabling long-term follow-up while not overburdening busy GPs. However, such routine data are only collected once a year, therefore causing a delay in data access. Detailed information on specific HIV-testing conditions in primary care practices and profiles of testers cannot be collected. Privacy issues impede further subanalyses (eg, sociodemographic characteristics of GPs associated with diagnosis of HIV). In addition, other interventions, such as the introduction of preexposure prophylaxis (PrEP) on a national scale in June 2017 might cause changes in the demand for HIV testing and subsequently in the number of HIV diagnoses, making comparisons over time difficult.

This study provides a valuable contribution to evidence-based HIV testing in primary care, since only few interventions for the promotion of HIV testing in primary care have been described in the literature [11,34,35]. These settings may play a greater role in HIV prevention and care continuum [10] in the future with outlined directions in provider-level education interventions [35]. The study's strong qualitative component will provide practice-based lessons on real-life experiences with HIV testing in primary care and insights into the mechanisms by which the intervention works. This will contribute to a nuanced interpretation of the results of outcome evaluation.

Authors' Contributions

HA and JL are responsible for the development, implementation, and evaluation of the intervention, supervised by CN. They have drafted and finalized the article. BV provided valuable inputs for the study design and developed the statistical analysis plan with TS; both contributed to the respective sections in the paper. JD and DVB provided valuable input during the intervention (study) development and provided feedback on the manuscript. JL carried out the work while at the Institute of Tropical Medicine, Antwerp and Domus Medica, Antwerp. She is now affiliated at Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

This randomized study was only retrospectively registered, explained by authors due to a conflict of definition of "clinical trial" (EU directive 2011/20/EC or EU Regulation 536/2014 versus WHO-definition). The editor granted an exception from ICMJE

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rules mandating prospective registration of randomized trials because the risk of bias appears low and the study was considered formative, guiding the development of the application [or other reasons for the exception, as argued by the authors]. However, readers are advised to carefully assess the validity of any potential explicit or implicit claims related to primary outcomes or effectiveness, as retrospective registration does not prevent authors from changing their outcome measures retrospectively.

Multimedia Appendix 1
Approval letter Institutional Review Board of the Institute of Tropical Medicine.
[PDF File (Adobe PDF File), 98 KB - resprot_v9i8e16486_app1.pdf]

Multimedia Appendix 2
Approval European framework HIV-ERA JTC 2014.
[PDF File (Adobe PDF File), 22 KB - resprot_v9i8e16486_app2.pdf]

Multimedia Appendix 3
Previous peer-review report from the Institute of Tropical Medicine.
[PDF File (Adobe PDF File), 33 KB - resprot_v9i8e16486_app3.pdf]

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Abbreviations

AB: advisory board
GP: general practitioner
HAK: HuisArtsenKring (GP-circle, local focal point for GPs)
HERMETIC: HIV European Research on Mathematical Modeling and Experimentation of HIV Testing in Hidden Communities
MSM: men who have sex with men
NIS: National Institute of Statistics
RIZIV: Rijksinstituut voor Ziekte en Invaliditeitsverzekering (Belgian National Institute for Sickness and Invalidity Insurance)
SAMs: sub-Saharan African migrants

Protocol

Evaluation of an Adaptive Implementation Program for Cognitive Adaptation Training for People With Severe Mental Illness: Protocol for a Randomized Controlled Trial

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Abstract

Background: Cognitive Adaptation Training is a psychosocial intervention that focuses on reducing the negative effects of cognitive disorders, especially executive functions such as planning and targeted action. International research has shown that Cognitive Adaptation Training enhances multiple aspects of daily functioning in people with severe mental illnesses. Despite this evidence, implementation of the intervention into routine care remains a challenge.

Objective: In this implementation research, a newly developed implementation program based on previous experience and scientific literature, is tested. The primary aim of this research is to assess the effectiveness of the implementation program. The secondary aim of this study is to evaluate the factors that impede or facilitate the implementation of Cognitive Adaptation Training.

Methods: To test the effectiveness of the implementation program, a multicenter cluster randomized controlled trial was conducted comparing the implementation program to a single training program in four mental health institutions in The Netherlands. Focus groups, semistructured interviews, and questionnaires were used at multiple levels of service delivery (service user, professional, team, organization) to identify factors that may hamper or facilitate implementation. The RE-AIM framework was applied to measure the implementation effectiveness. Following this framework, the primary outcomes were Reach, Intervention Effectiveness, Adoption, Implementation, and Maintenance. These are assessed before, during, and after implementation. The research had a total duration of 14 months, with a follow-up measurement at 14 months. Data will be analyzed using multilevel modeling.

Results: The study was funded in April 2018. Data collection occurred between November 2018 and January 2020. In total, 21 teams of 4 mental health institutions agreed to participate. Data analysis is ongoing and results are expected to be published in December 2020.

Conclusions: This implementation research may provide important information about the implementation of psychosocial interventions in practice and may result in a program that is useful for Cognitive Adaptation Training, and possibly for psychosocial interventions in general.

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Introduction

Modern views on psychiatric treatment for people with severe mental illnesses are fundamentally different from the treatment views and practices decades ago. Whereas the former treatment for people with severe mental illnesses was predominantly provided in large institutions, a paradigm shift towards recovery-oriented treatment aimed at increasing participation in the community resulted in a considerable decrease in hospital-based care [1]. Yet, a small group of people, presenting treatment resistant positive symptoms, persistent negative symptoms, cognitive impairments, and functional impairments, still require high levels of support and ongoing treatment in inpatient facilities for a longer period of time [2].

Treatment and support in these facilities mostly consist of support in daily living activities by psychiatric nurses, pharmacotherapy, psychological therapy such as psychoeducation and cognitive behavioral therapy, and occupation- and work-related daytime activities. Often, the available evidence-based psychiatric rehabilitation interventions, such as Individual Placement and Support [3] and the Boston Psychiatric Rehabilitation Approach [4], are not feasible due to the cognitive and communicative impairments of the service users. A rehabilitation intervention that has been found to be effective in this population is Cognitive Adaptation Training [5]. Cognitive Adaptation Training aims to reduce functional problems caused by cognitive deficits through the use of compensatory strategies and environmental supports. The compensatory strategies and environmental supports are set up based upon an evaluation of the environmental context and functional skills, an assessment of cognitive strengths/weaknesses, and an assessment of how the cognitive problems are expressed in daily life. The effectiveness of Cognitive Adaptation Training has been investigated in a number of randomized controlled trials in various contexts (outpatients and inpatients) with consistent positive findings [6,7].

Although there is a convincing body of evidence describing the clinical value of Cognitive Adaptation Training in different settings and target groups (community care, residential facilities, first-episode psychosis) [5-13], implementation of the intervention into routine care has yet to be established. Literature on the implementation of evidence-based practices shows that this so called science-to-service gap is a widespread problem in both somatic and mental health care [14]; treatment guidelines are often not followed and as few as 8%-32% of the people with schizophrenia in an inpatient and outpatient setting are offered psychosocial interventions such as family psychoeducation or supported employment, despite the fact that it is part of their treatment plan [15]. Furthermore, research on the

implementation of guideline recommendations in schizophrenia treatment showed that only 0%-7% of mental health care teams provide psychological or psychosocial evidence-based practices to more than 70% of the people in their caseload, even though these interventions were available to the teams [16]. After applying a series of structured activities aimed to implement evidence-based practices, these numbers increased to 10%-40% in the mental health care teams [16]. The reported factors that facilitated this implementation process were managerial support, a capable local team coordinator, and a motivated and skilled team of professionals. These studies show that dissemination of evidence-based practices alone does not lead to sustainable implementation, but when provided with the appropriate guidance, more sustainable implementation can be achieved.

To gain a better understanding of the processes involved in the implementation of Cognitive Adaptation Training, a posthoc process evaluation was conducted in a previous study [7] in order to clarify the providers' needs and perspectives regarding the intervention and its implementation. The mainly qualitative findings indicated 3 important barriers to implementation: (1) knowledge and skills of the nursing staff to provide the intervention in the appropriate way, (2) organizational preconditions such as time and support, and (3) motivation of the nursing staff to provide the intervention to the service users. These findings were in line with the factors outlined in the COM-B model [17] that was designed to understand, explain, and influence behavioral change. The model assumes that causal and reciprocal relationships exist between 3 factors: capability, opportunity, and motivation and that these concepts influence and determine behavioral change. *Capability* is defined as the mental and physical ability of an individual to perform a certain activity, such as knowledge and skills. *Opportunity* is defined as all factors that are beyond an individuals' sphere of influence yet enable or hinder the individual in performing certain behavior. *Motivation* is defined as all mental processes that bring about goal-directed behavior. It includes automatic and unconscious behavior, emotional reactions, and rational decision making that lead to certain behavior.

In this research, we propose and evaluate an implementation program that is based upon the results of our previous study's process evaluation [7] and is theoretically grounded in the COM-B model. By putting this implementation program into practice, we aim to achieve a sustainable implementation of Cognitive Adaptation Training in routine mental health care. The primary aim of this research was to assess the effectiveness of the implementation program, which is referred to as *implementation effectiveness* throughout the article. The RE-AIM framework [18] is used to assess and report the implementation effectiveness and is defined by reach, effectiveness of Cognitive Adaptation Training, which is

referred to as *intervention effectiveness* throughout the article, adoption, implementation (or fidelity), and maintenance. The secondary aim of this study was to evaluate the factors that impede or facilitate the implementation of Cognitive Adaptation Training.

Methods

Study Design

This study is a 2-arm multicenter cluster randomized controlled trial comparing the implementation program, consisting of tailored multifaceted implementation strategies to a preset program with single implementation strategies, using mixed methods. The total study duration was 14 months. The first 2 months are used to train the participating teams in Cognitive Adaptation Training. The assessments are administered at baseline (2 months; T0), 5 months (T1), and 8 months (T2). Long-term effects were assessed by a follow-up assessment at 14 months (T3).

Setting

In total, 21 rehabilitation teams of 4 mental health institutions across The Netherlands were included. The size and compositions of the teams differed: the team sizes ranges from 4 to 28 team members, and the number of service users they help in their day-to-day needs ranges from 9 to 35. Most of the team members were psychiatric nurses with a degree at bachelor or below bachelor level. All teams provide long-term daily clinical care in an inpatient setting to adult people diagnosed with a severe mental illness according to DSM-IV or DSM-5 criteria, depending on the date of diagnosis. The majority of the service users receiving treatment were diagnosed with schizophrenia or related psychotic disorders; other diagnoses included severe depression, bipolar disorder, personality disorder, and autism. The teams were different from those that participated in the randomized controlled trial evaluating the effectiveness of Cognitive Adaptation Training [7] but were similar with regard to the provided treatment, support, and living conditions. The teams aim to provide a combination of treatments such as pharmacotherapy, psychological, psychosocial, and nonverbal therapies. Examples are psychoeducation, cognitive behavioral therapy, trauma therapy, creative therapy, and work projects such as landscaping, catering, woodworking, and production work.

Participants

Participants in this study were members of the rehabilitation teams (including their managers) and service users. The members of the rehabilitation teams include nurses, social workers, peer support workers, and other professionals who provide day-to-day care to the service users. Treatment staff (psychiatrists, psychologists, and nurse practitioners) of the rehabilitation teams were excluded. The manager was defined as the person with managerial authority who monitors the functioning of the team members. Service users who receive outpatient treatment or those who were under the age of 18 were excluded from participation. No other inclusion or exclusion criteria were used.

Recruitment and Allocation

Two mental health institutions included in this study indicated that they were interested in Cognitive Adaptation Training before the start of the study. The managers of the rehabilitation teams of these mental health institutions and 2 other institutions were approached by the research group and were provided with information about the study. If they indicated that they were interested, an appointment was made to provide more in-depth information about the intervention, the research and the required investment in terms of time and effort. All managers of the participating mental health institutions were asked to sign a research statement. In this statement, the departments declared that the researchers and departments had sufficient expertise and facilities to conduct the research, that these facilities were available to the researchers, and that they would inform all people who were required to contribute to the research. In addition, a liability statement was included. The service users received both written and oral information about the research by the team members. All participants were asked to provide written consent to participation and were informed that their participation was voluntary and that withdrawal of consent was possible at any time without consequences.

To avoid contamination between the 2 treatment conditions, cluster randomization was applied at the team level. Teams were clustered if their members were situated in the same building or if they indicated that they interact with each other on a day-to-day basis. When these criteria did not apply, single teams were entered as a cluster. The teams were randomly allocated to either the experimental condition (multiple tailored implementation strategies) or control condition (single implementation strategies) by an independent staff member who blindly drew a ticket from a box containing a ticket for either condition.

Cognitive Adaptation Training

The intervention to be implemented in this study was Cognitive Adaptation Training, a psychosocial intervention aimed at reducing functional problems caused by cognitive deficits by using compensatory strategies and environmental supports. Cognitive Adaptation Training was provided by the nurses and other team members who provide day-to-day care to the service users. Individual Cognitive Adaptation Training plans were set-up and tailored to the individual through gathering information regarding: (1) daily functioning (Environmental and Functional Assessment) [19], (2) cognitive functioning (Modified Wisconsin Card Sorting Test; Letter fluency test) [20,21], and (3) reflection of cognitive impairments in daily life (behavior type: apathy versus disinhibition (Frontal Systems Behavior Scale) [22]. Goals are determined through shared-decision making and based upon the daily functioning outcomes. Behavior type is used as a basis for designing compensational strategies: for example, for apathy, strategies involve cueing and prompting behavior, while for disinhibition, strategies are focused on removing irrelevant or distracting stimuli from the environment where the activity takes place. Information on cognitive functioning was used to tailor the environmental supports to the level of cognitive functioning of the individual (ie, global or step-by-step description).

The Implementation Program

The implementation program was a 2-phase process with phase 1 being identical for all teams regardless of condition. This first phase included a local consensus meeting, a basic training in Cognitive Adaptation Training for all team members at site, and a specialist training in Cognitive Adaptation Training for a maximum of 2 team members per participating team. Phase 2 was offered to the teams in the experimental condition only and entailed the provision of multiple implementation strategies tailored to the needs and context of the individual teams. A graphical representation of the implementation program is presented in Figure 1.

Figure 1. Implementation program. CAT: Cognitive Adaptation Training.
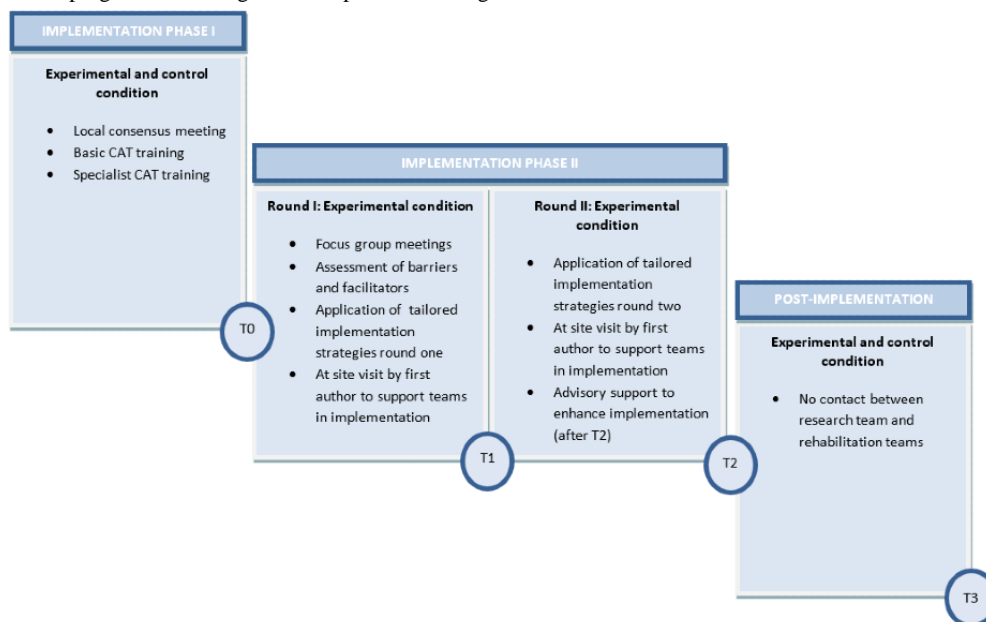
Implementation Phase 1: Experimental and Control Condition

Local Consensus Meetings

In all participating teams, a local consensus meeting was conducted by author MD to create a solid support base. In this meeting, information about Cognitive Adaptation Training, the implementation process, and the related research activities was provided to all team members. Moreover, this meeting was used to create commitment to the implementation study and for providers to decide whether to agree to participate.

Basic Cognitive Adaptation Training

Small educational group meetings were organized for all individual teams to educate them in the basic principles of Cognitive Adaptation Training. The basic training in Cognitive Adaptation Training was a single 90-minute meeting in which information was provided about the rationale behind Cognitive Adaptation Training and the steps involved to set up an individual Cognitive Adaptation Training plan. The educational meeting was provided on site by authors MD, LM, or a trained research assistant. It included an interactive component by training the team members in administering the Frontal Systems Behavior Scale, which is used for determining the compensational strategy.

Specialist Cognitive Adaptation Training

The qualitative results of the process evaluation as a part of the effectiveness study, which was conducted in a similar setting, showed that demoralization, indifference, and resistance of professionals to provide Cognitive Adaptation Training to the service users were important barriers to implementation. To overcome these barriers, local champions were recruited to promote the implementation process. The local champions were team members on site who were committed to the intervention and to performing the activities necessary to set up a Cognitive Adaptation Training plan. Two champions were recommended for each team and they were recruited on a voluntarily basis. They received 3-day specialist training provided by first author MD in which they gathered in-depth knowledge on Cognitive Adaptation Training–related constructs (ie, cognition, executive functioning, apathy, disinhibition), administering the interview and cognitive tests, on-the-spot training and supervision, designing a Cognitive Adaptation Training plan, and choosing appropriate environmental supports. At the end of the training, all champions received the materials and documents to provide Cognitive Adaptation Training to the service users.

Implementation Phase 2: Experimental Condition

The second part of the implementation study was exclusively provided to the teams randomized to the experimental condition. The teams in the control condition received no further implementation support. An overview of all measurement instruments and assessment schedule is presented in Table 1.

Table 1. Schedule of assessments.

Level, Construct	Instrument	Baseline (T0; 2 months)	5 months (T1)	8 months (T2)	14 months (T3)
Service user					
Demographical information		X	—	—	—
Effectiveness	LSP[a]	X	—	—	X
	NOSCA[b]	X	—	—	X
Mental health care staff					
Demographical information		X	—	—	—
Capability	CAT Fidelity[c]	—	X[d]	X	X
Opportunity	TCI[e]	X	—	—	X
	OCM[f]	X	—	—	X
Motivation	EPBAS[g]	X	—	—	X
Reach		—	—	X	X
Adoption	MIDI[h]	—	X[d]	X	X
Implementation	CAT Fidelity	—	X[d]	X	X
Maintenance		—	—	—	X
Manager					
Recovery-oriented care	ROPI[i]	X	—	—	X

[a]LSP: Life Skills Profile.

[b]NOSCA: Nurses' Observation Scale of Cognitive Abilities.

[c]CAT Fidelity: Cognitive Adaptation Training Fidelity Scale.

[d]Assessed for the teams in the experimental condition only.

[e]TCI: Team Climate Inventory.

[f]OCM: Organizational Climate Measure.

[g]EPBAS: Evidence-Based Practice Attitude Scale.

[h]MIDI: Measurement Instrument for Determinants of Innovation.

[i]ROPI: Recovery Oriented Practices Index.

Experimental Condition: Round 1

Focus Group Meetings

Two focus group meetings were organized by first author MD and a trained research assistant in each mental health institution for the teams in the experimental condition. The purpose of these focus group meetings was to collect qualitative data on the status quo regarding the quality of care that is provided to the service users and to gather additional information on barriers and facilitators to implement Cognitive Adaptation Training in the context of the COM-B constructs (capability, opportunity, motivation, and behavior change). For example, information was gathered on the perspective of the focus group participants regarding the extent to which the teams provide recovery-oriented care, how they support the service users in pursuing their own personal goals, how this is integrated in their day-to-day care, and what can be improved to optimize this process. The interview guide was developed by author MD and was modified in consultation with authors JW, MP, SC, and LM.

In a previous experience with combined focus groups (mental health professionals and service users), we noticed that service users could not keep up with the speed of the discussion. Therefore, we deliberately choose to split the focus groups. The first focus group included service users only, and the second focus group was organized for family members, caregivers, and mental health professionals. We aimed to include a minimum of 5 and maximum of 8 participants in each focus group.

Assessment of Barriers and Facilitators Based on COM-B

To assess implementation barriers and facilitators in each individual team, all team members who were involved in the day-to-day care of the service users received a set of questionnaires measuring different components of the COM-B model. The questionnaires were distributed by an email that included a personal link. The link to the questionnaires could only be used once after completion to avoid duplicate entries from the same individual. Responses were recorded automatically. Informed consent was obtained online. Online data collection was performed according to the guideline for

online surveys, where applicable [23]. The measurement instruments used in this assessment are described below.

Team and Organizational Climate

The *opportunity* of the local champions to implement Cognitive Adaptation Training in their teams was measured on 2 levels: team level and organizational level. The Team Climate Inventory [24] was used to measure team climate. It is a self-report questionnaire that measures 38 items on a 5-point scale (total score range: 38-190). The Team Climate Inventory consists of 4 scales, subdivided into 13 subscales: (1) participative safety (information sharing, safety, influence, and interaction frequency), (2) support for innovation (articulated support, enacted support), (3) vision (clarity, perceived value, sharedness, attainability), and (4) task orientation (excellence, appraisal, and ideation). The translated Dutch version has been validated and shows good psychometric properties [25].

The Organizational Climate Measure [26] is a self-report questionnaire measuring 82 items on a 4-point scale (total score range: 81-324). The scale contains 17 subscales, divided into 4 quadrants: (1) human relations (autonomy, integration, involvement, supervisory support, training, welfare), (2) internal process (formalization, tradition), (3) open systems (innovation and flexibility, outward focus, reflexivity), and (4) rational goals (clarity of organizational goals, efficiency, effort, performance feedback, pressure to produce, quality). The Organizational Climate Measure was translated to Dutch. The English version of the Organizational Climate Measure has good psychometric properties [26].

Motivation and Attitudes

To measure the *motivation and attitudes* of the team members to adopt evidence-based practices in the teams, the Evidence-Based Practice Attitude Scale [27] was used. The Evidence-Based Practice Attitude Scale is a self-report questionnaire consisting of 15 items measured on a 5-point Likert scale (total score range: 0-60) and consists of 4 subscales: (1) appeal, (2) requirements, (3) openness, and (4) divergence. The translated Dutch version of the Evidence-Based Practice Attitude Scale has good psychometric properties [28].

Implementation Strategies

The implementation efforts for the teams in the experimental condition included fixed and flexible implementation strategies based upon the literature [29]. The fixed implementation strategies were (1) a feedback meeting to discuss the results of the questionnaires measuring potential implementation barriers and facilitators, (2) collaboratively deciding on the implementation strategies in the teams, (3) on-site support by the first author in establishing the strategies, (4) a process evaluation at 3 months to measure the effect of the implementation strategies, (5) collaboratively deciding whether to change the implemented strategies, (6) a second on-site support visit by the first author to support the implementation strategies, and (7) an advisory report set up together with the local champions that describes potential implementation strategies. The flexible implementation strategies depended on the results of the feedback meeting and the process evaluation for each individual team. This part was context dependent and

had to be tailored to the needs and resources of the individual teams. If there was no budget or support base to implement a certain strategy, then we collaboratively had to find an alternative. Therefore, the flexible part could not be determined in advance but had to be decided during the course of the implementation period. For the implementation a process, progress, selection, and adaptation of strategies logbook was kept throughout the study period. The fixed and examples of flexible implementation strategies are described below.

In each individual team in the experimental condition, a feedback meeting was organized with the team members to discuss the results of the questionnaires measuring implementation barriers and facilitators. Implementation strategies that match the barriers and facilitators for each individual rehabilitation team were reviewed and were determined in consensus. For example, when team members indicated that there was limited time to implement Cognitive Adaptation Training in their daily working routine, we might discuss options to deimplement routines or tasks that have little or no beneficial effect. Or we might discuss options to alter Cognitive Adaptation Training in a way that it did not affect fidelity but would make it a group effort so that it was less time consuming for the local champions. Next, the tailored implementation strategies collaboratively selected in the feedback meeting were applied in practice. The researcher supported the individual teams in the implementation activities by visiting them once during the first 3 months.

Process Evaluation

After 3 months, a process evaluation was administered to assess the implementation progress and to re-evaluate the implementation strategies. If the results indicated that implementation barriers or facilitators had shifted or if the tailored implementation strategies did not show the desired results, new strategies were developed and applied. The process evaluation consisted of 2 interviews with each individual local champion by the first author or a research assistant: the CAT Fidelity Scale and the Measurement Instrument for Determinants of Innovation (MIDI) [30].

The *capability* of the local champions to provide Cognitive Adaptation Training as intended by the program developers is measured by the CAT Fidelity Scale. The CAT Fidelity Scale was developed in collaboration with research groups from the United States, Canada, Australia, Sweden and Finland (publication in preparation). Following the Delphi method [31], a multidisciplinary panel of experts was asked to reach consensus on the items. This resulted in a 6-point scale that comprises 44 items (total score range: 0-220) and measures various aspects related to Cognitive Adaptation Training: characteristics of the Cognitive Adaptation Training-specialist, administration and organizational requirements. Two raters score the CAT Fidelity Scale independently. If there is a disagreement among the raters on certain items, these items are discussed to reach consensus. A preliminary evaluation showed moderate interrater reliability of the scale ($\kappa=0.51$).

To gain a better understanding of the factors that influenced the implementation of Cognitive Adaptation Training, the MIDI [30] was used. The MIDI is a semistructured interview

measuring 27 determinants on a 5-point scale. The determinants are subdivided into 4 domains: determinants associated to the innovation, the adopting person, the organization, and the sociopolitical context (ie, whether the activities and procedures of Cognitive Adaptation Training are in accordance with legislation and regulations). The MIDI was developed based upon a systematic review and a Delphi study among implementation experts, thereby ensuring content validity. Although psychometric properties have not yet been established, other studies in mental health administering the MIDI among health care professionals showed an internal consistency (Cronbach α) between .61-.93 [32,33].

Experimental Condition: Round 2

The first author visited the individual teams of the experimental condition a second time after the process evaluation to provide support to the teams in the implementation activities. If new implementation strategies needed to be applied, this was discussed with the local champions. A second process evaluation was administered 6 months after the start of the implementation. Following this second process evaluation, an advisory report was set up by the first author in collaboration with the local champions in which suggestions for implementation strategies were described. The purpose of the advisory report was to provide suggestions to the local champions and the rest of the team that would help to better implement Cognitive Adaptation Training in their daily working routine. By providing them with advice, rather than physically guiding them as in the first 2 phases, we aimed to allow the teams to become more autonomous and inventive in setting up implementation strategies in the face of future barriers. Furthermore, as the advisory report was drafted based upon the results of the process evaluation, the advisory report in itself was an implementation effort as we informed the teams on the progress of implementation. The researchers and the teams in the implementation condition were not in contact with each other in between the advisory report and the follow-up assessment (T3) to discuss implementation problems or implementation activities.

Outcomes and Measures

The outcome evaluation of the implementation program was based upon the RE-AIM framework [18]. This framework describes implementation success as a combination of reach, intervention effectiveness, adoption, implementation, and maintenance. In addition to the instruments that were selected based upon the RE-AIM framework, the questionnaires described in Assessment of Barriers and Facilitators and Process Evaluation sections were also used as outcome measures.

Reach was measured by the proportion of service users who received Cognitive Adaptation Training in each team and by comparing these numbers between the 2 treatment arms. To detect possible selection bias, the representativeness of service users who received Cognitive Adaptation Training in the intervention condition was determined by comparing their demographic variables to those of the service users in the entire study population.

Intervention effectiveness refers to the clinical improvement of the service users as a result of Cognitive Adaptation Training. The effectiveness of Cognitive Adaptation Training was determined by the improvements of the service users on daily functioning and cognitive functioning measured by 2 observational questionnaires: Life Skills Profile [34] and the Nurses' Observation Scale of Cognitive [35]. The Life Skills Profile consists of 39 questions on a 4-point scale (total score range: 39-156) and measures various aspects related to daily life activities: self-care; nonturbulence; social contact; communication; and responsibility. Results on the Life Skills Profile from the previous research [7] evaluating the effectiveness of Cognitive Adaptation Training revealed a significant effect for people receiving Cognitive Adaptation Training in addition to treatment as usual compared to treatment as usual only. The Nurses' Observation Scale of Cognitive Abilities [35] measures cognitive functioning and includes 39 items (total score range: 0-121) subdivided into 8 cognitive domains (subscales): attention, perception, memory, orientation, higher cognitive domains, thoughts, language, and praxis. The Nurses' Observation Scale of Cognitive Abilities is scored on a 4-point scale. Both the Life Skills Profile and Nurses' Observation Scale of Cognitive Abilities have good psychometric properties [36,37].

Adoption was defined as the representativeness of participating sites and intervention agents that adopted the intervention. It is measured at the system level by comparing the determinants of the MIDI across the 2 implementation conditions.

Implementation refers to the Cognitive Adaptation Training specialists' fidelity to the elements of Cognitive Adaptation Training as described in the Cognitive Adaptation Training protocol. The level of implementation was measured by the CAT Fidelity Scale.

Maintenance, or sustainability of the intervention was evaluated at follow-up, which was 6 months after the final contact with the implementation researchers. Maintenance was measured by comparing the differences between postmeasurement and follow-up of the abovementioned constructs (reach, intervention effectiveness, adoption, and implementation) between the 2 conditions.

Demographic information was obtained from both service users (birth year, gender, nationality, level of education, main diagnosis, age of onset) and the team members (date of birth, gender, nationality, level of education, years working experience, years working with the target group population, years working in current team) and was completed at baseline assessment.

Recovery-Oriented Practice

To measure the extent to which the teams provided recovery-oriented care in general, the translated Dutch version of the Recovery Oriented Practices Index [38] was used. It consists of 26 items on a 5-point scale (total score range: 0-130), measuring 8 domains of recovery-oriented care. The domains include meeting basic needs; comprehensive services; network supports and community integration; service user involvement and participation; strengths-based approach; customization and

choice; self-determination; recovery focus. The Recovery Oriented Practices Index was administered and scored by one of the researchers through an interview with the management of the rehabilitation teams. The construct validity of the Recovery Oriented Practices Index has been reported as good [39].

Sample Size

Sample size was estimated for both intervention effectiveness of Cognitive Adaptation Training (based upon the Life Skills Profile) as well as implementation effectiveness (based upon the outcome variable Reach). To ensure enough power for both purposes, we used the highest estimated sample size. For intervention effectiveness, with a mean difference of 6 points on the Life Skills Profile (considered clinically relevant according expert opinions) and a standard deviation of 10.5 (based on the effectiveness trial of Cognitive Adaptation Training in residential settings [7], 78 service users needed to be included to detect significant improvements on the Life Skills Profile with a power of .8 and a significance level of .05. Accounting for a conservative attrition rate of 20%, a minimum of 98 service-users needed to be included in the study. For implementation effectiveness, based upon previous implementation research in the Netherlands [16], the expected proportion of service users reached in the experimental condition was set at 30%, compared to 5% in the control condition. To be able to detect a difference between conditions in proportion of service users reached with Cognitive Adaptation Training (with α=.05 and a power of .8), both groups (control and experimental) required a caseload of at least 34 service users each.

Statistical Analyses

To measure demographic and baseline differences between the 2 groups, chi-square tests will be performed for categorical variables, and 2-tailed independent sample *t* tests will be performed for continuous variables using SPSS software (version 24.0; IBM Corp). To assess the implementation effectiveness over time (outcome evaluation), mean differences in outcomes between the 2 arms on the dimensions of the RE-AIM framework were assessed using multilevel modelling [40]. A 3-level model will be built with team (level 3), subjects (level 2), and assessment (level 1) entered as levels. Significance of the fixed regression effects will be tested using the 1-tailed independent sample *t* test (=.05). The content of the focus group meetings and process evaluations will be transcribed verbatim and analyzed using a combined approach of inductive and deductive thematic analysis in ATLAS.ti (version 8.0; ATLAS.ti Scientific Software Development GmbH).

Ethics and Data Privacy

The Medical Ethics Review Committee of the University Medical Center Groningen in the Netherlands (file number: M17.220439) concluded that the study did not fall within the scope of the Medical Research Involving Human Subjects Act and waived the requirement for ethical approval. The study was conducted in compliance with local and international ethical standards and the Declaration of Helsinki [41]. Additional documents related to the ethical protocol can be requested from the corresponding author. The final and complete data set will only be accessible to members of the research team. Procedures regarding data management are in compliance with the Research Data Policy of the University of Groningen.

Results

The study was funded in April 2018 by a grant of the Foundation for Support (*Stichting tot Steun* VCVGZ; grant number: 247). The study was retrospectively registered at the Netherlands Trial Register in September 2019 (NL7989). Data collection occurred between November 2018 and January 2020. In total, 21 teams of 4 mental health institutions agreed to participation. Data analysis is ongoing, and the results are expected to be published in December 2020.

Discussion

The implementation of evidence-based practices in mental health care has received increased attention over the last few years. For example, funding agencies now request a detailed description of plans for implementation and dissemination activities to translate the research findings into clinical practice. Yet to date, evidence-based practices are rarely available for people with severe mental illness in various treatment settings [15,16]. One such evidence-based practice is Cognitive Adaptation Training, which aims to enhance independent daily functioning in people with severe mental illness. To improve implementation success of Cognitive Adaptation Training in clinical practice, a novel implementation program was developed that uses a systematic approach while considering context dependent factors. In this study, the effectiveness of this implementation program will be assessed. An effective implementation program will enhance the implementation success of Cognitive Adaptation Training on a broad scale and hence facilitate recovery in a group of people that is relatively underrepresented in the scientific literature.

An important strength of this study is its comprehensive design. The recruitment of departments in multiple mental health care organizations across The Netherlands increases the representativeness and the generalizability of the results. An additional strength in the study design is the use of mixed methods. This design enables us to explore and obtain an in-depth understanding of the processes involved during implementation, which will help to interpret the results at the end of the study. Furthermore, using both quantitative and qualitative measures to identify tailored strategies for implementation provides a more comprehensive perspective than either approach alone. By gathering this information on multiple levels of care (service user level, provider level, manager level), the Cognitive Adaptation Training program ensures a holistic approach in which all stakeholders' needs and perspectives are considered. Another strength of this study is that the implementation program is tailored to the needs of the individual teams. By matching the implementation strategies to the team and organizational context and collectively deciding which implementation strategies are acted upon and which strategies need reconsideration, rather than adopting a

one-size-fits-all approach, we aim to increase the implementation success.

We do not include cognitive performance in service users as an outcome measure. Given that we demonstrated cognitive improvements related to Cognitive Adaptation Training in another recent multicenter randomized controlled trial [7], one might consider this a minor limitation in this study. However, as it is not the goal of Cognitive Adaptation Training to improve cognition, but rather to bypass cognitive impairments, cognition is not included as a primary outcome measure in the aforementioned multicenter randomized controlled trial. Thus, since we focus upon implementation effectiveness in this study and to relieve the burden for service users, we felt it would be appropriate to use an observational questionnaire measuring cognition as a valid substitute. Although we did not find improvements on all cognitive domains in the randomized controlled trial evaluating the effectiveness of Cognitive Adaptation Training, the Nurses' Observation Scale of Cognitive Abilities predominantly measures domains related to frontal lobe functioning (thought processing, orientation, memory, attention, and consciousness). Since our previous study [13] on Cognitive Adaptation Training showed significant effects in visual attention and executive functioning, we considered it to be justified to include a measure that covers these domains and other cognitive domains related to frontal lobe functioning.

A second limitation to this study is the potential threat to nonresponse and selection bias. Even though the study was carefully designed to minimize the time-consuming burden of filling out questionnaires for both the health care professionals and service users, we recognize that it requires an extra effort in their already demanding day-to-day jobs. As a result, some health care professionals may not respond to the online questionnaires, causing nonresponse and selection bias. Also, as some of the included institutions showed interest in participation before the start of the study, this may influence the results and thus limit the generalizability. This should be taken into consideration while analyzing and reporting the final results.

The implementation program presented in this study can help to bridge the science-to-service gap in mental health care and may provide important information regarding facilitators and barriers to implementation for other mental health researchers and implementation scientists. Moreover, when proven effective, this implementation program may also be effective for the implementation of other psychosocial interventions or innovations in long-term psychiatric care.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer Review Report.
[PDF File (Adobe PDF File), 182 KB - resprot_v9i8e17412_app1.pdf]

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Abbreviations

CAT Fidelity Scale: Cognitive Adaptation Training Fidelity Scale
COM-B: Capability Opportunity Motivation–Behavior change
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)
DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)
MIDI: Measurement Instrument for Determinants of Innovation
RE-AIM: Reach Effectiveness Adoption Implementation Maintenance

<u>Protocol</u>

Impact of Co-Designed Game Learning on Cultural Safety in Colombian Medical Education: Protocol for a Randomized Controlled Trial

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Abstract

Background: Cultural safety encourages practitioners to examine how their own culture shapes their clinical practice and to respect their patients' worldviews. Lack of cultural safety in health care is linked to stigma and discrimination toward culturally diverse patients. Training in cultural safety poses considerable challenges. It is an unappealing subject for medical students and requires behavioral changes in their clinical practice. Game jams—collaborative workshops to create and play games—have recently shown effectiveness and engaging potential in university-level education.

Objective: The trial aims to determine if medical students' participation in a game jam to design an educational game on cultural safety is more effective than a standard lesson on cultural safety in terms of change in the students' self-reported intended patient-oriented behavior.

Methods: A parallel-group, 2-arm randomized controlled trial with a 1:1 allocation ratio will randomize 340 medical students and 60 medical interns (n=400) at the Faculty of Medicine at La Sabana University, Colombia (170 students and 30 medical interns to each arm). The intervention group will participate in an 8-hour game jam comprising (1) a preliminary lecture on cultural safety and game design, (2) a game building session where groups of students will create educational games about cultural safety, and (3) a play-test session in which students will play and learn from each other's games. The control group will receive a standard lesson, including a 2-hour lecture on cultural safety, followed by a 6-hour workshop to create posters about cultural safety. Web-based self-administered 30-item Likert-type questionnaires will assess cultural safety self-reported intended behavior before, immediately after, and 6 months after the intervention. An intention-to-treat approach will use a *t*-test with 95% CIs to determine the significance of the effect of the intervention, including within- and between-group comparisons. The qualitative most significant change technique will explore the impact of the intervention on the clinical experience of the students.

Results: Study enrollment began in July 2019. A total of 531 students completed the baseline survey and were randomized. Data collection is expected to be complete by July 2020, and results are expected in October 2020. The study was approved by the institutional review board of the Faculty of Medicine at McGill University (May 31, 2017) and by the Subcommittee for Research of the Faculty of Medicine at La Sabana University (approval number 445).

Conclusions: The research will develop participatory methods in game-based learning co-design that might be relevant to other subjects. Ultimately, it should foster improved cultural safety skills for medical students, improve the quality of health services for diverse cultural groups, and contribute to enhanced population health. Game learning may provide an innovative solution to

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a long-standing and neglected problem in medical education, helping to meet the educational expectations and needs of millennial medical students.

Introduction

Cultural Safety Training

Although cultural safety is an evolving term and lacks a formal definition [1], it is often described as a space "that is spiritually, socially, emotionally and physically safe for people; where there is no assault, challenge or denial of their identity, of who they are, and what they need" [2]. The concept originated in New Zealand to address the disconnect between the type of health care that indigenous Maori people were receiving and the culturally congruent care that they were advocating for [3].

Cultural safety has gradually gained attention because it offers a more comprehensive and respectful way to approach culture, in many settings replacing the current standard, which is cultural competence [4]. Cultural safety is distinct from cultural competence, in that it invites culturally diverse patients and their communities to co-design and evaluate culturally safe health care [1,5]. The notion of participation in health care design also differentiates cultural safety from cultural humility [6], another well-known approach to cultural diversity in health care.

The Royal College of Physicians and Surgeons of Canada will soon require all medical residency programs to provide mandatory cultural safety training [7,8]. There is, however, little research on how to implement this approach in medical education [9], and how health professionals acquire cultural safety skills is poorly understood [10].

There are additional challenges to promoting cultural safety in medical education. Educators might find cultural safety complicated to teach, and medical students might perceive it as dull or, given the altruistic tone of their chosen profession, unnecessary for them [11]. Contemporary medical training is overloaded almost everywhere, with little space to include an entirely new if very important subject. Millennial medical students—the birth cohort between 1979 and 2000 [12]—have new learning relationships with technology, creativity, and amusement that modern teaching strategies cannot overlook [13]. Finally, cultural safety training goes beyond mere knowledge acquisition; it must promote a *transformative* experience to impact students' behavior in clinical practice. The theory of transformative learning provides a framework to address these challenges [14].

Transformative Learning and Game Co-Design

Mezirow describes transformative learning as a process that changes frames of reference, "the structures of assumptions through which we understand our experiences" [14]. Frames of reference comprise habits of mind, which are habitual ways of

thinking and acting, and points of view, which are beliefs, values, and attitudes.

Mezirow argues that ethnocentrism, defined as "the predisposition to regard others outside one's own group as inferior" [14], is an example of a habit of mind. Ramsden, the Maori nurse who developed the concept of cultural safety, proposes that confronting ethnocentrism must be the first step in cultural safety training [3]. Transformative learning may, therefore, be suitable for providing cultural safety training to medical students.

Transforming frames of reference requires reflection on the assumptions upon which learners base their habits of mind and points of view [14]. In transformative learning, people become critically reflective of their assumptions through education that is participatory and interactive and through group problem solving or communicative learning [15].

Game jams provide an environment to foster learning through interacting and communicating with others [16], an essential aspect of transformative learning. These participatory events allow attendees to create games (digital or board games) in a time-constrained environment [17]. Unlike other educational approaches, game jams could offer a solution to the challenges of cultural safety in medical education by (1) engaging millennial students through a culture of creativity and learning, play testing, and idea sharing; (2) supporting a transformative process of learning-by-doing while enhancing creative thinking, problem solving, communication, and innovation; and (3) promoting transformative learning in less time, thus offering an alternative to overloaded medical curricula.

Fowler et al [16] recently found that game jam participation could improve the performance of computing students. However, we are not aware of any reported experience using game jams to train medical students. Our primary objective is to determine if medical students' participation in a game jam to design an educational game on cultural safety is more effective than a standard lesson on cultural safety in terms of change in students' self-reported intended patient-oriented behavior. Our secondary objectives are to (1) determine the impact of the intervention (game jam) compared with the control (standard lesson on cultural safety) on students' confidence in their general transcultural skills and (2) assess the impact of participation in the game jam through a narrative approach that identifies in their own words the effect of the learning on cultural safety in their clinical practice.

Methods

Trial Design

A parallel-group, 2-arm, randomized controlled trial (RCT) with 1:1 allocation will compare participation in a game jam with a standard lesson on cultural safety. The RCT will answer the following question:

- Among medical students and interns from La Sabana University, does participating in a game jam for cultural

safety training, in comparison with a standard lesson on cultural safety, result in an increased change in students' and interns' (1) self-reported intended behavior, (2) confidence in general transcultural skills, and (3) reported change in clinical practice?

Textbox 1 presents the population, intervention, contrast, outcomes, and time points components of the research question. This protocol description follows the standard protocol items: recommendations for interventional trials 2013 statement [18] (Multimedia Appendix 1).

Textbox 1. Population, intervention, contrast, outcome, and timing of the randomized controlled trial.

Population

- Undergraduate medical students and medical interns at La Sabana University in Colombia

Intervention

- Game jam aimed at fostering cultural safety in clinical practice

Contrast

- Standard lecture and workshop on cultural safety

Outcome

- (1) Cultural safety–intended patient-oriented behavior change outcomes from knowledge to action, (2) students' confidence in general transcultural skills, and (3) qualitative understanding of the change experienced by participants in their clinical practice

Timing

- Before the intervention, immediately following the teaching session, and 6 months after the intervention

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Study Setting

We will conduct the RCT at the Faculty of Medicine at La Sabana University in the municipality of Chía, Colombia. Chía is a small town located 15 km from Bogotá, the capital of Colombia. La Sabana University is a private higher education institution that has 8926 undergraduate students; 22% of these students come from a low socioeconomic level, 52% belong to the middle class, and the remaining 26% come from higher socioeconomic backgrounds [19]. Presently, there are 956 students enrolled in the medical school and 256 medical interns (n=1212) [19]. At La Sabana, the duration of the doctor of medicine program is 7 years. As part of this training, all medical students must undergo a one-and-a-half-year medical internship before graduating.

Eligibility Criteria

The inclusion criteria are as follows: (1) being a medical student or medical intern at any level of training and (2) providing informed consent. The exclusion criterion is not wanting to participate in the study.

Interventions

Game Jam

The intervention will consist of a game jam aimed at creating a low-technology prototype of an educational game to foster cultural safety in medical education. Groups of 5 or 6 students or medical interns will create an educational game prototype from scratch. We will follow the 6-step game jam protocol based on Macklin's *planning your game jam* guidelines [20] (Figure 1):

(1) Preliminary lecture session (1 hour): this comprises a 30 min lecture on cultural safety, based on a cultural safety curriculum co-designed with local community members knowledgeable about cultural and traditional health practices [21], and a 30 min lecture on game design.

(2) Opening ceremony: game jams usually start with opening comments from the host. We will welcome the participants and share the agenda and rules of the game jam.

(3) Game building (4 hours): this includes 6 steps:

Figure 1. Game jam protocol.
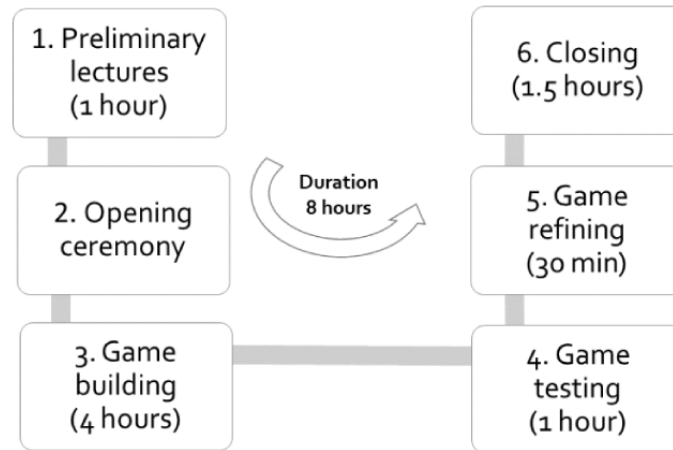
- We will invite participants to write a brief narrative of when they witnessed (or heard of) discrimination or disrespect against a patient because of their traditional health practices and the consequences of this discrimination.
- Participants will share their brief stories within their game jam group to discuss and select the story (based on consensus) that best describes discrimination or disrespect against a patient. A key component of this step is to imagine and brainstorm the fullest range of possible consequences—from trivial to life-threatening.
- Participants will anonymize the selected story as that of a fictional medical student who has to undergo a primary care clinical rotation in a local community where she or he faces intercultural tensions in clinical practice. The participants will then convert this narrative into a game and define a set of rules, rewards, and penalties.
- Participants will discuss the factors that hypothetically lead the medical student to be discriminatory or disrespectful toward his or her patient in the story. After the discussion, each group will select and integrate 5 to 10 factors into the game. The challenge here is that players have to become aware gradually that these factors can lead to disrespect or discrimination against culturally diverse patients as they play the game. Concretely, the jammers will be expected to add factors such as the hegemony of evidence-based medicine, colonization and ethnocentrism, and other factors defined in the co-designed cultural safety curriculum.
- Participants will discuss what can be done to address each of the selected factors that contributed to the disrespect or discrimination experienced by the patient in the narrative. Each group will select and integrate 5 to 10 actions to promote dialogue and respect toward culturally diverse patients in clinical encounters into their game. The *challenge* is that players learn to respect patients who use traditional health practices in clinical encounters as they play the game.
- The students will discuss and identify ideas to start working with the patient as a team in the health care decision-making process. This involves engaging in dialogue with the patient to invite them to bring their cultural and traditional practices to inform the health care decision-making process. Traditional practices will be predefined by our co-designed curriculum [21]. The *challenge* is that players of the game

have to learn how to work with traditional medicine users to make health decisions that are culturally safe jointly.

(4) Game testing (1 hour): groups will learn from each other's solutions, ideas, and resources, thus strengthening the cultural safety learning process. At least one member of each group will stay at their workplace to present their game. The remaining students of the group will rotate to play the games created by other groups, thus ensuring that participants from all groups will play at least two additional games. Before the end of the session and using Google Forms (Google LCC), we will ask the students to evaluate other groups' games in different categories aligned with each of the challenges.

(5) Game refining (30 min): after playing and testing other teams' games, each group will have new ideas for refining their own game. Groups will then return to their workplace and apply lessons to improve their own game. Each group will fill a form to register their game on Google Forms.

(6) Closing (1 hour 30 min): we will bring the full group together for the final presentation of the games. Each group will have to provide a brief description of their game and discuss how they solved each of the game building challenges. We will facilitate this session to highlight the underlying concepts of cultural safety. Finally, we will award prizes in 3 different categories aligned with each of the challenges.

Control Group

The control group will receive a 1 hour 30 min lecture on cultural safety in medical education by an expert in cultural safety. The lecture will be a standard lesson using PowerPoint slides and will cover the same key concepts used in the game jam, including (1) definition of cultural safety, (2) consequences of cultural tensions in health care, (3) self-awareness, (4) Colombian cultural health practices, and (5) respect for culturally diverse patients. The lecture will be based on our co-designed curriculum [21]. The session will be followed by a 15-min period to make comments and to ask questions and a 15-min break.

After the break, the students will participate in a 6-hour workshop based on cultural safety selected readings. Groups of 5 or 6 students or medical interns will answer 10 open-ended questions based on the lecture and the readings. They will create

a poster to graphically display their responses to other students. Similar to the game jam session, we will split each group and encourage a rotation process where participants from all groups will learn from at least two additional posters. Before the end of the session and using Google Forms, we will ask the students to evaluate the other groups' posters in 4 different categories: creativity, coverage of the topic, graphics and pictures, and layout and design.

In the closing session, the best groups will present their posters to the group at large. In this session, we will unpack and highlight the key concepts of cultural safety. Similar to the game jam session, we will award prizes in the 4 evaluated categories. Similar to that in the intervention group, the duration of participation in the control group will be 8 hours.

Criteria for Discontinuing or Modifying the Allocated Interventions

Participants are free to withdraw from the trial at any point. We will collect reasons for withdrawal from subjects who drop out of the trial.

Participants will not be able to switch groups once they have been randomized to the intervention or control arms, even if they request to do so. Using participants' lists, the facilitators will ensure that participants remain in their designated groups.

Strategies to Improve Adherence to Intervention

We will recruit 10 to 20 game jam facilitators to support participants and to ensure that all groups are able to meet the challenge of each step of the game jam protocol. The facilitators will be final-year medical students or medical interns interested in cultural safety research or game-based learning. We will train the facilitators for 1 month before the game jam to ensure that they will have the skills to support the game jam participants in their learning process successfully.

We will record attendance to the intervention and control arm activities. Along with the names of the participants, we will record the date, hour, and their signatures.

Relevant Concomitant Care and Interventions That Are Permitted or Prohibited During the Trial

Contamination is a concern of parallel-group RCTs in education. This occurs when individuals who are receiving the intervention *leak information*, which influences results in the control group. This usually reduces the measured intervention impact, making it more difficult to find a significant difference between groups [22].

In this study, we cannot guarantee that contamination will not occur. We will minimize this risk by asking students to avoid real-time communication with their peers (eg, using their cell phones), and we will conduct intervention and control activities simultaneously in different buildings. The groups will have different lunch breaks.

Outcomes

Primary Outcomes

The primary outcome is the self-reported intended patient-oriented behavior of students. This derives from the

response to the statement, "I will never be open to include my patients' cultural beliefs and practices in the health decision-making process." We are assessing students' *intended* behavior instead of actual practice/action. Our primary concern is sustained intention 6 months post intervention.

A supplementary analysis will examine the primary outcome in the context of a results chain using the conscious knowledge, attitudes, subjective norms, change intention, sense of agency, discussion, and behavior/action (CASCADA) model of planned behavior [23]. The model includes the following variables:

- *Conscious knowledge* was the response to the statement "I consider the cultural beliefs of my patients are not important for health decision-making."
- *Attitude to cultural safety* was derived from the statement "It is not worth considering the cultural beliefs of my patients to improve their health."
- *Subjective norm* used the statement "Although many physicians disapprove of cultural beliefs, I think that these beliefs could improve my patients' health."
- *Intention to change* was derived from the statement "I will never be open to include my patients' cultural beliefs and practices in the health decision-making process."
- *Agency* was the response to the statement "I feel prepared with the knowledge and skills to prudently incorporate my patients' cultural practices in the health decision-making process."
- *Discussion* derived from the response to the statement "I will discuss cultural safety with other students and physicians so they can prudently incorporate their patients' cultural practices in the health decision-making process."

Agency and discussion replace perceived behavior in the conventional theory of planned behavior [24]. Agency involves both self-efficacy and collective efficacy. The CASCADA model includes discussion as an additional element in the results chain toward behavior change [25]. Action as a clinician, of course, cannot be known while the student is still studying. We will extrapolate this in a supplementary analysis following the successful use of the CASCADA model to explore dengue prevention behavior [25].

Secondary Outcomes

Secondary outcomes comprise (1) students' confidence (transcultural self-efficacy) in their general transcultural skills and (2) qualitative understanding of the impact of the intervention in the clinical practice of medical students and medical interns through the most significant change technique. We will assess transcultural self-efficacy at baseline, immediately following the teaching session, and 6 months post intervention, and we will conduct a qualitative assessment in both groups 6 months after the intervention.

Output

Each student group of the intervention arm will create a co-designed low-technology prototype of a serious game to foster cultural safety in medical students. Some of these prototypes may serve as blueprints for future fully developed games or as input for future educational videogames.

In addition to the quantitative outcomes of the RCT, we will use the qualitative most significant change narrative technique [26] to collect and analyze stories of change from the medical students 6 months after the intervention. This technique will allow us to capture meaningful changes in the students' clinical

practice, which may not be apparent from the quantitative evaluation.

Participant Timeline

Figure 2 shows the consolidated standards of reporting trials flow diagram of the RCT [27].

Figure 2. Consolidated standards of reporting trials flow diagram of the randomized controlled trial.
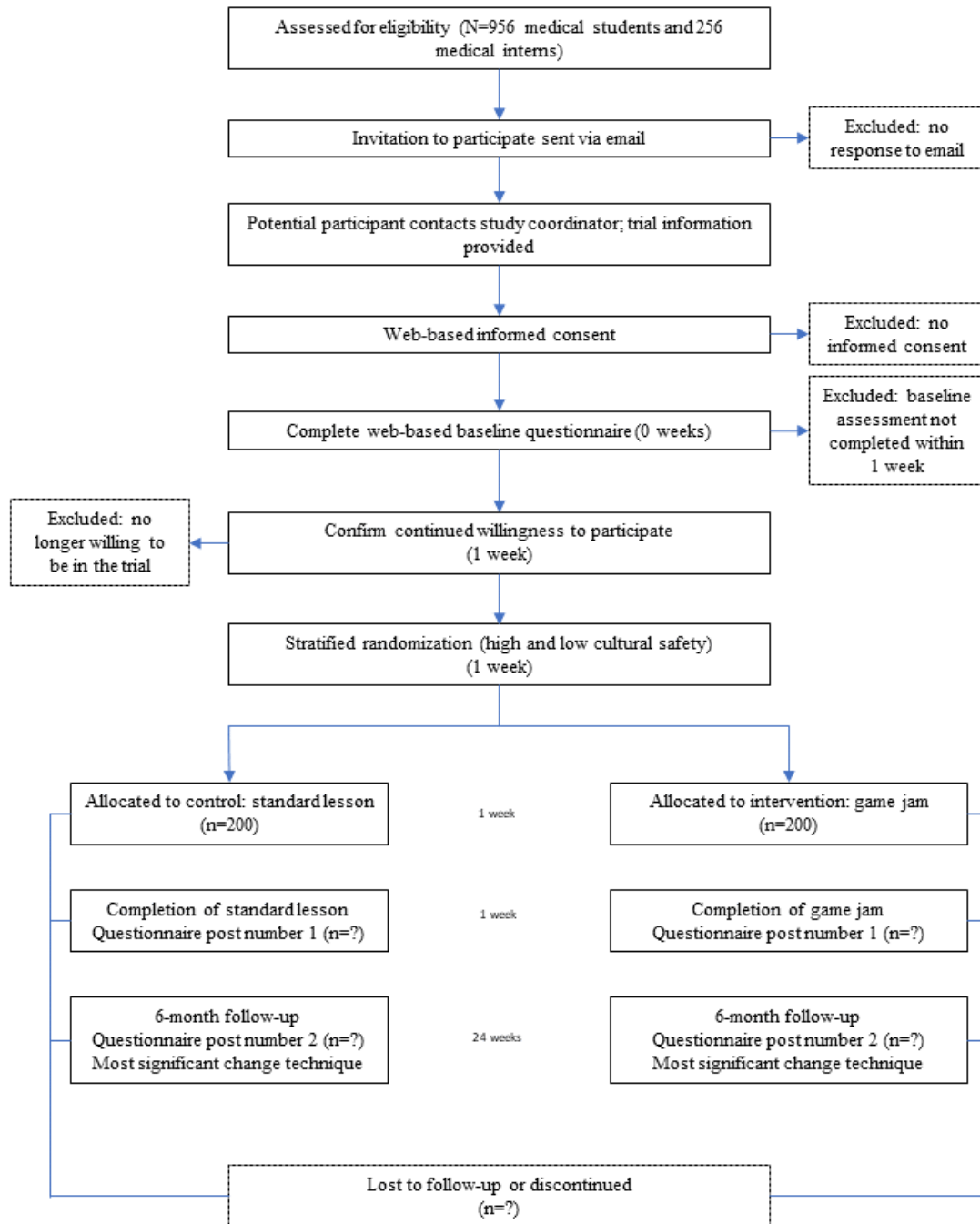
Sample Size

Our pilot RCT found an effect size (Cohen *d*) of 0.25 between the intervention and control arms after the teaching session (mean in the game jam group 26.9, SD 4.0; mean in the control group 25.9, SD 4.0). Using the *pwr* package in R [28], a group

size of 199 participants in the game jam group and 199 participants in the control group (sample size=398) will allow detection of an effect size of 0.25, with a 2-sided α of .05 and a power of 0.8 (Figure 3). As we observed considerable contamination in the pilot RCT, 0.25 is a conservative estimate of effect size.

Figure 3. One-arm power curve for sample size calculation.
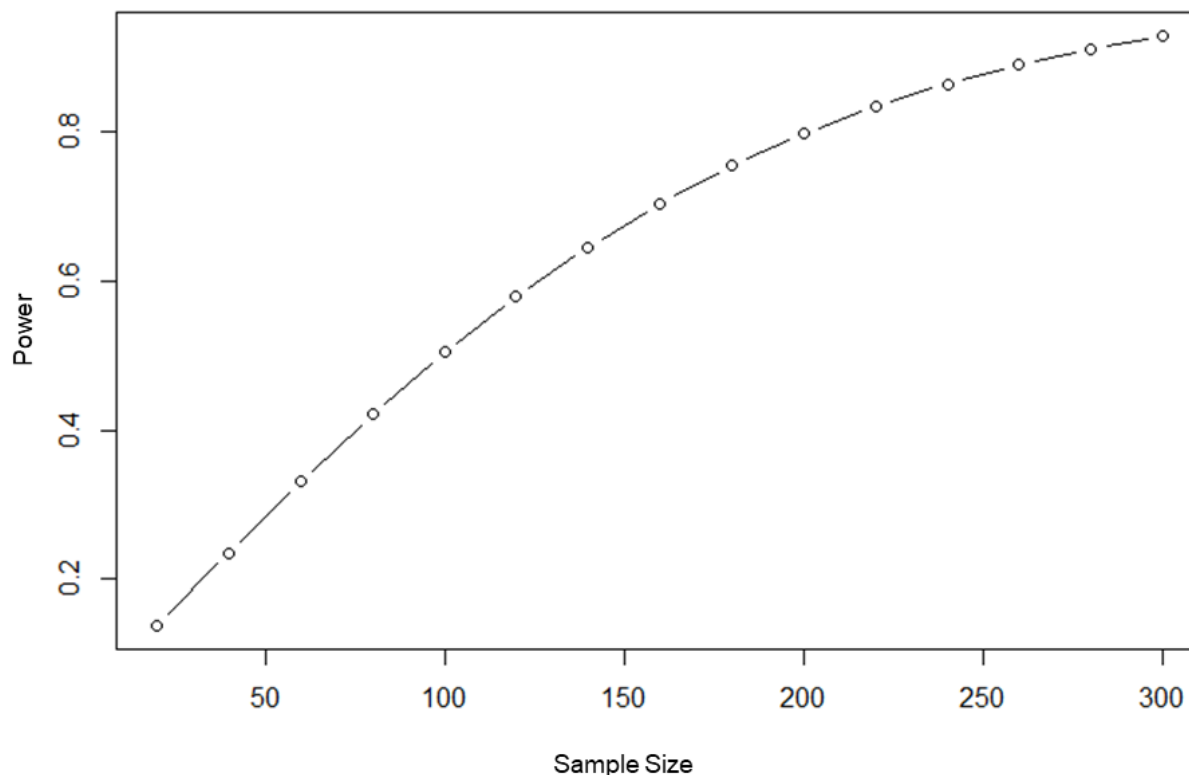
Recruitment

We will contact the medical students and medical interns using La Sabana University's mailing lists and email invitations for voluntary participation in the project. For those willing to participate, we will send further information about the project and the date and place of the intervention. We will ask interested students to complete the web-based informed consent and baseline questionnaire 1 week before the RCT.

Allocation

A potential source of bias in our study is a possible imbalance in the level of cultural safety training between the intervention and control groups before the intervention. The reason for this issue is that in Colombia, around 40% of the population uses cultural and traditional practices to maintain their health [29]. Therefore, some students will be familiar with traditional health practices, probably making them more likely to embrace the cultural safety approach compared with students not familiar with these practices.

To address this potential bias, we will use stratified randomization based on the cultural safety score at baseline. On the basis of the preliminary results of the baseline survey, we will split the group of medical students into 2 groups: low and high level of cultural safety knowledge. Computerized randomization will allocate the students either to the intervention or control arm, and we will use equal allocation between treatment arms. The study coordinator will be responsible for generating the allocation sequence, enrolling participants, and assigning participants to interventions.

Data Collection Methods

Data Collection

We will collect quantitative data at 3 time points: baseline, immediately after the intervention, and 6 months after the intervention, 'and will collect the narratives of change only 6 months after the intervention. Participants will enter quantitative data using mobile devices and SurveyMonkey self-administered questionnaires. Similarly, they will upload their stories of change using a predesigned format on Google Forms. We report our web-based instruments in accordance with the checklist for reporting results of internet e-surveys [30] (Multimedia Appendix 2).

Instrument and Quantitative Data to Be Collected

To the best of our knowledge, there are no validated research instruments to measure cultural safety outcomes in health care providers. A recent systematic review [31] exploring instruments to assess cultural competence (and aligned concepts) identified 10 instruments. All of them were self-administered and based on respondent perceptions. Half of these instruments (5/10) measured cultural competence; none of them were designed to measure cultural safety.

Our recently published scoping review identified that the transcultural self-efficacy tool—multidisciplinary healthcare provider version (TSET-MHP) has been used to assess the effectiveness of game-based learning interventions to promote cultural competence [32]. Researchers report a growing body of evidence supporting the validity and reliability of the instrument [33]. The instrument assesses cognitive, practical, and affective learning dimensions that can be categorized within the classic knowledge, attitudes, and skills behavior change outcomes.

Brascoupé points out that cultural competence provides a foundation for cultural safety [34]. Ramsden sees cultural safety training as a dynamic process moving from cultural awareness to cultural sensitivity to cultural safety [3]. Following this rationale, we will use a 30-item instrument comprising 3 parts. The first part (5 items) will explore the sociodemographic characteristics of the students. These includes sex, age, level of training, place of birth, socioeconomic status, and traditional health practices used in the family. The second part (15 items) will be based on the Likert-type TSET-MHP and will explore transcultural self-efficacy.

For the third part of the instrument (cultural safety), we developed a Likert-type preliminary version based on our CASCADA variables (*Primary Outcomes* section) and tested it for validity and reliability in our pilot RCT.

Validity and Reliability

Using data from our pilot RCT, we followed the process proposed by Jeffreys [35] to improve the validity and reliability of the third part of our instrument. In the pilot study, the questionnaire included the following open question: *How can we improve this instrument?* An inductive thematic analysis [36] of responses identified suggestions to adjust our survey. We shared the adjusted version of the instrument by email with 2 general practitioners, 1 medical intern, 6 medical students, and 4 cultural safety experts. We adjusted the instrument according to their comments and agreed on the content validity of the instrument by consensus.

To increase the construct validity of our instrument, we used the contrasted group approach, which explores the difference between 2 separate groups [35]. To increase the predictive validity of our instrument, we looked at the score difference between 2 time points [37]. Reliability explores the degree of accuracy and consistency in measurement. Using R Studio v1.1.419, we calculated Cronbach α [38] to determine the internal consistency of our instrument. As our instrument was short (<10 items), we expected a value of >0.5 [39]. We complemented the reliability exploration using the test-retest method to explore the stability of the instrument [35]. We report the validity and reliability results of our instrument in the pilot RCT, which is not yet published.

Qualitative Data to Be Collected

To explore students' stories of change after cultural safety training, we will use the most significant change approach, which is a narrative technique that allows participants to communicate changes that are most meaningful to them [40]. Using a predefined format in Google Forms, we will ask participants to write down and enter their stories based on the following instruction: "Please, tell me a story describing what you think is the most significant change in your clinical practice as a result of your participation in the activity [game jam or standard lesson] 6 months ago."

The instructions will clarify that participants should feel free to write down stories of negative changes or to say that they did not experience any change at all. Only medical students involved in clinical practice and medical interns (third to seventh year of medical school) will be invited to participate in this part of the RCT.

Methods to Maximize Completeness and Quality of Data

The study coordinator and facilitators will be physically present while collecting the data at each time point to ensure the completeness of data. In addition, we will use several validation options to increase the quality of the data: specific number range, specific character range, date validation, email address format, and prompts that alert participants when they enter incomplete or invalid answers.

In this study, the familiarity of millennial and generation Z medical students with technology and computer-based education supports using web-based questionnaires should decrease social desirability bias [41]. Assured of anonymity, respondents should be less concerned about what others may think about their responses, including peers and professors [42]. Data reliability in web-based questionnaires is reportedly equal to or better than that in traditional paper-based approaches [43]. Examples include data on self-reported perceived health status, oral contraceptive use, and smoking and alcohol use. Web-based questionnaires are also faster to complete and are typically cheaper than traditional approaches, making them ideal for our research.

Methods for Ensuring Secure Data

SurveyMonkey and Google Forms responses are stored in a worksheet that can only be accessed through an account log-in. Data transmission uses the secure sockets layer to encrypt information during transport. After downloading the data, we will delete it from the SurveyMonkey and Google Forms. We will store the data securely for 7 years and then destroy them in accordance with Centro de Investigación de Enfermedades Tropicales (Tropical Disease Research Centre) guidelines for security, storage, and eventual destruction of data records [44].

Methods for Analyzing Data

Primary Analysis

Using an intention-to-treat approach, we will perform a *t* test with 95% CIs to determine the effect of the intervention on change intention between parallel intervention and control groups 6 months after the intervention. We will assess the influence of this primary outcome in the results chain using the CASCADA approach developed by Andersson et al [25]. Transitive closure estimates the net influence of each element of the results chain on each other and on the final outcome—behavior change in practice [45].

Secondary Analysis

We will examine the residual impact of key baseline and sociodemographic baseline characteristics, including clustering (workgroup during the intervention or control activities), on the primary outcome. We will examine the residuals for the model assumptions and goodness of fit. This will rely on the Mantel-Haenszel approach adjusted for cluster and unconditional linear regression.

Supplementary Analysis

We will explore other parameters of impact, including within-group comparisons (baseline and postintervention 1 and 2) and between-group comparisons (treated versus control immediately postintervention). We will consider possible interactions with previous cultural safety training, family use of traditional medicines, and social class of participants. Planned subgroup analyses include gender, age, and social class, also using generalized linear mixed modeling with cluster as a random effect. All statistical tests will be 2-sided at a .05 level of significance. The Bonferroni method will adjust the level of significance for testing for secondary outcomes to maintain the overall level at α .05. We will express results as odds ratio/relative risk reduction for binary outcomes, standard errors, corresponding 2-sided 95% CIs, and associated P values.

Missing Data

There is no reason to expect differential missing data between game jam and standard lesson groups. We will document missingness and analyze missing data using Amelia II [46] to impute values for missing data with an expectation-maximization algorithm for the primary outcome. Estimates will reconcile data from 10 imputed datasets using Rubin's approach [47] in the R package Zelig [48]. In addition, we will provide an attrition diagram (eg, the proportion of participants completing the surveys in each group plotted over time) [49] demonstrating the engagement of participants over time.

Nonstatistical Methods

Students will enter their narratives of change on the web. Using ATLAS.ti 8, 2 research assistants will individually analyze the transcripts following a deductive thematic analysis approach. In a deductive analysis, a theory aligned with the researchers' interest drives the data analysis [36]; we will use the steps described by the CASCADA model to identify themes of change in the stories.

Ethics

This RCT applies the ethical principles in the tri-council policy statement [50] and was approved by the institutional review board of the Faculty of Medicine at McGill University (approval number A05-B37-17B) and by the Subcommittee for Research of the Faculty of Medicine at La Sabana University (approval number 445). We will explain the confidentiality and anonymity mechanisms and the voluntary nature of participation and obtain informed consent from participants before the study.

The facilitators will ensure that each participant has signed a web-based informed consent form before proceeding with any research activity. They will be available to explain the purpose of the study, potential risks and benefits, the confidentiality of responses, and the respondents' rights to not answer certain questions or to end their participation in the study.

Results

Study enrollment began in July 2019. A total of 531 students completed the baseline survey and were randomized. Data collection is expected to be complete by July 2020, and results

are expected in October 2020. The study was approved by the institutional review board of the Faculty of Medicine at McGill University (May 31, 2017).

Discussion

This will be the first medical education RCT using a game jam as an educational intervention. The focus of game jams to date has been on their products, which are generally video games. Our proposal is to explore the transformative engagement occurring as a result of participating in a game jam.

Answering our research question will advance the current knowledge on game jam research and participatory design in game learning. More importantly, implementing this project will contribute to the exploration of new strategies to solve the challenges of cultural safety training in medical education, taking into consideration the time pressure in medical studies and the expectations and needs of millennial medical students.

Some have recently advocated for the need to promote cultural safety rather than cultural competence [51]. To the best of our knowledge, this will be the first initiative using the cultural safety approach in South America. Similarly, cultural safety has been traditionally restricted to the indigenous context [34], and this will be one of the first experiences to apply cultural safety in a non-Indigenous setting.

Benefits from this project include medical students gaining broader tools for their future work, including openness and dialogue about cultural and traditional health practices. This aspect will be especially relevant for them as most Colombian medical students must work for at least 1 year in a rural area as part of their compulsory 1-year return service.

Long-term potential benefits derived from the project include enhanced quality in Colombian health services, improved reputation of health institutions (higher patient satisfaction, better physician-patient relationship, and better patient adherence), and reduced health disparities among culturally diverse patients in Colombia. Assessing these outcomes is, however, outside the scope of our study.

Challenges

We recognize several challenges. The participatory design of serious games is an emerging field, and evidence of its impact is scarce [52]. There are no agreed methodological frameworks or consensus on operational definitions. This could lead to unexpected challenges, hindering the research process. To address this issue, we conducted a pilot RCT with 79 final-year medical students to explore the acceptability and feasibility of cultural safety training through co-designed game learning, master the skills required to conduct a full-scale co-designed game learning session, pilot research methods and procedures, explore the validity and reliability of our research instrument, and identify logistical problems that might hinder the full-scale study. This helped us to understand and solve, in advance, some of the challenges. We will publish the results of the pilot RCT soon.

It is likely that only students interested in cultural safety, game learning, or research will agree to participate in the study. We

will implement measures suggested by Kahan et al [53] to prevent self-selection bias in our study. We will use computerized randomization, and all students will have equal probability to be randomized to the intervention or control arm. Although blinding is nearly impossible in RCTs applied to education research, the students will not be aware of the allocation sequence or what group they were allocated to. They will only have knowledge about the auditorium that each of them should attend on the day of the intervention. Our facilitators will prevent students from deliberately switching their allocation status. Finally, 5 facilitators in each study arm site will ensure that participants remain in their designated groups (game jam or standard lecture).

Some argue that the reproducibility of educational interventions is hard to ensure because of the *specific teacher effect* where the results of an intervention stem from the skills of a particular teacher [54]. To maximize the reproducibility and generalizability of our intervention, we will follow the recommendations provided by the *British Medical Journal* [55]. This involves describing the intervention rigorously enough to allow its reproducibility and scrutiny in the future. We will report details about the teachers (eg, background, years of experience, and fields of expertise) and the teaching interventions (duration, education content, and pedagogical approach).

In this project, we will assess education-related outcomes based on the theory of planned behavior. Experts in cultural safety training recommend, however, the use of patient-related outcomes such as evaluations of care, health outcomes, involvement in care, and health behaviors to assess cultural safety interventions [56]. Assessing patient-related outcomes would require a more complex approach that goes beyond our logistical and economic capacity. The impact assessment, however, will include a qualitative understanding through the most significant change evaluation. This will document the narratives of change in the clinical practice of medical students.

The findings of this project will be specific to the Colombian cultural context. In Colombia, exploring ethnocentrism and cultural safety is simplified by the widespread use of traditional health practices [29]. In other settings, where cultural and traditional health practices are not widespread, this approach will be less relevant, and it might be necessary to confront ethnocentrism in a more abstract way or through other stigmatizations.

Acknowledgments

Authors' Contributions

This study is part of the PhD work of JP. NA is the supervisor, and AC is the cosupervisor of JP. NA is the principal investigator, and JP is the study coordinator. NA conceived and advised on the development of the study. AC provided feedback on drafts of the paper. JP drafted this paper, and all authors adjusted it. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Standard protocol items: recommendations for interventional trials checklist of the study protocol.
[DOC File , 147 KB - resprot_v9i8e17297_app1.doc]

Multimedia Appendix 2
Checklist for reporting results of internet e-surveys.
[DOCX File , 23 KB - resprot_v9i8e17297_app2.docx]

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Abbreviations

CASCADA: conscious knowledge, attitudes, subjective norms, change intention, sense of agency, discussion, and behavior action
RCT: randomized controlled trial
TSET-MHP: transcultural self-efficacy tool—multidisciplinary healthcare provider version

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<u>Protocol</u>

Transdiagnostic Risk and Protective Factors for Psychopathology in Young People: Systematic Review Protocol

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Abstract

Background: Mental and substance use disorders are among the leading causes of burden of disease worldwide, with risk of onset peaking between the ages of 13 and 24 years. Comorbidity is also common among young people and complicates research, diagnosis and assessment, and clinical decision making. There is increasing support for empirically derived models of psychopathology that overcome issues of comorbidity and provide a transdiagnostic framework for investigating the specificity and generality of risk and protective factors for psychopathology.

Objective: This systematic review aims to identify transdiagnostic risk and protective factors for psychopathology in young people by synthesizing and evaluating findings from research investigating empirically based models of psychopathology.

Methods: Searches will be conducted in Medline, EMBASE, and PsycINFO databases. Reference lists of selected articles will also be hand searched for other relevant publications. All studies will be screened against eligibility criteria designed to identify studies that examined empirical models of psychopathology in relation to risk and/or protective factors in young people with a mean age between 10 and 24 years. Study quality will be assessed using the Joanna Briggs Institute Critical Appraisal Checklists for Cohort Studies and Analytical Cross-Sectional Studies. Findings will be summarized in a narrative synthesis, and a meta-analysis will be conducted if sufficient data are available.

Results: This review is ongoing. At the time of submission, full-text screening was completed, and hand searching of selected articles was underway. Results are expected to be completed by the end of 2020.

Conclusions: This protocol is for a systematic review of evidence for transdiagnostic risk and protective factors associated with empirically based models of psychopathology in young people. To our knowledge, the critical synthesis of this evidence will be the first to date and will provide a better understanding of the factors that contribute to the onset and maintenance of psychopathology in young people. Insights drawn from the review will provide critical new knowledge to improve the targeting of interventions to prevent or reduce mental health problems.

Trial Registration: This systematic review is registered with PROSPERO (CRD42020161368) and is available via Open Science Framework.

International Registered Report Identifier (IRRID): DERR1-10.2196/19779

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Introduction

Mental and substance use disorders are among the leading causes of burden of disease worldwide, and the mortality and morbidity of these disorders have not declined since 1990 [1]. These disorders often emerge during adolescence, with risk of onset heightened between the ages of 13 and 24 years [2,3]. A number of factors have been identified that increase (risk factors) or decrease (protective factors) the likelihood of young people experiencing mental health problems. Risk and protective factors help identify young people most at risk of developing mental disorders and guide intervention targets. Many risk and protective factors have been found to be associated with a number of different mental disorders [4]. However, it is unclear whether these associations are specific to certain mental disorders or transdiagnostic in nature.

Comorbidity among mental disorders is common, with estimates that up to two-thirds of adolescents with a mental disorder will also have at least one other mental disorder [3,5]. The prevalence of comorbidity makes diagnostic and treatment decision making complicated, as additional disorders can affect treatment outcome [6,7]. Furthermore, failing to account for comorbid mental disorders when investigating risk and protective factors could mean that relationships with mental disorders might be due to the compounding nature of overall psychopathology rather than any specific associations, hampering research, prevention, and treatment efforts.

Given the ubiquity of comorbidity, understanding risk and protective factors in relation to the development of mental disorders in young people is important for three reasons. First, comorbidity has been associated with greater symptom severity and poorer treatment outcomes [3,8]. Second, risk and protective factors may enhance identification and prediction of individuals with a greater likelihood of developing mental disorders [9]. Third, identification of the characteristics and processes that can be targeted and modified through intervention is critical to the development of efficacious prevention and treatment [10]. Much of the prior research investigating risk and protective factors has typically focused on associations with a single disorder or a single risk or protective factor [4]. As such, the relationships between the breadth of psychopathology and putative risk and protective factors are not clear, heralding the need for a different approach to examining these relationships.

Empirical Models of Psychopathology

The categorical, prototypical approach to organizing mental disorders used in traditional classifications systems, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM; now in its 5th edition) has a number of limitations, such as a lack of specificity as demonstrated by the prevalence of comorbidity [7]. In contrast, empirical models of psychopathology use a broad range of quantitative approaches to generate coherent arrangements of signs and symptoms of psychopathology and capture the high rates of psychiatric comorbidity [11]. What results is a quantitively organized framework that facilitates investigation of the specificity and generality of risk and protective factors for psychopathology that is not achievable with traditional classification systems

[9,12,13]. Two empirical models have emerged in recent years and received increasing attention in the literature.

Hierarchical Dimensional Models

Hierarchical dimensional models, such as the Hierarchical Taxonomy of Psychopathology (HiTOP) model, propose latent factors that capture covariance among commonly comorbid disorders. Early examination of comorbidity among common childhood disorders suggested the presence of two latent factors: internalizing (eg, mood and anxiety disorders) and externalizing (eg, substance abuse and antisocial, oppositional, and impulsive related disorders) factors [3,11,14]. However, internalizing and externalizing have also consistently been found to be positively correlated, suggesting the presence of a higher-order latent factor [3,12,15].

According to the HiTOP model, this association represents a general factor of psychopathology (the "p" factor). The "p" factor sits at the apex of the hierarchical structure and is thought to capture a latent vulnerability to all mental disorders (see Kotov et al [6]). Efforts to expand the internalizing-externalizing model to cover the breadth of psychopathology have flourished over the last two decades. Additional spectra that sit below the "p" factor have also begun to emerge, such as thought disorder (or psychoticism), detachment (eg, histrionic, avoidant, dependent, and schizoid personality disorders), and somatoform dimensions. Beneath each of these spectra sit a number of lower order dimensions, and beneath these sit a number of even more specific components and traits. In this framework, transdiagnostic risk and protective factors may be uniquely associated with the "p" factor or specific spectra, such as internalizing or externalizing.

Network Models

Network theory proposes that disorders arise from dynamic relationships between symptoms, resulting in a network of connected symptoms [13]. Disorders can therefore be seen as systems of causally related symptoms, rather than manifestations of latent vulnerabilities. Factors outside of the psychopathology network form what is referred to as the external field and can influence or activate symptoms, which in turn promotes the activation of other symptoms in a cascading system leading to the onset and maintenance of mental disorders [16]. Transdiagnostic risk and protective factors are therefore components of the network that are external to symptoms but are connected to symptoms from many symptom groupings within the psychopathology network.

Transdiagnostic Risk and Protective Factors

Two previous reviews have examined risk and protective factors in relation to internalizing and externalizing dimensions in children and adolescents; however, to our knowledge, no previous reviews have investigated other broadband dimensions [17,18]. A mega-analytic synthesis of child, family, school, community, and cultural risk and protective factors correlated with internalizing behaviors, externalizing behaviors, or both found 4 risk factors and 3 protective factors common to both internalizing and externalizing disorders [17]. Although this suggests that additional factors examined were specific to either internalizing or externalizing, it is unclear from the review

whether the studies included examined both internalizing and externalizing disorders simultaneously, only one of these, or specific behaviors or disorders within those disorder groupings. Thus, it is not possible to draw any conclusions about whether any of the identified risk and protective factors are transdiagnostic or disorder-specific.

McMahon and colleagues [18] conducted a systematic review of studies examining the relationship between internalizing and externalizing symptoms and a range of stressors, such as exposure to violence, abuse, poverty, and parental divorce, with the aim of evaluating the specificity of stressors. However, the review found little evidence that individual stressors were associated with specific internalizing or externalizing outcomes, with the exception of an association between sexual abuse and internalizing or post-traumatic stress disorder symptoms. This suggests that most stressors examined were transdiagnostic across internalizing and externalizing disorders. However, while stressors may be transdiagnostic risk factors and useful for identifying young people at risk of developing mental health problems, further investigation is needed to identify factors that can be addressed and modified through intervention. Further, it is unknown whether these transdiagnostic associations hold across other domains of psychopathology, such as psychotic-related disorders.

Research that takes into account a broad range of disorders and comorbidity is necessary to identify transdiagnostic risk and protective factors. Identifying the risk and protective factors for psychopathology in young people that occur across traditional diagnostic categories is of great clinical significance. Such factors may be useful for more efficient prediction and early identification of psychopathology, as some may provide useful targets for reducing overall risk for psychopathology, thus preventing a variety of mental disorders from subsequently emerging [19].

Review Aim

The aim of this systematic review is to identify transdiagnostic risk and protective factors for psychopathology in young people. This will be done by synthesizing and critically evaluating studies examining empirically based models of psychopathology.

Methods

This protocol conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) statement [20], which can be found in Multimedia Appendix 1, and is registered with PROSPERO (CRD42020161368). The protocol is also available via Open Science Framework [21].

Eligibility Criteria

The Population Exposure Comparator Outcome (PECO) framework was used to develop the research question and eligibility criteria for this review [22].

Population

The population of interest will be young people between 10 and 24 years of age, as defined by the World Health Organization [23]. Studies where the mean age of participants falls between 10 and 24 years will be considered for inclusion.

Exposure

Studies that have examined variables such as genetic, neurobiological, cognitive, social, and environmental characteristics and their association with an empirically based model of psychopathology will be considered for inclusion.

Comparison

Studies with or without a comparison group will be considered for inclusion as the dimensional nature of psychopathology implicit within contemporary knowledge precludes the need for control groups.

Outcome

Psychopathology outcomes derived from empirically based models of at least two broad groups of signs or symptoms, such as internalizing, externalizing, or thought disorders, will be included. Quantitative approaches typically used to organize signs and symptoms of psychopathology include factor analytic, class-based, and network approaches. Studies where validated measures of internalizing and externalizing have been used will also be included where findings for both dimensions have been reported.

Studies

Longitudinal and cross-sectional studies examining risk and protective factors associated with psychopathology in young people will be eligible. Although longitudinal studies provide stronger evidence for causation, cross-sectional studies will be included because they may help identify characteristics needing further research.

Studies must be peer-reviewed, be in English, and report original empirical findings. Reviews, opinion pieces, and other publication types that do not report original empirical findings will be excluded.

Search Strategy

Searches will be conducted in Medline, EMBASE, and PsycINFO databases. An example search string developed for Ovid PsycINFO is shown in Table 1, which will be replicated for EMBASE and Medline databases. Reference lists of selected articles will also be hand searched to identify additional relevant articles not captured by the initial search strategy.

Table 1. Sample search strategy developed for Ovid PsycINFO.

Search	Terms
1	SH[a]: Latent Variables/ or Latent Class Analysis/ or Latent Profile Analysis/ or Item Response Theory/ or Principal Component Analysis/
2	(general factor* or p-factor* or transdiagnostic* or psychopathology network* or symptom network* or bridge symptom* or comorbidity network* or latent* or factor mixture model* or multimode* or item response theory).mp[b].
3	1 or 2
4	SH: exp[c] Psychopathology/ or exp Psychiatry/ or exp Dual Diagnosis/ or exp Comorbidity/
5	(psychopatholog* or psychiatr* or comorbid* or co?occur* or dual diagnos*).mp.
6	4 or 5
7	3 AND 6
8	(Child* or adolescen* or teen* or youth* or pediatr* or paediatr* or young or emerging adult* or youth).mp.
9	SH: exp risk factors/ or exp protective factors/
10	((risk or protec* or resilienc* OR underlying or vulnerab*) adj4 (factor* or mechanism* or character*)).mp.
11	9 OR 10
12	7 AND 8 AND 11
13	Limit 12 to English language
14	Limit 13 to peer-reviewed journals

[a]SH: subject heading.

[b]mp: title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms.

[c]exp: explode.

Selection of Studies

All titles and abstracts will be screened by one reviewer (SJL); the other reviewers (CC, NN, MS) will screen 25% of the titles and abstracts, which will be randomly selected. For all studies identified in the initial screen, the full-text articles will be reviewed and assessed against the eligibility criteria by two reviewers (SJL and MS). Disagreements at each stage of screening will be resolved through discussion or by a third reviewer (CC). A PRISMA flow chart will be created to show the results of each stage of the screening process.

Review Procedure and Data Extraction

Citations will be imported into the Covidence systematic review software [24], which will be used to remove duplicates and screen tittles, abstracts, and full texts. The following information will be extracted by the primary reviewer (SJL): publication details (authors, year of publication, country), study design (eg, cross-sectional, longitudinal), sample characteristics (sample size, mean age, ethnicity, sex), psychopathology measures (measures used), informant type (parent, self, other), risk or protective factor measures, data analysis strategy (techniques used, model specification, indicator type), outcome statistics (eg, test statistics, P values, effect size, model fit statistics, network centrality statistics). For longitudinal studies, additional information will be extracted regarding follow-up intervals and frequency. A summary of main findings will also be recorded.

Assessment of Quality

Following data extraction, study quality will be assessed independently by two reviewers. Cross-sectional studies will be evaluated using the Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross-Sectional Studies, and longitudinal studies will be evaluated using the Joanna Briggs Institute Critical Appraisal Checklist for Cohort Studies [25].

Results

This systematic review is ongoing. At the time of submission, full-text screening was completed, and hand searching of articles for additional studies to be included was underway. Findings will be summarized in a narrative synthesis and grouped by research domain, such as genetic, neurobiological, cognitive, social, environmental, or any other broad themes that emerge from the review. Studies will also be summarized by statistical approach. Analysis of subgroups or subsets will be determined based on results of the review and availability of sufficient data. Results are expected to be completed by the end of 2020.

Discussion

Understanding how risk and protective factors are associated with empirical models of psychopathology is critically important to determining which factors will be most useful to target when developing treatment and preventative interventions. It may be that some transdiagnostic risk factors are associated with a general vulnerability to all mental disorders, while others may be more specific to certain dimensions or spectra (eg, internalizing, externalizing). Factors associated with a general liability may serve as fruitful targets for preventative interventions, whereas specific factors may be more useful in developing selective or indicated interventions.

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The results of this systematic review will provide a much-needed critical analysis of the risk and protective factors for mental and substance use disorders in young people derived from empirically based models of psychopathology. Findings will help guide and accelerate the development of transdiagnostic prevention programs. To our knowledge, this will be the first systematic review of the risk and protective factors associated with empirically based models of psychopathology in young people. The critical synthesis of this evidence provides an opportunity to better understand the factors that contribute to the onset and maintenance of psychopathology in young people. This information can provide a foundation upon which interventions can be designed that are better able to prevent or reduce mental health problems and in turn disrupt the cascade of psychopathological sequelae into adulthood.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRSIMA-P Checklist 2015.
[PDF File (Adobe PDF File), 153 KB - resprot_v9i8e19779_app1.pdf]

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Abbreviations

HiTOP: Hierarchical Taxonomy of Psychopathology
PECO: Population Exposure Comparator Outcome
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols

Proposal

The Parenting Education Needs of Women Experiencing Incarceration in South Australia: Proposal for a Mixed Methods Study

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Abstract

Background: The mother-child relationship is extremely important, and for mothers experiencing incarceration, this relationship has unique challenges. There is limited evidence currently available to identify the type and content of parenting education that would best suit women who are incarcerated.

Objective: This study aims to design and evaluate a parent education program for women experiencing incarceration in South Australia. The program must meet the specific needs of incarcerated women and considers the cultural needs of Aboriginal and or Torres Strait Islanders and migrant women. Hereafter Aboriginal and/or Torres Strait Islander peoples will be referred to as Aboriginal; the authors acknowledge the diversity within Aboriginal cultures.

Methods: This study will utilize a mixed methods approach, including six phases framed by a community-based theoretical model. This methodology provides a collaborative approach between the researcher and the community to empower the women experiencing incarceration, allowing their parenting education needs to be addressed.

Results: A scoping review was undertaken to inform this study protocol. This paper describes and discusses the protocol for this mixed methods study. Recruiting commenced in December 2019, results will be published in 2020, and the project will be completed by August 2022. This project has been supported by a Research Training Scholarship from the Australian Government.

Conclusions: The scoping review highlighted a lack of rigorous evidence to determine the most appropriate parenting education program to suit women experiencing incarceration specifically, and there was little consideration for the cultural needs of women. It also became clear that when quantitative and qualitative data are utilized, the women's voices can assist in the determination of what works, what will not work, and what can be improved. The data collected and analyzed during this study, as well as the current evidence, will assist in the development of a specific parenting education program to meet the needs of women experiencing incarceration in South Australia and will be implemented and evaluated as part of the study.

International Registered Report Identifier (IRRID): PRR1-10.2196/18992

Introduction

Background

It is estimated that there are more than 714,000 women and girls accommodated in corrective institutions globally, comprising 6.9% of the prison population worldwide [1]. The rate of women experiencing incarceration has increased by 53% since the year 2000. The female rate of incarceration is increasing faster than the male prison population, demonstrating a 20% rise. It is also estimated that millions of children worldwide have a parent

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who is incarcerated, and tens of thousands live in prison with their mother [2]. Australia is following a similar trend, increasing from 2349 women in 2014 to 3494 in 2020, a 48.7% percent rise in the past 5 years [3,4]. Notably, over half of these women had dependent children under the age of 15 years in their care before incarceration [4].

Women experiencing incarceration have commonly endured complex histories that often include child abuse, sexual abuse, neglect, domestic violence, and drug and alcohol addiction [5-10], leading to a high incidence of children being removed by child protection services [5]. These life events can result in complex trauma often exhibited by low self-esteem, inability to display emotions, physical or psychological agitation, self-injury, and suicide attempts [11]. Further, this impacts the woman's ability to maintain employment and may create issues with parenting, alcohol, and substance abuse, as well as affecting mental health [12]. These factors, combined with a lack of nurturing and inappropriate parental role modeling in childhood, can make parenting their children challenging [7]. Mothers who are incarcerated experience physical separation from their children and from their role as mothers, which impacts their identity as women [13]. Prison systems that do not provide support for mothers further damage and punish women, which can result in missed opportunities for rehabilitation, relationship building, and positive intervention [11]. Incarceration can be an important opportunity to offer women time to learn about parenting and strengthening relationships with their children [14,15].

Aim and Objectives

This paper outlines the study protocol for the development of a parenting education program for women experiencing incarceration. The study aims to explore the parenting education needs of women experiencing incarceration in South Australia and to determine the program's impact on the women participants. The study will address the following two questions: What are the parenting education needs of women experiencing incarceration? What is the impact of a specially designed parenting program for incarcerated women? The study will be conducted over six phases using a multiphase design, which will include a needs assessment, the development of an intervention program, and evaluation of the program.

Methods

Study Design

The study will utilize a mixed methods, multiphase design framed by a community-based theoretical model (Figure 1) [16]. This design and framework promote collaboration between the researchers, women who are incarcerated, and staff at the prison, in order to address specific problems in the target population. This methodology is an ideal fit for understanding populations that have been marginalized, giving them a voice [17,18]. A mixed methods approach using a multiphase design will involve multiple phases conducted over time with both concurrent and sequential data collection and analysis. This study will include six phases underpinned by a community-based theoretical model, involving six stages created by Stoecker [19], adapted by Badiee and Wang [17], and adapted further to suit this study by removing the medico-centric terminology.

Figure 1. Mixed method multi-phase design framed by a community-based theoretical model (CBT). Figure adapted from Nicolaidis and Raymaker [16].
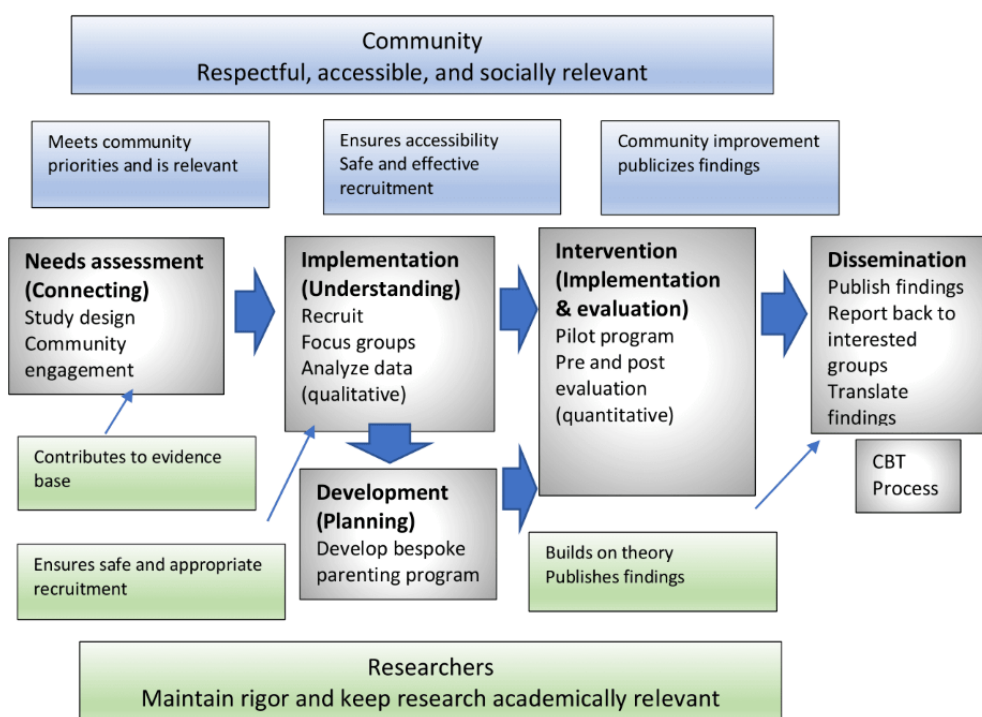
Phase 1

The connecting phase will involve building relationships with the prison staff to assist in developing a deeper understanding of the prison environment and build trust. Relationships will be established with Aboriginal and migrant communities to ensure the project is aligned with the principles of cultural safety considerations.

Phase 2

The understanding phase involved the undertaking and pending publication of a scoping review, utilizing the framework outlined in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) extension for scoping review checklist [20]. The scoping review was undertaken to determine the outcomes of existing prison parenting education programs for women experiencing incarceration and to provide key learning outcomes for improvement of future research and development. Eleven databases were searched, and two reviewers determined the full texts that would be included. A third reviewer resolved any conflicts.

Study Population

Incarcerated women in South Australia will be the target population of this study as well as prison employees. Participants will be eligible if they are incarcerated, able to understand and communicate English, and have a good understanding of what is involved in the study (this will be assessed when communicating with the woman). All women will have the participant information and written consent form read to them during a preparatory session, to help them understand what is involved when participating. Women who reside in two areas of the prison will be excluded from potential recruitment: women experiencing behavioral problems (8 beds) and women classified as high risk of self-harm or suicide (20 beds). Women without biological children will be included in the study, as they may also benefit from a parenting program, for example, they are currently pregnant, planning to have children in the future, or care for the children of family and friends. Staff participants will be included if they work at the prison in a role where they interact with women and are interested in being involved.

Method of Data Collection

Focus groups will be conducted by the primary researcher and a cofacilitator (researcher). An interview schedule (with prompts) will be used by the primary researcher, to help women focus and think about what their views and needs are around parenting and parenting education. Approximately 6-8 focus groups of between 4-8 participants will be conducted with women who have varying sentences and women on remand. Additionally, three specific focus groups will be conducted for Aboriginal women (where the presence of an Aboriginal Elder provides support), pregnant women, and migrant women. The focus groups will be recorded using a digital recorder. Preliminary information and ideas will be written on flip charts by the cofacilitator, and feedback to group members will be given at the end of each session to confirm that these represent what has been discussed. Focus groups will be conducted until data saturation has been reached. After the focus groups with the women, the prison staff will be invited to attend a focus group or face-to-face interview to contribute their ideas to the program and clarify any questions that the research may have uncovered.

Data Analysis

Descriptive thematic analysis will be used to analyze the data, which will enable a concise description of themes, allowing data organization and interpretation. Thematic analysis is a way of identifying, analyzing, organizing, describing, and reporting themes found within the data. This method of analysis provides flexibility while creating a rich, detailed, and complex interpretation of the data. This methodology will facilitate a clear and organized final report where similarities, differences, and potentially unexpected results will be presented [21]. Braun and Clarke [21] developed six stages of thematic analysis, which will be used as a guide for analyzing the data. Although this method of data analysis is a six-stage process, the analysis will involve reflection and the need to revisit stages over some time.

As guided by the Braun and Clarke [22] analytical framework, the first stage will involve transcribing the data where ideas and suggestions will be documented and cross-checked with the preliminary feedback. The second stage will involve the familiarization and immersion of data by the primary researcher and another researcher. Data that has meaning, is interesting, and contributes specifically to the development of the parenting education program will be identified and coded. The third stage will involve sorting data into themes and subthemes. During stage 4, the decision as to which themes will be combined, refined, or removed will be undertaken. This stage will ensure that data under each theme is significant, consistent, and that each theme is distinct. The next stage will involve naming the themes and creating definitions that summarise the themes. The results of the analysis will address the two research questions and create a comprehensive description of data collected, which will include direct quotes from women and staff at the study site prison.

Phase 3

The planning phase will involve the development of a parenting education program to suit the specific needs of women experiencing incarceration in South Australia, based on needs identified by the women. An expert working group will be assembled to guide program development based on their expertise and the findings from women and staff at the prison. The University of South Australia Human Research Ethics Committee and The Department of Corrections Research and Evaluation Management Committee will review the program before implementation.

Phase 4

A pilot program will be implemented with groups of 6-8 women in the prison, and the program will be conducted for at least one group of women.

Phase 5

The pilot parenting education program will be evaluated using a pre-post questionnaire for the women participants to complete. This questionnaire will be designed after the program has been developed to evaluate specific aspects of the program. A

combination of quantitative and qualitative data will be collected (ie, Likert scales and open-ended questions). Four to six staff members who have regular and consistent contact with the women will be interviewed after the women have participated in the program. The interviews will ascertain the program's impact on the women, including their behavior and attitude towards parenting and the program, giving further insight into the evaluation of the program to avoid relying on self-report from the women alone.

Phase 6

The results will be disseminated through publications and presentations. A results chapter will be written for a PhD student thesis. We envision at least four papers will be published during the undertaking of this research project, including a scoping review, the protocol, findings from focus groups, and program evaluation. Publications will be available to women and staff involved in the study and accessible via the prison library for those who are interested, and study findings and recommendations will be presented to parenting experts, female Aboriginal elders, and migrant support groups in the community.

Results

Phase 1

Phase 1 commenced in August 2018. The time spent building trusting relationships with the prison and the Aboriginal community was vital to this project. The effort allowed ethical approval, access to the prison, fine-tuning of research documentation, recruiting assistance, providing a space for interviews, allowing digital recording, connecting with key staff members, and engaging with key members of the Aboriginal community to ensure the project continues to follow guidelines for respectful research [23].

Ethical Considerations

This project was approved by the University of South Australia Human Research Ethics Committee on August 29, 2019, with approval until August 29, 2022 (application ID: 201956). The Department of Corrections Research and Evaluation Management Committee in South Australia also approved the project from November 12, 2019, to November 12, 2020. Ethics approval was gained by the Central Adelaide Health Local Health Network Human Research Ethics Committee from the 25th of June for one year. The approval includes the connecting, understanding, and planning phases of the research.

Prison staff will not be involved in recruiting women in order to avoid recruitment bias. The researchers will recruit women following an information session. This process will reduce power imbalance relationships with prison staff who may influence women's decision to participate. Written consent for all aspects of the project will be obtained. The vulnerability of incarcerated women has been taken into careful consideration in all phases of this research project. Women will be provided with an information session, as described earlier, where a detailed description of the study will be provided, ensuring that participation is voluntary and allowing the women to make an informed choice regarding whether they would like to be involved. Particular care will be taken to ensure confidentiality

of data collected and participants' anonymity. Pseudonyms will be used, and limited demographics will be collected to ensure that the women cannot be identified. The researchers will wear a duress alarm during the focus groups and will have the ability to contact security for immediate response. If the women become distressed, the researchers will refer the women to the appropriate supports, guided by a referral flow chart. The staff participants will be recruited via an email introduction from an administrator to reduce recruitment bias, which will include the participant information sheet and consent form to read. They will also be invited to an information session during which the researcher will explain the study, and the women can decide if they would like to attend a focus group. Deidentified electronic data will be stored on a password-protected computer, and written transcripts and demographic data will be stored in a locked cabinet in a locked office at the University of South Australia (C4-45). Documents will be stored for 7 years after the publication of the results, per the General Disposal Schedule No. 24, Universities of SA [24]. Digital recordings will be deleted after transcription.

Phase 2

The scoping review, unlike previous reviews, focused on the impact of parenting education for incarcerated women as well as highlighting the qualitative data and outlining the content of the programs to determine what can be learned for future program design. During this phase, challenges with the prison system, program content, what worked and what did not, was identified. The review identified limited rigorous research evaluating parenting education programs for women in prisons; currently, it is unknown what the most appropriate content of a parenting program for incarcerated women should entail. Limited consideration has been given to the specific cultural needs of incarcerated women and how these needs can be met. There are also very few programs developed after first identifying the needs of women. The challenges experienced by other researchers has been noted as a learning strategy for working in prisons. Cultural safety was not taken into consideration in the majority of studies. In studies that did adapt a program to suit the cultural needs of Aboriginal women, it was not specifically evaluated to determine if the needs of Aboriginal women were met. There were few programs where the input of women was sought in the development phase of a program, which would appear to be an ideal place to start designing a program for a population with unique needs. Therefore, in this study, a ground-up approach will be utilized, where women are questioned about their parenting education needs, and a parenting education program will be developed and designed around their specific circumstances and identified needs. The scoping review is expected to be published in 2020.

Focus groups will be conducted in the prison from December 2019 to December 2020, and the results of these interviews will be published in 2020.

Phases 3-5

These phases are reliant on the completion of the preceding phases.

Phase 6

Dissemination of the results will occur throughout the project. The project will be completed by August 2022. This project is funded by an Australian Government Research Training Scholarship for 3 years beginning in August 2018.

Discussion

Overview

Findings demonstrate a limited number of parenting programs for incarcerated women that have been developed with input from women in the target population. Many of the women who find themselves involved with the criminal justice system have experienced difficult childhoods themselves. It is, therefore, challenging for many of the women to parent their own children positively. The women may not have had the opportunity to access parenting support education in the community, and the challenges of separation can create further difficulties with the mother-child bond and relationship. Imprisonment is an opportunity for some women to change their lives and access learning opportunities that are offered in prison. One of the most important elements to improve outcomes for women is to initiate and maintain relationships with family and children [25,26]. Despite the many challenges that women encounter, children

are a strong motivator to avoid reoffense and substance abuse and the desire to regain custody [27].

The possible benefits of this study may result in women feeling positive and empowered about contributing their ideas and suggestions to a parenting education program, which may help women experiencing incarceration in the future. Some women involved in the preliminary phases may have the opportunity to attend the pilot parenting education program, which may have a positive impact on women's knowledge about parenting and, by extension, positively impact the next generation of children.

Conclusion

Parenting education is important as the separation between mothers and their children can have serious emotional, physical, and psychological effects on both the mother and child. Effective parenting programs have the potential to assist in the promotion of healthy relationships and reduce the intergenerational cycle of poor parenting and incarceration. This information must be disseminated to improve the education provided to women experiencing incarceration and their children. The data collected from participating women and staff in prison will be utilized in a ground-up approach to design a specific parenting education program to meet the needs of incarcerated women.

Authors' Contributions

All authors listed contributed equally to the development of ideas and the writing of the manuscript.

Conflicts of Interest

None declared.

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Proposal

Bahamas National Implementation Project: Proposal for Sustainability of an Evidence-based HIV Prevention Intervention in a School Setting

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Abstract

Background: Sustained implementation of school-based prevention programs is low. Effective strategies are needed to enhance both high-level implementation fidelity and sustainability of prevention programs.

Objective: This proposed study aims to determine if the provision of either biweekly monitoring and feedback and site-based assistance and mentorship or both to at-risk and moderate-performing teachers with monitoring through an enhanced decision-making platform by the Ministry of Education (MOE) and Ministry of Health (MOH) based on the real-time implementation data will increase national implementation fidelity and result in sustained implementation over time.

Methods: This study will target government schools including 200 grade 6 teachers in 80 primary schools and 100 junior/middle high school teachers (and their classes) on 12 Bahamian islands. Teacher and school coordinator training will be conducted by the MOE in year 1, followed by an optimization trial among teachers in the capital island. Informed by these results, an implementation intervention will be conducted to train using different levels of educational intensity all at-risk and moderate-performing teachers. Subsequently selected training and implementation strategies will be evaluated for the national implementation of Focus on Youth in the Caribbean and Caribbean Informed Parents and Children Together in years 2 to 5.

Results: It is hypothesized that a more intensive training and supervision program for at-risk and moderate-performing teachers will enhance their implementation fidelity to the average level of the high-performing group (85%), an HIV prevention program delivered at the national level can be implemented with fidelity in grade 6 and sustained over time (monitored annually), and student outcomes will continue to be highly correlated with implementation fidelity and be sustained over time (assessed annually through grade 9). The proposed study is funded by the National Institute of Child Health and Human Development from August 1, 2018, through May 31, 2023.

Conclusions: The study will explore several theory-driven implementation strategies to increase sustained teacher implementation fidelity and thereby increase the general public health impact of evidence-based interventions. The proposed project has potential to make significant contributions to advancing school-based HIV prevention research and implementation science and serve as a global model for the Fast Track strategy.

International Registered Report Identifier (IRRID): PRR1-10.2196/14816

Introduction

Background

Despite great progress over the past three decades in the prevention and treatment of HIV/AIDS, the global HIV epidemic remains a major cause of morbidity and mortality. HIV has become a disease of the young, with 40% of new infections worldwide occurring among those aged younger than 25 years. AIDS-related deaths increased among adolescents by approximately 50% between 2005 and 2012. Children and adolescents are significantly less likely to receive treatment than adults (23% versus 38%) [1-3]. The United Nations (UN) General Assembly has identified the pivotal role of young adults in the epidemic and is calling for comprehensive, evidence-based prevention approaches [4].

There has been much progress in curtailing the global HIV epidemic, however. The UN's Millennium Development Goals clearly articulate relevant target objectives with specific, trackable action plans and widely publicized annual progress reports [5]. The UN and nations across the world established Sustainable Development Goals including the ambitious but achievable goal of the Joint United Nations Programme on HIV/AIDS (UNAIDS) to end the AIDS epidemic as a global threat by the year 2030. This goal requires a 90% reduction of new HIV infections. Demographic groups that have not fully benefited from the advances in controlling the epidemic will need to be reached. The blueprint for this goal is the UNAIDS Fast Track strategy which states that "[v]ery high levels of coverage for programmes that promote correct and consistent condom use will be needed in all types of epidemics [1]."

Critical to the success of Fast Track are identifying and addressing the issues involved in maintaining the effectiveness of evidence-based HIV prevention programs as they are transformed from research to practice [6-8]. Primary prevention refers to actions or information aimed at preventing the onset of illness before the disease process begins or improving health through changing the impact of social and economic determinants on health. Most HIV prevention programs are designed to promote abstinence and/or condom use to prevent disease transmission. For an intervention that has been demonstrated to be effective in a research setting to become an effective public health tool, it must be implemented and sustained and delivered in a fashion that is likely to reproduce its effectiveness (fidelity). These concepts have been the source of substantial scientific inquiry [9,10]. Research to date indicates that sustained implementation (delivery of some or all of the intervention over time) of evidence-based behavioral interventions is low [11]. Studies assessing fidelity of implementation of effective programs report considerable deviance from the original, evidence-based curricula [12]. However, while fidelity of implementation is critical to success [12-14], many studies have found that some adaptation is inevitable and may signal commitment to the new program

[12,15,16] and/or strengthen the program's effectiveness [17]. Substantial literature underscores the importance of contextual fit of the new intervention within the local culture [18] that may be achieved through adaptation. These findings signal the importance of local, culturally appropriate implementation efforts for the next stage of HIV research [18,19].

Over the past decade, multiple disciplines have embraced the importance of moving evidence-based interventions into community settings in order to benefit society [20]. Numerous implementation and dissemination models have been developed, including the Exploration, Preparation, Implementation, Sustainment model by Aarons et al [21]. This model offers several strengths (logical, evidence-based) and specifies variables that may play crucial roles at different phases in the implementation process, impacting the ultimate success of intervention delivery [21]. It appears to be well suited as the platform for the research questions to be addressed.

Although implementation of evidence-based interventions in the school setting remains low [20,22], efforts to do so are increasing. Five factors found to be important are community-level aspects including politics and funding, implementer (teacher) characteristics, characteristics of the intervention program itself including adaptability and compatibility with the local environment, organizational capacity (including support from the leadership), and training and ongoing support [18,23,24]. Activities and materials supporting these concepts (eg, curriculum manuals and videos) appear to enhance the success of implementation. The implementation approach Fidelity Through Informed Technical Assistance and Training [23], consistent with the Exploration, Preparation, Implementation, Sustainment model and our own work [25,26], addresses threats to implementation fidelity through monitoring of implementation data provided by teachers and observers. In one study, the use of the Fidelity Through Informed Technical Assistance and Training approach was associated with an overall 98% curricular adherence [23]. Factors inconsistent with these supporting elements (such as lack of school time, competing priorities) undermine implementation [27]. Growing literature supports the evidence base for the utility of a social support network of practitioners or teachers (communities of practice) [28], confronting similar implementation challenges in working together [29,30]. In this study, communities of practice refers to a group of teachers who have ongoing interaction around the implementation of an effective HIV intervention. This social support network provides an environment in which teachers can share their experiences and discuss their progress and challenges in implementing HIV interventions in schools. Despite such advances, it is still not known if the public health outcomes anticipated from broad implementation of evidence-based programs are occurring and/or are sustained over time [31].

In the 1990s, with an HIV seroprevalence of 4%, the Bahamas embarked on an interagency approach targeting Bahamian

children and adolescents and involving the Bahamian Ministries of Health (MOH) and Education (MOE) to reverse the escalating rates of HIV [32]. Over the past two decades, Bahamas MOE and MOH and our research team have adapted a US Centers for Disease Control and Prevention "best evidence" HIV prevention program to produce the Focus on Youth in the Caribbean (FOYC) and Caribbean Informed Parents and Children Together (CImPACT) risk reduction programs to address the HIV epidemic in the Bahamas. Two randomized, controlled longitudinal trials of FOYC and FOYC+CImPACT found the programs to be effective in improving knowledge, condom-use skills, and/or self-reported risk behaviors. In 2010, the MOE included FOYC in the government grade 6 curriculum nationwide, with boosters in grades 7 and 8. The MOE now plans to expand the offering to the more effective but logistically more complex FOYC+CImPACT version.

The HIV prevalence rate in the Bahamas has been declining during the past 20 years. UNAIDS global AIDS monitoring found HIV prevalence among the general population to be 1.9% in 2017 (0.6% and 0.7% among young women and men aged 15 to 24 years, respectively) [33]. The Bahamas has been providing preexposure prophylaxis (PrEP) through the public health system since 2018 [33]. AIDS remains a leading cause of death among Bahamians aged 25 to 44 years [34].

In summary, data from the national implementation study conducted from 2011 to 2016 showed a strong, positive correlation between number of core activities delivered and positive student outcomes [14,25,26]. Nevertheless, only about 50% of core activities were delivered, consistent with the literature on implementation of school-based programs [12]. Our findings confirmed prior research indicating that sustained implementation is low and should be a research priority [35,36]. To address this challenge, research that explores several theory-driven implementation strategies (eg, innovative teacher training and support, implementation monitoring and feedback, role of a curriculum implementation committee) to increase sustained teacher implementation fidelity, and thereby increase the general public health impact of evidence-based interventions, is indicated.

Study Aims

Reflecting this background, our ongoing research aims to determine if the provision of either biweekly monitoring and feedback (BMF) or site-based assistance and mentorship (SAM) or both through a community of practice to at-risk and moderate-performing teachers with monitoring through an enhanced decision-making platform by the MOE and MOH based on the real-time implementation data will increase national implementation fidelity and result in sustained implementation over time.

Methods

Study Overview

FOYC+CImPACT is being implemented in grade 6 by approximately 200 grade 6 teachers. Annual FOYC boosters for the students will be conducted by the junior high school Health and Family Life Education (HFLE) teachers

(approximately 100). The research team includes the US researchers, the Bahamian research office, and the 45 school coordinators who will gather and transmit the data from the field to the research office. All decisions regarding implementation of FOYC+CImPACT are being made by the Bahamian MOE and MOH, but the researchers are available for consultation at any time and will be formally involved through the regularly scheduled Fast Track School-Term Implementation Committee (implementation committee) which has been designed specifically to integrate and coordinate the roles of data, operations, and decision making. The implementation committee will review the implementation data presented by the researchers and make decisions regarding the need for any changes in implementation of FOYC+CImPACT. The implementation committee will meet once per school term (3 times per year). Committee members will include representatives from the MOE, including those responsible for curriculum development for all subjects, and the MOH, including those responsible for the HIV prevention program. Inclusion of these high-level decision makers from the MOE and MOH in program rollout, monitoring, and decision making underscores the importance of the FOYC+CIMPACT training to the nation's Fast Track agenda. Researchers will present a summary of data collected, implementation status including any modifications made, and analyses prior to each meeting. The committee will discuss progress, decide if any implementation strategies require change, and identify data and programmatic needs to maximize FOYC+CImPACT's benefits to students and to the Fast Track initiative.

Evidence-Based Approaches to Increase Teacher Implementation

The MOE will give all teachers a FOYC+CImPACT 24/7 flash drive for point-of-care guidance as they prepare the lessons [37]. The MOE will deploy its peer-mentoring program for FOYC+CImPACT. High-performing teachers will serve as team leaders and provide guidance and onsite assistance to low- and moderate-performing teachers to increase their skills and self-efficacy [22]. High-performing and at-risk teachers will be identified through real-time implementation monitoring [23] and a pretraining 7-question screening tool [38]. As the goal is to achieve and sustain at least 85% implementation compliance (the average performance of the high-performing teachers) [25,38], implementation will be monitored biweekly with feedback provided to the teachers as per MOE policy. Decisions regarding the need for change will be made by the implementation committee based on data.

Measures

Measure Assessing Implementation and Student Outcome

We are using 9 measures and 1 student questionnaire (Health Risk and Protective Factors) that were developed and employed in our prior implementation study (Table 1), with some modifications (pilot-tested in the Bahamas) based on validated scales from school implementation studies [39-41]. The new scales include assessments of teacher autonomy (5 items), perceived principal supportiveness (4 items), teacher self-efficacy (3 items), teacher attitudes toward sex education

in schools (8 items), and teacher confidence (5 items). These scales are included in teachers' measures of impression before and after teaching and will be further tested in the proposed study. These measures will be administered to the teachers before and after implementing FOYC+CImPACT to assess factors influencing fidelity of intervention implementation.

Table 1. Flow of measures.

Measure	Description	Responsibility
Teacher checklist	The checklist includes the 30 activities contained in the FOYC[a] curriculum. Teachers indicate which activities they have/have not taught in each session and record whether they have taught each activity as outlined in the manual or have modified it and their level of comfort in teaching each activity and student engagement	Teacher
Observation log	This measure mirrors the teacher checklist. Approximately 10% of FOYC and 20% of CImPACT[b] classes for each teacher will be independently observed	School Coordinator
Workshop preevaluation	Assess whether all days of FOYC+CImPACT training were attended and perceptions before training and past experience about the curriculum	Teacher
Workshop postevaluation	Assess perceptions after training	Teacher
Impression before teaching	Assess factors influencing fidelity of intervention implementation including teacher perceptions of the importance of prevention programs, HIV prevention, and FOYC intervention; teacher confidence in teaching the FOYC intervention; teacher sense of ownership of the curriculum, and teacher education, years as a teacher, and training in interactive teaching	Teacher
Impression after teaching	Assess factors influencing fidelity of intervention implementation, teacher reasons for not being able to complete delivering the FOYC curriculum, and perceived student benefits from FOYC curriculum	Teacher
Workshop observer log	Assess training in the teacher training workshop given prior to teaching. These checklists assess whether each activity that should have been taught during the workshop was taught	Assistant project manager
School coordinator biweekly assessment	This measure is based on other real-time tracking measures assessing FOYC+CImPACT scheduling, teaching, and form-completion activities	School Coordinator
Programmatic assessment	This measure tracks program changes made by the senior education officers or the implementation committee	Project manager
HRPF[c] final exam	Assessing student outcomes as a function of teacher implementation fidelity and sustainability thereof over time. The HRPF[c] will be administered to the students prior to delivery of FOYC+CImPACT in grade 6 and at the end of the school year in grades 6, 7, and 8	Students

[a]FOYC: Focus on Youth in the Caribbean.

[b]CImPACT: Caribbean Informed Parents and Children Together.

[c]HRPF: Health Risk and Protective Factors.

Data Flow Management

Every teacher will be assigned to a school coordinator whose responsibility will be to collect the forms and return them biweekly by email, mail, in person, or carrier to the central data system at the research office. The school coordinator will also be responsible for completing the school coordinator biweekly assessment, which contains information about all scheduled activities and measures for each teacher assigned to her and their completion or otherwise. It is important to have this information independently observed and recorded so that the MOE and research team are able to determine the status of implementation at all times and the data forms are continually tracked. Project manager will review this data biweekly.

Field Work: Program Implementation and Research

Training Workshop

In the first quarter of year 1, all members of the research team including the 45 school coordinators participated in a 1.5-day training workshop, beginning with an overview of the Fast Track initiative and the FOYC+CImPACT program, followed by roles, responsibilities, data flow, ethical issues, and practice with the forms. Procedure manuals were distributed. A 1-day refresher training will be conducted in subsequent years for new and existing personnel.

Group Mentoring

Based on the principles of communities of practice, the MOE created SAM, a 2-tiered group mentorship program, to deploy the strength of high-performing teachers to help teachers who are struggling.

- General guidance and biweekly meeting: one high-performing teacher per school will serve as team leader and provide guidance to low- and moderate-performing teachers with their preparation and planning of FOYC+CImPACT sessions. The team leader will meet all grade 6 teachers and HFLE teachers (the middle school teachers involved) weekly to discuss their progress, identify challenges teachers are experiencing, and provide tips and guidance during the meeting. The team leader will promote

- group activities and enhance interaction among teachers in these meetings.
- Onsite assistance and observation: at-risk or moderate-performing teachers will be invited to observe while a session is being taught by a high-performing teacher/team leader in the classroom.

An additional program, enhanced SAM, will be offered to teachers who still have difficulties in teaching sensitive topics. As part of enhanced SAM, these teachers will be observed in the classroom by the team leader who will provide onsite assistance. These strategies, consistent with the principles of communities of practice [29,30], have evolved as part of the Bahamian school system's culture to support new/challenged teachers.

Multiphase Optimization Strategy Design-Based Trial

This trial examines the effect of each training/implementation component for at-risk and moderate-performing teachers and whether the presence or absence of a component has an impact on the performance of other components. An advantage of the multiphase optimization strategy (MOST) design is its ability to identify active components making significant contributions to the overall effect from those that are not doing so, hence not worth retaining. For our MOST trial, there are two intervention components, one with 2 levels (ie, BMF) and the other with 3 levels (ie, SAM), which corresponds to a full factorial with 6 experimental conditions (Table 2). We chose the teacher

implementation checklist to identify high-performing teachers as a measure of success (optimization criteria). Using our 7-item preimplementation school screening tool [38], we identified teachers who are at risk for not implementing the FOYC intervention curriculum and moderate- and high-performing teachers. All at-risk teachers and moderate-performing teachers were invited to participate in a factorial experimentation, using a MOST trial design. Workshop/video was provided to all teachers and treated as a constant component in the experiment. At the beginning of the trial, at-risk and moderate-performing teachers were asked to attend a 2-day curriculum workshop and each received an educational video. Following the teacher training, teachers were randomly assigned to 1 of the 6 experimental conditions and asked to teach the intervention curriculum for 1 semester. The primary outcome is implementation fidelity as assessed through the teacher implementation checklist and observer form. This effectiveness information is used to decide which set of components to select for at-risk or moderate-performing teachers. By conducting the proposed optimization phase of the MOST trial in year 1, we are determining the role of BMF and SAM (including enhanced SAM) and/or their combinations with the training workshop in improving implementation fidelity. The optimized teacher training and implementation packages will be used to train all at-risk and moderate-performing teachers for the subsequent national implementation of FOYC+CImPACT (12 islands in years 2 to 5).

Table 2. Multiphase optimization strategy design-based trial: optimization of training and implementation strategies.

Experiment condition	Workshop/video	Biweekly monitoring and feedback	Site-based assistance and mentorship
1 (n=15)	Yes	Yes	No SAM[a]
2 (n=15)	Yes	Yes	SAM
3 (n=15)	Yes	Yes	Enhanced SAM
4 (n=15)	Yes	No	No SAM
5 (n=15)	Yes	No	SAM
6 (n=15)	Yes	No	Enhanced SAM

[a]SAM: site-based assistance and mentorship.

Programmatic Implementation Including Change

Each stage of implementation will be assessed and tracked via the 9 measures. National implementation by grade begins in year 2 with grade 6 (full program). This will be followed in subsequent years by the grade 7 (boosters) as well as continued grade 6 full program, etc, such that by year 5, all classes of grades 6 through 9 in the 115 government schools nationwide will be participating. National implementation will begin with the teacher workshops. After the workshops, teachers will begin the actual implementation in the classrooms, beginning with the FOYC sessions during regular HFLE class time and scheduling the CImPACT sessions at a time when parents can attend. Data regarding the teaching process will be measured, including teacher perceptions before and after teaching FOYC+CImPACT, teacher checklist of what was taught, and observation by the school coordinator. Teacher compliance and success in scheduling, conducting at least 85% of all activities,

and completing all forms will be tracked in biweekly and programmic assessments by the school coordinator. The project manager will meet at least weekly with the national school coordinators to review and document on the programmatic assessments any changes made by MOE relevant to the implementation of FOYC+CImPACT. Three times per year, the implementation committee will review program progress. The research team will assemble, organize, and enter all of the data using the Autodata System's Scannable Office.

Statistical Analysis

Effectiveness of Training and Implementation Strategies

To test the main effects and interactions among intervention components, we will use a standard analysis of variance (ANOVA) using effect coding (for two level: –1 = no and +1 = yes; for three level: –1 = no SAM, 0 = SAM, and +1 = enhanced SAM) rather than dummy coding (0, 1 or 0, 1, 2, etc). Effect coding has several advantages over dummy coding. First,

effect coding produces estimates of main effects and interactions that are consistent with the classic definitions of ANOVA effects [42]. Second, effect coding preserves power for interactions [43].

We will make a preliminary selection of components that have achieved main effects (exceeding statistical significance or demonstrating medium-to-large effect size). This preliminary selection will then be reevaluated in light of any substantial interaction effects that have been detected to gain an understanding of how the components work in combination. Depending on the optimization criteria identified (implementing at least 85% of core activities), this would then be combined with other information (eg, cost, feasibility, scalability) to make a final selection of components [44]. This information will guide assembly of an optimized implementation package that achieves target outcomes with the least resource consumption and participant burden.

Sustainability of Implementation

Percentages of core activities (30 core activities in FOYC and 5 core activities in CImPACT) completed by all grade 6 teachers will be computed to assess whether the teachers can implement the prevention program with fidelity (delivery of more than 85% of core activities). For grade 7 to 9 teachers, percentages of core activities in booster sessions completed with fidelity will be computed to assess implementation fidelity

To assess whether delivery is sustained over time, percentages of core activities completed with fidelity by grade 6 teachers among the next cohorts of grade 6 students (and among grades 7 to 9 teachers, percentage of core activities in the boosters among the next cohorts of students) will be computed and compared across the cohorts of student classes. Sustainability refers to teachers' continued implementation of the intervention with fidelity (at least 50% of core activities) and adherence to program principles in 3 years (at 3 yearly follow-ups).

Student Outcomes

Bivariate analysis and mixed-effects modeling will be conducted to assess the relationship between implementation fidelity and student outcomes. In bivariate analysis, we will categorize the fidelity score into 3 levels: high fidelity (teachers complete more than 85% of core activities with fidelity), average fidelity (teachers complete 70% to 85% of core activities with fidelity), and low fidelity (teachers complete less than 70% of core activities with fidelity). The differences in grade 6 student outcomes at baseline and year-end follow-up across 3 levels of implementation fidelity and differences in the change scores between groups will be assessed using ANOVA (for HIV/AIDS knowledge, condom-use skills, perceptions) and Pearson chi-square tests (for self-reported behaviors). The test statistics (F score, chi-square) will be adjusted for the clustering effects of classroom and/or school using variance inflation factors.

The association of teacher implementation fidelity with student outcomes will be further examined using mixed-effects modeling (for knowledge, skills, and perceptions) and generalized linear mixed modeling (for self-reported behaviors), controlling for clustering effects of classroom/school, student age, sex, and baseline differences. Mixed-effects modeling analyses will be run using combined grade 6 teacher and grades 7 to 9 teacher fidelity score to assess overall effects of implementation fidelity of FOYC+CImPACT on student outcomes. Bivariate analysis and mixed-effects modeling will also be performed to assess the impact of different levels and types of curricular changes on student outcomes. To assess whether student improvements gained from grade 6 national implementation are sustained over time, a generalized estimating equation model will be used to examine the difference in student knowledge, skills, perceptions, and self-reported behaviors across the time points. Analyses will be performed using the SAS 9.4 (SAS Institute Inc) statistical software package.

Structural equation modeling analysis will be conducted to examine the relationships among factors influencing teacher fidelity of implementation and student outcomes using the Mplus 8 (Muthen & Muthen). We developed a hypothetical conceptual model (Figure 1) based on a synthesis of the empirical literature and our implementation work [21,45,46]. The model posits that teacher attitudes toward the intervention and self-efficacy in teaching the curriculum have a direct effect on fidelity of implementation, which will impact student outcomes. Ongoing interest and support from the school administration will reinforce teacher perception that this program is a high priority for their school administrators and indeed the nation. The identification of high-performing teachers as mentors will empower these teachers by increasing their sense of autonomy and role in the community. Given the importance of self-efficacy in implementation fidelity, components have been added to the implementation effort to increase real and perceived self-efficacy (workshop/video and site-based assistance and mentorship) [22,45]. Biweekly monitoring and feedback are hypothesized to increase teacher fidelity of implementation. The curriculum implementation committee is expected to improve teacher and school administrator attitudes toward the intervention. A starting model will be estimated to investigate the interrelationships among factors influencing fidelity of implementation. A full model will be constructed by including student outcome latent variables in the revised fidelity model, using the cluster option in Mplus. Standardized regression coefficients for all paths will be estimated using robust maximum likelihood estimation. A good model fit is indicated when the standardized root mean square residual and root mean square error of approximation are less than 0.05 and comparative fit index is greater than 0.95 [47,48].

Figure 1. Hypothesized conceptual model showing relationships among factors that influence fidelity of implementation and student outcomes. The implementation strategies are indicated by shadowed/italicized constructs.
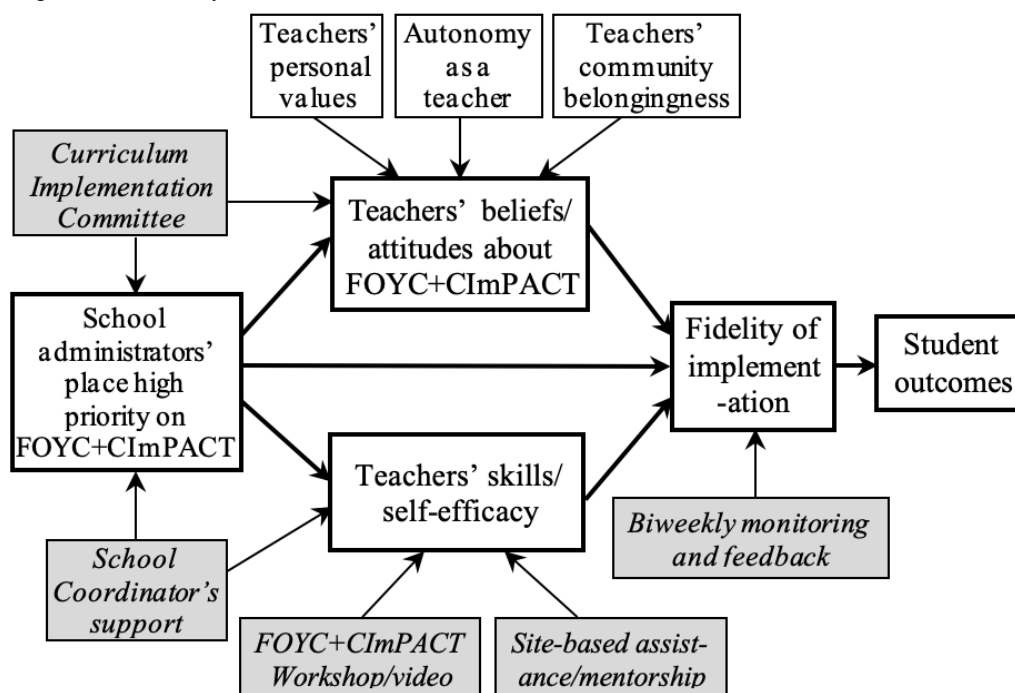
Results

The research protocol R01 HD095765 (BW and BS) was funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) for the period August 1, 2018, through May 31, 2023. Notice of award was received on July 23, 2018. Enrollment and teacher training began in October 2018 and will continue through September 2021. As of April 2019, 98 grade 6 teachers from two islands who teach HFLE classes completed a 2-day teacher training workshop. Twenty-four school coordinators (including 2 national school coordinators) were identified and trained for the purpose of tracking teacher implementation and progress biweekly, collecting teacher measures, and identifying and reporting issues and problems to the research office, located in New Providence. Seventy-two at-risk and moderate-performing teachers in 24 schools in New Providence participated in the MOST design-based trial from February to April 2019.

Teachers teach HIV intervention as part of the HFLE curriculum. Teacher participation in the project is voluntary. Parents are advised that the course will be taught to the students and they can request that their children not participate in the teaching sessions. While rare, these requests are accommodated.

At the beginning of the project, a small number of parents expressed concerns about the FOYC curriculum. The project coordinator met with these parents and explained the benefits of the sexual risk reduction intervention among adolescents in a nation such as the Bahamas with a national HIV prevalence among adults of 1.9% in 2017. The team did advise the parents that they could request that their children not participate in the teaching sessions. However, after this discussion, the parents were no longer concerned about the intervention curriculum. The research protocol was approved by the University of Massachusetts Medical School investigation committee and the institutional review board of the Bahamian Princess Margaret Hospital, Public Hospitals Authority.

Discussion

Implementation of evidence-based prevention programs in school settings remains low; sustained implementation is even lower. To address the important challenges confronting worldwide implementation of evidence-based programs in school settings, this research is designed to identify which structures effectively support high-level implementation fidelity and sustainability of prevention programs. This ongoing study explores several theory-driven implementation strategies to increase sustained teacher implementation fidelity to increase the public health impact of evidence-based interventions. The Bahamas has identified FOYC+CImPACT as one of the core evidence-based components of its UNAIDS Fast Track strategy to eliminate the global AIDS epidemic by 2030 and is committed to a data-based implementation plan to improve intervention delivery and maximize the program's impact among Bahamian students nationwide. The commitment and ongoing involvement of both the MOE and MOH will allow this nationwide research to serve as a global model for the UNAIDS Fast Track strategy. This research program has potential to make significant contributions to advancing school-based HIV prevention research and implementation science.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review reports.
[PDF File (Adobe PDF File), 164 KB - resprot_v9i8e14816_app1.pdf]

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Abbreviations

ANOVA: analysis of variance
BMF: biweekly monitoring and feedback
CImPACT: Caribbean Informed Parents and Children Together
FOYC: Focus on Youth in the Caribbean
HFLE: Health and Family Life Education
MOE: Ministry of Education
MOH: Ministry of Health
MOST: multiphase optimization strategy
NICHD: Eunice Kennedy Shriver National Institute of Child Health and Human Development
PrEP: preexposure prophylaxis
SAM: site-based assistance and mentorship
UN: United Nations
UNAIDS: Joint United Nations Programme on HIV/AIDS

Protocol

Discriminating Metabolic Health Status in a Cohort of Nursing Students: Protocol for a Cross-Sectional Study

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Abstract

Background: Obesity is currently a worldwide health crisis. Nurses are integral members of the primary health care team and have an important role in managing obesity and administering physical activity (PA) for patients. However, research shows that nurses tend to be overweight or obese, have poor metabolic health, and do not meet PA recommendations. This is problematic because PA is linked to both physiological and psychological well-being and may also influence how nurses counsel their patients. Nursing students are the next generation of nurses; however, there is limited research examining PA (among other lifestyle factors) and metabolic health in nursing students.

Objective: The goal of this research is to examine multiple lifestyle factors (including PA, nutrition, sleep, and stress) and determine whether these factors are associated with metabolic health in full-time undergraduate nursing students.

Methods: An estimated 320 nursing students (18 years of age and older) will be assessed for their metabolic health. Metabolic status will be determined by measuring body mass index (BMI), waist-to-hip ratio (WHR), body fat percentage [skinfold measures (FitSystems Inc)], resting blood pressure [automated oscillatory (Omron Healthcare Inc)], and fasting blood glucose (glucometer). Lifestyle factors will also be measured, including PA and sleep [the International Physical Activity Questionnaire (IPAQ) and 7-day accelerometry (wGT3X-BT, Actigraph LLC)], nutrition [3-day diet log (Nutritionist Pro, Axxya Systems)], and stress [the Depression Anxiety Stress Scale, heart rate variability assessments, and salivary cortisol (ELISA, Eagle Biosciences)]. The association between metabolic status and PA, sleep quantity and quality, nutrition, and stress will be examined by linear regression analyses. Differences by year of study in metabolic health status, PA, sleep, nutrition, and stress will be examined by 1-way analyses of variance (ANOVAs). To determine the ability of PA, sleep, nutrition, and stress to discriminate prevalent overweight and obesity or poor metabolic status, logistic regression and receiver operating characteristic (ROC) curves will be constructed. Statistical analyses will be performed in Stata (version 16.1, StataCorp LLC).

Results: Based on pilot data, we believe senior nursing students will have worse metabolic health (ie, higher BMI and WHR, increased body fat percentage, higher blood pressure, and increased fasting blood glucose) compared to first-year students. We hypothesize that poor PA participation, poor sleep quantity and quality, increased food intake, poor nutrition, and increased stress will be associated with worse metabolic health in full-time nursing students. The study received funding in February 2020. Due to the coronavirus disease 2019 (COVID-19) pandemic, work on this study has been delayed. We are currently completing our application for institutional research ethics approval. Data collection is projected to begin in January 2021, with data collection and analyses expected to be completed by May 2022.

Conclusions: This study will be the first published research to examine the relationship between lifestyle choices and metabolic status in nursing students attending a Canadian institution. More importantly, the results of this study will support the development of an informed intervention that will target the identified lifestyle factors, improving the physiological and mental health and well-being of nursing students.

KEYWORDS

nursing; students; metabolic health; physical activity; sleep; nutrition; stress

Introduction

Background and Rationale

Obesity is a current international epidemic [1], and it has become a global priority to reduce the burden of obesity [2]. Primary health care workers, which include registered nurses (RNs), interact closely with patients and therefore have an important role in managing an individual's obesity and associated secondary diseases. The critical role of nurses as agents of change in addressing the issue of obesity has been highlighted [3]. Unfortunately, research suggests that RNs themselves have a high level of obesity [4,5], more than the general population [6]. In addition to high rates of obesity, RNs do not meet international recommendations of 150 minutes per week [7] of moderate to vigorous physical activity (PA) [8,9]. One study reported that less than 30% of RNs sampled engaged in moderate-intensity PA [10]. Another study found that average body mass index (BMI) placed RNs (n=400) in the overweight category (>27 kg/m^2), and many had elevated waist circumference [11]. Furthermore, only 23% met the recommended PA guidelines [11]. Overall, research demonstrates that RNs tend to be overweight or obese and are not meeting exercise recommendations.

High obesity rates and sedentary behavior in RNs are particularly concerning for two reasons. First, a nurse's own behavior may influence their nursing practice. Indeed, RNs who exercise regularly are more likely to promote PA to their patients compared to those who are sedentary [10]. In addition to potentially impacting patient care, obesity and sedentary behavior in RNs are concerning because nurses are not optimizing their own physical and mental health. RNs who are overweight or obese suffer from impaired cardiovascular and metabolic health [11]. As well, the nursing profession is associated with high levels of psychological stress [12,13] and high rates of depression compared to the general population [14,15]. It is widely recognized that PA is important for maintaining both physiological and mental health [16,17]. Physical inactivity may actually worsen mental health in RNs; in one study, physical inactivity was associated with psychological distress, even after adjusting for age, job demands, and job control, among other factors [18]. Sleep also contributes to mental health and overall well-being [19], and RNs report being fatigued and having poor sleep habits [20-22]. Shift work is associated with higher BMI and waist-to-hip ratio (WHR) [23], while participation in PA is associated with improved sleep in non-nurse populations [24-27]. Thus, obesity, poor PA, and reduced sleep are concerning in RNs, considering the negative effect of such lifestyle choices on nurses' physiological and mental health.

Nursing students are a unique population of primary care providers as they are still engaged in education, and therefore, there is an opportunity to educate students regarding the importance of lifestyle choices for themselves and their patients. Unfortunately, research to date indicates that similar to RNs, nursing students also have poor physical fitness behaviors [28], and they tend to participate in less PA compared to non-nursing students [29]. However, there is limited published data that objectively characterizes obesity and PA in nursing students. Therefore, we recently conducted a pilot study that examined PA and overweight and obesity status in a small cohort of nursing students attending a Canadian institution [30]. BMI and WHR were measured, and PA was objectively assessed via 7-day accelerometry in 43 full-time nursing students. Participants were classified into 3 groups based on their nursing program year: first year (n=13), second year (n=10), and third/fourth year (n=20). Mean body weight was higher in second and third/fourth-year students compared to first-year students. Similarly, BMI was higher in second-year students (23.7 ± 1.9 kg/m^2) and third/fourth-year students (25.4 ± 2.5 kg/m^2) compared to first-year students (20.3 ± 2.3 kg/m^2; *P*=.005). Mean WHR was higher in third/fourth-year students (0.81 ± 0.06 cm) compared to first-year students (0.77 ± 0.04 cm; *P*=.04). Students were primarily sedentary (mean time spent sedentary was 81.7 ± 4.4%) and only engaged in an average of 9.9 ± 8.8 minutes of vigorous activity per day. Our pilot study results indicate that nursing students are highly inactive and that metabolic status based on BMI and WHR is worse in senior students [30].

We observed in our pilot study that nursing students are highly sedentary; however, it is important to note that PA is likely not the only factor that contributes to weight and obesity status in nursing students. For example, nutrition and food intake are directly correlated with BMI and WHR in RNs [31], and increased meal intake and poor nutrition are prevalent in shift workers [32]. As previously mentioned, poor sleep [33,34] and stress all likely contribute to worse metabolic health and overall well-being of nursing students. There is currently no study that examines the association of multiple lifestyle factors (including PA, nutrition, sleep, and stress) and metabolic health in a cohort of nursing students.

Purpose and Objectives

The current study will expand upon previous research [30] and will characterize the factors that discriminate metabolic health of undergraduate nursing students attending a Canadian university. To this end, the objective of this study is to determine what factors are associated with metabolic health (measured by BMI, WHR, body fat percentage, blood pressure, and fasting glucose) in full-time undergraduate nursing students. More specifically, we will examine whether objectively measured

PA, sleep, nutrition, or stress are associated with poor metabolic health status in a cohort of nursing students.

Based on pilot data [30], we believe that senior nursing students will have worse metabolic health (ie, higher BMI, higher WHR, increased body fat percentage, elevated blood pressure, and increased fasting blood glucose) compared to first-year students. We also hypothesize that poor PA participation, poor sleep quantity and quality, increased food intake, poor nutrition, and increased stress will be associated with worse metabolic health in full-time nursing students.

Significance

The current study will be the first published research to examine the relationship between lifestyle choices and metabolic status in nursing students attending a Canadian institution. More importantly, the results of this study will be used to inform a lifestyle intervention for nursing students. To our knowledge, there are only 2 published PA and lifestyle intervention studies that target nursing students. In one study, nursing students and student midwives (N=182) from the UK were randomized into a control or an intervention group. Students in the intervention group received an education package and created a nutrition and physical activity plan. Following the 4-month intervention, the BMI of the overweight participants decreased, indicating that education and accountability may influence exercise participation in nursing and midwifery students [35]. In a second study, a convenience sample of 30 nursing students from a university in the United States who wanted to increase their PA levels were invited to participate in an exercise intervention. Students were asked to exercise for 30 minutes at least 3 times per week. Following one university semester of the intervention, students had reduced body fat percentages and BMIs, and higher levels of self-reported PA [36]. These studies support the idea that a lifestyle intervention can positively affect metabolic health status in nursing students.

The results of this study will directly inform a lifestyle intervention for nursing students that targets the improvement of their health and well-being, specifically addressing the most prominent factors associated with their poor metabolic health status. For example, if reduced PA, poor nutrition, and lack of sleep are all associated with worse metabolic health in nursing students, the developed intervention will focus on improving these outcomes. The development of an intervention will target the improvement of both the physical and mental health of nursing students. This intervention has the potential to influence future nursing practice since research highlights that RNs who are physically active will be more likely to counsel their patients to be physically active [10].

Methods

Overview of Study Design, Timeline, and Participant Selection

In this cross-sectional study, students enrolled in a school of nursing in an Ontario university in Canada will be invited to participate. A member of the research team will approach students in multiple ways, such as through classroom announcements, a post on the online learning system portal, posters, and word of mouth. Members of the research team who will approach and consent students will have no association with the students' courses or academic work. Each year, the school of nursing enrolls approximately 200 students. We will aim to include approximately half of all students (ie, 80 students from each of the four years of nursing studies) to participate in the study (N=320). Our primary research objective is to examine multiple lifestyle factors (including PA, nutrition, sleep, and stress) and determine whether these factors are associated with metabolic health in full-time undergraduate nursing students; thus, we calculated our sample size based on our pilot data [30], which included an observed coefficient of determination value (R^2) of 0.25 when we conducted a linear regression that examined whether participation in sedentary, light, moderate, and vigorous activity was associated with BMI. We determined that for a 2-tailed regression analysis with 4 predictors, a total sample size of 87 is required to provide us with statistical power of 0.95. Since we may have more than 4 predictors (participation in sedentary, light, moderate, and vigorous activity; nutrition, which may include total kilocalories (kcals); sleep, which may include total sleep; and stress), we also determined that for a 2-tailed regression analysis with 7 predictors, a total sample size of 103 is required to provide us with statistical power of 0.95. Thus, our sample size of 320 students is more than adequate. We chose to target a total of 320 students as we wanted to have a sufficient representation of those attending the nursing program.

Ideally, we will recruit all participants during 1 academic year. If required, we will extend our recruitment and data collection over a second academic year. Specific inclusion criteria are (1) students enrolled in full-time nursing studies, (2) ≥18 years of age, and (3) signed informed consent. Only nursing students will be included in the current study (ie, there is no non-nursing student control group), since a comparison group is not required to address our research objective of examining discriminators of metabolic status in nursing students. Once the consent form is signed, students will meet with a member of the research team for their study visit (Figure 1). Only 1 study visit is required, which is estimated to take 60-90 minutes in total; therefore, this study involves minimal participant time commitment. Upon study completion, participants will receive a gift card to a popular snack or coffee location on the university campus.

Figure 1. Illustration of the study timeline; BP: blood pressure, DASS: Depression Anxiety Stress Scale, HRV: heart rate variability, IPAQ: International Physical Activity Questionnaire, PA: physical activity, WHR: waist-to-hip ratio.
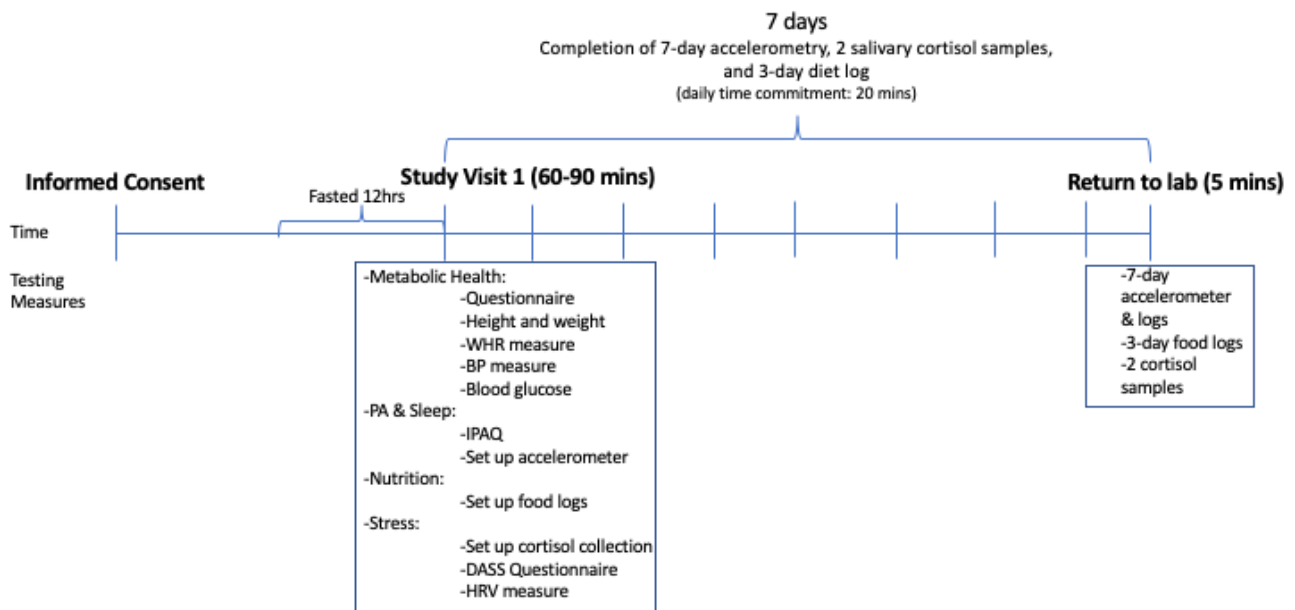
Assessments

Metabolic Health Measures

Metabolic health will be assessed by measuring obesity (BMI, WHR, body fat percentage), blood pressure, and fasting blood glucose, which are components of metabolic syndrome [37].

Participants will meet with a member of the research team and will complete a demographic questionnaire which includes information related to previous university or college studies, year of study in nursing, general health (ie, presence of any chronic diseases, use of medication), current living arrangements (ie, on-campus or off-campus with a commute), whether students are currently working or volunteering on the side, other health-related habits (such as drinking alcohol and smoking), as well as past history of PA participation. To further understand participation in PA over the past year, participants will complete the Modifiable Activity Questionnaire [38], which has been used to assess associations between physical activity and metabolic health in adults [39]. Participants will have their height (in centimeters) and weight (in kilograms) measured using a stationary research-grade stadiometer and scale. BMI will be calculated from the height and weight measurements: weight (kg)/height (m)^2 [40]. Waist and hip measurements will be recorded as per the World Health Organization's (WHO) guidelines using a Gulick tape measure [41]. At each site, 3 measurements will be taken, and they will be repeated if the measurements fall more than 1 centimeter away. The average value will be used to calculate the WHR: waist circumference (cm)/hip circumference (cm). Skinfold measures will be obtained using a Slim Guide skinfold caliper (FitSystems Inc). Measures will be obtained at the triceps, biceps, subscapular, suprailiac, and medial calf. Body fat percentage will be calculated using equations established by Durnin and Womersley (1974) [42].

Resting blood pressure (BP) will be measured using an automated oscillatory device (Omron Healthcare Inc) placed on the nondominant upper arm. Participants will be in a seated position for approximately 5 minutes prior to measurement. Two BP readings will be taken 60 seconds apart. An average of the 2 readings will be used.

Participants will be asked to fast (ie, to consume no food or drink other than water) for 12 hours prior to their study visit. Blood glucose will be measured using a standard glucometer; the third finger of the nondominant hand will be cleaned with an alcohol wipe and lanced using a single-use lancet. Blood will be collected on a test strip and measured via the glucometer.

Physical Activity and Sleep

Daily activity and participation in PA will be measured using 2 methods: (1) the International Physical Activity Questionnaire (IPAQ) and (2) objectively, via an accelerometer (wGT3X-BT, ActiGraph LLC).

Students will complete the IPAQ at their study visit. The IPAQ was developed in 1998 and is a validated questionnaire (across 12 countries) [43] that measures the PA and exercise that individuals complete as part of their everyday lives. It characterizes PA habits in the previous 7 days and considers physical activities of daily living, recreation, sport, and leisure time. The IPAQ contains 27 questions, is self-administered, and takes approximately 10 minutes to complete.

At their study visit, participants will be provided with an accelerometer (wGT3X-BT, ActiGraph LLC) to quantitatively measure activity and sleep. The wGT3X-BT accelerometer measures movement along 3 different axes: x-, y-, and z-axes. It is a valid PA measurement tool across many types and intensities of PA [44] that has been used previously to quantify PA in nurses [11] as well as in health professional students (including student nurses) [45]. Participants will wear the accelerometer on their nondominant hip (either clipped on their

clothes or using a provided monitor belt) for 7 consecutive days [46], and on their nondominant wrist (using a wrist attachment) during sleep [47,48]. Participants will be instructed to wear the monitor during all waking and sleep hours, and to only remove the device during a shower or to partake in water-based activities. They will be asked to keep a detailed activity and sleep log, recording information such as when purposeful exercise occurs, sleep quality, and tiredness. Participants will be encouraged to maintain their regular activity levels and sleep habits.

After the 7-day data collection, the participant will return the accelerometer and the activity and sleep log. The accelerometer data will be downloaded using ActiLife software (version 6.13.3, ActiGraph LLC), with data further exported to Excel (version 16.4, Microsoft) to complete analyses. We will require a minimum of 4 days of accelerometer wear (confirmed by activity logs) for a participant's data to be considered valid [49,50]. We will not exclude prolonged bouts of inactivity that is accounted for because students may be attending class or might study for prolonged periods of time in a stationary position. If necessary, we will compare activity logs to the daily accelerometry activity records and exclude days where the accelerometer was not worn for >60 consecutive minutes for unaccounted reasons. The intensity of PA will be determined by counts per minute using the Freedson Adult algorithm [51]. These intensity cut-offs were used by our pilot study [30] and another study that examined daily PA via accelerometry in health professional students [45]. Data from the accelerometer will show the total kcals expended per day and the amount of time engaged in sedentary, light, or moderate/vigorous-intensity activity per day, as well as data on sleep times, sleep latency, and sleep efficiency [47].

Nutrition

During the same week as their accelerometry data collection, participants will complete a consecutive 3-day diet log (which includes 2 days of the week and 1 day of the weekend) and record all food intake. A 3-day diet log is commonly used to assess nutritional intake [52,53]. Logs will be analyzed with Nutritionist Pro software (Axxya Systems) for multiple outcomes, including total kcal intake and macro and micronutrient content.

Stress and Psychological Health

Levels of stress will be assessed using 3 methods: (1) a biochemical analysis of levels of salivary cortisol; (2) resting measures of heart rate variability (HRV), which can provide information on autonomic balance (sympathetic and parasympathetic tone); and (3) the Depression Anxiety Stress Scale (DASS).

For the biochemical analysis of salivary cortisol, participants will be asked to submit 2 saliva samples. Participants will collect 2 saliva samples (4-5 ml) in provided sample tubes, once during the morning and once during the evening on the first full day of their accelerometry collection week. Participants will record the day and time of their saliva sample collection, and will keep the salivary samples in the freezer until they are able to return their samples to the research laboratory. Samples will be transported back to the lab in a cooler. Cortisol, which is

reflective of current stress levels, will be analyzed via ELISA (Eagle Biosciences).

For analysis of HRV, participants will have their heart rate monitored in lab at their study visit (following the collection of metabolic health measures) for 10 minutes in the supine position and 10 minutes in the standing position using a GPS sports watch (Polar V800). This information will be downloaded using Flowsync software (Polar) and analyzed using Kubios HRV software (Kubios Oy), which performs a fast Fourier transformation on the data collected to determine autonomic balance.

Students will complete the DASS at their study visit. The DASS is a widely used tool that has been validated in many populations to assess the emotional states of depression, anxiety, and stress [54]. There are reference values to which DASS scores can be compared [55]. It is important to note that the DASS does not measure clinical outcomes but rather the emotional states of anxiety, stress, and depression. The DASS is not intended to be used as a diagnostic tool for clinical cases. It considers how an individual has felt over the past week and is a 42-question scale that will take approximately 15 minutes to complete.

Statistical Analysis

The demographic characteristics of the participants will be assessed using descriptive statistics. The association between metabolic status (BMI, WHR, body fat percentage, blood pressure, and fasting blood glucose) and PA outcomes, sleep quantity and quality, nutrition, and stress will be examined by linear regression analyses. To examine differences by year of study, 1-way analyses of variance (ANOVAs) will be conducted comparing metabolic health status, PA, sleep, nutrition, and stress. Bonferroni post-hoc testing will be conducted if significant group differences are present. To determine the association between PA, sleep, nutrition, and stress with metabolic health (ie, BMI, WHR, blood pressure, blood glucose), we will conduct linear regression analyses in all nursing students, and by year of study.

To determine the ability of PA, sleep, nutrition, and stress to discriminate prevalent overweight and obesity, participants will be placed into one of 2 groups: overweight or obese versus not overweight or obese, based on the WHO's BMI and WHR cut-offs [40]. Logistic regression and receiver operating characteristic (ROC) curves will be constructed for each lifestyle variable [expressed as area under the ROC curves (AUROC) with 95% confidence intervals (CI)]. Similar analyses will be conducted using a composite indicator of metabolic status (incorporating obesity status, blood pressure, and fasting blood glucose). Additional analyses adjusted for age, gender, year of nursing study (including exposure to practicum), semester of school, and other potential confounding variables (such as prior physical activity habits) will be conducted as deemed necessary. Statistical analyses will be performed in Stata (version 16.1, StataCorp LLC).

Results

Following the completion of this study, we expect to characterize the metabolic status, PA habits, sleep quantity and

quality, food intake and nutritional status, and stress levels in nursing students attending a Canadian institution. We also expect to determine if PA, sleep, nutrition, or stress are associated with or discriminate obesity and metabolic status in nursing students.

The study received funding in February 2020. Due to the coronavirus disease 2019 (COVID-19) pandemic, work on this study has been delayed. We are currently completing our application for institutional research ethics approval. Data collection is projected to begin in January 2021, with data collection and analyses expected to be completed by May 2022.

Discussion

This study will be the first to examine multiple factors associated with metabolic health in a cohort of nursing students attending a Canadian institution. This paper describes a cross-sectional study designed to characterize PA, sleep, nutrition, and stress of nursing students, and it will determine which of these factors are associated with metabolic health (BMI, WHR, body fat percentage, blood pressure, and blood glucose). Ultimately, the goal of our research program is to develop a supported and informed intervention that targets the improvement of the most prominent factors associated with poor metabolic health status in nursing students. This cross-sectional study is necessary as it will allow us to identify the factors impacting the metabolic health of Canadian nursing students and, therefore, to determine which factors should be targetted with an appropriate intervention. The use of "exercise as medicine," among other lifestyle intervention approaches, has gained attention from researchers and health care professionals, since exercise is a potent method of reducing the prevalence of obesity and improving multiple health outcomes [56].

It is important to note that although we are measuring some important lifestyle factors (such as diet, physical activity, sleep, and stress), the current study does not consider all individual-environment interactions or structural environmental factors that may impact the metabolic health of nursing students. For example, one study in the UK that examined food intake in (non-nursing) university students suggested that university policies aimed at improving student diets should incorporate student engagement in food preparation and increased access to healthy, low-cost food [57]. Thus, socioeconomic status may play a role in the lifestyle and health of university students. Similarly, the distance a student lives in relation to their university campus may impact their health. One study of over 700 university students examined the presence of metabolic syndrome in students who were active commuters (ie, walked to campus) versus students who took motorized transport to campus (such as a car or bus); the prevalence of metabolic syndrome was almost 9% higher in the students who did not actively commute to school [58]. Therefore, students who are able to live close to campus (due to a variety of reasons, including socioeconomic ones) and engage in active commuting may have better metabolic health. Another factor that may influence participation in physical activity at the university level is the presence of a disability; one research study demonstrated that a large number of university students with an identified disability did not meet the WHO's physical activity guidelines; therefore, special consideration of students who identify with a disability (and not just physical disabilities) is needed [59]. As well, higher academic achievement has been associated with better PA habits in university medical school students [60]. Thus, it is important to recognize that there are additional factors that are not being explored in the current study that may independently influence the metabolic health and lifestyle choices of university students, including nursing students. This study is a preliminary study characterizing some of the metabolic health and lifestyle factors in nursing students.

There are additional limitations to this study. This study will allow us to determine which factors correlate with the metabolic health of nursing students; however, we will be unable to determine whether these factors are directly causative (although it is likely that there are multiple factors that contribute to poor metabolic health of nursing students). Furthermore, we are not following students longitudinally; rather, we are examining the profile of the student population at one given time. Since we intend to use the results of this study to inform a lifestyle intervention, we believe these limitations are not problematic, as we are interested in learning which factors might be best to target with our intervention.

In conclusion, this study will provide valuable data describing the nursing student cohort at a Canadian institution. It will ultimately support an informed lifestyle intervention that will target the improvement of the physiological and mental health and well-being of nursing students, as well as education related to the importance of lifestyle choices for themselves and their future patients.

Authors' Contributions

SLW, HB, and IKM designed the study. JW will lead data collection, and SLW, HB, and IKM will oversee data collection and analyses. SLW wrote the initial manuscript draft, and HB, JW, and IKM significantly contributed to the revision of the manuscript. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review reports from Trent/Fleming School of Nursing Research Grant Program.
[DOCX File , 26 KB - resprot_v9i8e21342_app1.docx]

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Abbreviations

ANOVA: analysis of variance
AUROC: area under the receiver operating characteristic curve
BMI: body mass index
BP: blood pressure
COVID-19: coronavirus disease 2019
DASS: Depression Anxiety Stress Scale
HRV: heart rate variability
IPAQ: International Physical Activity Questionnaire
kcal: kilocalorie
PA: physical activity
RN: registered nurse
ROC: receiver operating characteristic
WHR: waist-to-hip ratio
WHO: World Health Organization

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<u>Protocol</u>

Closing the COVID-19 Psychological Treatment Gap for Cancer Patients in Alberta: Protocol for the Implementation and Evaluation of Text4Hope-Cancer Care

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Abstract

Background: Cancer diagnoses and treatments usually engender significant anxiety and depressive symptoms in patients, close relatives, and caregivers. Providing psychological support during the coronavirus disease (COVID-19) pandemic presents additional challenges due to self-isolation and social or physical distancing measures in place to limit viral spread. This protocol describes the use of text messaging (Text4Hope-Cancer Care) as a convenient, cost-effective, and accessible population-level mental health intervention. As demonstrated in previous research, this evidence-based program supports good outcomes and high user satisfaction.

Objective: We will implement daily supportive text messaging as a way of reducing and managing anxiety and depression related to cancer diagnosis and treatment in Alberta, Canada. Prevalence of anxiety and depressive symptoms, their demographic correlates, and Text4Hope-Cancer Care–induced changes in anxiety and depression will be evaluated.

Methods: Alberta residents with a cancer diagnosis and the close relatives of those dealing with a cancer diagnosis can self-subscribe to the Text4Hope-Cancer Care program by texting "CancerCare" to a dedicated text number. Self-administered, anonymous, online questionnaires will be used to assess anxiety and depressive symptoms using the Hospital Anxiety and Depression Scale (HADS). Data will be collected at onset from individuals receiving text messages, and at the mid- and endpoints of the program (ie, at 6 and 12 weeks, respectively). Data will be analyzed with parametric and nonparametric statistics for primary outcomes (ie, anxiety and depressive symptoms) and usage metrics, including the number of subscribers and user satisfaction. In addition, data mining and machine learning analysis will focus on determining subscriber characteristics that predict high levels of symptoms of mental disorders, and may subsequently predict changes in those measures in response to the Text4Hope-Cancer Care program.

Results: The first research stage, which was completed in April 2020, involved the creation and review of the supportive text messages and uploading of messages into a web-based text messaging service. The second stage, involving the launch of the Text4Hope-Cancer Care program, occurred in May 2020.

Conclusions: Text4Hope-Cancer Care has the potential to provide key information regarding the prevalence rates of anxiety and depressive symptoms in patients diagnosed or receiving care for cancer and their caregivers. The study will generate demographic correlates of anxiety and depression, and outcome data related to this scalable, population-level intervention. Information from this study will be valuable for health care practitioners working in cancer care and may help inform policy and decision making regarding psychological interventions for cancer care.

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Introduction

Background

Cancer is a leading aspect of the global burden of disease [1] and the second leading cause of death internationally [2]. In 2018, 1 in 6 deaths worldwide (9.6 million deaths) were attributed to cancer [2]. The total annual economic cost of cancer in 2010 was estimated to be approximately USD $1.16 trillion, and the economic impact of cancer is significant and increasing [3]. The same trend exists in Canada, where cancer is the leading cause of death, responsible for about 30% of deaths [2]. Based on 2015 estimates, 1 in 2 Canadians are expected to develop cancer during their lifetime and 1 in 4 are expected to die from it; current figures estimate 225,800 new cancer cases and 83,300 deaths in 2020 [4]. In Alberta, about 1 in 2 Albertans will reportedly develop cancer, with 20,473 anticipated cases [5]. Furthermore, mental illnesses are the most prevalent disabilities in Canada, generating at least 70% of documented costs with a cumulative annual economic impact of approximately CAD $8 billion in direct costs (ie, hospital and physician visits and medications), and CAD $11-50 billion in indirect costs [6].

A new cancer diagnosis places significant emotional strain on individuals and their caregivers and is associated with an increased risk for common psychiatric disorders [7]. After cancer diagnosis, emphasis is necessarily placed on physical treatment, with limited attention on associated psychological complications [8].

The prevalence of anxiety and depression amongst patients with cancer varies; mean depression prevalence estimate from diagnostic interviews is 13% among cancer patients, with a range from 4%-49% depending on context and assessment methods [9]. An estimated 20%-30% of diagnosed patients develop depression and anxiety [10,11]. Patients with incurable disease report higher levels of anxiety and depression, compared with patients who can be cured [12]. Depression and anxiety may adversely impact treatment and outcomes for patients with cancer [7,8,13]. For patients with cancer diagnoses that exhibit poorer outcomes, such as lung cancer, the risk of suicide is higher than in the general population, and more so within the first 6 months postdiagnosis [14,15]. Patients who previously accessed mental health services are at increased risk of poorer outcomes, including greater risk of mortality after a cancer diagnosis [16]. As such, early assessment and treatment of these mental health conditions may produce a beneficial effect, particularly with respect to anxiety symptoms [2,17,18].

While determinants of the development of psychological distress or mental illness in cancer patients are not well understood [8,19], several factors have been proposed, including age, gender, lack of social support, unemployment, and fewer educational qualifications [8,20]. Several factors related to the cancer itself may also lead to the development of mental illness, including the type and stage of cancer, prognosis, and treatments offered and received [8]. Stigma arising from certain types of cancers (eg, lung cancer and tobacco use) and associated guilt may increase anxiety, interfere with sleep, and lead to depression [21,22]. The availability of clinical support and clear, simple communication can help reduce cancer patient confusion and distress [8].

A recent review showed that anxiety was more prevalent among cancer survivors than controls across all cancer types [23]. With survival rates for cancer improving with early detection and treatment, the failure to address psychological issues for cancer patients may reduce cancer survivor productivity and economic viability, thereby increasing the overall illness burden for patients, caregivers, and the health care system [24].

Several studies demonstrate correlations between levels of psychological distress in cancer patients and their families [25]. Cancer causes emotional distress in patents' and their families' lives. While the emphasis is on treating the physical symptoms of patients with cancer, families and caregivers who are also affected have limited support and/or restricted access to psychological treatment for their distress. This is a treatment gap that needs filling.

Provision of psychological services from diagnosis through treatment and rehabilitation may help cancer patients, families, and caregivers address the burden of psychological distress arising from their diagnosis. It is likely that significant and ongoing barriers to cancer patients accessing psychological supports have increased during the coronavirus disease (COVID-19) pandemic. Presently, cancer psychological services are either embedded in the cancer service itself, offered through community mental health services, or accessed privately. In Canada, these specialized services are usually located in urban areas, forming service clusters, thereby limiting access for patients, families, or caregivers who are remotely situated or self-isolating. In times of crisis, the mental health needs of cancer patients are anticipated to increase, but their service access may be restricted by medical service and public health constraints related to COVID-19. This creates a critical gap in service provision and care for these patients. To bridge this gap,

there is a global call to embrace and adopt nontraditional means to service the mental health needs of vulnerable populations. Options include incorporating existing technologies such as telepsychiatry, internet-based cognitive behavior therapy (CBT) [26], and mobile messaging services [27]. Patients located in less populated or rural communities may find these services helpful in bridging the gap in care and provision of services.

The use of cellphones has become an integral part of daily living for a majority of the population. Mobile messaging services can be asynchronous, geographically independent, tailored, and contextualized for vulnerable groups. Text messaging is often economical (cents per message) or free for end users and does not require technical skills for use or expensive data plans; furthermore, almost 90% of Canadians own a smartphone [28]. Supportive text messages are associated with positive clinical outcomes in community settings, including a reduction in depressive symptoms and increased abstinence duration in alcohol use disorder [27,29]. In two user satisfaction surveys, over 80% of subscribers reported that a supportive text messaging program improved their mental health [27,30]. It is also a low-cost adjuvant to care that can be received at home when self-isolating and may be used to bridge the psychological treatment gap for medically vulnerable patients, including cancer patients, and particularly for those in remote or rural areas to improve service accessibility.

To help address the potential stressors and mental health difficulties that inevitably arise during emergencies, Alberta Health Services (AHS), in collaboration with six health foundations and the Department of Psychiatry at the University of Alberta, launched the Text4Hope-Cancer Care program. Text4Hope-Cancer Care is an evidence-based tool providing daily free CBT-based text messages for 3 months to individuals who self-subscribe to the program. It evolved from the pre-existing program infrastructure supporting the Text4Mood program, initially launched in January 2016 to support individuals in the aftermath of the 2016 Fort McMurray fires [27]. It was launched as Text4Hope [31] in March 2020 during the COVID-19 pandemic in order to improve access to psychological care in a cost-effective and timely manner to individuals who are self-isolating. For cancer patients in remote areas and for those self-isolating, there is an even greater urgency to support them, particularly when access to services is restricted. As an evidence-based bridge to achieve this, the Text4Hope-Cancer Care program is a distinct arm of the Text4Hope program. The messages are intended to help individuals identify and adjust negative thoughts, feelings, and behaviors arising from a cancer diagnosis and treatment as well as the COVID-19 pandemic.

Objective

This protocol describes the implementation and evaluation of a low-cost, evidence-based, supportive text message service for cancer patients in Alberta. The objective of the project is to implement a self-subscribing daily supportive text message program to close the psychological treatment gap and reduce anxiety and depression related to cancer diagnosis. Research questions include:

1. Will the supportive text message program help to reduce anxiety and depressive symptoms among Albertan cancer patients and their caregivers?
2. What are the prevalence rates of anxiety and depressive symptoms in cancer patients and their caregivers who subscribe to the program?
3. What are the demographic correlates of anxiety and depressive symptoms in cancer patients and their caregivers who subscribe to the program?
4. Do demographic variables affect anxiety and depression amongst cancer patients and their caregivers when quarantined?
5. Will cancer patients and their caregivers be satisfied with receiving this method of care and support during the pandemic?

Methods

Evaluation Methodology and Measurement Plan

Patients diagnosed or receiving treatment for cancer and their caregivers can self-subscribe to receive daily supportive text messages for 3 months by texting the word "CancerCare" to 393939. The messages align with a cognitive behavioral framework and were developed by a clinical psychologist (MH), then reviewed and revised by a multidisciplinary team consisting of psychiatrists, mental health therapists, and counselors who work with cancer patients and their caregivers. Examples of the Text4Hope-Cancer Care messages are shown in Textbox 1.

Textbox 1. Text4Hope-Cancer Care messages.

- Advocate for your needs using assertiveness. Assertiveness is being respectful to you and the other person. Be direct, non-aggressive, and specific.
- Do things you enjoy. These activities can remind you who you are, and take your mind off cancer for a while.
- Cancer affects the whole family. To help you and your family cope, try to: maximize quality time together, communicate, and create a schedule together.

Messages are preprogramed into a web-based text messaging service for online delivery at 12 PM each day. At the onset, and via the first message, respondents are welcomed to the service and invited to complete an online baseline survey capturing demographic information, COVID-19–related self-isolation/quarantine information, and self-reported responses on the Hospital Anxiety and Depression Scale (HADS) [32].

HADS is comprised of 14 questions, each of which has four answer options, with a total score calculated out of a possible 21 points. A total score of 0-7 is considered *Normal*, 8-10 is considered *Borderline Abnormal (Borderline Case)*, and 11-21 is considered *Abnormal (Case)*. HADS is the main measurement tool for the effectiveness of the Text4Hope-Cancer Care program.

Survey questions will be programed into Select Survey, an online survey tool, operated by AHS. Respondents will receive no incentives or inducements for participating in the program. Participation in the program is voluntary, and completion of the survey will not preclude receipt of subsequent supportive text messages. Subscribers may opt-out at any time by texting "Stop" to 393939. Survey responses will be stored on an AHS server and data will be exported and analyzed by the research team. Ethics approval has been granted by the University of Alberta Health Research Ethics Board (Pro00086163).

Sample Size Considerations

Based on annual cancer diagnoses in Alberta, we expect about 20,000 patients with cancer and their caregivers to subscribe to the supportive text message program over the next year. Given a previous response rate of 21.7% for the Text4Mood survey [33], we anticipate around 4000 survey responses over the next 12 months.

Outcome Measures

The primary outcome is changes in HADS scores at 6 and 12 weeks from baseline. The secondary outcomes are (1) interaction between primary outcomes and the demographic characteristics of subscribers and self-isolation/quarantine status during the pandemic; and (2) subscriber satisfaction and experience.

We will implement and evaluate the Text4Hope-Cancer Care program 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: Acceptability (subscriber satisfaction/experience), Accessibility (number of cancer patients and their caregivers that subscribe to and complete the program and ease of subscription to and utilization of Text4Hope-Cancer Care), Appropriateness (subscriber feedback related to how helpful the daily messages have been during the COVID-19 pandemic), and Effectiveness (6- and 12-week changes in the HADS). It may also be possible to examine Efficiency (cost avoidance and efficiencies through the reduced need for face-to-face counseling) and Safety (self-reports of decreased crisis and urgent service calls and decreased emergency medical services utilization rates).

Hypotheses

Our hypotheses, based on previous research, are that: (1) higher rates of anxiety and depression will be reported among cancer patients and their caregivers who subscribe to the program compared to rates of these disorders in the general population; (2) specific risk factors will be found for the experience of anxiety and depression, such as female gender, self-isolation and quarantine status, and social determinants of health (eg, employment, housing); (3) the intervention will result in a 25% or greater reduction in anxiety and depressive symptoms (as measured by the HADS) at 6 and 12 weeks from baseline; (4) at least 80% of subscribers will express satisfaction with the supportive text message program and perceive the daily supportive text messages as contributing to their overall mental well-being.

Data Analysis

We will evaluate the impact of Text4Hope-Cancer Care by analyzing the change of anxiety and depression symptoms at 6 and 12 weeks as reported on the HADS by subscribers. Data analysis will include 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 [27,29,36-39] indicates sufficient effect size for the expected Text4Hope-Cancer Care program subscriber sample size.

Results

The first research stage, which was completed in April 2020, involved the creation and review of the supportive text messages and uploading of messages into a web-based text messaging service. The second stage, involving the launch of the Text4Hope-Cancer Care program, occurred in May 2020. The remainder of the project will focus on data analysis and reporting.

Discussion

This research study proposes supportive text messaging to address a critical gap in psychological care for patients with cancer. The identification and management of emergent mental health issues for cancer patients has neither been addressed for Canadian nor other global jurisdictions during the COVID-19 pandemic. Similarly, the use of supported text messaging as a means of bridging the psychological treatment gap for cancer patients with mental health issues has not been studied previously. This study will offer support, independent of geographic location (urban, rural, or remote) or physical distancing, to cancer patients at a time when their mental health needs may be exacerbated by the COVID-19 pandemic. This approach will seek to ameliorate potential negative effects of self-isolation and social distancing measures in cancer patients and their access to psychological care in a cost-effective and responsive way. The study will make accessible and available psychological supports that would otherwise be inaccessible, risky, or significantly burdensome for patients to use, given their physical location, disease condition, or position on a waitlist. A significant portion of cancer patients do not take part in traditional psychological supports offered to them [40]. A plausible explanation for this may be an increased physical and mental tiredness, logistic difficulties getting to service locations, and geographic distance from the clinic, which may preclude their engagement in traditional, face-to-face, psychological support approaches. Using supportive text messaging to provide CBT-based psychological treatment at the individualized level may increase chances of participation and possibly improve engagement and outcome. This approach offers a nimble support system that may reach an individual at virtually any location and enables scalable access to a larger, geographically disparate population, fitting the demography of Canada and many other nations, including low and middle-income countries and the Asia-Pacific Economic Cooperation community.

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A limitation of the study design is that it may selectively appeal to younger cancer patients and caregivers who have greater flexibility with the use of text messages, thereby producing selection bias. As well, phone service coverage may not be uniform throughout the province, with denser coverage for city populations, which may skew the findings toward a more urban population with a higher educational level. Finally, rates of anxiety and depression to be reported in our study will be based on a standardized self-rated scale (ie, the HADS) rather than clinical interviews using the Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition (DSM-5).

Acknowledgments

Authors' Contributions

VIOA conceived and designed the study, including the Text4Hope-Cancer Care program. MH created the bank of supportive text messages. RS contributed to creating the Text4Hope-Cancer Care program. VIOA and NN drafted the initial manuscript. All authors critically reviewed the manuscript and contributed to the final draft. All authors reviewed and approved the final draft of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AHS: Alberta Health Services
CBT: cognitive behavior therapy
COVID-19: coronavirus disease
DSM-5: Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition
HADS: Hospital Anxiety and Depression Scale
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance

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Protocol

Effect of Ankle Plantar Flexor Spasticity Level on Balance in Patients With Stroke: Protocol for a Cross-Sectional Study

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Abstract

Background: The lower limb spasticity after stroke can affect the balance and gait of patients with stroke.

Objective: The aim of this study is to assess the effects of ankle plantar flexor spasticity level on balance in patients with stroke.

Methods: Patients with stroke were recruited from neurology and physiotherapy clinics in Tehran, Iran. Based on the level of ankle plantar flexor spasticity according to the Modified Modified Ashworth Scale (MMAS), the eligible patients with stroke were divided into 2 groups: high spasticity (MMAS score≥2) and low spasticity (MMAS score<2). The primary outcome measures were the MMAS scores, Activities-Specific Balance Confidence questionnaire scores, eyes-open and eyes-closed posturography measures, and Timed Up and Go test results. The secondary outcome measures were the ankle passive range of motion and ankle joint proprioception. The t test, mixed model univariate analysis of variance, and Spearman rank correlation were used for statistical analysis.

Results: Data collection and statistical analysis are complete. The interpretation of results is underway. We expect the results to be published in winter 2020.

Conclusions: We believe that patients with high ankle plantar flexor spasticity after stroke will demonstrate greater balance dysfunction, which will worsen with impaired proprioception, passive range of motion, and eyes closed.

International Registered Report Identifier (IRRID): RR1-10.2196/16045

Introduction

Stroke is the most common cause of disability in adults worldwide. Spasticity is one of the most important motor complications after stroke and negatively affects patients' quality of life [1,2]. Spasticity is a velocity-dependent increase in muscle tone, resulting from hyperexcitability of the stretch reflex [3]. The lower limb spasticity has a critical role in balance and gait dysfunction of patients after stroke [4]. It decreases the joint range of motion (ROM) and increases the stiffness of the muscles and tissues around the joints. The impairment in balance and postural control is an important symptom in patients after stroke, because it can delay the recovery process in performing

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daily activities and increases the risk of falling [5]. A reduced balance control is associated with greater disability [6].

The somatosensory system, especially proprioception, is impaired in patients with stroke [7]. This impairment affects the motor function of the patients and prolongs their rehabilitation period. Consequently, the balance control is difficult for the patients with stroke due to impaired proprioception and inappropriate ankle strategies [8].

The evaluation of balance and of the factors contributing to the balance disorders, such as balance nonconfidence, in patients after stroke is necessary. The balance confidence indicates the patients' confidence to maintain their balance and stability. Balance nonconfidence can affect both static as well as dynamic balance and subsequently increases the chance of falling and disability. Decrease of static and dynamic balance is a significant risk factor of falling and a functional limitation of daily activity [9,10]. Balance has a direct relationship with functions such as walking and climbing the stairs [11]. Balance in patients with stroke is the key factor in the prediction of rehabilitation period and functional outcomes [12].

The lower limb spasticity can affect the gait quality and balance of patients after stroke [13]. The role of spasticity in falling and the direct relationship between the severity of spasticity and the history of falling have been demonstrated [14,15]. Rahimzadeh Khiabani et al [16] evaluated the relationship between spasticity severity and balance in patients with stroke. However, this study had several drawbacks. The severity of spasticity was measured based on the Modified Ashworth Scale (MAS), despite the debate on the scale's reliability and validity [17] and the caution against its use for assessing spasticity [18]. Furthermore, only static balance, not proprioception and ankle ROM, was evaluated. Therefore, the main objective of this study protocol is to investigate the effects of ankle plantar flexor spasticity level on the balance of patients with stroke. We hypothesized that the patients with high level of ankle plantar flexor spasticity have greater balance dysfunctions, especially in the eyes-closed condition, and that their balance confidence is lower than that of the patients with a low level of spasticity in the eyes-open condition.

There are no optimal tools for assessing balance in patients with stroke. This study assessed the balance using valid clinical tools and instrumented posturography, as the objective measurement of balance is important to detect dysfunctions. Instrumented posturography that uses a force plate is inexpensive and easily available. Therefore, it was used to quantify postural sways through the measurement of center-of-pressure displacements during quiet standing. Balance dysfunctions in the patients with stroke are frequently characterized by deviations and instability of the center of pressure. Therefore, using the instrumented posturography for assessing the static balance is relevant.

Methods

Study Design

A cross-sectional study was designed to compare the static as well as dynamic balance, balance confidence, ankle proprioception, and passive ROM between 2 groups of patients

with the high and low levels of ankle plantar flexor spasticity after stroke.

Setting

The measurements were be taken at the Biomechanics and Analysis of Human Motion Laboratory, School of Rehabilitation, Tehran University of Medical Sciences in Iran.

Approval of Study Protocol

The study protocol was approved by the Review Board, School of Rehabilitation, Tehran University of Medical Sciences and the Ethics Committee of Tehran University of Medical Sciences (Reference number: IR.TUMS.FNM.REC.1397.012).

Informed Consent

All eligible participants provided a written formal consent after receiving information about the research procedure. We explained the study details to participants before taking the measurements.

Participants

Participants with stroke were recruited from the neurology and physiotherapy clinics in Tehran, Iran. Participants were screened for eligibility. The patients were divided into 2 groups based on their level of ankle plantar flexor spasticity according to the Modified Modified Ashworth Scale (MMAS): high spasticity (MMAS score≥2) and low spasticity (MMAS score<2).

The inclusion criteria were as follows: first-ever unilateral stroke (hemorrhagic/ischemic), ankle plantar flexor spasticity≥1 based on the MMAS, walking ability, no fixed contracture in the ankle, independent standing with eyes open/closed, ability to understand and follow the commands, and no pain in the lower limbs. Participants with vision problems or depression as well as those taking antispastic medications or undergoing a rehabilitation program focused on balance and proprioception were excluded.

The physiotherapy and neurology clinics in Tehran were contacted for referring the patients with stroke who were willing to participate in the study. The principal investigator and physiotherapist responsible for assessing the patients and performing the experiments called the heads of these clinics to request cooperation and to describe the eligibility criteria. Moreover, the study aims and eligibility criteria for inclusion of patients were provided in the written form to the heads of the clinics.

Sample Size

Considering the data from the previous study [16], the sample size was estimated to be 28 (n=14 in each group; Z_α=1.96; α=.05; Z_β=.842; standard effect size=1.067).

Procedures

The patients were interviewed to collect demographic data, including age, gender, height, weight, time since the onset of stroke, etiology (ie, ischemic or hemorrhagic), and the affected side. Patients were assigned to one of the following groups: high spasticity (MMAS score≥2) and low spasticity (MMAS score<2). The severity of ankle plantar flexor spasticity was measured after making the patients rest in bed for 5 minutes in

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supine position with their shoes taken off [19]. Subsequently, the Activities-Specific Balance Confidence (ABC) questionnaire [20] was administered, followed by the measurements of affected ankle proprioception, passive ROM, posturography, and Timed Up and Go (TUG) test (Figure 1). An experienced physiotherapist performed all the tests.

Figure 1. Representation of the study protocol. ABC: Activities-Specific Balance Confidence; ROM: range of motion; TUG: Timed Up and Go.
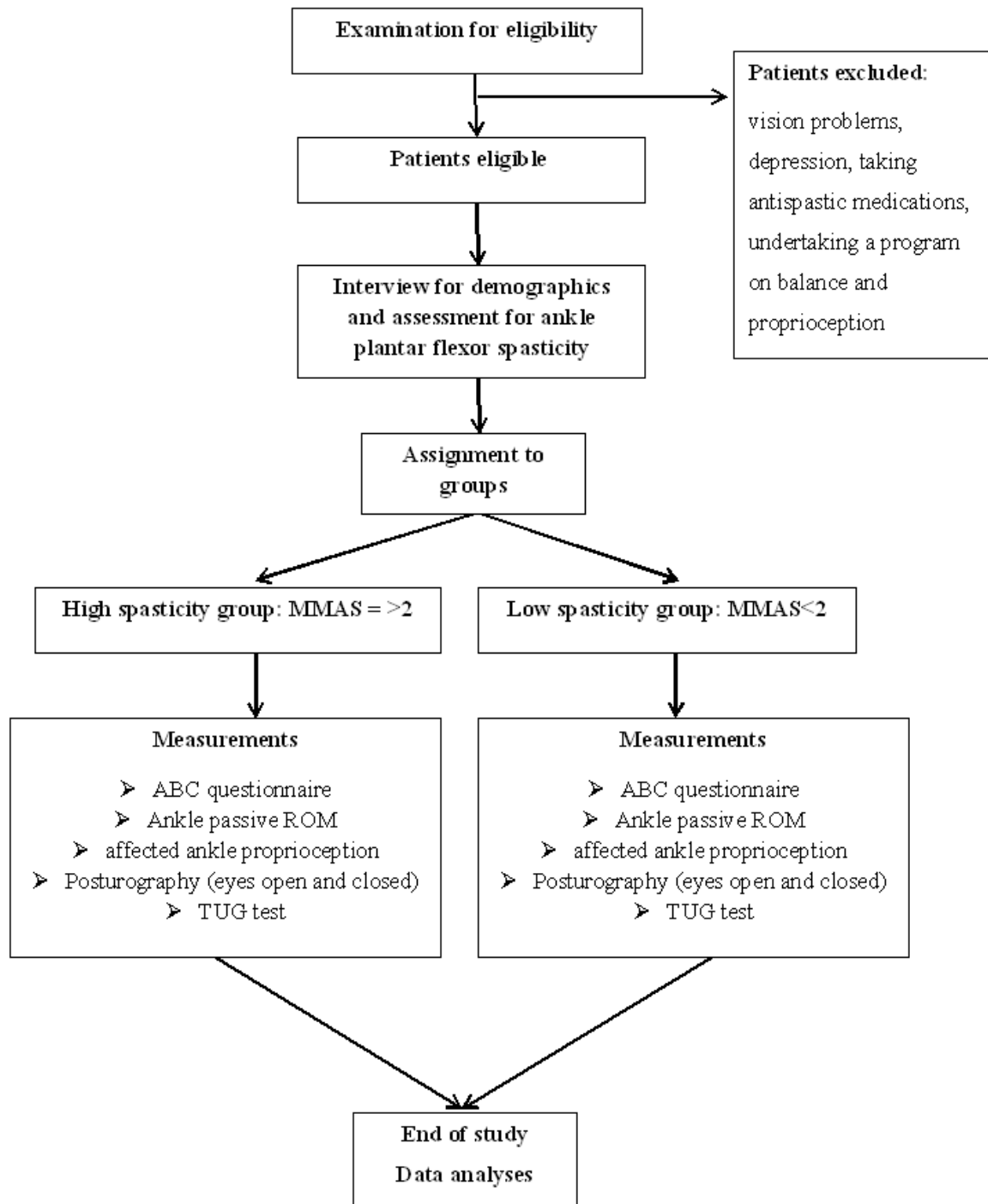
Outcome Measures

The primary outcome measures were the MMAS scores, ABC questionnaire, posturography measures in open- and closed-eyes conditions, and TUG test. The secondary outcome measures were the ankle passive ROM and ankle joint proprioception. Table 1 summarizes the outcomes and how they were measured in the study.

Table 1. Summary of the outcome measures.

Outcomes	Scale of measurement
Primary outcomes	
Spasticity	MMAS[a]
Balance confidence	ABC[b] questionnaire
Static balance	Posturography with eyes open and closed
Dynamic balance	TUG[c] test
Secondary outcomes	
Passive ROM[d]	Standard goniometer
Ankle proprioception	Electrogoniometer

[a]MMAS: Modified Modified Ashworth Scale.

[b]ABC: Activities-Specific Balance Confidence.

[c]TUG: Timed Up and Go.

[d]ROM: range of motion.

Spasticity

The affected ankle plantar flexor spasticity was assessed by an experienced physiotherapist using the reliable and valid MMAS [21,22]. To assess the spasticity severity, the physiotherapist stood on the affected side, stabilized the affected ankle with one hand, and moved it from maximum possible plantar flexion to maximum possible dorsiflexion, counting to 1001 [23]. The definitions of spasticity grades of MMAS are presented in Table 2.

Table 2. Modified Modified Ashworth Scale (MMAS) to assess the level of spasticity [17].

Grades	Definitions
0	No increase in muscle tone.
1	Slight increase in muscle tone, manifested by a catch-and-release or by minimal resistance at the end of the ROM[a], when the affected part(s) is moved in flexion or extension.
2	Marked increase in muscle tone, manifested by a catch in the middle range and resistance throughout the remainder of the ROM, but affected part(s) is easily moved.
3	Considerable increase in muscle tone; passive movement is difficult.
4	Affected part(s) is rigid in flexion or extension.

[a]ROM: range of motion.

Balance Confidence

The ABC questionnaire, which is reliable and valid, was used to assess the balance confidence of patients with stroke in performing their daily activities [20,24]. The ABC questionnaire included 16 questions asking the subjects to score their confidence from 0% (no confidence) to 100% (complete confidence). To calculate the total score in percent, the following formula was used: (total score/16)×100.

Posturography

The static balance of patients was evaluated by posturography. The use of force plate in balance measurement of the patients with stroke has been demonstrated [25]. The physiotherapist asked each patient to stand on the force plate with bare feet, heels apart by 9 cm and at 30° angle, and upper limbs comfortably along the body. The patients were asked to look at a point on the wall at a distance of 2 m during the test with eyes open as well as with eyes closed. Open- or closed-eyes condition was randomly applied with 2-minute rest interval between the conditions. Each condition was repeated 3 times (with a 20-second interval), and the duration of each repetition was 20 seconds. Velocity (in centimeters per second) and the anteroposterior and mediolateral displacements (in centimeters) were recorded 3 times, and an average was calculated [25].

TUG Test

Dynamic balance of patients was measured by TUG Test, which has been proven reliable in patients with stroke [26]. The patient was asked to sit comfortably on the chair with feet resting on the floor. Then the patient was asked to get up from the chair, walk a 3-meter distance, turn around, go back to the same chair, and sit down. The time in seconds was recorded using a stopwatch from the moment the patient got up from the chair to the moment he or she sat back on the chair.

Ankle ROM

The ankle passive ROM in degree was measured in the supine position with knee extended using a standard goniometer. Axis of the goniometer was located on the lateral malleolus; the stable arm, along the head of the fibula; and the moving arm, along the fifth metatarsal. The physiotherapist stabilized the affected

leg by one hand and moved ankle passively to maximum possible dorsiflexion by the other hand [27].

Ankle Joint Proprioception

The ankle joint proprioception was measured with the patient sitting on the edge of bed with eyes closed. The electrogoniometer was connected to the longitudinal axis of the tibia and the fifth metatarsal. The physiotherapist slowly and randomly moved the ankle to one of the following angles: 5° plantar flexion, 15° plantar flexion, or 15° dorsiflexion angles. The examiner then held the ankle in that position for 5 seconds and asked the patient to note the ankle position. The ankle was moved passively to the starting position. The ankle was moved again to the desired position, and the patient was asked to report the position. The difference between the starting and the patient-reported position was recorded as an error value. These steps were repeated for 3 times, and the average error (in degree) over those 3 repetitions was considered as a reconstruction error of that angle [28]. The same procedure was performed for all angles with 1-minute rest interval, and the average error was recorded for each angle.

Statistical Analysis

SPSS version 22 (SPSS Inc) was used for the data analysis. The normal distribution was analyzed using the Shapiro-Wilk test. The t test was used to examine the differences between 2 groups. Mixed model univariate analysis of variance (ANOVA) was used to analyze the effect of spasticity level of ankle plantar flexor muscles on the postural sway indicators in open- and closed-eyes conditions. The relationship between the severity of spasticity with the ABC scores, ankle proprioception, passive ROM, and TUG test were analyzed with Spearman rank correlation. The statistical significance was defined at $\alpha<.05$.

Results

Data collection and statistical analysis are complete. The interpretation of results is underway. The demographic characteristics of the participants will be calculated and provided. Descriptive results for all clinical and posturography measures will be reported and illustrated in the tables. The differences between 2 groups on the outcome measures will be analyzed and reported. The results of correlation coefficients between spasticity severity and clinical measures will be calculated and reported. We expect results to be published in winter 2020.

Discussion

This study protocol will compare the static and dynamic balance in patients with stroke with high and low levels of plantar flexor spasticity. The results of this study would be relevant to clinicians addressing the challenges of spasticity and neurorehabilitation in patients after stroke.

There are a few studies focusing on the role of severity of spasticity on the poststroke balance dysfunction. Depression, gait asymmetry, and spasticity are 3 independent factors for predicting falls in patients with stroke [15]. Spasticity is a contributing factor to gait asymmetry [29,30]. It follows that the spasticity may be considered as one of the main predictors of falling, impairment in independent walking, and disability. Therefore, considering the role of lower limb spasticity in balance and gait dysfunctions of patients after stroke, the findings of this study will be important for both clinicians and patients to manage the plantar flexor spasticity, improve the balance, and enhance the walking ability and quality of life of the patients with stroke.

We have hypothesized that the balance dysfunction will be greater in the patients with high ankle plantar flexor spasticity than in the patients with low ankle plantar flexor spasticity. Further, the balance dysfunction will be greater with eyes closed than with eyes open. Additionally, the proprioception is reduced in the patients with stroke [31]. This impairment in proprioception is greater in the patients with higher ankle plantar flexor spasticity [32]. Consequently, we expect that the balance confidence will be lower in the group with high ankle plantar flexor spasticity. If the role of spasticity level in motor function of the patients with stroke is verified, it can help physiotherapists take necessary interventions to manage the ankle plantar flexor spasticity and improve proprioception. Such interventions can reduce the risk of falling and improve balance and mobility.

This study used a single-force platform. Thus, posturography measure was a net characteristic of both affected (paretic) and nonaffected feet. With 2 force plates (1 for each limb), the posturography characteristics of the affected foot and the nonaffected foot can be assessed for the 2 groups. These results can be then compared with those of neurologically healthy subjects.

The patients with high ankle plantar flexor spasticity will demonstrate greater static and dynamic balance dysfunctions than those of the patients with low spasticity, particularly, with eyes closed. The findings of this study will have implications for practice and research in the treatment of balance dysfunctions in patients with ankle plantar flexor spasticity after stroke.

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Authors' Contributions

NNA, SN, and AM contributed to the study conception and the design. AM drafted the manuscript. NNA read and revised the manuscript critically. All authors reviewed and commented upon the manuscript for important intellectual content and gave approval of the final manuscript for submission.

Conflicts of Interest

None declared.

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Abbreviations

ABC: Activities-Specific Balance Confidence
ANOVA: analysis of variance
MAS: Modified Ashworth Scale
MMAS: Modified Modified Ashworth Scale
ROM: range of motion
TUG: Timed Up and Go

Protocol

Binocular Vision, Visual Function, and Pupil Dynamics in People Living With Dementia and Their Relation to the Rate of Cognitive Decline and Structural Changes Within the Brain: Protocol for an Observational Study

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Abstract

Background: Visual impairment is a common comorbidity in people living with dementia. Addressing sources of visual difficulties can have a significant impact on the quality of life for people living with dementia and their caregivers. Depth perception problems are purportedly common in dementia and also contribute to falls, visuomotor task difficulties, and poorer psychosocial well-being. However, depth perception and binocular vision are rarely assessed in dementia research. Sleep fragmentation is also common for people living with dementia, and binocular cooperation for depth perception can be affected by fatigue. Pupillary responses under cognitive load also have the potential to be a risk marker for cognitive decline in people living with dementia and can be combined with the above measures for a comprehensive evaluation of clinical visual changes in people living with dementia and their relation to changes in cognitive status, sleep quality, and cortical structure or function.

Objective: This study aims to characterize the nature of clinical visual changes and altered task-evoked pupillary responses that may occur in people living with dementia and evaluate whether these responses relate to changes in cognitive status (standardized Mini Mental State Examination [MMSE] score), Pittsburgh sleep quality index, and cortical structure or function.

Methods: This proposed exploratory observational study will enroll ≤210 people with recently diagnosed dementia (within the last 24 months). The following parameters will be assessed on 3 occasions, 4 months apart (plus or minus 2 weeks): visual function (visual acuity and contrast sensitivity), binocular function (motor fusion and stereopsis), task-evoked pupillary responses (minimum and maximum pupil size, time to maximum dilation, and dilation velocity), cognitive status (MMSE score), and sleep quality (Pittsburgh Sleep Quality Index). A subset of patients (n=30) with Alzheimer disease will undergo structural and functional magnetic resonance imaging at first and third visits, completing a 10-day consensus sleep diary to monitor sleep quality, verified by sleep actimetry.

Results: This research was funded in February 2018 and received National Health Service Research Ethics Committee approval in September 2018. The data collection period was from October 1, 2018, to November 30, 2019. A total of 24 participants were recruited for the study. The data analysis is complete, with results expected to be published before the end of 2020.

Conclusions: Findings will demonstrate how often people with dementia experience binocular vision problems. If frequent, diagnosing and treating them could improve quality of life by reducing the risk of falls and fine visuomotor task impairment and by relieving psychosocial anxiety. This research will also demonstrate whether changes in depth perception, pupillary responses,

and quality of vision relate to changes in memory or sleep quality and brain structure or function. If related, these quick and noninvasive eye tests help monitor dementia. This would help justify whether binocular vision and pupillary response testing should be included in dementia-friendly eye-testing guidelines.

Introduction

What We Know About Dementia and Vision

People living with dementia (PWD) experience unique difficulties in coping with comorbidities, including visual impairment. A recent large-scale study [1] identified visual impairment as more prevalent among PWD compared with older people, generally. Overall, 19% of PWD had a remediable form of visual impairment, and other studies have identified potential links between poor visual acuity (VA) and cognitive decline [2-5]. Recent reviews highlighted that sensory deterioration such as vision and hearing loss can both contribute to or be a consequence of cognitive decline through both direct and indirect mechanisms [6]. For example, dementia-related cortical vision processing abnormalities may give rise to such a link [4,7], but visual problems have also been found to precede cognitive decline and increase the risk of dementia [5,8,9]. However, the mechanisms suggested for this association are being debated, including functional disability affecting engagement with cognitively stimulating activities [5,8,10] and interaction with depressive symptomology [8]. Overall, it is suggested that addressing global sensory deterioration may significantly impact the quality of life for PWD and their caregivers [9-11], with some studies suggesting that routine sight-restoring treatments such as cataract surgery have the potential to modify the trajectory of cognitive decline [12] or increase gray matter volume [13].

Assessment of visual function within larger studies [1,5] was limited to high-contrast VA, excluding another potential source of debilitating visual symptoms—disorders in binocular vision (BV), leading to asthenopia, strabismus, and diplopia. This, with the associated loss of depth perception, can contribute to falls in older people [14], impact fine motor task performance [15], and affect psychosocial well-being [16]. Problems with BV increase in prevalence with advancing age [17] and are often remediable with simple treatments where the etiology is related to oculomotor control, known to be disrupted in some types of dementia [7,18]. However, the literature on the prevalence of BV disorders for PWD is limited; only 3 small-sample studies have evaluated the quality of stereoacuity [2-4], with other grades of BV (eg, motor fusion) unconsidered. The findings in these studies are conflicting, potentially due to differing stereotests used between studies as the upper limit of normality [19], and the impact of refractive blur varies between stereotests [15].

Stereopsis in People Living With Dementia

A pilot study explored the measurement of BV among people with cognitive impairment (n=7; Table 1). Although the sample size precludes a formal statistical analysis, the raw data suggest difficulty in attempting static random dot stereotests in comparison with real depth (Frisby) or dynamic (Accurate STEReotest: ASTEROID [20]) stereotests, particularly the Preschool Randot (PSR) stereotest, which lacks a monocular control to facilitate an understanding of the test.

Data were collected from council day center attendees with no history of amblyopia, strabismus, or ocular trauma, scoring ≤21 on the Mini Addenbrookes Cognitive Examination, a score highly likely to have come from someone with dementia. Near tests were conducted at 33 cm, the distance VA test was conducted at 3 m, and all stereotests were performed according to the manufacturer's instructions. The ASTEROID stereotest was not performed in 1 patient (002) due to a history of seizures. The ethical approval reference number is 18/YH/0152.

Depth perception problems are a commonly cited aspect of living with dementia [21], and there are known impacts of Alzheimer disease on oculomotor nuclei [7], important in binocular eye coordination, and the parietal lobe, integral to binocular processing for depth perception [22]. It is reasonable to hypothesize that the strength of depth perception would deteriorate as dementia progresses, but no studies have attempted to confirm this. Visual perception problems have been proposed as a unique risk factor for falls in PWD [23,24]. Falls are more common in PWD [24], including injurious falls such as hip fractures [25], and hospitalization of older adults carries an increased risk of further cognitive decline [26]. Delirium is a common mechanism for progression of dementia following hip fracture [27]. As such, monitoring of visual functions could identify those living with dementia who are at greater risk of injurious falls and hospitalization that could exacerbate the progression of dementia. Recent reviews have called for more research into the role of visual functions as a less costly and invasive biomarker for the progression or severity of dementia [28,29]. However, the interaction among primary visual function (VA and contrast sensitivity), binocular functions such as stereopsis and horizontal fusional vergence range, and rate of cognitive decline (eg, cognitive test score) in PWD is yet to be evaluated formally. Consideration of strength of depth perception as a potential contributor to visual difficulties in dementia may therefore add predictive value to this suggested marker of disease progression.

Table 1. Small-sample pilot data trialed multiple stereotests with individuals who had cognitive impairment (n=7).

ID	Gender	Age (years)	Mini Addenbrookes Cognitive Examination II score	Distance acuity (log-MAR)		Near prism fusion amplitude (Δ BI[a]-BO[b])	Near heterophoria size (Δ)	Frisby stereotest (arcsec)	TNO[c] stereotest (arcsec)	Preschool Randot stereotest (arcsec)	ASTEROID stereotest (arcsec)
				RE[d]	LE[e]						
001	F[f]	84	20	0.08	0.00	16BI-20BO	12	75	120	60	160
002	F	81	9	0.20	0.00	12BI-25BO	14	215	2480	Not measurable	Not performed
003	M[g]	82	4	0.50	0.40	16BI-40BO	8	Not measurable	Not measurable	Not measurable	1200
004	F	87	10	0.00	0.10	10BI-20BO	4	75	2480	Not measurable	570
005	M	84	13	0.15	0.45	20BI-40BO	8	40	2480	Not measurable	140
006	F	82	21	0.08	0.10	16BI-35BO	4	75	2480	400	140
007	M	70	9	0.08	0.10	6BI-16BO	20	215	2480	800	1200

[a]BI: base in.

[b]BO: base out.

[c]TNO: The Netherlands Organisation for Applied Scientific Research.

[d]RE: right eye.

[e]LE: left eye.

[f]F: female.

[g]M: male.

Monitoring Vision to Index Dementia Progression

Emerging evidence suggests that pupil dynamics could also index the progression of dementia, potentially serving as a biomarker for early diagnosis [30]. Pupillary responses (maximum dilation velocity, average dilation, minimum and maximum size) are mediated by brainstem structures showing early pathological changes in PWD [7]. Measuring task-evoked pupil changes for PWD during a memory task (varying cognitive load level) in addition to monitoring visual, binocular, and cognitive function over time enables a comprehensive evaluation of clinical visual changes in PWD and their relationship to changes in cognitive status via indicators such as the standardized Mini Mental State Examination (MMSE) score.

The addition of structural and functional magnetic resonance imaging (MRI) would enable preliminary evaluation of potential relationships between clinical visual changes, cognitive decline, and cortical structure or activation in PWD. This can be coupled with an evaluation of sleep quality, which is an emerging area of interest in Alzheimer disease due to sleep fragmentation being identified as a risk factor for cognitive decline [31]. Anatomically, the visual system has important input into circadian rhythms [7], with cataract surgery being reported to improve sleep quality because of better light transmittance [32,33]. Furthermore, a recent cross-sectional study identified visual impairment as being associated with the presence of sleep problems in institutionalized individuals with dementia [34]. Despite the known clinical relationship between sleepiness and deterioration of binocular coordination, research in this area has focused on the effects of major or total sleep deprivation [35-37].

No study to our knowledge has attempted to formally explore the relationship between quality of sleep measures, such as sleep latency and fragmentation, and clinical measures of BV. The mapping rate of brain atrophy (on structural MRI) and blood oxygenation level dependent (BOLD) activation levels in visual areas (on functional MRI) against visual function, binocular function, rate of cognitive decline, and baseline sleep quality may help determine whether clinical visual changes possess predictive or diagnostic potential as well as identify possible mechanisms for such an interaction.

This proposed exploratory observational study attempts to address these gaps in the literature based on the study aims presented above. Performing this study on an exploratory basis enables the inclusion of multiple dementia types because of the overall dearth of literature on the occurrence of BV disorders and pupillary changes among dementia types other than Alzheimer disease. Answering these research questions will determine whether changes in BV and pupil dynamics, in addition to changes in visual function, should be given further consideration as potential markers or predictors of both changes in cognitive status (indexed by standardized MMSE, found to agree substantially with the Clinical Dementia Rating for mild-to-severe dementia [38]) and cortical changes in structure or function during the course of recently diagnosed dementia.

Methods

Aims

This study aims to do the following:

1. Determine the relationship between changes over time in cognitive status (standardized MMSE score) and the following measures: binocular function (stereoacuity, motor fusion, and convergence near point [NPC]), visual function (VA and contrast sensitivity), pupillometry measures (maximum dilation velocity, average dilation, minimum and maximum size), and sleep quality (Pittsburgh Sleep Quality Index).

2. For individuals with Alzheimer disease, relate changes in the above to sleep onset latency, efficiency, and fragmentation (actigraphy and sleep diary) and structural changes in brain volumes and functional changes in cortical activation patterns within visual areas for a subgroup with Alzheimer disease.

3. Establish the prevalence of BV disorders and abnormal pupillometry measures among people with recently diagnosed dementia.

Study Design

The study is an exploratory observational study.

The inclusion criteria for all participants (maximum, n=210) included the following:

1. Confirmed diagnosis, within the last 24 months, of Alzheimer disease, vascular dementia, mixed Alzheimer and vascular dementia, Lewy body dementia, or posterior cortical atrophy.

2. Baseline corrected distance VA ≤0.300 logMAR binocularly—that is, no significant bilateral visual impairment [1] affecting the ability to fixate pupillometry targets or participate in BV tests.

3. No pathology affecting pupil function, for example, ocular trauma.

4. No history of childhood amblyopia or strabismus.

5. No history of alcohol or substance misuse.

6. No significant neurological or psychiatric history excluding dementia, for example, focal brain lesion and schizophrenia.

7. Not currently taking miotic or mydriatic medications (eg, for glaucoma).

8. If taking medication that may impair cognitive function, to have been taking this medication for at least 6 weeks at a stable dose.

9. Spectacles, if worn, are up-to-date prescriptions (within the last 2 years).

10. Fundus and media check within the last 12 months, with permitted diagnoses: no apparent defect, age-related macular degeneration, diabetic retinopathy, and cataract [1].

The inclusion criteria or the subset of PWD receiving MRI (n=30; comprising a suitable subsample for the pilot study [39]) included the following:

1. Capacity to provide informed consent, as determined by the 3-Item Capacity Questionnaire or in discussion with the direct care team (this criterion is in place for this subset of participants because of the requirement for the person with dementia to be alone in the scanner room during scanning and only be addressed by intercom).

2. No contraindications for MRI, for example, embedded metals.

3. Confirmed diagnosis, within the last 24 months, of Alzheimer disease—dementia type selected for established structural MRI disease progression markers [40].

Frontotemporal dementia was excluded because of the higher likelihood of challenging behavior being exhibited [41], presenting a risk for the lone researcher during testing. Parkinsonian dementia was also excluded as the binocular function and oculomotor deficits in Parkinson disease are well documented [42-44]. A diagnosis window of 24 months was selected over the use of a cognitive test score cap to permit heterogeneity in dementia severity across the sample to explore the prevalence of BV disorders while also minimizing skew toward people with more severe dementia, which may limit the ability to effectively evaluate changes in cognitive status over time. Such heterogeneity can occur within this window because of known diagnostic delays for dementia (18-30 months [45]).

No upper or lower age limits were applied to maximize recruitment, although it was anticipated based on previous audits of the case pool of the recruiting National Health Service (NHS) Trust that the majority of potential participants were likely to be aged 60 years. Research on the prevalence of BV disorders in association with advancing age is limited and excludes PWD, but one large sample study found a 19.1% difference in the prevalence of BV disorders between adults aged between 60 and 69 years and those aged 80 years. To minimize the possible impacts of an unrestricted age range leading to a preponderance of one particular age group affecting the anticipated prevalence of BV disorders within the sample, an average prevalence for binocular vision disorders was calculated for adults aged 60 years using the data from this study and was used to inform the choice of sample size. Previous studies [46,47] have commented on the difficulty in distinguishing visual problems arising from the presence of dementia from those arising as a consequence of advancing age, but fundus or media pathologies such as cataracts and age-related macular degeneration are known to be prevalent in this patient group [1]. Studies evaluating the relationship between the presence of these pathologies and the presence of cognitive impairment or Alzheimer disease have presented conflicting results [7,48,49]. Attempting to restrict recruitment on this basis may limit the generalizability of the study findings and reduce sample size and the ability to explore the data collected.

As the proposed study focuses on tracking clinical changes in visual, pupillary, binocular, and cognitive functions within a restricted time frame, the emphasis is less on the underlying cause of these changes (ie, dementia vs fundus or media pathology) and more on exploring the relationships between them. Thus, for this study, the inclusion of individuals with certain fundus or media pathologies per a previous large-scale study (diabetic retinopathy, cataract, and age-related macular degeneration) [1] can be permitted. This enables the possibility for a subgroup analysis while still achieving the research aims.

Recruitment

Eligible participants, identified by their direct care team within participating NHS Trust community mental health clinics or from a database of research volunteers held by the research & development (R&D) department, will be provided with study

information during their clinic appointment or by post following telephone contact if they express an interest to participate.

Sample size is justified on a pragmatic basis, balancing recruitment feasibilities with the research aims of exploring potential relationships between cognitive status and visual, binocular, and task-evoked pupil function. It is anticipated that up to 210 participants could be reasonably tested within a 10-week period, determined by funding constraints to allow completion of the study within 12 months. This assumes a 60-min consent and testing slot per participant, 7 participants per day, 3 days per week. A maximum target sample of 210 participants was permitted.

The participating NHS Trust receives approximately 1890 referrals annually for people with dementia, and diagnoses up to 160 individuals with dementia monthly, providing a large pool of potential participants commonly aged 60 years (unpublished data). Among older people aged 60 years without dementia, the average prevalence of BV disorders was 31.6% [17]. If >200 PWD are recruited, approximately 63 PWD could have reduced binocular function, suitable for exploratory analysis of BV disorders and altered pupil responses with a standard error <3.5% based on the hypothesis that PWD may have greater proportions of abnormal test results than people without dementia.

PWD eligible for MRI subgroup inclusion will be serially recruited during the initial study visit until the subgroup sample size was achieved (n=30). If withdrawing after the first scan, they will not be replaced in recruitment.

Procedures

Informed consent will be sought from participants or a consultee process will be employed where appropriate, with the capacity to consent determined by a validated brief questionnaire [50] where indicated. Ongoing consent [51,52] will be determined on a per-visit basis. The consent form also includes provisions for the participant to express their wishes concerning participation in the study, should they experience a loss of mental capacity before the study is completed, as an adjunct to these considerations.

A case history (caregiver supported if required), including dementia type and diagnosis date, ensures eligibility criteria are met. Dementia type and diagnosis date, previous ocular history, and previous imaging findings will be corroborated using the patient's medical records after consent is obtained.

Eligibility screening is supported by optometric information (VA, current prescription, and fundus/media check findings), obtained from the patient's optometrist, or a monocular distance VA test if the last NHS sight test was >1 year ago. If the latter satisfies the eligibility criteria, an updated sight test can be arranged by the researcher (by written agreement) or the participant or their caregiver with a provider of their choice. If eligible to participate, the researcher will contact the participant to organize the initial study visit as well as an MRI scan if eligible.

All participants will be invited to complete the Pittsburgh Sleep Quality Index at each study visit—or this can be proxy-completed by a caregiver with knowledge of the participant's sleep patterns.

The following clinical tests will be performed at a community clinic or in the participant's home by the researcher (registered orthoptist) at all study visits:

1. MMSE: this test was selected as a global measure of cognitive status that is highly relevant to clinical dementia care and is commonly used in memory clinics and other clinical consultations in the United Kingdom. Current research suggests weaker performance of the standardized MMSE when used to monitor individuals with early cognitive impairment; however, our participants had an existing diagnosis of dementia and will have held this for up to 2 years. This limitation was balanced against the need to seek a short, global measure already familiar to PWD and their caregivers, to keep the scope of the research broad, minimize distress during cognitive testing, and keep visit durations within an acceptable time limit as advised by patient involvement volunteers. The researcher was trained by a consultant neuropsychiatrist to conduct the test and score it

2. Monocular near VA (Sonksen logMAR).

3. Monocular distance VA (Early Treatment of Diabetic Retinopathy Study: ETDRS logMAR chart or Lea acuity paddles).

4. Binocular contrast sensitivity (Cardiff contrast test).

5. Cover test (testing distances: 33 cm and 6 m).

6. Suppression (Bagolini glasses; testing distances: 33 cm and 6 m).

7. Ocular motility.

8. Binocular function: horizontal phasic prism fusion range (PFR; testing distances: 33 cm and 6 m) and stereotests (Frisby and ASTEROID; administered on a glass-free 3D tablet). Note that test selection was informed by the raw data shown in Table 1, suggesting that individuals with cognitive impairment could perform these stereotests more easily in comparison with the static random dot TNO and Preschool Randot stereotests.

9. Near point of convergence.

10. Prism cover test (testing distances: 33 cm and 6 m).

11. Pupillometry (testing the dominant eye under standard room lighting): participants attempt the Wechsler Memory Scale-III Digit Span subtest for 3 digits (low cognitive load, 4×) and 6 digits (high cognitive load, 4×); digits presented by the computer aurally at a rate of 1 digit per second, with *Ready* and *Repeat* at start and finish; and pupil diameter and dynamics recorded when participants repeated digit sequences, using Tobii X2-60 (Tobii Ltd; 9-point calibration, dimmed lighting, 20-second calibration data stream recording followed by a total of 8 × 15-second data stream recordings—video recordings of the iris and pupil are not saved).

The testing time is approximately 60 min in total (including computer setup), with breaks offered if required. All tests are low-risk, quick, noninvasive, and (except for pupillometry) routinely performed in orthoptic practice.

All participants will return for 2 follow-up assessments, 4 months apart (plus or minus 2 weeks), repeating the above tests. Adaptations required to enable performance of a test will be documented, for example, change in test target, use of matching card, demonstration of testing procedure, and instances where performing tests was not possible.

The MRI subgroup (n=30; diagnosis of Alzheimer disease) will also receive an MRI scan (within 2 weeks of the first and final study visits) using a 3T TIM Trio MR scanner (Siemens) with a 32-channel array head coil.

Whole-brain scans performed included the following:

1. Structural MRI (11 min in total): T1-MPRAGE, FOV 192 mm, matrix 256 × 256, 1 mm isotropic spatial resolution, TR=2250 ms, TE=2.98 ms, flip angle 9°, GRAPPA factor 2, and acquisition time 4 min 32 seconds. T2-TSE, 29 × 4 mm slices, slice gap 1.2 mm, FOV 220 mm, matrix 320 × 320, 0.7 mm isotropic spatial resolution, TR=5060 ms, TE=102 ms, flip angle 140°, GRAPPA factor 2, acquisition time 1 min 38 seconds FLAIR-TSE, 25 × 4 mm slices, slice gap 1.2 mm, FOV 220 mm, matrix 256 × 256, 0.9 mm isotropic spatial resolution, TR=9000 ms, TE=100 ms, flip angle 150°, acquisition time 4 min 32 seconds.
2. Functional MRI (25 min in total): BOLD T2–EPI, 32 × 3 mm descending slices, slice gap 0.75 mm, FOV 192 mm, matrix 64 × 64, voxel size 3 × 3 × 3 mm, spatial resolution 3 mm × 3 mm, TR=2000 ms, TE=30 ms, flip angle 78°, bandwidth 2112 Hz per pixel, echo spacing 0.54 ms.

Viewing comprised the following:

1. Multifocal polar and eccentricity retinotopic mapping stimuli (4 runs of 31 × 8000 ms mini blocks alternating between 2 stimulus sets comprising sectional checkerboard wedge and ring stimuli) [53]. Acquisition time of 4 min 16 seconds per run. This paradigm was selected to enable shorter scan times and reduce the risk of fatigue while still facilitating a good signal-to-noise ratio.
2. Suprathreshold static red-green anaglyphic stereoscopic targets [22] presented using MATLAB (Matrix Laboratory; Mathworks) and Psychtoolbox-3. The target was a random dot 6 × 6 checkerboard presented against a 50% gray background, comprising interleaved black and white checks to equalize luminance across the image and ensure visibility of a consistent pattern was maintained between disparity and zero disparity viewing conditions. A checkerboard design was selected to ensure that the stimulus contained an equal number of disparity-defined and nondisparity-defined regions [54]. The black checks were disparity defined. Overall, 3 runs of 6 condition blocks and 1 control block (blank 50% contrast screen with fixation target) were performed. Each condition block sequentially displayed 6 targets, randomized for stimulus duration (2.2, 2.5, 2.9, 3.2, 3.4, and 4 seconds) and inversion (checks inverted and checks not inverted), with an interstimulus interval of 0.3 seconds. Block duration was 20 seconds, block order was randomized by drawing the test disparity in pixels from a shuffled array (control, –26, –13, 0, 0, +13, +26; minus disparities are crossed and plus disparities, uncrossed). One pixel subtended 0.031° or 111.6 arcsec at

75 cm viewing distance (projector resolution 1280 × 720, in-scanner screen size 52 cm width × 44 cm height). Thus, crossed and uncrossed disparities of 1451" arc and 2901" arc were displayed. Each run was initiated after a wait of 4× TR to allow stable magnetization to be reached. Acquisition time was 7 min. Test disparities were selected based on data [54] showing that these produced the strongest BOLD signal differences when compared to zero disparity, which is important for limiting the scan duration while still producing valid data, and verified with a pilot scan of 2 young healthy subjects without cognitive impairment. They also correlate well with our pilot data (Table 1), suggesting that people with cognitive impairment manage more gross disparities with red-green anaglyph random dot static stereotests.

The minimum duration between scans is 8 months. Visits last no more than 90 min, of which no more than 45 min will be spent in the scanner. A mounted frame and padding will be used to minimize head movement for participants. As all participants must pass a capacity assessment before entering the scanner, it is not anticipated that artifacts such as head motion are any more likely to occur than they would be for any other individual of similar age. A break will be offered between the retinotopic mapping and stereoscopic functional MRI sections to minimize fatigue. The scan order is as follows: T1, retinotopic mapping functional MRI; T2, fluid-attenuated inversion recovery; and stereoscopic target functional MRI. The researcher will speak to the participant via intercom between each of the scans to ensure that the participant is comfortable, understands what is about to happen, and is still awake.

This subgroup will also be invited to wear a sleep-tracking watch (Actiwatch, Camntech) and complete a consensus sleep diary during a 10-day period following the first and final study visits, returning the watch and diary by post in a prepaid envelope.

Data Analysis

Abnormal test results will be determined using the criteria adapted from Leat et al (Table 2) [17].

To establish the prevalence of BV disorders, the proportion of abnormal test results will be reported and compared by age group, dementia severity, and dementia type as well as against the data in Leat et al [17]. Pupillometry measures (maximum dilation velocity, average dilation, and minimum/maximum size) for high and low cognitive loads will be similarly compared with age-related norms collected in a separate study of adults aged 50 years with a normal standardized MMSE score (>26 out of 30) using the same paradigm.

MRI data will be visually inspected for quality, and participants with excessive head motion (>3 mm in any axis or >3) will be excluded. Functional MRI data will be preprocessed and analyzed in SPM8 (Wellcome Department of Imaging Neuroscience) using the standard generalized linear model approach. Preprocessing will correct for slice timing and head motion. Smoothing will not be performed to preserve spatial resolution and, because of the within-subject design, spatial normalization will not be required. In each participant's design

matrix, the timing of the stimulus blocks will be entered as regressors of interest and convolved with the canonical hemodynamic response model; head motion parameters will be included as covariates of no interest. To analyze the multifocal retinotopic mapping results, the procedure outlined by Henriksson et al [53] will be followed: coregistration between anatomical and functional data will be performed in SPM before transfer to Freesurfer using each participant's T1-weighted structural scans and the preprocessed functional MRI data. Eccentricity and polar angle retinotopic maps will be visualized using Freesurfer and used to denote regions of interest (ROIs) for primary visual areas V1, V2, V3, V4, and V3A. For stereoscopic image viewing, within-subject change between the first and final visits in the regional BOLD signal will be calculated for occipital and parietal lobe ROIs. Structural analyses will be conducted using Freesurfer; changes in cortical thickness in the occipital and parietal lobe ROIs and changes in the medial temporal lobe volumes will be calculated at the within-subject level.

A linear mixed model approach will assess, at the within-subject level, changes in the following variables at the level of time (visit number): pupillometry measures (time to maximum dilation, percentage maximum dilation from baseline, percentage maximum constriction from baseline, and baseline pupil size), visual function (VA and contrast sensitivity), binocular function (PSR and Frisby stereoacuity, NPC, and PFR), and standardized MMSE. Linear mixed modeling enables the consideration of repeated measures with the selection of a suitable covariance matrix. It is also effective in the presence of missing data for individual tests, making it an ideal approach to accommodate instances where PWD may, for example, be able to complete the high-load task-evoked pupillometry assessment at one visit but not the next.

Models that control for dementia type will determine relative contributions made by changes in pupillometry measures, visual function, and binocular function to changes in standardized MMSE, regional BOLD activation percentages, brain volume, and cortical thickness (first vs final visit). Results will be contrasted between PWD with and without a diagnosed BV disorder. Further subgroup analyses by presence/absence of fundus/media pathology or BV disorder will be performed depending on prevalence.

For participants who complete sleep actigraphy, linear mixed models will examine the level and rate of change in binocular function measures, standardized MMSE, regional BOLD activation percentages, brain volume, and cortical thickness (first vs final visit) as a function of sleep quality at baseline, adjusted for age, sex, and education, and their interactions with time.

Table 2. Criteria for abnormal test results.

Test	Abnormal result
CT[a]	• Heterotropia
PCT[b]	• Horizontal heterophoria >10Δ • Vertical heterophoria >2Δ
PFR[c]	• Horizontal: <2× heterophoria size on PCT (Δ, Sheard criterion) • Vertical: >4Δ
OM[d]	• Anomalous pursuit movements and/or underaction or restriction ≥–2 in any direction
NPC[e]	• >10 cm
Stereopsis	• Frisby: >210" arc [55] • ASTEROID: ASTEROID data collected for feasibility testing only; normative data currently unavailable

[a]CT: computerized tomography.

[b]PCT: prism cover test.

[c]PFR: prism fusion range.

[d]OM: ocular motility.

[e]NPC: convergence near point.

Results

Current Status

This research was funded in February 2018 and received approval from the NHS Research Ethics Committee in September 2018. The data collection period was from October 1, 2018, to November 30, 2019. A total of 24 participants were recruited for the study. Data analysis is complete, and the results are expected to be published before the end of 2020.

Anticipated Impact

Binocular, visual, and pupil function tests are routine, low-risk, quick, and noninvasive; if found to be interlinked markers of cognitive decline, monitoring their change over time could be an important aspect of future dementia care. Orthoptists, as allied health professionals, are well-placed to take on this role because of their ability to conduct objective assessments of visual function in people with cognitive difficulties, thereby obtaining robust clinical data.

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If BV disorders are found to be more prevalent in this group than in older people, further research could explore the impact of treating BV disorders on quality of life for PWD and their caregivers, potentially evidencing to commissioners the need for dedicated orthoptic services for PWD. This would also provide evidence for the inclusion of assessment and treatment of BV disorders within the College of Optometrists [56] and Royal College of Ophthalmologists [57] dementia guidelines and the proposed Dementia Eye Care Pathway [58], where it does not currently feature.

Discussion

Ethical Considerations

Risks of Participation

All participants have a confirmed diagnosis of dementia as part of the inclusion criteria; thus, disclosure of diagnosis through study information materials has very low impact risk. All clinical tests used are noninvasive, quick, and low-risk, and, except for the ASTEROID stereotest and pupillometry, are routinely conducted in orthoptic practice with minimal distress to patients. The ASTEROID stereotest requires the participant to simply look at some dots on a computer screen and has been successfully performed with older people who have cognitive impairment in another study, with no distress (Table 1). Similarly, pupillometry measurement is simple and has been used extensively in people who have dementia or cognitive impairment in the past [30,59,60].

Medical imaging is a routine and well-accepted aspect of clinical care for people with dementia attending the participating NHS Trust's community mental health clinics. Therefore, the inclusion of MRI scans for a subgroup of participants (n=30) is not anticipated to cause a significant burden. A panic button will be provided for the participant to use and their caregiver will be able to communicate with them via intercom during the scan, to provide reassurance.

If a symptomatic BV problem is diagnosed at the baseline visit, or VA deteriorates by a clinically significant amount during the study period (ie, reduction >0.200 logMAR), a report letter will be generated and sent to their general practitioner (GP) or optometrist. This allows participants, if they wish, to initiate further investigation or seek onward referral to the hospital eye service to explore treatment options. Similarly, if a gross abnormality is identified on MRI scanning, a letter will be sent to the GP, copied to their memory clinic consultant if appropriate, to prompt further investigations. This is per the standard operating procedures for the MRI facility.

Symptomatic BV disorders are associated with an increased risk of falls [14]; therefore, providing the option to seek further treatment is an important ethical consideration to mitigate this risk. As the study is exploratory and examining the relation between changes in the parameters of interest over time, rather than the etiology underlying such changes (eg, initiation of orthoptic treatment), it is still possible to include data from participants who have sought onward referral or received orthoptic treatment within analyses.

Financial Incentives

A nominal honorarium shows recognition and appreciation of the time and effort made by participants to attend study visits and undergo testing. As study participation involves 3 study visits and, for some participants, 2 additional visits for MRI scans, it was felt that including this honorarium was appropriate to acknowledge this burden of participation. Travel expenses are also reimbursed to ensure participants are not left out of pocket by participating in the research.

It is recognized that as part of the Health Research Authority (HRA) guidance on payments for research [61], incentives or financial inducements should not be offered where adults cannot consent. Although the research is limited to individuals with a diagnosis of dementia made in the last 24 months, there may be instances where ongoing consent changes or diagnosis is made after dementia has substantially progressed. The University of Surrey's Research Integrity and Governance Office will also provide input and advice in these instances. Procedures regarding honorariums are explained within the study information materials.

Data Protection and Confidentiality

All participants will be assigned a number upon entry to the study. All paper and digital study records will use this number instead of the participant's name to preserve anonymity. Paper project data (related to the administration of the project, for example, consent forms and record sheets) will be kept in a locked filing cabinet in a lockable room in the R&D office at the participating NHS Trust. Electronic data (primarily data sets) will be stored and pseudonymized by participant number on the university's secure research storage server for a minimum of 10 years. Data will be disposed of securely via confidential shredding or electronic formatting after these times.

Participants will not be personally identifiable in any publication material. Participants can give permission on the consent form for their anonymous data to be deposited in a repository. Participants will be able to withdraw their data, without giving a reason, until the point at which their data is published in an anonymized form.

Anonymous data may be published with consent in data repositories (eg, Dementias Platform UK or the UK Data Archive) or as required by scientific journals to accompany article publication. These data may contain raw data or summary data (eg, means and SDs) from any measures collected. No identifiable information (eg, names, date of birth, etc) will be published. Anonymous data may be used for future research purposes by the research team or other researchers, provided the research has ethical approval.

Patient/Public Involvement

Study information materials have been developed with 3 patient involvement representatives who have dementia or care for someone with dementia. Designing study materials with this patient group ensures that they are suitable for use in the informed consent process. This involvement work supported timely ethics review and has also assisted in developing the best

method of approaching people with dementia to participate in the study.

We consulted with our involvement representatives about several issues pertaining to the study, such as the best approach toward eligibility screening and redistribution of funds allocated for honorariums where a participant does not have the capacity and is unable to receive it. We also sought advice from the patient involvement staff at the Alzheimer's Society to ensure that our approach reflected best practices.

For honorariums, it was recommended that a discussion take place at the point of entry to the study, in instances where the participant has capacity to consent, to establish their preferences for distribution of the honorarium in the event that their capacity deteriorates. Another alternative suggested where capacity was not present at the point of enrolment in the study was reallocating the honorarium amount toward reimbursement of other costs associated with study participation as appropriate, for example, meal vouchers and increased travel budget.

For eligibility screening, our representatives shared their experiences of having their eyes tested and felt that offering to organize the test would be acceptable to avoid inducing the burden of participation, provided potential participants and their caregivers are also given the option to organize their own test if they wish and they have given consent for contact details or test results to be exchanged for this purpose.

Our patient involvement volunteers remain involved throughout the study, with additional patient involvement meetings scheduled for after data collection, to discuss any issues with the recruitment approach or study methods that may require an amendment, and at the end of the study to present the findings, establish the key take-home messages relevant to people with dementia and their caregivers, and to develop a lay summary of the findings. The Health Research Authority and INVOLVE patient involvement standards [62] were used to develop the initial recruitment materials and information pack for being involved in the study and are being used for communications with our involvement representatives throughout the study. HRA guidance on discussing public involvement embedded within the Integrated Research Application System application form was also followed.

Conflicts of Interest

None declared.

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Abbreviations

BOLD: blood oxygenation level dependent
BV: binocular vision
GP: general practitioner
HRA: Health Research Authority
MMSE: Mini Mental State Examination
MRI: magnetic resonance imaging
NHS: National Health Service
NPC: convergence near point
PFR: prism fusion range
PSR: Preschool Randot
PWD: people living with dementia
R&D: research & development
ROIs: regions of interest
VA: visual acuity

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Protocol

Evaluation of More Stamina, a Mobile App for Fatigue Management in Persons with Multiple Sclerosis: Protocol for a Feasibility, Acceptability, and Usability Study

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Abstract

Background: Multiple sclerosis (MS) is one of the world's most common neurologic disorders leading to severe disability in young adults. MS-related fatigue directly impacts on the quality of life and activity levels of people with MS. Self-management strategies are used to support them in the care of their health. Mobile health (mHealth) solutions can offer tools to help symptom management. Following a user-centered design and evidence-based process, an mHealth solution called More Stamina was created to help persons with MS manage their fatigue.

Objective: The overall study aims are to explore the feasibility, acceptability, and usability of More Stamina, a mobile app for fatigue self-management for persons with MS.

Methods: A mixed-methods, multicenter study will be used to assess the feasibility, acceptability, and usability of More Stamina. The study will take place during the third and fourth quarters of 2020 (Q3-Q4 2020) in 3 locations: Argentina, Spain, and Switzerland. A longitudinal cohort study will take place, and think-aloud protocols, open-ended interviews, and short answer questionnaires will be used. Persons with MS will be recruited from the different locations. This study seeks to enroll at least 20 patients that meet the criteria from each site for the longitudinal cohort study (total n=60).

Results: Ethical approval has been granted in Argentina and is pending in Spain and Switzerland. Outcomes will be published in peer-reviewed medical journals and presented at international conferences.

Conclusions: Findings from this study will be used to help understand the role that mHealth can play in fatigue management in MS.

Trial Registration: ClinicalTrials.gov NCT04244214; https://clinicaltrials.gov/ct2/show/NCT04244214

International Registered Report Identifier (IRRID):   PRR1-10.2196/18196

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Introduction

Background

Multiple sclerosis (MS) is one of the world's most common neurologic disorders leading to severe disability in young adults. More than 2.3 million people live with MS in the world, with higher incidences in Northern Europe and in temperate climates [1]. MS is a chronic condition with high self-management needs [2] that require significant support [3-5] since the majority of self-management occurs at home [6]. MS symptoms range from simple visual disturbances and altered sensation to severe fatigue and cognitive problems with mobility issues [2]. Persons with MS can also go through stretches of periods in which symptoms worsen, called "attacks" or "relapses" [1,2]. Fatigue is the most common and disabling symptom of MS, affecting up to 80% of patients [7-12]. There seems to be some association between MS fatigue and environmental conditions such as the time of the day and weather [13] but it is still unknown how much of an influence these factors have. MS fatigue has a huge impact on quality of life [8,9] and socioeconomic status for persons with MS and is the major reason for early retirement [14]. As a result of MS, persons with MS are typically less active [15] and have reduced levels of physical activity [16-18].

Mobile health (mHealth) is the delivery of health care or health care–related services through the use of portable devices [19]. The use of mHealth software apps has grown in recent years, to the point where commercial app stores hold thousands of health care–related apps [20]. Several digital and remote communication technology apps have been developed for MS clinical monitoring and management, to complement traditional clinical approaches [21]. Wearable devices, including actigraphy, gyroscopes, and body temperature or heart rate monitors, have been used to obtain a more comprehensive assessment of different body functions and to monitor disability in persons with MS [22]. A recent review [21] showed that the use of apps for MS as complements to traditional in-clinic care can improve outcomes and increase access to care, disease information, and support. The use of mHealth could help persons with MS to be more active in their self-management, for example, by tracking adherence to treatment, changes in bladder and bowel habits, and activity and mood.

However, digital health technologies have low adoption rates by patients with chronic diseases, in part explained by an inappropriate fit of these technologies with patients' daily lives and the high patient burden associated with digital self-monitoring [23]. Studies regarding the attitudes of persons with MS toward using smartphone apps highlight the benefits of tailoring apps to specific patient needs [24,25]. Further, involving patients and health care professionals in the design of technology is a need that has been often raised [26-32] and could be helpful in increasing adoption rates [33-35].

In previous studies, we explored available mHealth apps for persons with MS and found that only a handful exist [31,36]. This prompted the user-centered design (UCD) process of an mHealth solution specifically tailored for this target population called More Stamina.

User-Centered Design

UCD is a design philosophy that places the needs and characteristics of end users in the center of software design and development [37-39]. Through the use of UCD, solutions that are specific to the characteristics of the intended users are designed with higher acceptance and fewer user errors [38-40]. The overall process of UCD comprises the specification of the context of use (understand users and their characteristics and environment), specification of the requirements (identify the granular requirements and needs), production of solutions (start an iterative process of design and development), and evaluation (testing to find critical feedback on the product) [37,41].

The evaluation of usability entails a wide array of methodologies that vary in terms of research design, complexity, cost, and duration [42]. Different methods can be used to evaluate a system design on its usability, such as expert-based inspections and user-based testing [43]. Following UCD ensures that mHealth apps are more likely to meet end user needs and expectations [44,45].

More Stamina

More Stamina is a gamified task organization tool designed to help persons with MS manage their energy, to minimize the impact of fatigue on their daily life. The tool acts as a to-do list where users can input the tasks they want to accomplish that day in a simple manner (Figure 1). More Stamina is currently available in English, Spanish, Finnish, and German.

The overall concept is that a person's energy is represented through a visual metaphor (progress bar) and a symbolic unit that quantifies the amount of estimated effort a given activity might take (Stamina Credits). Users start their day with 100 Stamina Credits and assign them to new activities for that day. As users go through their day and complete the activities, they mark them as done, and the system prompts them to assess whether their effort was underestimated, overestimated, or properly estimated. More Stamina keeps track of these answers as data points and starts analyzing and creating a trend for each activity (eg, "shopping"). Repeated use of More Stamina allows it to learn about the user's habits, and once sufficient information is gathered on "shopping," a recommendation feature starts reminding users of their own tendencies.

The app logs user activity through the in-built sensors of the device and is able to monitor the number of steps, walking pace, distances, and GPS positioning. Patient-reported outcomes are available and optional in More Stamina. Standardized tools such as the Fatigue Severity Scale [46] and Chalder Fatigue Scale [47] are loaded into the system. Usage statistics are gathered locally for each added activity to keep track and collect assessments; the user can choose to share these statistics to a secure server for analysis. Users have control as to which information to disclose and with whom, whether it's personal, clinical, or treatment-related. Additionally, they can opt-in to send de-identified information for research purposes.

Figure 1. More Stamina screenshots.
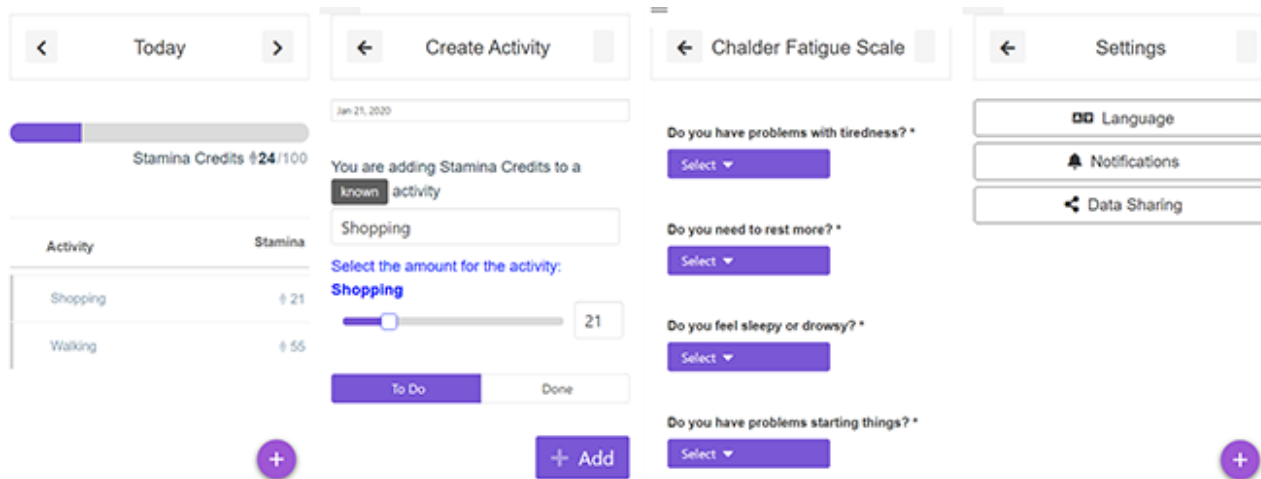
Current Status

The More Stamina app was created following the UCD approach through iterative development, allowing continuous improvement of the app. The progress of the solution through the different phases of the UCD process is reported in our previous studies. The state of the practice of health apps for MS was studied through a systematic app review [31,36]. The needs, barriers, and facilitators of mHealth apps for persons with MS were explored using focus groups and interviews [25]. User profiles, or "personas," were created to aid the design process [25,48], and the design process, prototyping, and initial usability testing have been described [49].

The work intended in this phase will assess the feasibility, acceptability, and usability of the mHealth solution with persons with MS (see Figure 2).

Figure 2. Phases of the user-centered design for the More Stamina app. The green boxes indicate the areas of focus for the current study. mHealth: mobile health; MS: multiple sclerosis.
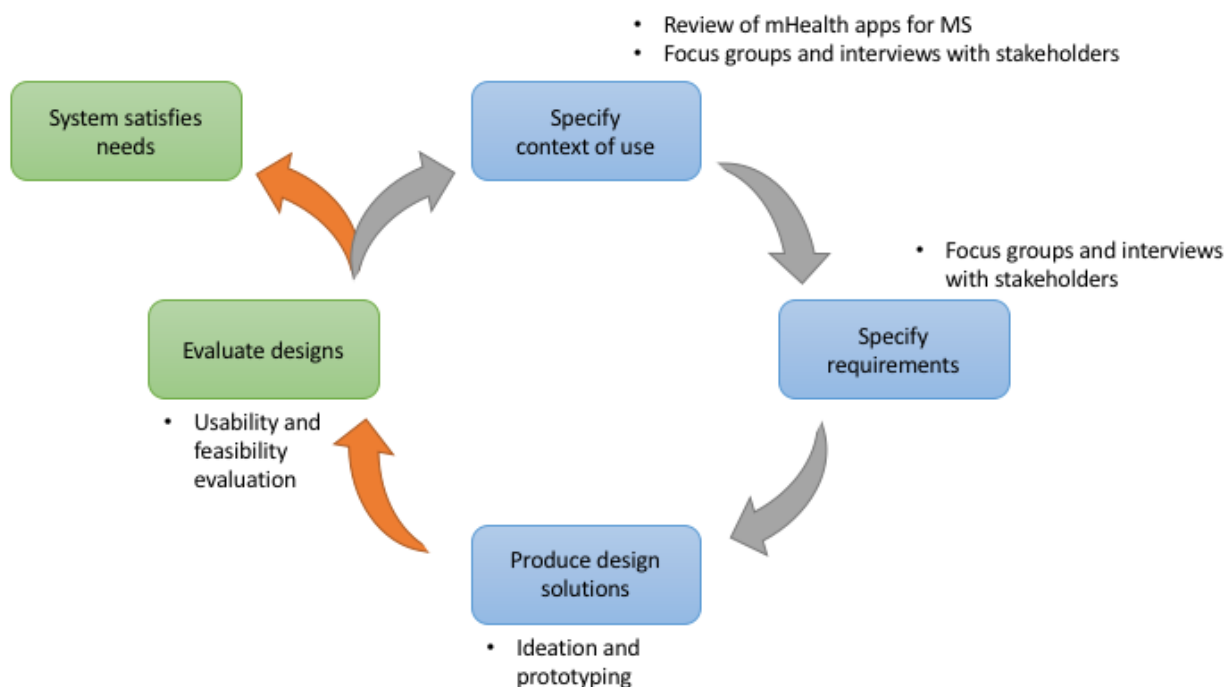
Objectives

The overall study aims are to explore the feasibility, acceptability, and usability of More Stamina, a mobile app for fatigue self-management for persons with MS.

The specific objectives are to estimate adherence to the use of More Stamina; estimate the effect of More Stamina adherence on behavior change, measured through changes in the amount of activities and amount of estimated energy per activity; estimate the effect of adherence to the use of More Stamina on the perception of fatigue management; validate the value proposition of More Stamina; identify More Stamina user activity patterns of persons with MS; and identify factors associated with the use of More Stamina.

Methods

Study Design

A mixed-methods, multicenter study will be used to assess the feasibility, acceptability, and usability of More Stamina. The study will take place during the third and fourth quarters of 2020 (Q3-Q4 2020) in 3 locations: Argentina, Spain, and Switzerland.

A longitudinal cohort pilot study will be conducted using a series of well-established standardized tools for user-based evaluations and surveys (see Standardized Tools). Participants' background information regarding health information, quality of life, and familiarity with mobile technologies will be collected. Potential cultural differences will also be explored through qualitative approaches. System usage logs will quantify patient engagement with the system [50].

Settings

This study is part of a collaborative project between researchers and different institutions across the globe. The work will take place in 3 locations with local teams. Sessions will be conducted by a native language facilitator. Overall study coordination will be carried out by Dr. Guido Giunti from the University of Oulu as part of the More Stamina research project.

Argentina

Hospital Italiano de Buenos Aires (HIBA) is a university general hospital in the Autonomous City of Buenos Aires that includes 2 hospitals (Central Hospital and Hospital Italiano de San Justo Agustin Rocca) and 22 primary care centers. This organization has 750 beds, conducts approximately 2.5 million outpatient visits per year, and includes a health maintenance organization that delivers prepaid health care to approximately 150,000 members per year.

The Argentinian local team will be composed of researchers from HIBA.

Spain

The Vithas Nisa Sevilla Hospital (VNH) ranks as the number one private center in Andalusia and fourth in all of Spain with a specialized unit aimed at researching and treating MS. This unit is composed of a multidisciplinary team, including neurologists, neuropsychologists, physical therapists, clinical researchers, nurses, and administrative staff.

The Universidad de Sevilla is the main house of learning in the Andalusian province of Spain and provides superior education by means of studies, teaching, and research, as well as the generation, development, and diffusion of knowledge to serve citizens and society.

The Spanish local team will be composed of researchers from the Universidad de Sevilla and VNH.

Switzerland

Kliniken Valens is a center specializing in neurological rehabilitation services located in Valens, Switzerland. Kliniken Valens employs a multidisciplinary staff, including neurologists, physiotherapists, occupational therapists, speech therapists, and sports therapists. In 2019, a total of 550 persons with MS were admitted for neurological rehabilitation, of which 70% suffered from fatigue and this was the primary focus of their stay.

The Swiss local team will be composed of researchers from Kliniken Valens and the University of Oulu.

Recruitment and Sample Size

Persons with MS will be recruited from patient databases at HIBA, VNH, and Kliniken Valens and invited to participate in the study. Inclusion criteria will require each participant to be >18 years old, have received a confirmed MS diagnosis according to McDonalds criteria [51] at least 1 year prior to the study, have none to moderate physical disability (Expanded Disability Status Scale [EDSS] <6.5) at the time of recruitment, have no major cognitive or haptile impairment influencing the ability to use the app, be fluent in one of the languages in which More Stamina is available, and be the owner or user of a compatible smartphone device with internet access.

Exclusion criteria include refusal to participate, cognitive or physical impairment that prevents the use of mobile phones, and inability to attend the follow-up encounters.

This study seeks to enroll at least 20 patients that meet the criteria from each site for the longitudinal cohort study (total n=60). The sample size is an adequate number because of the methods used that provide extensive, detailed data [52].

Standardized Tools

The following is a description of the standardized tools that are used in this study. Language-appropriate and culturally validated versions will be used accordingly.

Expanded Disability Status Scale

The EDSS is a method of quantifying disability in MS and monitoring changes in the level of disability over time. It is widely used in clinical trials and the assessment of persons with MS [53]. The EDSS scale ranges from 0 to 10 in 0.5-unit increments that represent higher levels of disability. Scoring is based on an examination by a neurologist.

Quality of Life in Neurological Disorders

Neuro-QoL (Quality of Life in Neurological Disorders) is a measurement system that evaluates and monitors the physical, mental, and social effects experienced by adults and children living with neurological conditions [54].

Chalder Fatigue Scale

The Chalder Fatigue Scale is a self-administered questionnaire for measuring the extent and severity of fatigue within both clinical and nonclinical epidemiological populations. Although originally developed to measure the extent of chronic fatigue symptoms within clinical populations, the scale was revised and is now more widely used to measure the severity of "tiredness" rather than just chronic fatigue syndrome [47].

eHealth Literacy Scale

The eHealth Literacy Scale (eHeals) is an 8-item scale that tends to measure perceived skills at finding, evaluating, and applying electronic health information to health problems [55]. The

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instrument has been proven to be a reliable and easy-to-use self-report tool and has been used in some studies. The scale is based on a model that distinguishes between 6 types of literacy skills: traditional literacy, health literacy, information literacy, scientific literacy, computer literacy, and media literacy. Accordingly, the eHeals aims to measure a broad overview of literacy skills, which might make it a potential instrument to assess the effects of electronic health literacy–tailored strategies to deliver online information and apps.

System Usability Scale

The System Usability Scale provides a "quick and dirty," reliable tool for measuring a product's usability [56]. It consists of a 10-item short questionnaire with 5 response options for respondents, ranging from "Strongly agree" to "Strongly disagree."

Think-Aloud Protocol

Think-aloud is a well-established technique for usability assessment, commonly used to determine users' thoughts and opinions while they perform a list of specified tasks with a system [57]. A think-aloud protocol asks users to express their immediate thoughts and reactions during their interactions with a system. The sessions are normally recorded, or notes are taken [58]. Minimal intervention from the usability tester assures users' thought processes are not interrupted except to remind them to keep talking. The focus is on understanding users' decision-making processes and on how users experience the system in their own words. Only a small sample of users is needed due to the extensive, detailed data it provides [59,60].

To guide the usability evaluation, case scenarios were created for what would be considered as normal everyday user interactions with the More Stamina solution. A panel of neurologists, physiotherapists, and designers validated the different scenarios. The specific scenarios patients will have to perform will consist of (1) completing their user profile, (2) creating a new activity for themselves, (3) managing previously recorded activities, (4) planning for a future activity, and (5) responding to one of the integrated surveys (Multimedia Appendix 1).

Participants will be instructed to assess the More Stamina app using the think-aloud method, stating out loud what they are doing, what thoughts come to their minds, and how are they interacting with the app. The facilitator will record comments and actions of the participants with screen-capturing software and an audio recorder.

Open-Ended Interviews

Qualitative inquiries are useful to provide insight into complex and multifaceted experiences of individuals when a rich description is the main goal of the study [61]. Participants of our study will be interviewed with open-ended questions to explore their experiences with the mHealth solution. They will be asked to comment on sections of the system they thought were well designed, to comment on sections that were inadequately designed, and to provide any further comments they might have about system usability.

User Behavior

Within More Stamina, Stamina Credits are a numeric continuous variable that ranges from 0 to 100 to represent the estimated effort of an activity. This variable is used to gauge how effective the user is in predicting the effort of each individual activity.

User activity patterns over time will be aggregated per week and described. Adherence will be estimated in each follow-up meeting. Adherence with app use will be estimated using the frequency of weekly use throughout the tracking period.

Study Flow

Persons with MS from each location will be invited to be part of the study and go through the process of informed consent where they will be briefed about the overall study and their rights as participants (see Ethical Considerations). After providing informed consent, participants will be part of a series of 4 workshops. Prospective monitoring will be carried out for 2 months for all participants at all sites, and daily measurements of More Stamina during that period will be considered.

Encounter 1 will be used to set up user accounts for participants, introduce the More Stamina solution, and install it on their smartphones. Monitoring will begin after the installation of More Stamina. All participants will complete the following standardized tools: EDSS, NeuroQoL, Chalder Fatigue Scale, eHeals, and System Usability Scale.

A subgroup of up to 5 participants per site (total n=15) will be selected for convenience to represent the main themes of this study: time since diagnosis (prolonged or recent), digital health literacy (expert user or beginner user), and disease burden (high or low). This subgroup will go through the think-aloud protocol by performing the specific scenarios and be interviewed about ease, utility, and perceived benefit. The sessions will be digitally audio recorded and video recorded, capturing on-screen navigation on screens.

There will be 3 face-to-face follow up meetings: day 15 (Encounter 2), day 30 (Encounter 3), and at the end of the follow-up at day 60 (Encounter 4). In these meetings, feedback will be obtained on the use of the More Stamina app regarding its functionality, usability problems, daily use, and information concerning disability, quality of life, and adherence. The overall study flow that will be replicated in each site is shown in Figure 3.

Figure 3. Study flow. SUS: System Usability Scale.
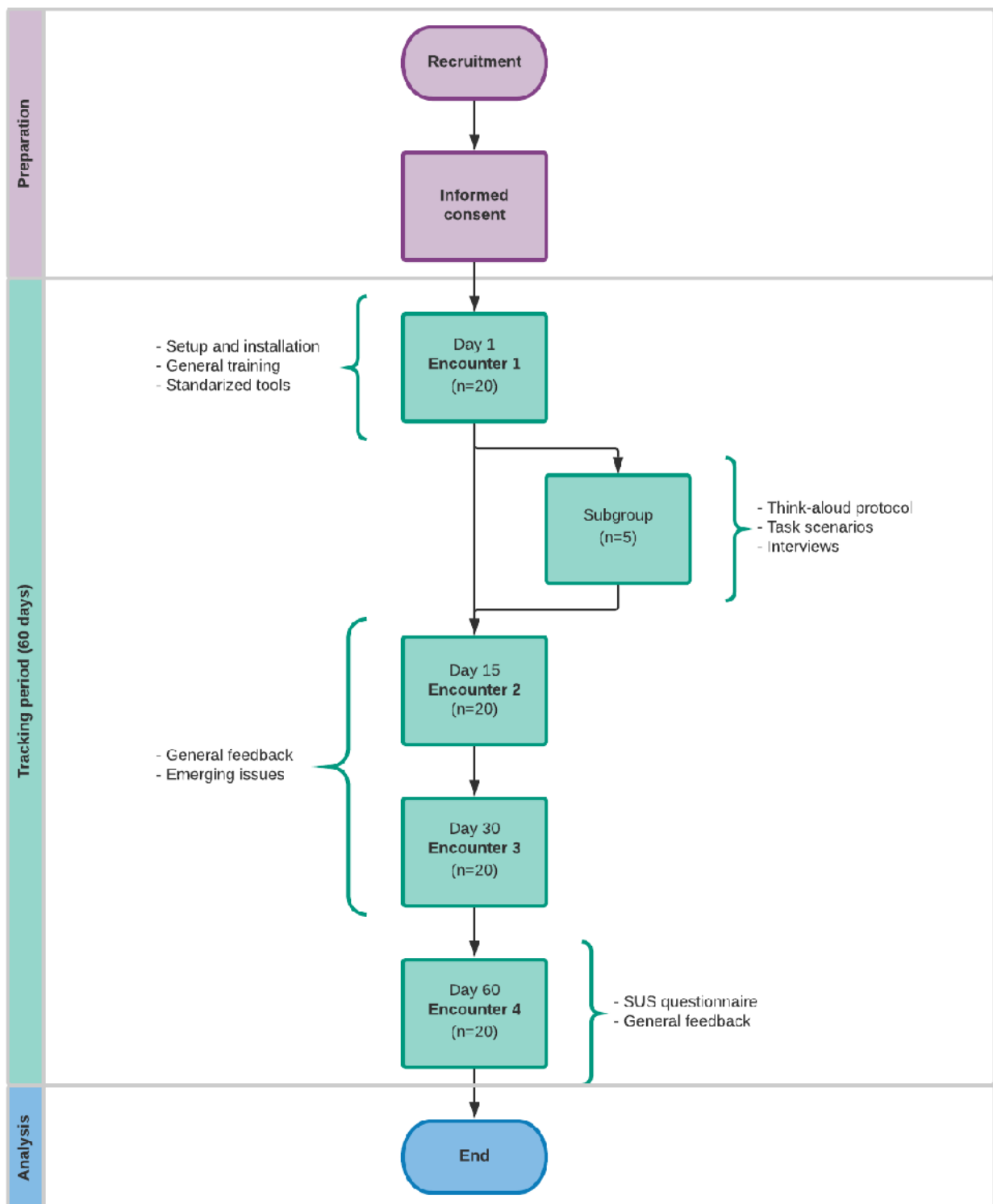
Data Analysis

Quantitative Analysis

Descriptive statistics will be used to summarize the participants' background and characteristics. Categorical variables will be presented as absolute and relative frequencies. Continuous variables will be presented as mean and standard deviation or median with interquartile range depending on distribution. A *P* value <5% will be considered statistically significant. Statistical analysis will be performed using STATA v15.

Quantitative analysis will be performed on the data collected through the mHealth solution. A linear regression model will be used to assess the association between the degree of adherence to the app, changes in the amount of activity, and changes in the amount of estimated stamina per activity. The outcome variables will be changes between baseline and final activities, changes in estimated stamina per activity for specific

activities selected by the researcher team based on frequency and relevance, and changes in fatigue self-perception. Changes will be calculated considering the baseline measurement and final measurement after the 3-month tracking period. A multivariate linear regression model adjusted for age, sex, and eHEALS will be used. The need for inclusion of other potential confounders will be evaluated.

Participants who are above the median usage of the app will be defined as heavy users. The median is less affected by outliers and skewed data and is usually the preferred measure of central tendency when the distribution is not symmetrical. Potential factors associated with the use of the app will be explored with a univariate logistic regression model.

Qualitative analysis will be performed on the data collected through the think-aloud protocol, individual interviews, and focus groups by using thematic analysis to identify emerging themes [62]. Each transcript will be reviewed and coded independently by 2 researchers. The themes will be combined by agreement of the 2 researchers, involving a third researcher in the event of a disagreement. Major themes and subthemes will be developed via an iterative review process. In order to help ensure the integrity of the content analyses, the guidelines recommended by Shenton [63] will be followed, which include collecting and analyzing data in an iterative process to identify themes and generating an audit trail, among others.

Crosscultural Aspects

Cultural contexts influence the way users choose, utilize, and conceptualize products and technology [64]. According to Evers and Day [65], culture is a discernible variable in interface acceptance, and it seems to play some role in perceiving subjective preferences in design [66]. Crosscultural partnerships can positively influence product development, but the use of traditional usability testing techniques in crosscultural settings can be problematic and may produce unexpected or spurious results [67].

Qualitative and quantitative data will be explored, paying attention to potential differences that pertain to cultural and geographical contexts such as traditions, habits, and weather conditions. In order to mitigate the risk of spurious results in usability testing due to crosscultural settings, we will use native speakers who are in a trusted position related to the participants.

Data Handling

Access to personal information will be restricted to the investigators of the study, health authorities, the Research Ethics Committee, and the monitors and auditors of the study. They will be subject to the duty of secrecy inherent to their profession, when necessary, to verify the data and procedures of the study, but always maintaining the confidentiality of the same according to the current legislation. Participants may exercise their rights of access, rectification, cancellation, and opposition of data according to the European Union General Data Protection Regulations [68].

The information and personal data of the participants will be kept in a completely confidential form with all the rigor of the law. Participants will be asked to not use any names during group discussions. Reports of study results will not include any identifying information. The paper questionnaires used will be digitized. The audio recordings of the group discussions will be typed and kept in secure servers at the University of Oulu. After the transcriptions are finished, the audio recordings will be destroyed. The typed transcripts will remain on password-protected computers, and any hard copy will be kept in a closed filing cabinet. Only members of the research team will be able to listen to the recordings or read the typed versions.

Ethical Considerations

The ethical research guidelines of the University of Oulu [69] and University of Seville [70] will be followed. Ethical approval will be obtained to ensure that the research is done in accordance with the Declaration of Helsinki and in line with the current local legislations from the respective authorities: HIBA's Institutional Review Board (Argentina), the Ethics Committee of the Regional Ministry of Health of the Government of Andalusia (Spain), and the Swiss Ethics Committee on Research Involving Humans (Switzerland). The study has been registered in ClinicalTrials.gov with the identifier NCT04244214.

The participants will be informed about the nature of the research project; the reasons for their participation; risks, benefits, and alternatives associated with the research; and their rights as research subjects before agreeing to participate. Steps will be taken to ensure that data gathered from participants will be kept under strict security, anonymity, and privacy.

Results

The study will take place during the third and last quarters of 2020 (Q3-Q4 2020). Outcomes will be published in peer-reviewed medical journals and presented at international conferences.

Discussion

Overview

This protocol presents the work intended to take place to assess the feasibility, acceptability, and usability of a fatigue management mHealth solution for persons with MS.

Persons with MS have a different attitude than other people towards physical activity [18] and are typically less active than healthy persons [15]. The proposed approach of More Stamina for fatigue management is in line with common approaches in energy conservation education programs and fatigue management for MS [71,72]. The goal is to help the patient save energy through the implementation of different strategies such as work simplification or the use of task prioritization.

By tracking and collecting use and contextual information, the present study will also help to understand underlying factors and causes for MS fatigue.

The goal of this pilot study is to further our understanding of the potential issues and challenges that will be used as the foundations for a larger randomized control study.

Limitations

It is possible that the differences between the patient group who participated in the UCD and the target groups of this study are significant enough that there is a preference mismatch. For example, the importance of fatigue management could vary depending on cultural factors or adherence, or interest could even be radically different depending on economic factors. This is expected, and understanding potential differences is part of the aims of the study. Finally, the nature of the study does not allow the assessment of health outcomes due to the lack of randomized exposure and monitoring period. Such explorations will be the subject of future studies.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Case scenarios.
[DOCX File , 13 KB - resprot_v9i8e18196_app1.docx]

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Abbreviations

EDSS: Expanded Disability Status Scale
eHeals: eHealth Literacy Scale
HIBA: Hospital Italiano de Buenos Aires
mHealth: mobile health
MS: multiple sclerosis
SUS: System Usability Scale
UCD: user-centered design
VNH: Vithas Nisa Sevilla Hospital

Protocol

An Evaluation of Parents' Experiences of Patient Engagement in Research to Develop a Digital Knowledge Translation Tool: Protocol for a Multi-Method Study

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Abstract

Background: The last decade has seen increasing calls for patient and public involvement in health-related research due to an ideological shift toward more equitable methods of knowledge development and an effort to increase the usability and relevance of knowledge by improving outcomes in clinical practice. Patient engagement includes simply informing patients to offering complete decision-making autonomy to individuals, groups, communities, caregivers, friends, and families who have personal experience and knowledge of a health issue. Despite the use of patient engagement methods in research, evaluation has lagged, resulting in a knowledge gap that makes it difficult to foster capacity and sustainability for patients and researchers alike since little is known about how effective patient collaborations in research are built, maintained, or improved. This study centers on pediatric functional constipation, a common condition that affects children and families. Since parents play a pivotal role in treatment, they are an optimal group to engage in improving the resources and support available to them.

Objective: This study aims to use patient-engagement methods to establish a research collaboration with parents to cocreate a digital knowledge translation tool for parents caring for a child with functional constipation and formally evaluate the patient engagement processes within this project to build the science of patient engagement in research.

Methods: Members of the parent collaborator group will be recruited from previous participants who expressed interest in the development of a digital knowledge translation tool. The group will collaborate with the research team to create a tool to address patients' support and information needs when caring for a child with functional constipation. The parent collaborator group will then be evaluated in a multimethod study design. Data will be digitally and anonymously collected from all members of the parent collaborator group, using the validated Public and Patient Engagement Evaluation Tool (PPEET) patient questionnaire. Descriptive statistics will be used to report group characteristics and question responses. Qualitative analysis will be used to understand open-ended question responses. Specifically, directed content analysis will be used to assess themes of the Patient Engagement in Research (PEIR) Framework with a combination of deductive and inductive analyses. Findings will be integrated into the discussion if there are sufficient commonalities and inter-relationships. The final manuscript will include reporting of each element as described by the Good Reporting of a Mixed Methods Study criteria.

Results: Recruitment is planned for June 2020. Data collection for the evaluation of patient engagement processes will occur upon completion of the digital knowledge translation tool. The results of this study are expected to be published by the end of 2020.

Conclusions: This study will provide valuable information about parents' experiences participating in child-health research and is a fundamental step in building the science of patient engagement in research.

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Introduction

Health research programs have historically been considered the exclusive domain of professional scientists. Whereas families' experiential knowledge and input in the clinical environment has been prioritized for many years, the research context has been slower to consider patients as contributors to knowledge development. Despite the intention to create clinically relevant knowledge, research programs have continued to develop knowledge in isolation from patient input. Consequently, patients and families have been at the center of a paradox between the ideological positions of clinical practice and research [1], while questions about the usability and relevance of research findings to improve clinical care have persisted. Over the past ten years, there have been increasing calls for patient and public involvement in health-related research. The impetus for this shift is twofold; an ideological shift towards more equitable and less hierarchical methods of knowledge development [2,3] and an effort to increase the usability and relevance of knowledge as evidenced by improved outcomes in clinical practice.

Although terminology varies around the world, in Canada, the terms *patient-oriented research* and *patient engagement* are commonly used in health care, aligning with guidance from the Canadian Institutes of Health Research. Patient engagement is defined as "meaningful and active collaboration in governance, priority setting, conducting research and knowledge translation [3]." Furthermore, the word patient is an umbrella term that includes individuals, groups, communities, caregivers, friends, and families who have personal experience and knowledge of a health issue [3]. Although including patients and families as part of the research team is a fairly straightforward ideal, diversity in operationalization has slowed knowledge development related to effectiveness and best-practices of patient engagement [4-6]. Similarly, evaluation of the processes and outcomes of patient engagement in research has lagged, resulting in a meager evidence base for patient-oriented research [2,4,7-10]. The current lack of evidence regarding patient engagement in research makes it difficult to foster capacity and sustainability for patients and researchers alike since little is known about how effective patient collaborations in research are built, maintained, or improved.

Furthermore, parents are a unique subgroup of the patient engagement population that merits further exploration because of their dual roles, inherently representing both themselves as caregivers and their children as patients [11-13]. Specifically, in this study, we are engaging with parents caring for a child with functional constipation. Functional constipation is a type of constipation that occurs without underlying medical or physiological causes. Prevalence rates amongst North American children are reported in the range of 9%-18% [14], and these patients often have higher rates of emergency department visits and specialist care. Specifically, pediatric functional constipation accounts for upwards of 25% of pediatric gastroenterology visits [15,16]. Parents of children with functional constipation are critical stakeholders in the successful management of pediatric functional constipation because the treatment regime is ideally provided and monitored at home. As such, collaborating with parents of a child with functional constipation offers an innovative approach to ensure clinicians can provide proper support, and parents have resources tailored to their needs. We are engaging with patients in pediatric functional constipation research both to improve clinical care for families and to evaluate parents' experiences participating in child-health research, as a fundamental step in building the science of patient engagement in research. That is, the patient engagement process is widely applicable, meaning others can use this protocol to guide patient engagement processes and evaluation in any number of study populations.

There is a significant body of literature that helps conceptualize and operationalize the elements of patient engagement within this study [3,8,17-19]. Patient engagement is often considered a spectrum ranging from informing stakeholders to giving stakeholders complete decision-making autonomy. The intention for patient engagement in this project aligns with the term collaboration; wherein a partnership is formed, decision-making is a shared responsibility between the researchers and the patient group, and is inclusive of their knowledge, experience, and preferences. The process goal for our patient engagement approach is based upon identified metacriterion [8] of respect, trust, legitimacy, fairness, competence, and accountability in the development of knowledge. To operationalize this intent, we will use the Patient Engagement in Research (PEIR) framework [17] (Figure 1) to guide the actions and strategies of our patient engagement approach. Whereas the metacriteria help guide the goals of patient engagement, the PEIR framework highlights key themes that can be used as scaffolding for *how* to conduct meaningful patient engagement in research. Therefore, explicit planning and reporting of the patient engagement approach and activities within the project will be an important foundation of this study.

The purpose of this study is to (1) use patient engagement methods to establish a research collaboration with parents to cocreate a digital knowledge translation tool for parents caring for a child with functional constipation and (2) formally evaluate the patient engagement processes within this project to build the science of patient engagement in research.

Figure 1. Organizing themes of the Patient Engagement in Research Framework with examples of corresponding elements (reprinted with permission from authors) [17].

Organizing themes	Example of elements
Procedural requirements—Procedural details involved in managing the inclusion of patient partners in a research project to ensure their experiences are rewarding and productive Overall, this theme highlights the importance of engaging early, sharing activities, having diverse patient partner representation, ensuring alignment between a research project and patient partners' interests, having funding to support and compensate patient partners, being clear about the engagement process and having open communication	1. The research project has an appropriate number of patient partners 2. Patient partners agree on the goals of the project 3. Patient partners clearly understand their roles on the project
Convenience—Emphasizes the importance of choice and accessibility, including sufficient time to engage, and the flexibility to choose how and when to contribute	1. Patient partners have sufficient time to contribute 2. Patient partners, preferences are considered when meetings are being planned
Contributions—Pertains to the roles of and tasks assumed by patients. Patient partners want to contribute their perspectives and experiences to research	1. Patient partners provide their perspectives 2. The contributions are a good use of the patient partners' time
Team interaction—Focuses on aspects of positive research team interaction that are important to patient partners, which involves communication style and rapport	1. There is mutual respect among team members 2. Trust becomes established within the research team
Research environment—Emphasizes the importance of having a positive and an inclusive organizational/team culture that allows patients to feel comfortable and accepted as equal team members working together	1. Patient partners are treated as an equal partner 2. There is a general openness to receiving the views of patient partners
Support—Pertains to the valuable resources, including financial and skills/instructional support offered to patient partners Highlights the importance of using financial and non-financial resources to support and encourage patient partners' contributions	1. Patient partners receive the training needed for their role 2. Patient partners are offered sufficient reimbursement for out-of-pocket expenses
Feel valued—Focuses on ensuring that patients feel equally important on the research team by demonstrating appropriate recognition and respect	1. Patient partners contributions are acknowledged 2. Patient partners are offered sufficient compensation for their contributions
Benefits—Highlights that it is important to patient partners that they derive benefits from their engagement	1. Patient partners see how their contributions can benefit other people 2. Patient partners gain or improved their knowledge

Methods

Patient Engagement

This study forms part of a multistage research project to improve care and resources for families living with pediatric functional constipation (see diagnostic criteria in Multimedia Appendix 1) [20,21]. The preceding stage of qualitative, Interpretive Descriptive [22] research frames this proposed patient engagement phase and will be the primary recruitment source of our collaborators. The purpose of the qualitative research stage was to develop an in-depth understanding of parents' experiences and information needs when caring for a child with functional constipation. Recruitment was through community and social media information posts shared in the summer and fall of 2019. Interested parents contacted the research team for further details. We recognize that parents who volunteer for such research are unlikely to reflect the general population, and we will explicitly cite this limitation in our findings. After sharing the information letter and discussing any questions, 18 parents consented and participated in semistructured interviews. After the interview, parents were asked if they would like to allow the research team to keep their contact information and be notified about the subsequent stage; patient-engagement to cocreate a digital knowledge translation tool.

The operationalization of patient engagement in this project is through the creation of a parent collaborator group and is detailed as follows. A parent collaborator group will be formed by inviting all participants from the qualitative portion of the research to move forward in a new role as a member of the parent collaborator group. Through collaboration, we will work together to establish priorities and cocreate a digital knowledge translation tool for parents caring for a child with functional constipation. This stage of the research fits within the *tailoring knowledge* portion of the Knowledge-to-Action (KTA) framework [23]. The patient engagement process and activities described in this stage are meant to provide a framework rather than a rigid protocol because the parent collaborator group has not been formed, and their contributions to shaping the research process are critical to upholding the legitimacy of parents' collaborative role in this stage.

We did not locate any evidence to support best practice about the optimal group size for patient engagement in research. Instead, we will build the parent collaborator group based on practical considerations and recommendations of coauthors with extensive experience working with parent groups. Specifically, the size of the group should foster meaningful engagement. That is, we strive to develop a group that is large enough to be able to have a discussion, and everyone has the opportunity to share ideas. Conversely, we do not want a group so large that it is unmanageable. Lastly, we remain cognizant that these are parents with children, and they may not be able to attend every session, so we aim to have enough flexibility in our meetings to accommodate for all of these factors (online synchronous and asynchronous access). We anticipate a reasonable target

size of between four and twelve members will be sufficient to build meaningful engagement. Although the primary source of collaborators in this stage will be from the preceding qualitative stage of the project, additional parents who have experience with childhood functional constipation will be welcomed to join the parent collaborator group as they become known to other members of the group (friends or community members known to have a child with functional constipation).

At our first meeting, detailed verbal and written information about the commitment required by the study will be provided. Informed consent will be sought from interested participants. Members may revoke their consent to participate at any time. The first meeting will be facilitated by a registered professional (psychologist or social worker) with extensive group facilitation experience to establish group norms and support an effective group process. Subsequent meetings will be cofacilitated by the researcher and parents. The aim of the project will be discussed, including the following key points. First, parent participation is explicitly being sought to ensure this project will accurately address the challenges and improve the experiences of families living with pediatric functional constipation. Second, parents will be supported to develop new skills if desired, but their experiential knowledge already qualifies them as valuable partners in this project. Third, parents will share decision-making responsibility with the researchers for the content, form, and style of the knowledge translation tool. Decision-making processes within the group will be documented and determined by the group. For example, the group may choose to use a modified Delphi technique [24] or focus on a robust discussion to generate consensus. Fourth, although individual input is desired, participation will also involve interacting with other parents affected by pediatric functional constipation. Fifth, differing perspectives amongst group members are expected and considered beneficial because the aim is to advocate for the needs of the larger parent community as a whole. That is, participants need not aim for unanimous agreement on topics of discussion. Finally, the concepts of respect, trust, legitimacy, fairness, competence, and accountability will be our guideposts for the work of the parent collaborator group.

Expectations for the activities and commitment of the parent collaborator group will also be discussed. The time commitment is based on previous experience of coauthors and is anticipated to be approximately one-hour meetings held every 3-4 weeks for 1-3 months. This timeline is flexible and will be adapted based on the progress and needs of the parent collaborator group. Meeting locations will be central to parents, accessible by public transportation, and include childcare and light refreshments. The content of the digital knowledge translation tool will stem from (1) best practice guidelines and clinical recommendations for the management of pediatric functional constipation, and (2) the themes and experiences generated from the qualitative inquiry of the preceding stage. The methods and process for developing the knowledge translation tool are based on existing literature [25-28] and previous experience with creating knowledge translation tools for parents. This research is situated within a larger program of research in a nationally funded knowledge mobilization network, Translating Emergency

Knowledge for Kids (TREKK) [29], where a clinical team develops bottom line recommendations, developed by exploring practice guidelines and the best available synthesized research evidence. All bottom line recommendations are vetted through a large, clinical focused national committee. The format of the knowledge translation tool will be determined by the parent collaborator group while building on the strengths of a narrative-based medium. For example, previously successful knowledge translation tools have been whiteboard videos and digital storybooks. A graphic designer and creative writer will be available to support the development of a high-quality digital knowledge translation tool. The design team of the writer and graphic designer will be provided with a story outline that reflects the combined experiences and most salient themes from the qualitative inquiry. The parent collaborator group will work with the design team to revise and build the knowledge translation tool through iterations to address questions of clarity, potential bias or marginalizing factors, ease of use, relevance, and other factors as determined by the parent collaborator group. Upon completion of the knowledge translation tool, the final component of the project will be to evaluate the process of patient engagement in the project. Although not directly part of this stage of the research project, the knowledge translation tool (after completion) will be formally evaluated and tested for usability. The knowledge translation tool will also be made widely available on digital and social media platforms.

Evaluation Design

The evaluation of the parent collaborator group will use a multimethod design with both quantitative and qualitative components. A multimethod design was chosen to answer two related but distinct research questions. First, the quantitative component will use the Public and Patient Engagement Evaluation Tool (PPEET) participant questionnaire [30,31], which includes survey questions with Likert response options to examine the question, "To what degree did the patient engagement processes of the research meet the intended meta-criterion of respect, trust, legitimacy, fairness, competence, and accountability [8]?" The qualitative component will use open-ended questions to explore in more detail, "Why or how did/didn't the patient engagement processes of this research project meet the meta-criterion?" The rationale for using quantitative and qualitative methods in this stage of the research aligns with the purpose of *expansion* or *enhancement* by using an additional method to augment and further detail the findings [32,33]. Due to the focused nature of the evaluation and the small size of the parent collaborator group, both the quantitative and qualitative aspects of the study will be limited to descriptive methodologies.

Sample

All caregivers who participate in the parent collaborator group will be invited to participate in the evaluation phase. Parents who did not continue for the full duration of the project will also be included in the sample if they are willing. Parents who were invited to participate in the group but declined will be asked if they are willing to share any feedback about what may have influenced their decision not to join the group.

Data Collection

Data collection will occur after the completion of the knowledge translation tool development. The PPEET patient questionnaire [30,31] will be copied into a digital format by entering the questions and response fields into the secure surveying platform SimpleSurvey. Parents will receive digital access to the questionnaire, which can be completed anonymously. Demographic questions which are considered indirect identifiers will be optional data fields. The survey instructions will include an explanation that if the demographic questions are answered, the respondent's data will remain confidential but may no longer be anonymous (to the researchers). The tool aims to generate data concerning the key features of the engagement approach and the participants' perceptions of impact [31]. The PPEET includes 14 survey questions with five Likert-scale response options ranging from strongly agree to strongly disagree. The tool includes open-ended questions querying how the results may be used, the best aspect of the engagement, and areas for improvement. Qualitative analysis will be used to understand the open-ended question portion of the PPEET to generate more in-depth data. Documents from the parent collaborator group meetings such as agendas, minutes, and decision processes will be used as additional data sources to more fully answer the research questions.

Analysis

The two types of data collected will be analyzed and reported separately. The findings from the quantitative and qualitative data will be integrated into the discussion if there are sufficient commonalities and inter-relationships.

Data from the Likert-scale questions will be entered into SPSS version 25. Descriptive statistics will be used to report group characteristics and question responses, including mean, median, and/or the mode (as appropriate), and range (or IQR, as appropriate). Frequency and percentages will be reported for categorical demographic information. No further analysis is planned because there is no comparative element of the design.

We will use directed content analysis [34] to explore participant responses relative to the themes of the PEIR Framework [17] using a combination of deductive and inductive analyses. Documents from parent collaborator group meetings (agendas, minutes, decision processes) will also be used as data sources for qualitative analysis. Data will be cleaned and transferred into NVIVO version 11 (QSR International). All responses will be categorized according to the PEIR framework codes: *procedural requirements*, *convenience*, *contributions*, *support*, *team interaction*, *research environment*, *feeling valued*, and *benefits* [17]. Text that cannot be coded into one of these categories will be coded with another label that captures the meaning of the response. Finally, we will compare the extent to which the data fit within the PEIR framework versus other themes. Interested members of the parent collaborator group will also be invited to contribute to the analysis and dissemination of the evaluation findings in order to maintain engagement in the collaborative relationship. The manuscript produced from this stage of the research will include reporting each element described by the Good Reporting of A Mixed Methods Study criteria [35].

Ethics

Approval from the appropriate University Health Research Ethics Board is complete for this project (#Pro00087548). Each participant will receive an information sheet that will provide details on the purpose of the study, identify the potential risks/benefits, and explain the voluntary nature of their participation. Participants may choose not to answer particular questions and can revoke consent from participating in the parent collaborator group at any time. Evaluation data will be collected anonymously; therefore, individual participant data cannot be removed after it is collected. Data will be kept confidential, except for the duty to report any information relating to child welfare. Any information disclosed that falls under mandatory reporting laws (eg, safety and well-being of a child) would be shared first with the disclosing participant. Eligible participants will receive a written consent form to be read and signed before enrolling in the study. All data will be stored using secured software on a password-protected server.

Data Management

Survey data will be collected on participants' computer or tablet devices through the SimpleSurvey platform. SimpleSurvey is a secure online platform with secure servers in Canada, protected by several firewalls and three physical layers of security. Data collected through the online platform is completely anonymous and cannot be traced back to any one individual. The data is stored on SimpleSurvey servers until data collection for the specific survey/project is complete. Once data is downloaded onto the University of Alberta servers, it will be deleted from SimpleSurvey storage. Data will be stored on a secure drive, which is hosted by the University of Alberta, Faculty of Nursing, secure server system. The server is backed up twice a day. Files can be recovered if accidentally deleted/lost/corrupt. In the event of system-wide corruption, an external hard drive is used to back up the data once a month. This hard drive is kept in a locked area within a locked office.

Results

Recruitment for the parent collaborator group is planned for June 2020. Once the group is formed, the development of the digital knowledge translation tool for parents caring for a child with functional constipation is expected to take 3-4 months. Data collection for the evaluation of patient engagement processes will occur when the digital knowledge translation tool has been built and is expected to take 2-4 weeks to optimize the number of responses. The results of this study are expected to be published by the end of 2020.

Discussion

This study will include the development of a relevant and accessible digital knowledge translation tool created *with* and *for* parents caring for a child with functional constipation. The findings will also fill gaps in the evidence supporting the processes of patient engagement in research. Our reported patient engagement processes are widely applicable, meaning others can use this protocol to guide patient engagement and evaluation in a variety of contexts. Specifically, the results can

inform future research collaborations to ensure that contributions by patient stakeholders are optimized, and challenges recognized and planned for accordingly. For example, avoiding tokenism, fostering inclusivity, and building capacity are knowledge gaps within patient engagement methods in research that may be better understood through widespread evaluations and dissemination. The results of this study can help build the science of patient engagement in research. Limitations of the study and findings will be discussed. Despite our planning and intentions, this study may face challenges such as small sample size or significant attrition. We commit to full disclosure of the barriers encountered and the potential implications for the results. Given the emergent nature of PE evaluation, we suggest that studies with negative or limited findings are equally important to understand the barriers to further development of this field.

This study fits within the KTA framework [23] as a component of *tailoring knowledge* by creating a knowledge translation tool.

Future projects related to this research will plan and examine the integration of the knowledge translation tool into the *action cycle* of the KTA framework [23]. For example, assessing usability by a broader audience contributes to adapting the knowledge to the local context and can also help identify potential barriers to use. In addition to the creation of a digital, patient-direct knowledge translation tool, knowledge translation activities will be woven throughout this research. Specifically, the topic of functional constipation aligns with priority areas of research identified by a national needs assessment of care providers; therefore, the foundation for this research stems from an existing relationship with clinical knowledge stakeholders. The use of a patient engagement approach in this research allows for explicit and ongoing inclusion of stakeholders; thus, integrating end-users of the knowledge into the development processes. Lastly, the dissemination of the findings from this study will include tailored presentations to stakeholder groups and manuscript publication to target healthcare researchers.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Diagnostic criteria for functional constipation.
[PDF File (Adobe PDF File), 14 KB - resprot_v9i8e19108_app1.pdf]

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Abbreviations

KTA: Knowledge-to-Action
PEIR: Patient Engagement in Research
PPEET: Public and Patient Engagement Evaluation Tool

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Protocol

Using Machine Learning to Optimize the Quality of Survey Data: Protocol for a Use Case in India

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Abstract

Background: Data quality is vital for ensuring the accuracy, reliability, and validity of survey findings. Strategies for ensuring survey data quality have traditionally used quality assurance procedures. Data analytics is an increasingly vital part of survey quality assurance, particularly in light of the increasing use of tablets and other electronic tools, which enable rapid, if not real-time, data access. Routine data analytics are most often concerned with outlier analyses that monitor a series of data quality indicators, including response rates, missing data, and reliability of coefficients for test-retest interviews. Machine learning is emerging as a possible tool for enhancing real-time data monitoring by identifying trends in the data collection, which could compromise quality.

Objective: This study aimed to describe methods for the quality assessment of a household survey using both traditional methods as well as machine learning analytics.

Methods: In the Kilkari impact evaluation's end-line survey amongst postpartum women (n=5095) in Madhya Pradesh, India, we plan to use both traditional and machine learning–based quality assurance procedures to improve the quality of survey data captured on maternal and child health knowledge, care-seeking, and practices. The quality assurance strategy aims to identify biases and other impediments to data quality and includes seven main components: (1) tool development, (2) enumerator recruitment and training, (3) field coordination, (4) field monitoring, (5) data analytics, (6) feedback loops for decision making, and (7) outcomes assessment. Analyses will include basic descriptive and outlier analyses using machine learning algorithms, which will involve creating features from time-stamps, "don't know" rates, and skip rates. We will also obtain labeled data from self-filled surveys, and build models using k-folds cross-validation on a training data set using both supervised and unsupervised learning algorithms. Based on these models, results will be fed back to the field through various feedback loops.

Results: Data collection began in late October 2019 and will span through March 2020. We expect to submit quality assurance results by August 2020.

Conclusions: Machine learning is underutilized as a tool to improve survey data quality in low resource settings. Study findings are anticipated to improve the overall quality of Kilkari survey data and, in turn, enhance the robustness of the impact evaluation. More broadly, the proposed quality assurance approach has implications for data capture applications used for special surveys as well as in the routine collection of health information by health workers.

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Introduction

Data quality is vital for ensuring the accuracy, reliability, and validity of survey findings. Traditional approaches to monitoring data quality have sought to consider both the *intrinsic* (the data collection tool, implementation and support systems governing its use) and *extrinsic* factors (weather, enumerator-respondent dynamics, community environment) underpinning survey implementation, and in turn, data quality [1]. The quality of survey data starts with the selection of the survey institutions that will support the design and development, sampling, and implementation of the instrument. Decisions on survey tool content, including the selected indicators, language used, and phrasing of both questions and response options, as well as the length of the tool and the broader implementation strategy (tablets versus paper tools, sampling, training, profile, and the number of enumerators, workload), and support structures including supervision and reliability checks, may also influence quality.

Strategies for ensuring survey data quality have traditionally used quality assurance (QA) procedures—defined as "any method or procedure for collecting, processing or analyzing survey data that is aimed at maintaining or enhancing their reliability or validity" [2]. QA procedures usually focus on the intrinsic factors which influence data quality, starting with the sampling (overview of population composition, sampling frame, stratification, size), tool development (reliability of questions, accuracy, understandability of translation), enumerator selection (experience and profile) and training (length, methods, and content of training; enumerator and supervisor evaluation) [2]. These are followed by the piloting and refinement of tools and, ultimately, main survey implementation. QA procedures during implementation concentrate on survey personnel (enumerators, supervisors, coordinators), logistics (travel and team organization), contact procedures (respondent identification/introduction, consent, refusal rates), enumerator remuneration, supervisor checking procedures, data transfers and checks [2]. Examples of QA procedures during implementation may include reliability checks from supervisors, site visits from senior study personnel, as well as routine data analytics.

Data analytics is an increasingly vital part of survey QA, particularly in light of the increasing use of tablets and other electronic tools which enable rapid, if not real-time, data access. Routine data analytics are most often concerned with outlier analyses that monitor a series of data quality indicators, including response rates, missing data, and reliability of coefficients for test-retest interviews. Dashboards may be used to visualize key tracking indicators and provide a snap-shot of survey implementation status. Collectively, while these procedures help ensure basic data quality, they fall short of optimizing the full potential of rapid data access borne from the use of electronic tools during survey implementation.

Machine learning is emerging as a tool with the potential to enhance real-time data monitoring by identifying trends in data collection that could compromise quality [3]. Machine learning covers a broad array of computationally-intensive methods aimed at detecting patterns in the data, including outliers and subtle trends that would not always be noticed via manual data cleaning and analysis. In the context of QA for survey monitoring, machine learning can be used to classify the data by the severity of outliers using either supervised techniques—with labeled training or pilot data—or a variety of unsupervised techniques [4].

Household surveys are expensive, time-consuming, and resource-intensive. Recognizing this, to date, applications of machine learning as part of household surveys have sought to reduce the expense of surveys by using satellite or phone data to predict socioeconomic distribution in a country [5]. However, little work has been done using machine learning techniques to improve the monitoring of surveys. To address this gap, we aim to outline a comprehensive strategy for monitoring the quality of data emerging from a large population-based household survey in rural India, including the use of machine learning techniques. Study findings are anticipated to shed light on the feasibility and effectiveness of advanced monitoring using machine learning as compared to traditional monitoring techniques.

Methods

Survey Description

In late 2018, as part of an impact evaluation of the maternal messaging program Kilkari, a randomly selected sample of 5095 women 4-7 months pregnant, with access to a mobile phone were identified across four districts of Madhya Pradesh, India: Rewa, Rajgarh, Hoshangabad, and Mandsaur [6]. Identified women were administered a structured baseline survey tool that sought to measure their knowledge of reproductive, maternal, newborn, and child health (RMNCH) practices and observe their digital literacy. Following the baseline survey, women were randomized to receive Kilkari messages or not (status quo). In this paper, we focus on the QA procedures for the endline survey administered to women enrolled in the study at 12 months postpartum. The endline survey will be used to capture RMNCH decision making, discussion, knowledge, and practice.

Study Setting and Population

The study setting in Madhya Pradesh is characterized by disparities in access to education, mobile phones, and health services by gender and geographic location (rural/urban). With a population of over 75 million, Madhya Pradesh is home to over 20% of India's population. Madhya Pradesh ranks as one of the worst-performing states in India economically (gross domestic product per capita of US $1100 versus US $1709 nationally) and in terms of health outcomes, particularly concerning child nutrition. In 2015, only 35% of children were breastfed within one hour of birth, and 58% of children were exclusively breastfed until 6 months [7]. While over half of

pregnant women attended antenatal care (ANC) in the first trimester, only 36% received the recommended four ANC visits [7]. Health behaviors and care-seeking practices differ markedly between urban/rural areas and are underpinned by high rates of illiteracy (41% of women, 18% of men) and poor access to mobile phones among women [7]. In 2015, 19% of rural and 50% of urban women reported having access to a mobile phone [7].

Our trial population consists of women who have given birth in the past 1 year after being enrolled while they were 12-34 weeks of gestation, and all participants are at least 18 years of age, speak and understand Hindi, and own or have access to a mobile phone during the morning or afternoon. Our sample ranges from the ages of 18-44 years, with 61% of the sample being between the ages of 20-25. In terms of socioeconomic profile, 21% of our sample is "general class," which is socially privileged, 47% are "other backward class," which is somewhat

marginalized, and the remainder are from highly marginalized groups—scheduled caste (20% of the sample) and scheduled tribe (11% of the sample). Hindu individuals comprised 95% of the trial sample, and 11% had not received any formal education, 6.5% had 1 to 4 years of schooling, 17.8% had between 5 and 7 years, 56.0% had between 8 and 12 years, and 8.7% had more than 12 years.

Overview of Quality Assurance Procedures

The household survey monitoring strategy aims to identify biases and other impediments to data quality and includes seven main components: (1) tool development, (2) enumerator recruitment and training, (3) field coordination, (4) field monitoring, (5) data analytics, (6) data feedback loops for decision making, and (7) outcome assessment. In the framework below, we have outlined the processes we aim to complete in an effort to ensure survey data quality (Figure 1).

Figure 1. Conceptual Framework of methods to improve data quality from Kilkari womens' household survey.
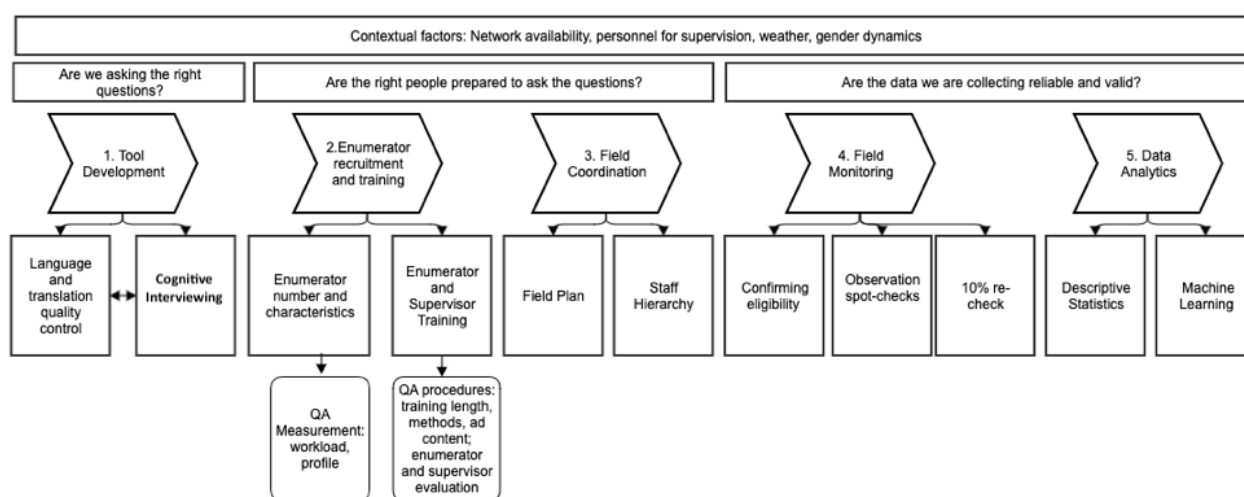
Tool Development

Tool development assumed six essential steps: (1) linking intervention content with key indicators across behavior change outcomes for decision making, discussion, knowledge and practice, (2) drawing survey content from standardized and/or validated survey tools, literature, and/or expert review, (3) translation, (4) cognitive interviewing, (5) pilot testing, and (6) computer-assisted personal interviewing (CAPI) checking.

Our tool development began with looking at our key indicators on knowledge, practice, discussion, and decision making around topics relevant to pregnant and postpartum women such as family planning, infant and young child feeding, and newborn care. We then chose to assess these indicators using selected questions from previously completed standardized surveys. These questions were reorganized, reworded, and translated. The survey was a close-ended quantitative survey with single-answer multiple-choice questions as well as multiple-answer multiple-choice questions. Questions for which other options could be provided had an "other specify" text box. We chose to go beyond the traditional pilot testing methods and also use cognitive interviews to test our tools. Cognitive interviewing involves first asking the survey question as it is

written, recording the respondent's answer, then using verbal probes to determine if the respondent is understanding the question and providing an answer in the manner intended by the researchers [8]. We used this method to assess if our tool's major sections on knowledge and behavior of family planning and infant and young child feeding were accessing the cognitive domains we intended them to [9]. Through this work, we revised our questions to improve their comprehensibility for our sample population (women in rural Madhya Pradesh).

During training, we spent time reviewing the paper versions of the tool as well as ensuring that our CAPI tablet versions, programmed using CSPro software, mirrored them well and adhered to the skip logic we had outlined. Both paper and tablet versions of the survey took on average about 1.5 hours to complete. The tablet version of the survey had just one question at a time appear on the screen. The process of checking the tablet version of the tool continued before and after piloting these versions in the field to ensure we had made all necessary changes in both language and logic before data collection with our end-line sample began. All survey data will be collected on tablets.

As part of the tablet-based data collection forms, we added a few parameters that were not part of the paper tools. These included time-stamps for the start and end of modules and time flags at the beginning and end of questions involving in-depth probing. GPS fields were added to the end of the tablet-based tool to track location.

Enumerator Recruitment and Training

Enumerator recruitment depends on survey size and timeline, as well as the characteristics of the enumerator. The experience and characteristics, including age, gender, caste, ethnicity, education, and geographic origins of an enumerator can influence not only their understanding of survey questions but also the implementation of the survey, including how they explain questions to and interact with respondents. Survey enumerators will be women fluent in Hindi, between 21-35 years of age, with education levels ranging from current college students to current PhD students, and 0-12 years of survey experience. To monitor the effects of enumerator characteristics and experience on data quality, we will start by administering a short survey during training to formulate their profile, and then as survey data are collected, use these profile data to understand potential associations between profile data and survey data quality.

To ensure that adequate numbers of enumerators are recruited, we have projected the number of interviews that need to be completed weekly by geographic area and considered the time it takes to administer each survey coupled with the time required to travel to and locate respondents. Additional factors such as enumerator attrition, along with the need to conduct repeat visits to locate respondents or complete partially completed surveys, will be factored in.

Once an adequate number of enumerators and supervisors are recruited, training will be key to optimizing survey implementation and ensuring data quality. Training will be led by the in-country field manager, a physician with >30 years of survey management experience. Additional support will be provided by study team members who participated in the development of the tool in its early stages. The training spanned 14 days and involved classroom-based lectures, quizzes, role-playing exercises, and field-based piloting. The tool covered multiple modules, including family planning methods, infant and young child feeding, and the immunization schedule. First, the didactic lectures covered the information on the domains covered in the tool. Then the field manager, along with support from various members of the study team who were instrumental in developing the tool, walked through the tool, including the questions, responses, and how to administer the question in a detailed manner. The session leader verified the data collectors'

understanding and asked them to clarify any lingering questions they may have had. After explaining and discussing the questions with the group, the enumerators conducted mock-interviews amongst themselves. A few quizzes on these topics were administered to ensure that the enumerators and supervisors were familiar with these health areas and associated vocabulary. In order to provide more real-world practice, there were two field pilot days in nearby villages that resembled the study population but were outside the study population, one with paper forms and another with the tablet version of the surveys with which the enumerators could practice. These pilot test days allowed the enumerators to become comfortable using the tool with live respondents, as well as allowing them an opportunity to comment on any issue in the tool, including language and flow.

Field Coordination

Beyond the development of the tool and enumerator selection and training, the quality of data is improved by strong field coordination. Field coordination is built on two main components: field and logistics planning as well as coordinating the monitoring of data collection through supervisors and checks. First, key eligibility criteria for interviews need to be kept in mind when planning field logistics. Women will be interviewed if they have completed 12 months postpartum or longer; thus, field planning will require that enumerators be spread across four districts of Madhya Pradesh to capture women as they reach their expected date of eligibility. Confirming women's eligibility will require reliability monitoring, as outlined below. Once an eligible woman is identified, supervisors are given her identification and location information so they can coordinate their team of enumerators to her location and manage any follow-up visits as necessary depending on her availability.

A clear hierarchy in quality assurance activities as part of field operations is key for ensuring the collection of high-quality data. The field team will include 35 enumerators, 9 supervisors, and 2 coordinators, a survey coordinator, and a field manager. The male supervisors will be paired with a team of enumerators, consisting of 3-4 female enumerators, and will be in charge of checking the data as it is collected. The coordinators track adverse events and logistics and will conduct spot checks. The survey coordinator will monitor the data and relay any issues back to the larger research team. The field manager will handle training as well as ensure the field plan is in place. With clear roles in place, the field manager and survey coordinator will be best able to plan the fieldwork and monitoring, respectively. The data flow and feedback processes are outlined below (Figure 2).

Figure 2. Data flow and feedback in Kilkari women's survey.
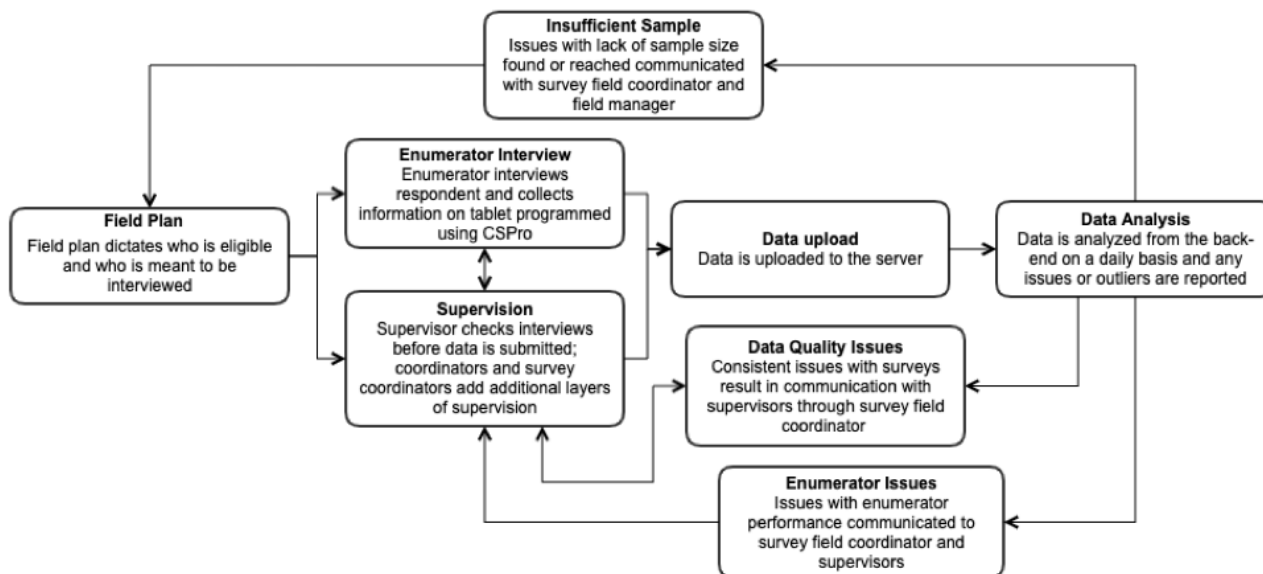
Field Monitoring

Field monitoring consists of both confirming the eligibility of respondents as well as spot checks. Both these aspects happen at each of the five levels of field hierarchy: (1) enumerator, (2) immediate field supervisor, (3) coordinator, (4) field-level data quality supervisor, and (5) back-end data quality supervisor. At the enumerator level, any issues or red flags identified by enumerators will be reported back to their immediate supervisor who assigned them to the interview; these could include issues of eligibility or issues with tablets or other interview processes. Immediate field supervisors will focus principally on locating respondents and monitoring interviews. The former occurs based on the respondents the field coordinators give each supervisor—the respondent is located, and eligibility is confirmed. Then the supervisor may monitor part or all of the interview either through spot-check observation or form check and keep track of completion or any needed follow-up visits. The coordinators will manage larger village/block level logistics to ensure all eligible participants in an area have at least been visited once on a trip and also complete random spot-checks as their logistics duties allow. The field level quality supervisor will complete spot-checks as well as follows-up on any systemic issues found in both eligibility checking or back-end data monitoring either by individually speaking with enumerators/supervisors or discussing any data quality issues during debriefing meetings with the team. Finally, the back-end data quality supervisor will check weekly data uploads for any entry errors relating to eligibility, such as incompatible birth age or incorrect unique identifier. They will also assess mechanistic indicators such as time to interview completion or rate of skips or "don't know" responses that warrant further observation of participating enumerators. The larger research team will conduct monthly checks on the field teams.

Beyond eligibility confirmations and observation spot-checks, our second stage of reliability monitoring will involve a 10% resample to ensure enumerators are asking the questions correctly so that we are getting consistent answers. A set of 15-25 questions will be randomly selected from a bank of 30, and the 10% sample will also be randomly selected from the total eligible population that has completed interviews. The recheck will be completed by a different enumerator either later in the day or a day later after the original interview has taken place.

Data Analytics

Data analytics will focus on descriptive and outlier analyses.

Descriptive analyses will focus on the conduct of basic frequencies across all questions in the survey to ensure that questions are not being unexpectedly skipped. Beyond checking the frequencies across the variables, we will also examine any anomalies, such as incorrect unique identifiers or ineligible respondents based on date, every week. These frequencies will be examined after each district in the survey is halfway complete.

The outlier analysis aims to identify anomalies in the data, which could indicate gaps in quality. Outlier analysis will start with the selection of features, and depending on these features and their distributions (parametric/non-parametric), several techniques will be explored for outlier detection including numerical outliers, Z-score, linear models, probabilistic and statistical models, as well as unsupervised machine learning (k-means clustering). Analyses will draw from the following data sources: enumerator completed survey tools from piloting, enumerator completed survey tools from the main field implementation, enumerator profile survey, and the recheck survey. The following steps will be undertaken:

1. Selecting Features Necessary to Examine Gaps in Quality

Data features will be identified from the enumerator collected survey tools during implementation. They may include (a) time to complete the overall questionnaire, select modules, and individuals questions, (b) frequency of enumerator selection of the response option 'don't know,' and (c) skip patterns. While time-stamping all individual questions in the data collection tools will not be possible, select priority questions (eg, dietary

recall) will be time-stamped, along with the start-stop times by module and for the overall time to complete the tool in its entirety. Data from enumerator collected survey tools during implementation will be linked with data on the enumerator profile and descriptive statistics used to identify outliers and as needed feedback data requiring follow-up. Each of these features and the indicator proposed to measure each is summarized in Table 1. Machine learning algorithms will ultimately be developed through the additional steps described below.

2. Obtaining Labeled Data

Labeled data are essential in supervised machine learning. Labeled data can assume a variety of forms; in this case, we have data from enumerators completed on their own without a respondent as fast as they possibly can. These data are then labeled as 'false' data to be used in our supervised learning algorithms. By comparison, another labeled dataset will come from data captured during the pilot testing of tools. An alternative strategy for obtaining labeled data through data augmentation will also be explored. Data augmentation is the process of supplementing a dataset with similar data that is created from the information in that dataset.

3. Building Models

This data will be split randomly into a training set and a testing set. As predictors of the models, we will use the features listed in step 1, and the data will be labeled as "false" or "true."

Two steps will be undertaken to build models: (1) develop the best models for each learning algorithm using the training dataset and cross-validation methods and (2) apply the best performing algorithm on the test dataset for an unbiased evaluation. During the learning (training) process, k-fold cross-validation methods will be used to avoid overfitting and assess model performance. The k-fold cross-validation method involves splitting the dataset into k-subsets, which are, in turn, held out while the model is trained on all other subsets. The process is complete when accuracy has been determined for each instance in the data set, and an overall estimate of accuracy has been generated. Once the learning step is accomplished on the "training" set, we have trained models. Each model will be tested using the originally withheld testing set.

The algorithms under consideration are listed below in Table 2. We aim to train using all methods to identify the best algorithm for our data. Methods to assess the models, compare their attributes, and formulas to compare the results of the learning algorithms are similar to those presented in a study by Mohan et al [3]. That study also describes comparisons of the strengths of these various algorithms [3].

Table 1. Biases in survey completion that can be captured using machine learning.

Biases	Indicator	Numerator	Denominator
Rushed completion	Percent of time to complete survey, sections, and individual question as compared to time recorded during piloting	Time measured during the pilot—actual time in seconds	Pilot time
CAPI[a] entry error/ Fabricated responses	Percent difference from 10% resample	Questions that are different in 10% resample	Total number of questions resampled
Respondent bias	Mean time taken to complete questions among respondents in differing sociodemographic characteristics	N/A[b]	N/A
Skipping of sections	Percent of skips across all potential skip options throughout the tool	Opportunities where a skip was implemented	Total opportunities where a question or section can be skipped
Misunderstanding of content	Percent of "don't knows" across all questions and by section per respondent or enumerator	Questions with "don't know" answers	Total number of questions with "don't know" options

[a]CAPI: computer-assisted personal interviewing.

[b]N/A: not applicable.

Table 2. Machine learning algorithms.

Algorithm	Description	Intended application
Supervised		
Logistic regression	Classification (nonlinear model)	Classification of times, "don't knows," and skips used by enumerator characteristics and respondent characteristics
Linear discriminant analysis	Classification (linear model). It is a linearization of Gaussian naïve Bayes.	Classification of times, "don't knows," and skips used by enumerator characteristics and respondent characteristics
Support vector machines	Support vector machines are techniques based on the calculation of the maximum margin hyperplane for classification problems.	Classification of times, "don't knows," and skips used by enumerator characteristics and respondent characteristics
Classification and regression trees	A predictive model that consists of leaves that represent the target and branches that represent conjunctions of input features. Considered a subset of decision trees. Random forests operate by constructing multiple decision trees during training and aggregating their results to avoid overfitting by single trees.	Classification of times, "don't knows," and skips used by enumerator characteristics and respondent characteristics
Naïve Bayes	Classification model based on probabilities.	Classification of times, "don't knows," and skips used by enumerator characteristics and respondent characteristics
Neural networks	Neural networks are powerful models for machine learning. They are a generalization of linear and nonlinear models	Classification of times, "don't knows," and skips used by enumerator characteristics and respondent characteristics
Unsupervised		
K-means	K-means clustering is a way to use data to uncover natural groupings within a heterogeneous population	Grouping of Enumerators' times, "don't knows," and skips used by enumerator characteristics and respondent characteristics

Feedback Loops for Decision Making

Data quality issues identified during analysis will be fed back to the survey coordinator and survey team in the field. The immediate strategy for feedback will require that the data quality supervisor identifies the problem and communicates with the study coordinator via phone and email; the coordinator will then speak with the team supervisor and the enumerator (Figure 2). The study team is also exploring the possibility of automated feedback loops to capture data quality gaps identified by the machine learning algorithms and send QA issues via email or text to the study coordinators, customized calls or text alerts to team supervisors, and provide the monitoring and supervision teams with access to a web-based dashboard for data visualization (Figure 3).

Depending on the magnitude of the issue identified and its frequency, an appropriate response will be devised and may include trouble-shooting issues with CAPI/tablets, enumerator retraining or encouragement as needed, or in serious circumstances, re-interviewing the respondent. A more pervasive issue may require a team meeting where a problem with a certain question or set of the respondent population needs to be dealt with differently. Depending on the severity of the issue, the survey coordinator will be in charge of deciding how best to handle it and recheck the data to ensure the problem has been resolved.

Figure 3. Automated feedback loops.
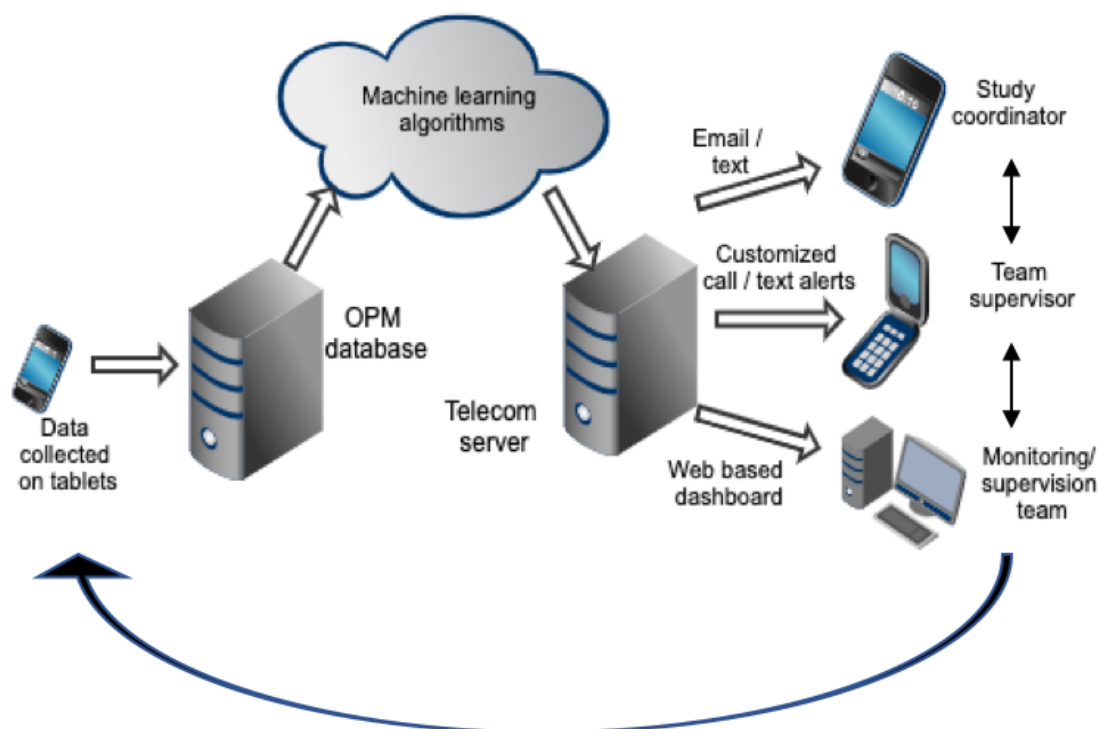
Outcome Assessment

Given that this is a small pilot study of this SMS feedback system, we will be assessing acceptability and feasibility. To examine if the SMS system reduces the amount of time to address errors, we will look at the difference between the date the error was made and the date it was resolved. Additionally, we plan on conducting qualitative interviews with the coordinators and supervisors to understand their perceptions of the SMS format of feeding information back and soliciting data on feasibility and acceptability. We hope to conduct in-depth interviews and focus group discussions with field staff towards the end of the data collection period to learn this information from them after they have been using the SMS system for an extended period.

Results

This study has been approved by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board and the India-based Sigma Research and Consulting review.

Discussion

Machine learning has the potential to enhance routine QA methods for surveys, as well as the routine capture of health information through data capture applications. The proposed QA strategy for the Kilkari Impact Evaluation aims to comprehensively improve data collection quality through innovations in the tool development stage, such as cognitive interviewing, as well as in the monitoring stage through the use of machine learning. By complementing traditional monitoring back-end checks, machine learning has the potential to enhance

survey monitoring by identifying biases in survey data collection, which may hamper data quality and, in turn, emerging findings. The potential use of automated feedback loops via text and email may serve to enhance the timeliness of feedback at the point of data collection and, in turn, improve efficiencies in data collection by minimizing the need to return to geographic areas after teams have left. The QA approach outlined in this protocol may have additional implications for study teams comprised of researchers spread across wide geographies, enhancing remote QA and enabling greater confidence in emerging data.

The limitations of this approach include the parameters used for the machine learning approach—ideally more time-stamps and information on tapping forward or back off a screen would provide more detail on the timing and mechanics of each survey completed. In some cases, an interview may be interrupted by factors outside the enumerator's and respondent's control such as a baby crying or a neighbor calling; however, the enumerators are encouraged to do their best to complete the survey in one sitting and include comments on hindering circumstances that extend the length of the interview at the end of the survey. Additionally, some skips in the surveys and "don't know" responses are necessary and unavoidable; thus, these measures could be ambiguous at times. Given the nature of our multi-select tool, we expected enumerators to be probing for answers and using "other specify" for ambiguous answers and using the "don't know" option minimally. However, this parameter is specific to our survey, and it could be that in another type of tool, other parameters are used to indicate rushed or low-quality interviews. This difference is true of other steps as well, such as which time-stamps to collect, what kind of labeled data to obtain, and the types of responses that are useful

for quality control. Quality assurance needs to be tailored for each survey.

In large surveys, such as the Demographic and Health Surveys (DHS) and Multiple Indicator Cluster Surveys (MICS), traditional monitoring techniques are used. DHS quality checks during fieldwork focus on assessing quality based on the number of questions answered, recoding, and eligible sample met. Additional measures such as age displacement, response rates, and completeness of data are relayed back to the data collectors to improve quality during the period of data collection [10]. After data entry, the number of questionnaires is checked against the number expected according to the sample design, and double entry is conducted to minimize entry mistakes. The entered data are checked for further issues, and variables determined to be missing at random are calculated using needed imputations. MICS follows similarly strict guidelines with interview teams headed by supervisors and accompanied by measurers who are in charge of taking measures of weight and water quality. Data quality checks focus on the number of respondents, deviations from the average weight of children interviewed, ages of respondents, and nonresponse rates [11]. While these monitoring approaches are widely used and time-tested, machine learning could further strengthen the monitoring approaches used in these large surveys.

Thus far, the use of machine learning in household surveys in Lower-middle-income country settings is limited. One set of researchers has used tree-based machine learning methods to model and predict nonresponse in surveys [12]. Similarly, a working paper from the United Nations Economic Commission for Europe examined the use of machine learning methods to develop data editing and imputation [13]. Both these studies focus on the use of machine learning to counteract and improve household surveys with sparse data. Another study with objectives similar to ours sought to measure the rate of enumerators falsifying information in Tanzania using machine learning [14]. Our study is an extension of the work done in Tanzania by automating the process of quality assurance to send survey errors back to the field team.

Machine learning holds great value for other aspects of international development beyond survey work as well. In 2016, Goldblatt et al used satellite imagery in India to examine areas of urbanization in a rapidly developing country [15]. A World Bank Group additionally reported using natural language processing to study differences between genders when deliberating topics in village meetings transcripts across Tamil Nadu [16]. Given the expanding use of these methods in international development and survey work, it is only fitting that we take them a step further to assist with monitoring incoming data.

Conclusions

The comprehensive QA strategy outlined in this protocol aims builds on traditional approaches to survey QA through the use of machine learning methods to improve data monitoring, and in turn, quality. The approach undertaken is anticipated to improve the rigor of impact evaluation data currently being collected in four districts of Madhya Pradesh, India, as part of the Kilkari Impact Evaluation. Broader learnings are anticipated as this protocol is additionally envisaged as a use case for the application of similar methods to improve the quality of data emanating from data capture digital health solutions currently being used by health workers throughout India.

Conflicts of Interest

None declared.

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Abbreviations

ANC: antenatal care
CAPI: computer-assisted personal interviewing
DHS: Demographic and Health Surveys
QA: quality assurance
RMNCH: reproductive, maternal, newborn and child health
MICS: Multiple Indicator Cluster Surveys

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Protocol

A Combined Digital and Biomarker Diagnostic Aid for Mood Disorders (the Delta Trial): Protocol for an Observational Study

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Abstract

Background: Mood disorders affect hundreds of millions of people worldwide, imposing a substantial medical and economic burden. Existing diagnostic methods for mood disorders often result in a delay until accurate diagnosis, exacerbating the challenges of these disorders. Advances in digital tools for psychiatry and understanding the biological basis of mood disorders offer the potential for novel diagnostic methods that facilitate early and accurate diagnosis of patients.

Objective: The Delta Trial was launched to develop an algorithm-based diagnostic aid combining symptom data and proteomic biomarkers to reduce the misdiagnosis of bipolar disorder (BD) as a major depressive disorder (MDD) and achieve more accurate and earlier MDD diagnosis.

Methods: Participants for this ethically approved trial were recruited through the internet, mainly through Facebook advertising. Participants were then screened for eligibility, consented to participate, and completed an adaptive digital questionnaire that was designed and created for the trial on a purpose-built digital platform. A subset of these participants was selected to provide dried blood spot (DBS) samples and undertake a World Health Organization World Mental Health Composite International Diagnostic Interview (CIDI). Inclusion and exclusion criteria were chosen to maximize the safety of a trial population that was both relevant to the trial objectives and generalizable. To provide statistical power and validation sets for the primary and secondary objectives, 840 participants were required to complete the digital questionnaire, submit DBS samples, and undertake a CIDI.

Results: The Delta Trial is now complete. More than 3200 participants completed the digital questionnaire, 924 of whom also submitted DBS samples and a CIDI, whereas a total of 1780 participants completed a 6-month follow-up questionnaire and 1542 completed a 12-month follow-up questionnaire. The analysis of the trial data is now underway.

Conclusions: If a diagnostic aid is able to improve the diagnosis of BD and MDD, it may enable earlier treatment for patients with mood disorders.

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Introduction

Background

Mood disorders affect approximately 400 million people worldwide, with bipolar disorder (BD) and major depressive disorder (MDD) representing the 17th and the 2nd leading causes of years lost to disability, respectively [1]. Affected individuals experience debilitating and often recurrent symptoms [2,3] as well as an association with high levels of both psychiatric and somatic comorbidities [4,5], culminating in decreased quality of life [6,7] and increased mortality [8]. In addition, caregivers of patients with mood disorders experience a substantial burden associated with this role, expanding the direct impact of these conditions [9,10]. Economically, recent estimates of the annual European-wide costs associated with BD are €21.5 billion (US $24.1 billion), whereas those associated with MDD are €91.9 billion (US $102.9 billion) [11].

Existing diagnostic methodology, based on subjective reports and observations gathered during clinical interviews that are referenced against symptom checklists [12], leads to frequent misdiagnosis and underdiagnosis of mood disorders [13,14]. Patients with BD often initially present with depressive episodes that can be indistinguishable from depressive episodes in the context of MDD [15,16], leading to approximately half or more of patients with BD initially being misdiagnosed with MDD [17,18]. The approximate 8- to 10-year delay before a BD diagnosis includes the delay from initial symptom manifestation until psychiatric evaluation as well as the delay from initial assessment until correct diagnosis [19,20]. MDD diagnosis faces issues of both over- and underdiagnosis. These issues overlap with one another and include patient reluctance to seek help for emotional distress [21], short consultation times, and limited focus on mental health in primary care [22]; a shortage of mental health practitioners [23,24]; and the difficulty of identifying patients who fulfill the clinical threshold for MDD [25].

Although pharmacological and psychological treatments can be effective when correctly prescribed [26-28], inaccurate or delayed diagnosis limits the effective use of these treatments. For BD, a delay before correct diagnosis and treatment is associated with poorer outcomes [29], whereas a diagnostic delay for MDD compounds the time associated with the identification of an effective therapy, which can lead to months of trial and error treatment testing [27,30]. By shortening the period before the administration of appropriate treatment, early and accurate diagnosis of mood disorders represents the first step on the path to lessen the burden experienced by patients with BD and MDD.

Psychiatry is increasingly turning to a variety of digital tools, which are already in use in many forms [31], to improve symptom-based diagnosis [32]. One reason for this approach is the unprecedented data gathering opportunities that digital platforms represent for researchers [33]. However, despite the optimistic projections of technology's potential to increase the accessibility and efficacy of psychiatric interventions, these goals are not yet fully realized [34,35]. With digital solutions in psychiatry still in an early phase of research and development, they may be most immediately clinically applicable in areas with fewer barriers to validation and adoption. One such area is psychiatric questionnaires, for which digitization has already begun. In particular, the increased convenience of digital questionnaires [36] may overcome clinicians' stated obstacles of time and difficulty of implementation [37]. As the majority of these questionnaires have shown interformat reliability, meaning the digital and paper versions are comparable [38], the next steps for digital questionnaire development may be the personalization of questions to individual patients through dynamic question selection. With the digitization of previously existing psychiatric questionnaires ongoing, digital psychiatric questionnaires represent a promising field for further innovation.

In conjunction with the progression to digital tools to evaluate patient history and symptoms, a paradigm shift to biomarker-based diagnosis in psychiatry is underway [39]. This shift is facilitated by both the growing understanding of the biological basis of mood disorders [40,41] as well as advances in technology that allow large amounts of biological information to be collected and analyzed. Biomarkers are defined by the National Institute of Health's Biomarker Working Group as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention," with diagnostic biomarkers representing one of a number of categories of biomarkers, alongside prognostic and predictive biomarkers [42]. It is important to note, however, that the clinical utility of diagnostic biomarkers is not dependent on a full understanding of the complex and interrelated factors culminating in psychiatric illness. Despite the growing research into biomarkers, to date, no diagnostic biomarkers for psychiatric disorders have been implemented in routine clinical use. In pursuit of this goal, efforts for biomarker discovery and validation are widespread, supported by initiatives such as the National Institute of Mental Health's Research Domain Criteria project [43].

Proteomics is a promising area for biomarker development because of its ability to detect disease-related alterations in readily accessible bodily fluids such as blood. This potential has been supported by research on candidate biomarkers and preliminary results both in mood disorders and other psychiatric conditions [44]. However, because of the complexity and heterogeneity of psychiatric disorders [45-47], there is a high threshold for progress in identifying and validating diagnostic psychiatric biomarkers. It is, therefore, likely that a panel of multiple biomarkers, rather than a single one, will be necessary for the validation of a psychiatric diagnostic aid [44]. Although much research on biomarkers has been previously conducted using serum or plasma, dried blood spots (DBS) represent a novel and clinically promising methodology for validating psychiatric biomarkers, given the multiple advantages of DBS that decrease barriers to implementation. These advantages include lower cost, minimal invasiveness, decreased blood volume required, simplified shipping and storage, and the ability of patients to provide a sample in a nonclinical setting [48]. When analyzing DBS samples, the strengths of mass spectrometry (MS), such as the ability to quantify large numbers of analytes in parallel, high sensitivity and specificity, and reproducibility [48,49], make it an ideal technique for validating

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a psychiatric diagnostic panel. By leveraging existing proteomics research in psychiatry with the complementary strengths of DBS and MS analysis, the goal of validating a biomarker-based diagnostic aid for mood disorders could be achieved.

To validate new approaches and tools to advance the process of psychiatric diagnosis, large-scale diagnostic trials are required [49-51]. However, the difficulty of reaching trial recruitment goals makes recruitment an obstacle to consider in its own right. Although the proportion of research trials reaching their recruitment goals seems to be improving, slightly under half of the publicly funded clinical trials still fail to reach these benchmarks [52-54]. This issue has been specifically documented in mood disorder trials, with multiple trials in recent years having failed because of under-recruitment [55,56]. The substantial time and cost devoted to failed trials [57] and the high proportion of trials that experience recruitment extensions [52] divert resources from clinical objectives. Beyond reaching a target number of trial participants, a representative participant population is required to ensure the generalizability and reproducibility of findings [58]. This is of particular concern in psychiatry, as the generalizability of research trials and clinical usefulness of findings has been questioned and remains under scrutiny [59-62]. In the case of web-based recruitment in psychiatry, it is also unclear how closely a trial population reflects the population of interest, as some groups may face digital exclusion [63]. Executing web-based trial recruitment in a timely and cost-effective manner could provide a roadmap for recruitment for other psychiatric trials.

Diagnostic tools must both accurately identify conditions and encourage appropriate follow-up action to improve treatment and outcomes for patients. Given the difficulty of effective communication between clinicians, academic researchers, and patients in psychiatry [64,65], the inclusion of service users in trial conception, planning, and design is increasingly considered essential to achieve this aim [66]. Specific to diagnostic trials, considering the trial in the broader context of the health care delivery pathway contributes to the clinical effectiveness of the diagnostic tool that is eventually developed [51]. By investigating the relationships between diagnostic information, caregiver decision making, and patient perceptions, the gaps in the mood disorder care pathway may be better understood and narrowed.

This study describes the objectives, methods, and recruitment results for the Delta Trial, which was launched in April 2018 and closed in February 2020 by the University of Cambridge's Cambridge Centre for Neuropsychiatric Research (CCNR). The aim of the trial is to develop algorithms based on a digital questionnaire and proteomic biomarker data to be used as a diagnostic aid for mood disorders in patients presenting with depressive symptoms. Participants were recruited through the internet and completed the trial remotely in a manner that may provide a useful roadmap for future psychiatric trials. The analysis of these data is now underway. The creation of a diagnostic aid for mood disorders that combines questionnaire and biomarker data could contribute to reducing the significant individual and societal burden of mood disorders by facilitating early diagnosis, leading to effective treatment.

Objectives

Primary Objective: To Reduce the Misdiagnosis of Bipolar Disorder

The primary objective of the Delta Trial is to develop a diagnostic algorithm based on a digital questionnaire and proteomic data to identify individuals with BD who have been misdiagnosed with MDD. The target population for the primary objective was participants who had received a recent MDD diagnosis from a general practitioner or psychiatrist and were experiencing some depressive symptoms at the time of recruitment (baseline MDD). *Recent* was defined as a diagnosis within the last 5 years, during which time it would be more likely that a patient with BD remains misdiagnosed with MDD [67,68]. Depressive symptoms were measured using the Patient Health Questionnaire (PHQ-9) [69], with a score of 5 or greater required for inclusion in the trial.

Secondary Objective: To Achieve a More Accurate and Earlier Diagnosis of Major Depressive Disorder

The secondary objective of the Delta Trial is to develop a diagnostic algorithm, also based on a digital questionnaire and proteomic data, to identify symptomatic help seekers with MDD. The target population for the secondary objective was participants who had not had a previous mood disorder diagnosis (baseline low mood) and scored 5 or greater on the PHQ-9 at the time of recruitment. Diagnoses predicted by the algorithms developed for the primary and secondary objectives will be compared with the diagnoses obtained through the World Health Organization World Mental Health Composite International Diagnostic Interview (CIDI), which is assumed to represent the participant's true diagnosis [70].

Follow-Up Objectives

Follow-up objectives for investigating participants' response following the receipt of a results report were also established to understand the response to, and effectiveness of, a diagnostic aid such as that under investigation in the Delta Trial within existing mental health care pathways. These follow-up objectives, informed by data from digital 6- and 12-month follow-up questionnaires, are to understand whether trial participation (1) impacts the quality of life for participants, as measured by the Warwick-Edinburgh Mental Wellbeing Scale [71]; (2) leads to new or changed mood disorder diagnoses; or (3) results in a recommendation of new or changed mood disorder–related medications and interventions.

Statistical Calculations

We assumed that we could detect at least 80% of both participants with BD who had a baseline MDD diagnosis and of baseline low mood participants who had undiagnosed MDD. In addition, based on previous studies [72-75], we assumed that 20% or more of participants in the trial with a baseline MDD diagnosis would have BD and that 30% or more of the baseline low mood participants would have MDD. Power calculations estimated that we would need to recruit at least 200 participants for each of the primary and secondary objectives to have more than 80% power to detect noninferiority to a prediction model with an area under the receiver operating characteristic curve

of 0.8 at the 5% significance level. To account for participant attrition and other factors, we decided to recruit 300 participants for each of the primary and secondary objectives to form the training sets for algorithm development. To provide test sets to validate the algorithms to be developed, a further 100 participants for each objective as well as 40 participants with a baseline BD diagnosis (baseline BD) who scored 5 or greater on the PHQ-9 at the time of recruitment were added to the data collection targets. The recruitment for these groups was also stratified to reflect the observed gender ratios of the relevant conditions: two-thirds women for the baseline MDD and low mood groups and evenly split between men and women for the baseline BD group [76].

Methods

Recruitment

Participant recruitment for the Delta Trial was executed through emails to suitable participants from previous trials who had consented to be recontacted, paid Facebook advertisements, organic and paid promoted posts on the CCNR Facebook page [77], and updates to the CCNR laboratory website [78]. The choice of exclusively using Facebook for paid advertising was based on experience from a previous pilot study (unpublished), demonstrating its superior effectiveness over other digital advertising options. Both static imagery and animated videos were created and used as advertising materials for the trial.

Eligibility Screening, Consent, and Enrollment

Inclusion criteria and consent requirements for participants are listed in Table 1. These criteria were kept to a minimum within the bounds of safety and resource constraints to ensure that representative samples from the target populations were recruited. Participants were able to complete an eligibility screening, including the PHQ-9, and were provided with a participant information leaflet as well as the opportunity to ask questions about the trial before consenting to participate through the Delta Trial website [79]. To maximize the safety of those individuals who were interested in participating in the Delta Trial but were not eligible because of current suicidal ideation, we provided specific resources and contact information when they felt unsafe. Eligible participants who provided consent were sent a confirmation email to ensure that they had registered with an email address to which they had regular access. Acknowledgment of receipt of this email was considered the final step of enrollment in the trial.

Table 1. Delta Trial inclusion criteria and consent process.

Participants are eligible to perform	Inclusion criteria or actions required
Adaptive digital questionnaire (selection through eligibility screening, consent, and enrollment)	• Age 18-45 years • UK resident • Not pregnant or breastfeeding • Not suicidal • Patient Health Questionnaire 9 score ≥5 • Consent to having read participant information sheet • Consent to voluntary participation • Select link in the confirmation email
DBS[a] and CIDI[b] (selection through consent, digital questionnaire responses, and internal analysis; only eligible once the digital questionnaire is completed)	• Consent to provide DBS samples and complete CIDI • No blood-borne illness • No previous diagnosis of schizophrenia • Recruiting target not yet reached for baseline mood disorder diagnosis group (major depressive disorder, bipolar disorder, or low mood[c])

[a]DBS: dried blood spot.

[b]CIDI: Composite International Diagnostic Interview.

[c]Low mood: no mood disorder diagnosis.

Delta Trial Digital Platform

Once participants were enrolled in the trial, they were able to access the Delta Trial digital platform by logging on to the Delta Trial website. The Delta Trial digital platform incorporated input from a service user advisory group on features such as the tone of written materials, frequency of communication, and participant journey through the platform and was developed under Medical Device Directive 93/42/EEC. An individualized dashboard on this web platform guided each participant's progress through the trial. All digitized steps of the trial were completed through this platform, which automatically recorded and visualized every step through the trial for participants. The Delta Trial digital platform was designed for ease of use to encourage completion of the trial, and specific functionality of the digital platform that facilitated this goal included automated reminder emails for each step of the trial that were sent to participants at different intervals, the ability to stop and later restart the adaptive questionnaire after any question, and the option to change from one device to another at any time.

Adaptive Digital Questionnaire

Once enrolled, the first step for all participants in the trial was to complete an adaptive digital questionnaire on the Delta Trial digital platform. A novel adaptive digital questionnaire was created for the Delta Trial. This questionnaire was designed following an analysis of existing questionnaires for mood disorders, the *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition [80], and the *International Classification of Diseases and Related Health Problems,* Tenth

Revision [81], as well as input from psychiatrists and a service user group. A wide range of studies and questionnaires were analyzed [70,82-90] to ensure the inclusion of well-validated symptoms of BD and MDD, symptoms to discriminate conditions between and within the BD and MDD spectra, and further symptoms and lifestyle factors of potential interest for analysis. The 6 sections of the questionnaire focused on the following topics: (1) demographic information and personal history; (2) manic and hypomanic symptoms; (3) depressive symptoms; (4) personality profiling; (5) medication, treatment, and substance use history; and (6) other psychiatric conditions. Each section of the questionnaire was estimated to require an average of 12 (SD 3) min to complete, although actual times varied because of the adaptive nature of the questionnaire, which directed participants to relevant questions based on their previous answers. The questionnaire database contained a total of 635 distinct questions, with the longest possible route through a questionnaire consisting of 382 questions.

After completion of the digital questionnaire, participants were either asked to provide DBS samples or were marked to receive a results report. This decision was made through a two-step process: first requiring consent from participants during enrollment that they were willing to perform DBS sampling and a telephone interview, followed by selection based on the fulfillment of the second set of inclusion criteria, as listed in Table 1. Participants who had not consented to do so or were not eligible to provide DBS samples and perform a telephone interview were delivered a nondiagnostic results report through the digital platform that described the most likely conditions according to their answers to the digital questionnaire.

Dried Blood Spot Collection for Proteomic Analysis

Participants selected to continue with the trial were asked to input an address through the digital platform, to be sent a DBS sample collection kit. The DBS sample collection kit used in the Delta Trial was a Conformité Européene-marked device under Article 22 of the Medical Device Regulation 2017/745 and contained relevant materials and instructions to allow participants to complete and submit DBS samples.

A standardized MS-based targeted proteomic biomarker screening method, based on previously published work [48,91], was developed for the Delta Trial. For this method, 203 candidate peptides representing 120 proteins were selected for inclusion, in many cases based on their previous association with psychiatric disorders, including depression, BD, and schizophrenia [91]. These proteins were first extracted and digested from the DBS samples [48], and then, unique surrogate peptides representing candidate proteins were monitored through multiple reaction monitoring using an Agilent 1290 liquid chromatography system coupled with an Agilent 6495 Triple Quadrupole Mass Spectrometer.

Composite International Diagnostic Interview

For the Delta Trial, predictions from the algorithms developed for the primary and secondary objectives will be compared with the result of a CIDI, which is assumed to represent the participant's diagnosis [70]. These interviews were conducted over the telephone and using the CIDI 3.0 software version,

developed by the World Health Organization. For these interviews, the only sections of the CIDI software that were operationalized were the screening section questions related to demographics or mood disorders as well as the depression and mania sections. All interviewers received in-person external training from a CIDI-certified instructor as well as internal training and monitoring. After completion of the CIDI, participants received results reports similar to those received by participants who only completed the digital questionnaire. The reports for these participants were identical to those received by participants who only completed the questionnaire, except that these reports reflected the mood disorder condition suggested by the CIDI. Only participants who completed all 3 steps—comprising a completed digital questionnaire, DBS samples, and CIDI—fulfilled the recruitment targets from the statistical calculations.

Feedback

Following receipt of a results report, all participants were asked to complete a short feedback survey through the digital platform. This survey was intended to guide future trial design and gain insight into participant perceptions related to the trial.

Follow-Up

The final step in the trial is follow-up questionnaires to be completed through the digital platform at 6 and 12 months from the date that a participant received a results report. These questionnaires were designed to provide answers via patient self-reports to the follow-up objectives related to the impact of Delta Trial participation. These objectives are to analyze and understand whether trial participation (1) impacts the quality of life for participants, (2) leads to new or changed mood disorder diagnoses, or (3) results in a recommendation of new or changed mood disorder–related medications and interventions.

Ethics and Data Handling

All trial-related materials and methods were ethically approved by the University of Cambridge Human Biology Research Ethics Committee (approval number HBREC 2017.11) and conducted in accordance with Good Clinical Practice and International Organization for Standardization (ISO 14155:2011). All participants in the Delta Trial had access to a downloadable participant information sheet as well as other information related to the trial and general psychoeducation via the Delta Trial website and were emailed their digitally signed and dated consent forms and the participant information sheet on enrollment in the trial. All trial data are stored securely at the University of Cambridge's CCNR, and confidentiality is maintained using unique participant ID numbers and digitally separating trial data from participants' personal information. Personal information, which is only accessible by a selected number of trial staff, is kept solely for the purposes of recontacting participants who have opted in for future CCNR studies or as dictated by the General Data Protection Regulation and Human Tissue Authority and will not be shared with any other organizations.

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Results

Timeline

The recruitment for the Delta Trial was launched on April 27, 2018, and closed on September 28, 2018. All participants who returned DBS samples before October 16, 2018, were asked to perform a CIDI, and the final CIDI was conducted on October 24, 2018. Outstanding results reports for participants who had progressed to the end of the digital questionnaire were delivered on October 26, 2018. Feedback on trial processes and perceptions of the trial was submitted by 1289 participants following receipt of a results report. A total of 1780 participants also completed a 6-month follow-up questionnaire and 1542 completed a 12-month follow-up questionnaire, the last of which was completed in November 2019. These participants did not necessarily overlap with those who provided DBS samples and completed a CIDI. The trial was officially closed on February 6, 2020.

Recruitment Results

To achieve training and validation datasets for the diagnostic algorithms as dictated by the power calculations for the primary and secondary objectives, 5422 participants were enrolled in the trial. The observed progress of the participants is documented in Figure 1 and Table 2. The results reports were delivered to 3232 participants who completed the digital questionnaire, and an average of 284 questions were answered by each participant who completed the questionnaire. One step of the trial for which the participant completion rate was notable was in the return of DBS sample collection kits, as 79.14% (1377/1740) of kits that were posted to participants were completed and returned to CCNR. In addition, 962 participants with a diagnosis of MDD that was established greater than 5 years before enrollment but otherwise fulfilled enrollment criteria were enrolled and completed the digital questionnaire. These participants did not progress to further stages of the trial.

Figure 1. Delta Trial flow chart. This figure illustrates the number of individuals who completed each step of the Delta Trial and the reasons for attrition between each step. Abbreviations: DBS: dried blood spot; CIDI: World Health Organization World Mental Health Composite International Diagnostic Interview.
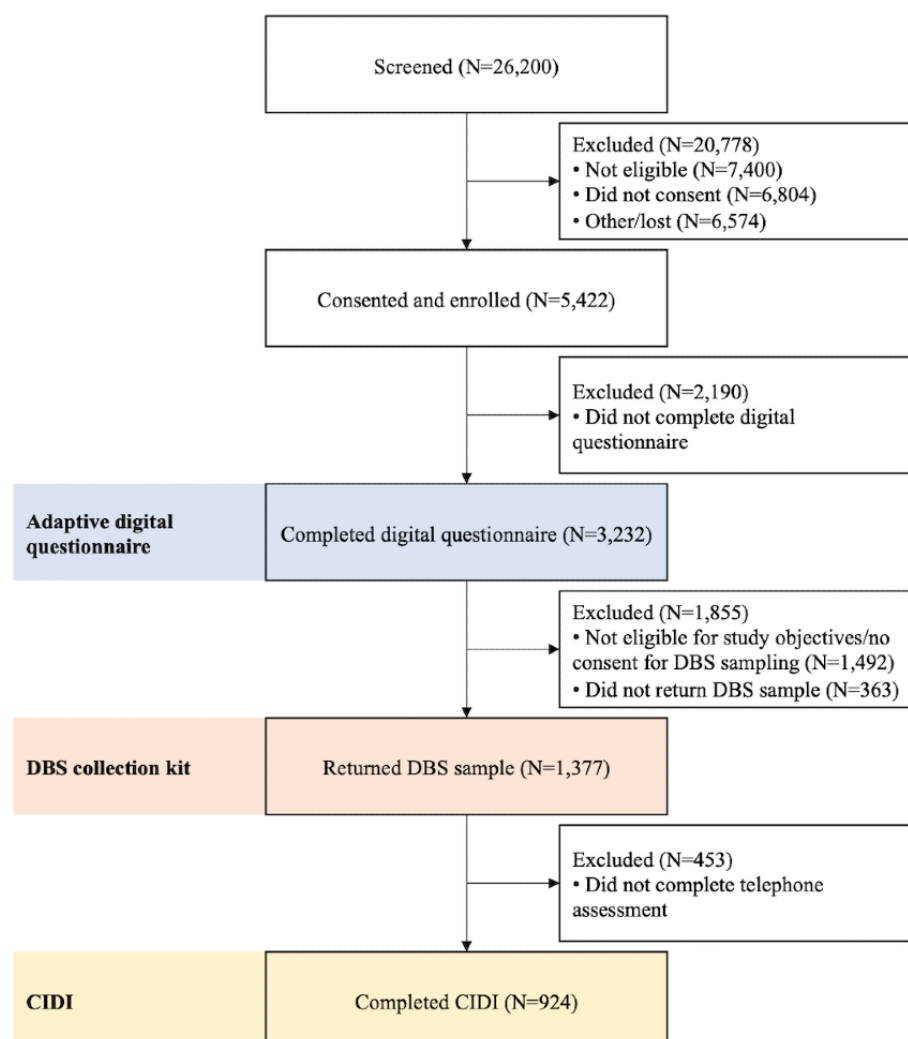
Table 2. Delta Trial participant progress, grouped by baseline mood disorder diagnosis group (N=5422).

Mood disorder diagnosis group	Trial steps and overall completion rate from previous step, n (%)			
	Completed digital questionnaire 3232 (59.61)	Sent DBS[a] sample collection kit 1740 (53.84)	Returned DBS sample collection kit 1377 (79.14)	Performed Composite International Diagnostic Interview 924 (67.10)
Major depressive disorder, n (%)				
Female	676 (71.9)	610 (71.3)	467 (69.7)	301 (68.4)
Male	264 (28.1)	246 (28.7)	203 (30.3)	139 (31.6)
Bipolar disorder, n (%)				
Female	144 (64.0)	26 (34)	23 (34)	21 (39)
Male	81 (36.0)	50 (66)	45 (66)	33 (61)
Low mood[b], n (%)				
Female	668 (68.58)	534 (66.6)	411 (64.8)	277 (64.6)
Male	306 (31.42)	268 (33.4)	223 (35.2)	152 (35.4)
Other[c,d], n (%)				
Female	837 (76.58)	5 (83)	4 (80)	1 (100)
Male	256 (23.42)	1 (17)	1 (20)	0 (0)

[a]DBS: dried blood spot.

[b]Low mood: no mood disorder diagnosis.

[c]Other: not in one of the major depressive disorder, bipolar disorder, or low mood baseline mood disorder diagnosis groups.

[d]Participants from this group were able to progress beyond the digital questionnaire because of operator error in the trial progression selection process.

A completed digital questionnaire, DBS samples, and a CIDI were gathered from 924 participants. There were 440 participants in the baseline MDD group, 54 participants in the baseline BD group, and 429 participants in the baseline low mood group. The gender ratios of these groups also generally reflected pretrial targets, as the percentage of female participants in the groups was 68.4% for baseline MDD, 39% for baseline BD, and 64.6% for baseline low mood. Any noteworthy differences in group characteristics will be accounted for in future statistical analyses.

Discussion

Principal Findings

The Delta Trial was designed and launched with the ultimate aim of contributing to early and accurate diagnosis of mood disorders to enable effective treatment for patients. Specifically, the objectives of the trial are to develop and validate diagnostic algorithms to reduce the misdiagnosis of BD as MDD and achieve more accurate and earlier diagnosis of MDD in a population of participants with depressive symptoms who completed the trial remotely. To this end, processes and techniques that can be implemented in a real-world setting were established, such as the creation of a novel adaptive digital questionnaire and the use of self-collected DBS samples for proteomic analysis. More participants than were dictated by data collection targets for the primary and secondary objectives were recruited and enrolled in the trial over the course of 5 months. In addition, the trial population approximately matched baseline mood disorder diagnosis groups and the level of gender stratification that were targeted before launching the trial. These successes are emblematic of the opportunities that are possible through leveraging a combination of digital tools and a consideration of the viewpoints of multiple stakeholders, including a service user group and clinicians.

Strengths and Limitations

However, the design and execution of the Delta Trial also introduced potential bias in the participant population, most notably through (1) recruitment techniques, (2) the use of self-reports of medical history, and (3) the selection of participants to progress through the various stages of the trial. With recruitment conducted on the web and mainly through Facebook, the participants in the trial are likely to be more regular internet—and specifically Facebook—users than the target population. In addition, variables such as age, gender, and interests used in displaying advertising materials may have shaped the composition of participants according to the recruitment targets described earlier. Self-reports of medical history for participants and their families may have been incorrect or incomplete and could have been improved by using medical records. In addition, the progressive nature of the trial, in which participants had to consent for the DBS and CIDI steps of the trial and were then selected to perform those steps, shaped the trial population to further conform to the recruitment targets and population assumptions underlying those targets. Finally, the time commitment required to complete the questionnaire, submit DBS samples, and perform a CIDI required a level of interest in the trial that may have been higher in people who were very concerned about their mental health symptoms or history, enriching the levels of undiagnosed conditions in the trial population.

Conclusions

The Delta Trial was launched in April 2018 with the aim of creating a diagnostic aid to improve the diagnosis of mood disorders. Demographic and symptom data have been gathered from 3232 participants who completed an adaptive digital questionnaire that was designed and created for the trial. Of these participants, 924 also submitted DBS samples for proteomic analysis and completed a CIDI. With follow-up questionnaires completed in November 2019 and the trial closed in February 2020, the analysis of the trial data has now begun. We hope to share our results to contribute to reducing the significant burden of mood disorders through early and accurate diagnosis. We also hope to gain insight into follow-up actions taken by participants after receiving a results report and the process of digital recruitment for psychiatric trials.

Conflicts of Interest

SB, DC, GO, LF, and EB have financial interests in Psyomics Ltd SB, PE, and TO could benefit financially from any products that arise from work performed in the Delta Trial.

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Abbreviations

BD: bipolar disorder
CCNR: Cambridge Centre for Neuropsychiatric Research
CIDI: Composite International Diagnostic Interview
DBS: dried blood spot
MDD: major depressive disorder
MS: mass spectrometry
PHQ-9: Patient Health Questionnaire

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Protocol

Feasibility of the Internet Attachment–Based Compassion Therapy in the General Population: Protocol for an Open-Label Uncontrolled Pilot Trial

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Abstract

Background: Compassion-based interventions delivered over the internet are showing promising results for the promotion of psychological health and well-being. Several studies have highlighted their feasibility, acceptance, and preliminary efficacy. However, this is an incipient field of research, and to the best of our knowledge, there are no data available from Spanish-speaking countries.

Objective: The aim of this study is to investigate the feasibility, acceptance, and preliminary efficacy of the Internet Attachment–Based Compassion Therapy (iABCT), a web-based version of the Attachment-Based Compassion Therapy, in Spanish speakers from the general population.

Methods: This feasibility study features a single-arm, uncontrolled, within-group design with an embedded qualitative and quantitative process evaluation at baseline, immediately after the intervention and at the 3-month follow-up. A minimum of 35 participants from the general population will be allocated to iABCT. Feasibility measures will include attrition rate, patterns of use of the web-based system, and participants' acceptability, usability, and opinion. The primary outcome was measured using the Pemberton Happiness Index. Secondary outcomes were measured using the Compassion Scale, Self-Compassion Scale, Forms of Self-Criticizing/Attacking and Self-Reassuring Scale-Short form, Five Facets of Mindfulness Questionnaire, Relationships Questionnaire, General Health Questionnaire, Non-Attachment Scale, International Positive and Negative Affect Schedule Short Form, Purpose-In-Life Test, and difficulties regarding the practice of compassion (Compassion Practice Quality Questionnaire). Mixed models will be used to evaluate primary and secondary outcome measures. A qualitative content analysis of the participants' qualitative responses will also be performed.

Results: Enrollment started in February 2020 and will be finished in April 2020. Data analysis will start in October 2020.

Conclusions: To our knowledge, this study will, for the first time, show data on the feasibility, acceptability, and preliminary efficacy of web-based compassion (and self-compassion) training—that is, the adapted iABCT—in Spanish speakers from the general population. Further aspects of their implementation (ie, facilitators, barriers, and unwanted effects) and mechanisms of

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change will be investigated. This study will allow the revision and fine-tuning of the developed intervention, study design, and planning procedures, as well as the initiation of a future randomized controlled trial.

Introduction

Compassion-Based Interventions

Compassion-based interventions (CBIs) focusing on cultivating compassion and self-compassion have recently been developed with promising results for the general population as well as for the treatment of a number of different psychological disorders [1-5]. In particular, *self-compassion*, which involves the directing of compassion toward oneself, is emerging as a strong predictor of well-being, psychological health, and quality of life [6-10]. A recent meta-analysis study of randomized controlled trials (RCTs), for the clinical and nonclinical population, showed significant between-group differences with moderate effect sizes with regard to cultivating compassion (d=0.55; k [number of studies]=4; 95% CI 0.33-0.78), self-compassion (d=0.70; k=13; 95% CI 0.59-0.87), and mindfulness (d=0.54; k=6; 95% CI 0.38-0.71), reducing depression (d=0.64; k=9; 95% CI 0.45-0.82), anxiety (d=0.49; k=9; 95% CI 0.30-0.68), and psychological stress (d=0.47; k=14; 95% CI 0.19-0.56) and improving satisfaction with life and well-being (d=0.51; k=8; 95% CI 0.30-0.63), which remained when active control comparisons were included [4]. Kirby [3] found 8 face-to-face established CBIs with 6 of them having RCTs and meta-analysis evidence [4]. Those 6 CBIs were Compassion-Focused Therapy [11], Mindful Self-Compassion [12,13], Compassion Cultivation Training [14,15], Cognitively Based Compassion Training [16-18], Cultivating Emotional Balance [19,20], and Compassion and Loving-Kindness Meditations [21,22]. The other 2 CBIs pending the publication of evidence were the ReSource Training Protocol [23] and the Being with Dying Programme [24]. Another systematic review and meta-analysis investigated the effectiveness of self-compassion–related therapies (ie, CBIs, mindfulness-based cognitive therapy, and acceptance and commitment therapy). It found greater improvements in promoting self-compassion (g=0.52; 95% CI 0.32-0.71) and in reducing psychopathology (depression: g=0.40, 95% CI 0.23-0.57; anxiety: g=0.46, 95% CI 0.25-0.66) in clinical and subclinical populations, although the results did not remain when analyses were restricted to the comparison between self-compassion–related therapies and active control conditions [2].

Attachment-Based Compassion Therapy

To the best of our knowledge, the attachment-based compassion therapy (ABCT) program is the first CBI to have been originally developed and validated in the Spanish language [6]. To date, ABCT—in the face-to-face group format, specifically—has shown its efficacy and applicability in a nonrandomized controlled study of healthy people (ie, adults not having a psychological disorder and not receiving any psychiatric treatment) [1] and in an RCT for the treatment of fibromyalgia [5]. In a study on the general population, Navarro-Gil et al [1] found significant improvements in self-reported measures of self-compassion, dispositional mindfulness, and secure attachment style, as well as significant reductions in psychological disturbance, experiential avoidance, and levels of anxiety and avoidance toward social relationships as compared with the waiting list control group. Moreover, the authors pointed out that the significant increments in secure attachment style in the ABCT group were mediated by changes in self-compassion. The results of the RCT on patients with fibromyalgia revealed greater improvements in general health status, clinical severity, anxiety, depression, quality of life, and psychological flexibility in the ABCT group (combined with treatment as usual [TAU]) compared with an active control group (relaxation combined with TAU) at postintervention and 3-month follow-up. An interesting finding was that the effect sizes found were larger than those obtained when treating fibromyalgia using cognitive behavioral therapy (CBT) or mindfulness-based interventions (MBIs). Moreover, psychological flexibility partially mediated the relationships between the experimental condition (ABCT and TAU vs relaxation and TAU) and overall health status, pain catastrophizing, anxiety, and depression at follow-up. Nevertheless, these studies did not include any specific well-being outcomes, indicating that further research is needed in this regard.

Internet-Delivered Compassion-Based Interventions

There are promising results that suggest the potential utilities of web-based compassion training. One of the first studies is the research conducted by Krieger et al [25], testing the feasibility of a web-based version of the Mindfulness-Based Compassionate Living program in self-referred participants suffering from harsh self-criticism (N=39). Authors found high levels of satisfaction with the program; significant increases in self-compassion, mindfulness, reassuring self, and satisfaction with life; and significant reductions in inadequate self, hated self, perceived stress, and fear of self-compassion from pretreatment to posttreatment and from posttreatment to follow-up at 6 weeks, with medium-to-large within-effect sizes (d=0.50-1.50). A replicated RCT in 122 participants supported the preliminary evidence, including the maintenance of the effects at 6-month follow-up. The dropout rate was 11.6%. Other adherence outcomes (ie, number of completed modules and self-reported number of completed exercises per week) predicted postintervention scores for self-compassion but not for

depressive, anxiety, and distress symptoms in the intervention group.

Finlay-Jones et al [26] gathered preliminary data on the feasibility and effectiveness of the Internet-Based Self-Compassion Cultivation Program for Psychology Trainees (N=37) in a pilot study. After completing the 6-module program, participants reported significant changes in self-compassion, happiness, depression, perceived stress, and emotion regulation difficulties at postintervention and 3-month follow-up. Program feedback from participants revealed high average levels across modules for enjoyableness, relevance, comprehension, and learning and low-to-moderate average levels for difficulty. Recently, Eriksson et al [8] pointed out the effects of a brief web-based mindful self-compassion program on stress and burnout symptoms in a group of practicing psychologists (N=81) and the relationships between changes in self-compassion and self-coldness and changes in stress and burnout symptoms in an RCT. After the 6-week training (15 min per day of an online exercise), the results showed significant increases in self-reported self-compassion and reduced burnout symptoms, perceived stress ($d=0.59$), and self-coldness levels. Measures of distress were strongly related to self-coldness rather than self-compassion.

In summary, there is incipient evidence that supports the feasibility, acceptance, and preliminary effectiveness of CBIs delivered over the internet. However, to our knowledge, the existing research has mostly been conducted in English-speaking countries. Data regarding how Spanish speakers would accept CBIs are needed to determine the feasibility to apply it in this population, to cover this gap, and explore the potentialities and advantages of delivering compassion via the internet to promote personal resources and well-being beyond geographical barriers. According to *the Mental Capital and Wellbeing: Making the most of ourselves in the 21st century* project, it is expected that achieving small changes in overall well-being levels of the general population would consequently lead to higher decreases in percentages of mental health illness and subclinical disorders [27]. Thus, emphasizing positive psychological states, such as compassion, would act as protective factors for social, physical, and mental health. Specifically, Neff and Costigan [28] pointed out that treating oneself with care and compassion is a powerful way to enhance intrapersonal and interpersonal well-being.

In this regard, although the ABCT protocol was developed to be applied in Spanish speakers, there are no data available on its effects on the well-being outcomes of this population or on whether it could be delivered in a feasible way through the internet. Therefore, there is a need to continue exploring ways of approaching the general population with these effective resources, which is one of the main advantages of delivering self-applied interventions over the internet.

Aims and Hypotheses

The main aim of this study is (1) to investigate the feasibility of the Internet Attachment–Based Compassion Therapy (iABCT), a web-based version of ABCT, in the general population. Additional objectives are (2) to analyze the preliminary effects of iABCT on happiness, compassion, self-compassion, dispositional mindfulness, general health,

purpose in life, nonattachment, attachment styles, self-criticism, and positive and negative affects at postintervention and 3-month follow-up; (3) to explore cost-effectiveness by means of changes in overall health status levels; (4) to investigate the mechanisms of change, predictors, and associations between outcomes; and (5) to assess adverse or unwanted effects and facilitators and barriers to the intervention received.

The principal hypothesis is that iABCT will be feasible and well accepted by participants in terms of attrition, expectations, satisfaction, usability, and opinion. Second, iABCT will show efficacy in promoting significant changes with moderate-to-large within-group effect sizes in self-reported measures of happiness, compassion, self-compassion, dispositional mindfulness, self-criticizing, nonattachment, purpose in life, attachment, and overall health status. We also hypothesize that gains will be maintained at 3-month follow-ups. Third, changes in overall health levels will demonstrate the cost-effectiveness of iABCT. Fourth, significant associations will be found between changes in compassion, self-compassion, dispositional mindfulness, general health, purpose in life, nonattachment, attachment styles, self-criticism, positive and negative affects, and happiness. Specifically, improvements in happiness scores and overall health status will be predicted by self-reported self-compassion. Increments in secure attachment style would mediate the relationship between self-compassion and happiness. Finally, low rates of adverse or unwanted effects are expected.

Methods

Study Design

This feasibility study and open trial features a single-arm, uncontrolled, within-group design with 3 measurement points at baseline (preintervention), immediately after the intervention (postbaseline), and 3-month follow-up with an embedded qualitative and quantitative assessment. Participants will be allocated to iABCT. The study was registered under Clinicaltrials.gov (NCT03918746) and will be conducted following the extension of the Consolidated Standards of Reporting Trials (CONSORT) statement for pilot and feasibility studies [29], the Consolidated Standards of Reporting Trials of Electronic and Mobile HEalth Applications and onLine TeleHealth guidelines [30], and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (Multimedia Appendix 1) [31]. The SPIRIT checklist was used as a guide for reporting this study protocol (version 1; March 6, 2019).

Eligibility Criteria

The sample will consist of healthy adults from the community. Inclusion criteria are participants should (1) be aged 18 years or older, (2) have adequate knowledge and an understanding of spoken and written Spanish, (3) have a computer with speakers and internet access in a secure setting (home or private office), (4) have an email account, and (5) be able to use a computer and browse the internet. Exclusion criteria are (1) a diagnosis of a mental disorder according to the Diagnostic and Statistical Manual for Mental Health Disorders-Version 5 (DSM-5) [32], (2) alcohol or other substance abuse or dependence, (3) receiving psychiatric or psychological treatment, (4) engaging in ongoing

formal meditation training (eg, mindfulness or compassion intervention), (5) presence of heart disease, cardiorespiratory illness, or other severe medical condition, (6) history of epileptic crisis, and (7) unavailability to complete the internet intervention because of surgery or medical intervention.

The study will include participants with and without prior meditation experience. Meditation experience and frequency of meditation will be registered and considered in the data analysis.

Sample Size

A minimum of 35 participants is considered sufficient to cover the aims of this feasibility study and to provide precise and efficient estimations of parameters (ie, means, standard deviations, effect size, and confidence intervals) for the powering of a larger RCT. Sample estimation is based on the recommended range in the literature (eg, 24 and 50) [33-35] and in line with existing feasibility studies in this field [25,26].

Recruitment

Recruitment will be conducted online using professional and nonprofessional social media (ie, Facebook, LinkedIn, and Twitter), on the website where the internet intervention will be developed and hosted [36], and through advertisements in local newspapers and radios. The study will also be announced in the Master in Mindfulness program at the University of Zaragoza (Spain) and emailed to lists of contacts interested in meditation issues (eg, students on the master's program and former students, and people subscribing to the newsletter published by the Mindfulness and Compassion Research Group [37]). In addition, posters will be placed in the following locations: Universitat Jaume I, the University of Valencia, the University of Zaragoza (Teruel, Huesca, and Zaragoza campuses), Miguel Servet Hospital (Zaragoza), and the Arrabal Health Centre (Zaragoza). All participants will access the study voluntarily, and no reimbursement for their participation will be provided in any case. The internet intervention aims to promote psychological well-being but not treat any mental disorders or medical conditions.

People who are interested in the study will be asked to contact the research team, and they will be scheduled for an admission telephone interview to screen for the inclusion and exclusion criteria—including a diagnostic telephone interview—and an explanation of the research terms (ie, study design, intervention length, and intervention rationale). Participants meeting the eligibility criteria and giving their informed consent will be allocated to the web-based intervention. A user account and password will be provided via email to each participant for individual use. Baseline assessment will be completed on the website and via a telephone interview before the intervention commences. Participants will be free to withdraw from the intervention or study at any time and without providing justification. In such cases, the research group will endeavor to contact them to ask for reasons and collect data regarding the feasibility of the internet-based intervention developed.

Internet Attachment–Based Compassion Therapy

The intervention will consist of an internet-delivered version of ABCT [7]. ABCT is a compassion protocol based on the attachment theory and thus includes practices to raise awareness and/or address maladaptive aspects, where appropriate, of attachment styles developed with parents [6]. This process is taught as a form of both compassion and self-compassion to improve present-day interpersonal relationships and well-being in general [1]. ABCT consists of 8 group sessions, each of which has a 2-hour duration (1 session per week), including theory and both formal and informal compassion and self-compassion exercises and practices such as receiving and giving compassion to oneself, friends, unknown people, and people deemed to be problematic; identifying their own attachment style; and understanding how it influences their current interpersonal relationships, together with daily homework assignments that should take 15 to 20 min to complete [1,6].

iABCT will follow along the lines of the original model [6,7], and it will be adapted and developed to be totally self-applied over the internet via the website (Figure 1) [36], designed by the Laboratory of Psychology and Technology, Universitat Jaume I, and the University of Valencia. This platform allows several internet interventions including online assessments to be developed and hosted.

iABCT will consist of 8 sequential modules with the same structure: (1) module agenda; (2) theoretical contents of the module; (3) exercises and activities (including formal and informal practices) to put what is learned in the module into practice; (4) assessment of the knowledge acquired during the module; (5) tasks to be completed before advancing to the next module (homework assignments); and (6) summary of the module. The content will be presented through text, audios, videos, pictures, vignettes, and interactive exercises. Downloadable PDF files will be made available so that users can review them offline. Formal practices (guided meditations) will be delivered through audios with specific guides and instruction for each meditation. Furthermore, transcriptions of each guided meditation will be included as downloadable PDF files.

Figure 1. A screenshot of the "Psicología y Tecnología" (Psychology and Technology) Web platform.

Table 1 presents the contents of each module. In comparison with the original ABCT, the adapted web-based version includes module 0, "Introduction to attachment-based compassion therapy," to introduce to the participant the basics of the attachment-based compassion model and the program contents. Module 0 also includes tips about the use of formal and informal compassion (when/where/how much/how meditate) and on the importance of progressiveness in compassion training and of home practice between modules. Specific content has been added about "managing guilt" (formal meditation in module 4), "embarrassment" (theoretical component and formal practice in module 5), and "envy" (theoretical component and formal practice into module 7). Moreover, the term, "the figure of affect," has been replaced by "basic affection" to make it easier to understand and so that participants will not confuse this with "the figure of secure attachment." Other practices that have been eliminated are "showing forgiveness for the hurt caused

by loved ones" (for people with grief experiences) and the "the illusion of labels" because they were not considered relevant for this protocol. Finally, module 8 on equanimity ("Beyond compassion: equanimity") [6] has not been included in the web-based version because it was considered a different and advanced aspect of compassion.

The length of the interventions will depend on the pace of each participant, who will be advised to complete 1 module per week, taking the days between sessions to complete homework assignments. Each module has been optimized to allow it to be completed in approximately 1 hour. It is estimated that the web-based intervention can be completed in 8 weeks. However, each participant will be free to advance at his/her own pace with a maximum period of 10 weeks. Formal telephone support will not be systematically provided, but participants will be able to make contact for technical assistance (eg, web accessibility problems or forgotten passwords) if necessary.

Table 1. Structure and contents of Internet Attachment–Based Compassion Therapy.

Module	Theoretical component	Formal practice	Informal practice
0: Introduction to attachment-based compassion therapy	• What is compassion? • Contexts of application • Attachment-based compassion therapy: structure and rationale • Meditation and compassion: formal and informal practice • Tips about meditation practice: when/where/how much/how meditate • The importance of progressiveness in compassion and homework	• N/A[a]	• 3-min compassionate practice
1: Preparing ourselves for compassion. Kind attention	• The workings of our brain • The reality of suffering: primary and secondary suffering • What is and is not compassion?	• Compassionate breathing and compassionate body scan • Compassionate in coping with difficulties	• Self-compassion diary • Savoring and giving thanks
2: Discovering our compassionate world	• Going deeper into compassion and mindfulness terms • Compassion and related terms • Fear of compassion	• Connecting with basic affection • Developing a safe place • The compassionate gesture • Identifying the figure of secure attachment	• The object that joins us to the world • Diary of compassion practice • What are we good at?
3: Developing our compassionate world	• How compassion works • The figure of secure attachment • Efficacy of compassion • Self-criticism	• Developing the figure of secure attachment • Developing the compassionate voice	• Writing a letter to the figure of secure attachment
4: Understanding our relationship with compassion	• The biological bases of compassion • Attachment styles • Guilt • Importance of these styles in everyday life	• Becoming aware of our attachment style • Ability to receive affection: friend, indifferent person, and enemy • Guilty repair practice	• Letter to your parents • Observing our attachment styles in daily life
5: Working on ourselves	• The importance of the affection toward ourselves and others • Embarrassment	• Showing affection to friends and indifferent people • Showing affection to ourselves • Reconciliation with our parents • Repairing embarrassment	• The greatest display of affection (in general and from our parents) • 3 positive aspects and 3 negative aspects of our parents
6: Understanding the importance of forgiveness	• The concept of forgiveness • Phases of forgiveness • Utility of forgiveness • Basic resistances to generate forgiveness • Resources to generate forgiveness • The recapitulation (optional)	• Forgiving yourself • Asking others for forgiveness • Forgiving others and showing compassion to enemies	• Interdependence • Compassion in daily life
7: Consolidating the practice of compassion	• Working in 3 periods (past, present, and future) • Envy • Usefulness of being our attachment figure • Difficult relationships • How to keep up the practice of compassion for a lifetime	• Working with envy • Becoming our own attachment figure • Handling difficult relationships	• Not taking anything personally • Our values and their relationship with compassion • What would our lives be like if we started over?

[a]N/A: not applicable.

Outcome Measures

Participants will be assessed at baseline (preintervention), postintervention, and 3-month follow-up after they complete the intervention. Assessments will be conducted online via the website [36], where the iABCT will be hosted, and via a telephone interview at pre- and postintervention, except for the 3-month follow-up that will be conducted only via the website. Both participants and researchers will receive email reminders

of each assessment time. The study variables and assessment times are summarized in Table 2.

Table 2. Study measures, time of assessment, and source of measurement.

Measures	Aim	Assessment point	Assessment source
Admission interview	Screen eligibility criteria (inclusion/exclusion)	Pre[a]	Phone interview
Sociodemographic data	Sex, age, educational level, occupation, and civil status	Pre	Phone interview
M.I.N.I. 7.0.2.[b]	Psychological diagnosis (exclusion criterion)	Pre	Phone interview
Meditation data	Source of learning, frequency, duration of each session (in minutes), lifetime practice (in years), and context of practice	Pre	Phone interview
PHI[c]	Well-being	Pre, post[d], and FW[e]	Web
SCS-26[f]	Self-compassion	Pre, post, and FW	Web
Compassion scale	Compassion	Pre, post, and FW	Web
FSCRS-SF[g]	Two forms of self-criticism: inadequate self and hated self and the ability to self-reassure	Pre, post, and FW	Web
FFMQ-15[h]	Dispositional mindfulness and mindfulness facets	Pre, post, and FW	Web
RQ[i]	Attachment styles	Pre, post, and FW	Web
GHQ-12[j]	Mental health recent symptoms, feelings, or behaviors	Pre, post, and FW	Web
NAS-7[k]	Nonattachment	Pre, post, and FW	Web
I-PANAS-10-SF[l]	Positive and negative affects	Pre, between modules, post, and FW	Web
PIL-10[m]	General sense of meaning and purpose in life	Pre, post, and FW	Web
Compassion Practice Quality Questionnaire	Difficulties related to the practice of compassion meditation	Between modules, post, and FW	Web
Expectations and Satisfaction Questionnaires	Participants' expectations before the intervention and their satisfaction after it	Pre and post	Web
UAQ[n]	Usability and acceptability of the internet-based intervention	Post	Web
Qualitative opinion interview	Opinions on the internet intervention, the modules, and unwanted or unexpected effects	Post	Phone call
Attrition rate	Percentage of participants that drop out of the intervention after accessing it for the first time	Post	Web
Patterns of use for each participant	Length of the intervention, time spent on each module, and how many times they enter the modules	Between modules	Web

[a]Pre: preintervention.

[b]M.I.N.I. 7.0.2.: Mini International Neuropsychiatric Interview version 7.0.2 for DSM-5.

[c]PHI: Pemberton Happiness Index.

[d]Post: postintervention.

[e]FW: 3-month follow-up.

[f]SCS-26: Self-Compassion Scale.

[g]FSCRS-SF: Forms of Self-Criticizing/Attacking and Self-Reassuring Scale-Short form.

[h]FFMQ-15: Five Facets of Mindfulness Questionnaire.

[i]RQ: Relationships Questionnaire.

[j]GHQ-12: General Health Questionnaire.

[k]NAS-7: Non-Attachment Scale.

[l]I-PANAS-10-SF: International Positive and Negative Affect Schedule Short Form.

[m]PIL-10: Purpose-In-Life Test.

[n]UAQ: Usability and acceptability Questionnaire.

Diagnosis, Screening, Sociodemographic, and Meditation Experience Data

An admission interview will be conducted to screen for inclusion and exclusion criteria. Sociodemographic data of participants will be recorded regarding sex, age, educational level, occupation, and civil status. Variables regarding overall meditation practice will be recorded as follows: any or no meditation experience, source of learning (ie, self-taught, therapy context, teacher or secular training course, and religious context), frequency of meditation (daily, 3 or 4 times a week, once a week or less, 2 or 3 times per month, sporadically, never), duration of each session (mean time in minutes), and lifetime practice (in years), and for participants with experience, the amount of time (in months) of meditation practice interruption and context of practice (secular or religious). Frequency, duration of each session (in minutes), and lifetime practice (in years) will also be asked for different meditation practice types (ie, focused attention meditation, open monitoring meditation, compassion or loving-kindness meditation, values mediation, deconstructive meditations, and informal mindfulness practices). A brief description of each meditation practice will be provided to guarantee the understanding and standardization of the concepts among participants.

Screening for exclusion criteria owing to the diagnosis of a psychological disorder will be performed using the *Mini International Neuropsychiatric Interview* (M.I.N.I. 7.0.2.) [38]. A copyright license for use of the standard M.I.N.I. 7.0.2 in Spanish, based on DSM-5 criteria, will be requested from the authors.

Feasibility Outcomes

Feasibility outcomes will assess the implementation of iABCT regarding adherence (ie, attrition rate), patterns of use for each participant (eg, length of the intervention, time spent each in each module, how many times they enter the modules), participants' acceptability (*Expectations and Satisfaction Questionnaires* adapted from Borkovec and Nau [39]), usability (*The Usability and Acceptability Questionnaire* [40,41]), and opinion (qualitative interview).

The *qualitative opinion interview* has been specifically developed to assess participant opinions on the web-based intervention. This semistructured telephone interview includes 14 questions with both quantitative and qualitative open questions: 7 of which refer to the usefulness of the intervention, components, modules, information provided, and multimedia elements (eg, images, audios, videos, PDF files) rated on a scale of 1 to 5 (1=not at all; 2=not very; 3=somewhat; 4=very; 5=extremely) and 2 dichotomous questions ("yes" or "no") regarding whether they would consider it useful to have the program at their disposal for additional time after completion of the treatment, as well as whether they would like to have longer access. Additionally, interviewers would request to expand on the participants' qualitative responses for each question. Finally, 2 open questions will be included to assess adverse or unwanted effects and facilitators and barriers to the intervention received.

Psychological and Mental Health Outcomes

The primary outcome is well-being, which will be assessed using the *Pemberton Happiness Index* [42].

Secondary outcomes include the following: the *Compassion Scale* [43] and the *Self-Compassion Scale* [44] will be used to assess compassion and self-compassion, respectively. Self-criticism will be measured using the *Forms of Self-Criticizing/Attacking and Self-Reassuring Scale-Short form* [45]. Dispositional mindfulness will be assessed using the short *Five Facets of Mindfulness Questionnaire* [46]. The *Relationships Questionnaire* [47,48] will be used to assess attachment styles (ie, secure, preoccupied, dismissive, and fearful). The *General Health Questionnaire* (GHQ-12) [49,50] will be included to measure general mental health status. Nonattachment (eg, I can let go of regrets and feelings of dissatisfaction about the past when pleasant experiences end, I am fine moving on to what comes next) will be assessed using the *Non-Attachment Scale* [51], and positive and negative affects will be measured using the International Positive and Negative Affect Schedule Short Form [52]. The *Purpose-In-Life Test* [53] will assess the general sense of meaning and purpose in life. Difficulties related to the practice of compassion meditation will be assessed using the *Compassion Practice Quality Questionnaire* (adapted from Del Re et al [54]) that has been specifically developed for this study, which includes 10 items that participants score on a scale ranging between 0 and 100, indicating the percentage of the time that their experience reflects each statement.

Ethics and Dissemination

This trial received approval from the Ethics Committee of Universitat Jaume I (Castellón, Spain; March 6, 2019; file number CD/006/2019) and will be conducted in compliance with the study protocol, the Declaration of Helsinki, and good clinical practice. Data security/confidentially will be guaranteed according to Spanish Organic Law 3/2018 of December 5 on the Protection of Personal Data and Guarantee of Digital Rights; all relevant EU and Spanish privacy laws will be observed and respected. Access will be granted to the internet platform via a unique username-password combination, and all transferred data will be secured using the advanced encryption standard polynomial $m(x)=x^8+x^4+x^3+x+1$. Data collected via the website will be stored on secure servers at Universitat Jaume I, with personal data and user-generated data stored in separate databases on different servers. The consent form will be explained and required from all participants by researchers at the initial phone call. Written consent will be obtained before the start of the intervention.

A data monitoring committee (DMC) will be set up, comprising a psychiatrist, the principal investigator, and an independent clinical psychologist familiarized with the administration of internet-based interventions. The DMC will meet 3 times throughout the trial—after the baseline, posttreatment, and at follow-up measurements—but will be available on request at any time to provide support and information to all parties where necessary. The DMC will function independently of the sponsors and funders and will oversee and safeguard all trial participant interests, monitoring the overall conduct of the trial and ensuring

the safety of participants by systematically checking negative events and reacting to any extreme distress or risk. In the case of an adverse event emergency, participants will be contacted and encouraged to receive additional help and counseling. Interim analyses are not contemplated in this study, although the DMC could request them if considered necessary for proper conducting of the trial and/or participant safety. Important protocol modifications will be communicated to relevant parties (ie, trial participants, trial registries, journals, ethical committee, and researchers). Results will be disseminated to relevant health care and professional communities and the general population via social media, in peer-reviewed and popular science journals, and at scientific and clinical conferences. Authors of the works derived from this study will be the investigators collaborating in this clinical trial, and there is no intention of using professional writers. A professional native English-speaking editor will check the language and grammar of English written content. Data generated in this trial (ie, full protocol, participant-level data set, and statistical code) will be made available upon reasonable request to the corresponding author.

Patient and Public Involvement Statement

There was no involvement in the design and development of this trial by patients or the public. The public will be involved in the dissemination of the research. An end of study report will be developed to communicate study results to all participants, and a study newsletter will be sent to participants via email.

Statistical Analysis Plan

Normality and homoscedasticity data assumptions will be checked using Kolmogorov-Smirnov (K-S) and Levene tests. Significant differences on categorical variables (eg, sex, educational level, occupation, etc) will be assessed using a chi-square test. Attrition and dropout rates will be calculated by reporting percentages and patterns of missing data. The Little missing completely at random (MCAR) test will be used to assess the assumption that data are MCAR [55]. Means and SDs will be reported for all the measures at each assessment point. A preliminary efficacy analysis will be performed using means of comparison for related samples based on intention-to-treat and per-protocol analyses. Mixed model analyses for primary and secondary outcome measures will be implemented using the linear mixed-effects models (MIXED) procedure with 1 random intercept per subject. *Time* will be treated as a within-group factor, and significant effects will be followed up with pairwise comparisons (adjusted by a Bonferroni correction). Sensitivity analyses will be performed to assess the robustness of the findings in terms of different methods for handling missing data (ie, mixed models with and without imputation, maximum-likelihood estimation, and maximum-likelihood multiple imputation) [56]. Within-group effect sizes (pre vs post and pre vs 3-month follow-up) will be reported using Cohen *d* and its 95% CI. For the analyses of associations between the intervention outcomes, predictors of change, and mechanisms of actions, several statistical tests will be performed such as Pearson correlation, multiple regressions, and mediation analysis using the bootstrapping approach [57]. A cost-effectiveness and cost-utility analysis will be conducted using the GHQ-12 based on literature proposals [58,59]. The

mapping technique proposed by Lindkvist and Feldman [59] will be used to predict health state utility values using a crosswalk transformation algorithm from the GHQ-12 to the health utility measure (EuroQoL–5 dimension [EQ-5D]). Spanish tariffs of EQ-5D will be used as the reference population [58,60]. Additionally, participants' qualitative responses regarding adverse or unwanted effects and facilitators and barriers to the intervention received will be explored using a qualitative content analysis and coding and the categorizing data approach by counting the frequency of words with NVivo software (QSR International). Statistical analyses of quantitative data will be performed using SPSS version 23 for Windows (IBM Corp). The statistical analysis plan (SAP) will be revised by all the study team members before the database is locked for use in the final statistical analysis. Any discrepancies or changes made between the analysis plan in this protocol and final SAP will be explained and reported.

Results

Enrollment started in February 2020 and will be finished in April 2020. Data analysis will start in October 2020.

Discussion

There is incipient evidence that supports the feasibility, acceptance, and preliminary effectiveness of CBIs delivered over the internet. However, to our knowledge, the existing research has mostly been conducted in English-speaking countries.

This paper describes the study protocol to investigate the feasibility of iABCT, a web-based version of the ABCT adapted to be completely self-applied over the internet for the general population. Results from this study will, for the first time, show data regarding the feasibility, acceptability, and preliminary evidence of web-based compassion (and self-compassion) training—that is, the adapted iABCT—in Spanish-speaking countries on a sample of healthy people. Moreover, further aspects of their implementation (ie, facilitators and barriers) and mechanisms of change will be investigated.

ABCT, in a face-to-face group format, has shown its efficacy and applicability for healthy people and for patients with fibromyalgia. This intervention focuses on training compassion and self-compassion to build a secure individual attachment style, which has been considered key for therapeutic efficacy [6,61]. It is expected that those improvements in compassion, self-compassion, and secure attachment will also promote an increased sense of well-being. In this study, specific measures of well-being and mental health (ie, happiness, overall health status, purpose in life, and positive and negative affects) have been included. Findings from this study will be congruent with the growing research supporting the benefits of using the internet to deliver evidence-based interventions [62-64] and will add valuable data to the incipient research field on the potential of self-applied CBIs via the internet [8,25,26,65].

We would like to highlight the relevance of conducting a feasibility study before designing a larger RCT due to the novelty of cultivating compassion via the internet (ie, CBIs).

Moreover, despite the wide use of meditation-based interventions (eg, MBIs and yoga-based programs) over the last decade, compassion in the sense with which it is used here—the feeling that arises in witnessing another's suffering and that motivates a subsequent desire to help [66]—is a relatively new concept for the general population in Spanish-speaking countries, where it is traditionally associated with a "feeling of commiseration and pity for those who suffer hardship or misfortune" [67]. However, the entry for this term in the official Spanish language dictionary of the Royal Spanish Academy has recently had its definition updated to a "feeling of pity, tenderness, and identification toward others' afflictions" [68], which is closer to the psychological definition and the evolutionary perspective of compassion [66] and may reflect the assimilation of and re-conceptualization of the term.

This trial has been designed to cover the 8 areas of feasibility as suggested by Bowen et al [69]: *acceptability* (ie, how the intended individual recipients react to the intervention); *demand for the intervention* (ie, assessed by gathering data on estimated use or by actually documenting the use of a selected intervention); *implementation* (ie, the extent, likelihood, and manner in which an intervention can be fully implemented as planned and proposed, often in an uncontrolled design); *practicality* (ie, the extent to which an intervention can be delivered when resources, time, commitment, or some combination thereof is constrained in some way); *adaptation* (ie, to assess the necessity of changing program contents or procedures to be appropriate in a new situation); *integration* (ie, to assess the level of system change needed to integrate a new program or process into an existing infrastructure or program, as in our case using the website of Psychology and Technology); *expansion* (ie, to examine the potential success of an already-successful intervention with a different population or in a different setting, such as the original ABCT); *limited-efficacy testing* (ie, to test an intervention in a limited way, such as using a convenience sample, with shorter follow-up periods or with limited statistical power). In addition, this research will use a combination of methods (ie, qualitative and quantitative approaches) that best suit its feasibility study design based on author recommendations [70]. Key aspects of possible barriers to its implementation (ie, difficulties and unwanted or unexpected effects of the compassion meditation practice) will be directly asked and investigated.

Finally, based on recent literature findings, several constructs that have been associated with the promotion of well-being will be assessed together with compassion and self-compassion outcomes (eg, mindfulness, self-criticism, attachment styles, nonattachment, or purpose in life) [1,10,45,47,71-73]. Specifically, we would highlight the role of self-criticism (inadequate self and hated self and the ability to self-reassure), which is linked to various forms of psychological disorders [45,74]. Findings from this study would also provide preliminary data on associations between these variables.

Authors' Contributions

DC drafted the manuscript, with important contributions from SQ, PH, AC, and JG. DC in collaboration with SQ, YL, and JG, designed and planned the study. DC, PH, and LM developed the internet-based adaptation of the intervention protocol, with important contributions from SQ, MN, and JG. DC developed the iABCT program on the website with important contributions and oversights from DVC. ER and LB adapted the traditional paper-and-pencil questionnaires to the internet system. All authors participated in the review and revision of the manuscript and approved the final manuscript for publication.

Conflicts of Interest

The authors declare that they have developed the iABCT, the web-based version of ABCT developed and validated by JG and MN in the conventional format. DC was provided with grants from the Generalitat Valenciana (VALi+d program; APOSTD/2018/055) to carry out the project, "Compassion-based Therapy and wellbeing: development of an Internet-based intervention". The authors declare that the research is conducted in the absence of any commercial or financial interests.

Multimedia Appendix 1
Standard Protocol Items: Recommendations for Interventional Trials checklist.
[PDF File (Adobe PDF File), 66 KB - resprot_v9i8e16717_app1.pdf]

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Abbreviations

ABCT: attachment-based compassion therapy
CBI: compassion-based intervention
CONSORT: Consolidated Standards of Reporting Trials
DMC: data monitoring committee
DSM-5: Diagnostic and Statistical Manual for Mental Health Disorders-Version 5
GHQ-12: The General Health Questionnaire
iABCT: Internet Attachment–Based Compassion Therapy
M.I.N.I: Mini International Neuropsychiatric Interview
RCT: randomized controlled trial
SAP: statistical analysis plan
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TAU: treatment as usual

Protocol

Toi Même, a Mobile Health Platform for Measuring Bipolar Illness Activity: Protocol for a Feasibility Study

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Abstract

Background: The diagnosis and management of bipolar disorder are limited by the absence of available biomarkers. Patients with bipolar disorder frequently present with mood instability even during remission, which is likely associated with the risk of relapse, impaired functioning, and suicidal behavior, indicating that the illness is active.

Objective: This research protocol aimed to investigate the correlations between clinically rated mood symptoms and mood/behavioral data automatically collected using the *Toi Même* app in patients with bipolar disorder presenting with different mood episodes. This study also aimed to assess the feasibility of this app for self-monitoring subjective and objective mood/behavior parameters in those patients.

Methods: This open-label, nonrandomized trial will enroll 93 (31 depressive, 31 euthymic, and 31 hypomanic) adults diagnosed with bipolar disorder type I/II (Diagnostic and Statistical Manual of Mental Disorders, 5th edition criteria) and owning an iPhone. Clinical evaluations will be performed by psychiatrists at the baseline and after 2 weeks, 1 month, 2 months, and 3 months during the follow-up. Rather than only accessing the daily mood symptoms, the *Toi Même* app also integrates ecological momentary assessments through 2 gamified tests to assess cognition speed (QU*i*CKBRAIN) and affective responses (PLAY*i*MOTIONS) in real-life contexts, continuously measures daily motor activities (eg, number of steps, distance) using the smartphone's motion sensors, and performs a comprehensive weekly assessment.

Results: Recruitment began in April 2018 and the completion of the study is estimated to be in December 2021. As of April 2019, 25 participants were enrolled in the study. The first results are expected to be submitted for publication in 2020. This project has been funded by the Perception and Memory Unit of the Pasteur Institute (Paris) and it has received the final ethical/research approvals in April 2018 (ID-RCB: 2017-A02450-53).

Conclusions: Our results will add to the evidence of exploring other alternatives toward a more integrated approach in the management of bipolar disorder, including digital phenotyping, to develop an ethical and clinically meaningful framework for investigating, diagnosing, and treating individuals at risk of developing bipolar disorder or currently experiencing bipolar disorder. Further prospective studies on the validity of automatically generated smartphone data are needed for better understanding the longitudinal pattern of mood instability in bipolar disorder as well as to establish the reliability, efficacy, and cost-effectiveness of such an app intervention for patients with bipolar disorder.

Trial Registration: ClinicalTrials.gov NCT03508427; https://clinicaltrials.gov/ct2/show/NCT03508427

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Introduction

Background

In clinical practice, the diagnosis and management of mood/behavioral symptoms in bipolar disorder rely on subjective information and clinician's evaluations, thereby raising issues, including patient recall bias, decreased illness insight during acute affective episodes, and differences in clinical assessment experience [1]. In patients with bipolar disorder, mood changes are often accompanied by shifts in other behavioral patterns such as motor activity, energy, sleep, and cognitive functions [2]. In addition, many patients with bipolar disorder experience significant daily or weekly mood swings, which do not fulfill the criteria of an acute episode but are above the levels of mood/behavioral changes experienced by nonpsychiatrically ill individuals [3,4].

Mood instability in bipolar disorder increases the risk for relapse [5] and impairs daily functioning over time [6-8], indicating that the illness is still active. Evidence has shown that patients with bipolar disorder in remission who presented with emotional hyper-reactivity, which was assessed as a proxy of mood instability by using an analog self-rated scale, had significantly increased risk for cardiometabolic dysfunction and poor cognitive functioning [9,10]. A recent study using a smartphone-based mood self-monitoring in patients with bipolar disorder has shown that mood instability was associated with significantly increased perceived stress, decreased quality of life, and impaired functioning, although most of these patients were in remission during the 9-month study period [11]. These findings highlight that mood instability could provide unique additional variance in predicting bipolar illness activity. However, the longitudinal pattern of mood instability is poorly understood as it is difficult to assess validly [12,13]. Therefore, the ability to assess mood/behavior changes continuously in real time and in more ecological conditions may be an opportunity for better understanding the clinical progression of bipolar disorder and for monitoring individual treatment outcomes.

Digital Phenotyping in Bipolar Disorder

Currently, more than 35% of the world's adult population owns and uses a smartphone [14]. Smartphones offer the opportunity to collect a vast amount of objective, fine-grained information (eg, data on phone usage, voice features, GPS data) in real time, which may reflect behavioral patterns, thereby providing novel insights into physical and mental illnesses [15-17]. As stated by the World Health Organization, "the use of mobile and wireless technologies to support the achievement of health objectives (mobile health [mHealth]) has the potential to transform health service delivery across the globe" [18].

Different mHealth interventions have been developed and used for various medical conditions such as diabetes, cardiovascular disease, asthma, and headache [19]. In psychiatry, mHealth systems for depression, anxiety, eating disorders, schizophrenia, and bipolar disorder have been gaining traction [20-26].

Several studies have evaluated the possibility of providing remote mood monitoring for patients with bipolar disorder by using diverse digital technologies [27-37]. For example, the ChronoRecord study included daily mood charting by using a computer [36,37]. In the AMoSS (Automated Monitoring of Symptoms Severity) study, participants monitored their moods daily by using a study-specific smartphone app, and they completed their weekly mood measures by using the True Colours system [38] and by wearing movement-sensing devices to monitor multiple physiological parameters [37]. This study has demonstrated that mood and activity monitoring were well accepted and tolerated by the participants who also reported that mood monitoring assisted them in the early recognition of their mood states [34]. The MONARCA (MONitoring, treAtment and pRediCtion of bipolAr Disorder Episodes) studies showed correlations between the severity of depressive and manic symptoms self-reported by patients with bipolar disorder who were using an electronic device and the clinically rated symptoms measured using standard mood rating scales [16]. The OpenSIMPLe feasibility study, which used a smartphone-based psychoeducation program for bipolar disorder, reported high percentages of perceived helpfulness, well-being, and general health among all the participants [33]. Moodswings, an internet-based self-help program for bipolar disorder, which includes psychoeducational material and cognitive behavioral therapy elements, has reported significant reductions in mood symptoms and improvements in the quality of life and medication adherence in patients with bipolar disorder who were using this platform [27].

Despite the fast growing development of digital technologies and the excessive hype for their use in psychiatry, robust evidences in this emerging field are lacking. For example, compelling pilot results of many app studies have not translated into clinical practice [35,39]. Standardized methods to collect, analyze, and report digital mood/behavioral data as well as clear frameworks regarding privacy and security of data are still not available [40,41], making the implementation of feasibility and validation studies an important step of this process.

Objectives of This Study

In order to tackle some of these questions as well as to contribute to the evidence on digital phenotyping in bipolar disorder, we developed the *Toi Même* mHealth platform, which comprises the *Toi Même* smartphone app to self-monitor subjective and objective parameters of bipolar illness activity. The name of

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this project was inspired by the foreword engraved on the frontispiece of the Temple of Delphi—"Know thyself" (ie, *Connais toi toi-même,* in French). This expression was adopted by the philosopher Socrates who uttered it in his dialogues with his mentor Platon: "Know thyself as the dweller of the mind, senses, and the body" [42]. Our research protocol was carried out in real-world clinical settings with patients with bipolar disorder and we aimed to investigate the correlations between the clinically rated mood symptoms and mood/behavioral data that were automatically collected using the *Toi Même* app in patients with bipolar disorder presenting with different mood episodes. This study also aimed to assess the feasibility of this app for self-monitoring subjective and objective mood/behavior parameters in these patients.

Methods

Study Design

This is an applied research study on digital technology, software development, and analysis of app feasibility through an open-label, prospective, and multicenter clinical trial. The 3 investigation centers involved in this study are The Therapeutic Center for Bipolar Disorder (Centre Thérapeutique de Jour-Troubles Bipolaires, CTPJ-TB), Clinique Bellevue, Meudon, France; Clinique du Château de Garches, Garches, France; and the Service Hospitalo-Universitaire GHU Sainte-Anne, Paris, France.

Study Population

The enrollment of the patients started in April 2018 at the CTPJ-TB investigation center. The inclusion criteria for this study were male or female adult patients with bipolar disorder (age, 18 years and above), diagnosed with bipolar disorder type I or II (Diagnostic and Statistical Manual of Mental Disorders, 5th edition [DSM-5] criteria), owning an iPhone (iPhone operating system 9.0 or higher) with wireless internet access, and with a sufficient level of understanding to follow the research protocol. All patients were assessed using a standardized semistructured clinical interview and self-reported questionnaires conducted by a trained psychiatrist. The exclusion criteria were the current DSM-5 diagnosis of schizophrenia, psychotic disorders, dementia, or mental retardation, and patients presenting with suicidal behavior/ideation. At the CTPJ-TB, an independent psychiatrist researcher (AAD) asked the patients if they would like to participate in the study and explained the aims of the study. If the patient agreed to participate, an informed consent form was handed out and signed by both the participant and the psychiatrist investigator (EM) who was blinded to the smartphone data. No rewards or incentives were offered to the patients for participating in the study, and all interviews and follow-up assessments were carried out by the same investigator. The Research Ethics Committee (Comité de Protection des Personnes, Ile-de-France VII) approved the study protocol ID-RCB: 2017-A02450-53, which is also registered at www.clinicaltrials.gov (Identifier: NCT03508427).

Clinical Assessments

Data on sociodemographic and clinical assessments were performed at baseline and after 2 weeks, 1 month, 2 months,

and 3 months. These are the time points at which clinical evaluation is routinely performed at the CTPJ-TB. Hence, the study assessments did not add any extra burden on the participants or extra contact time with the staff.

The severity of the depressive and manic symptoms was evaluated using the Montgomery-Åsberg Depression Rating Scale (MADRS) [43], a 10-item questionnaire, ranging from 0 to 60, with higher scores indicating more severe depression, and the Young Mania Rating Scale (YMRS) [44], a 11-item questionnaire, ranging from 0 to 60, with higher scores indicating severity of (hypo)manic symptoms. Overall functioning was assessed using the Functioning Assessment Short Test (FAST), which encompasses 24 items to evaluate 6 functional domains: autonomy, occupational functioning, financial issues, interpersonal relationships, leisure time, and cognitive functioning. FAST scores range from 0 to 72, and higher scores indicate poorer functioning and greater disability [8].

In addition to the clinical evaluations, participants completed self-report evaluations of mood symptoms, behavior, and sleep patterns by using validated instruments. Depressive and manic symptoms were self-assessed using the 16-item Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR) [45] and the Altman Self-Rating Mania, a 5-item scale [46], respectively. Sleep patterns were assessed using the Pittsburgh Sleep Quality Index [47], which differentiates "poor" from "good" sleep by assessing 7 sleep domains, that is, quality, latency, duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. A global score of 5 or greater indicates sleep disturbances. Levels of activation were measured using the Multidimensional Assessment of Thymic States, a 20-item self-report instrument that assesses the levels of activation uncoupled from mood during the preceding week [48]. It quantitatively evaluates 5 dimensions, namely, emotional reactivity, sensory perception, psychomotor activity, motivation, and cognition, each of which can vary from hypoactivation to hyperactivation [7]. At the end of each evaluation, the investigators asked patients to give feedback regarding the overall satisfaction, ease of use, and perceived helpfulness of the *Toi Même* app (ranging from 1=not at all to 5=extremely).

The clinical data were collected using the Research Electronic Data Capture (REDCap) software [49], which is a widely used data collection platform. REDCap follows the international rules for validation, qualification, and security gold standards, which are also aligned with the Pasteur Institute's privacy/security rules for data collection.

Toi Même App

Rather than only accessing the categories of mood symptoms, the *Toi Même* app expands on the existing digital self-assessments for bipolar disorder by integrating ecological momentary assessments of the fundamental dimensions of behaviors (eg, motor activity, cognition, affective response) in the same tool through 2 gamified tests, which were created and adapted by the first author (AAD) in order to assess cognition speed (QU*i*CKBRAIN) and affective responses (PLAY*i*MOTIONS) in real-life contexts. These games also

passively collect data regarding user's response time (seconds) and the number of hits/errors in each game trial, continuously measure the daily motor activities (eg, number of steps, distance) using the smartphone's motion sensors, and perform a comprehensive weekly assessment, including validated self-rating scales [45,46,48]. Moreover, this app is special because *Toi Même* is the first app developed in France without commercial purposes, and it has been developed specifically for monitoring bipolar illness activity.

The principles, content, and the specifications of the *Toi Même* app were conceived by AAD. After a year of collaborative work among psychiatrists, neuroscientists, software engineers, and designers, the *Toi Même* app 1.0 version used in this study was available in French and was free of charge for the study participants. The information technology department of Pasteur Institute provided all the technical support for coding the app and the platform's back office. The *Toi Même* app functionalities are intended to be minimally invasive to the users' daily routine and normal smartphone usage. After the patients were included in the study, patients received an email with a link to install the *Toi Même* app in their own smartphones. Once the app was installed, users could configure it to receive a notification to perform their daily/weekly assessments. The system automatically sends a reminder notification once if the users have not completed their assessments. The app allows collecting mood/behavior information in both active (ie, need the user's action) and passive ways (ie, without the user's action), which is captured using the smartphone sensors. Once a day, the app prompts the user to score a short graphic 8-item test, including the assessment of subjective levels of mood, energy, emotion, irritability, anxiety, motor activity, speech, and thought speed on a scale from –3 to +3. Sleep time (hours), daily events (yes/no), and medication intake (yes/no) are also assessed daily.

The app also randomly delivers to the users each one of the games twice a week.

The game QU*i*CKBRAIN randomly offers a series of 7 trials, each one containing a pair of word image or a simple calculation. The user's action is to analyze and answer if the word matches (or not) with the image (Figure 1A) or in case a calculation is presented, the user must answer if the result of the calculation is correct (or not) (Figure 1B). Correct and incorrect buttons are present in each trial. The QU*i*CKBRAIN task contains about 1000 different trials.

The game PLAY*i*MOTIONS is intended to assess the user's affective response to the images. This test comprises about 1000 color images depicting a broad spectrum of themes, including humans, animals, objects, and scenes along with normative ratings on the affective/valence dimension (ie, the degree of positive, neutral, or negative affective response that the image evokes). In each game trial, an image appears on the smartphone screen for approximately 5 seconds (Figure 2A). Thereafter, the image fades away, after which a colored circle and 2 buttons appear: one button contains the name of the color of the circle written in the same color (or in a different color) as that of the circle and another button contains the name of a color different from that of the color of the circle. In this task, the user's action is to analyze the 2 options offered and choose the one that corresponds with the color of the circle displayed on the screen (Figure 2B).

At the end of the daily assessment, the *Toi Même* app provides an intuitive dashboard reflecting some of the daily scores, the user's mood/behavioral patterns during the last 7 days and, by data push, during the last 30 days (Figure 3). No diagnostic or therapeutic feedbacks are provided. All data recorded by the app are encrypted, synchronized, and stored in a deidentified format within the *Toi Même* server.

Figure 1. Example of a cognitive speed assessment by the QU*i*CKBRAIN task.
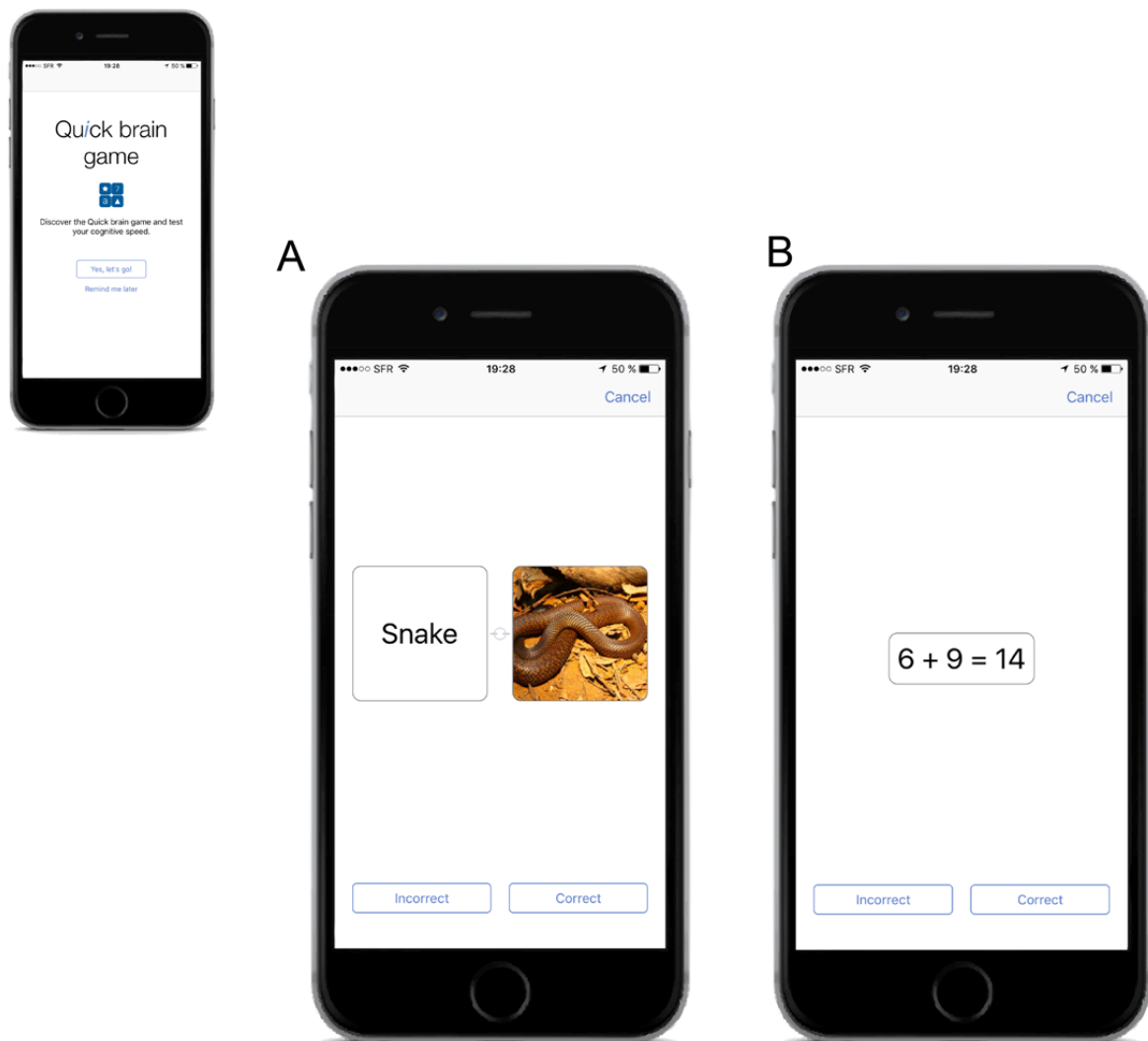
Figure 2. Example of an affective response assessment by the PLAY*i*MOTIONS task.
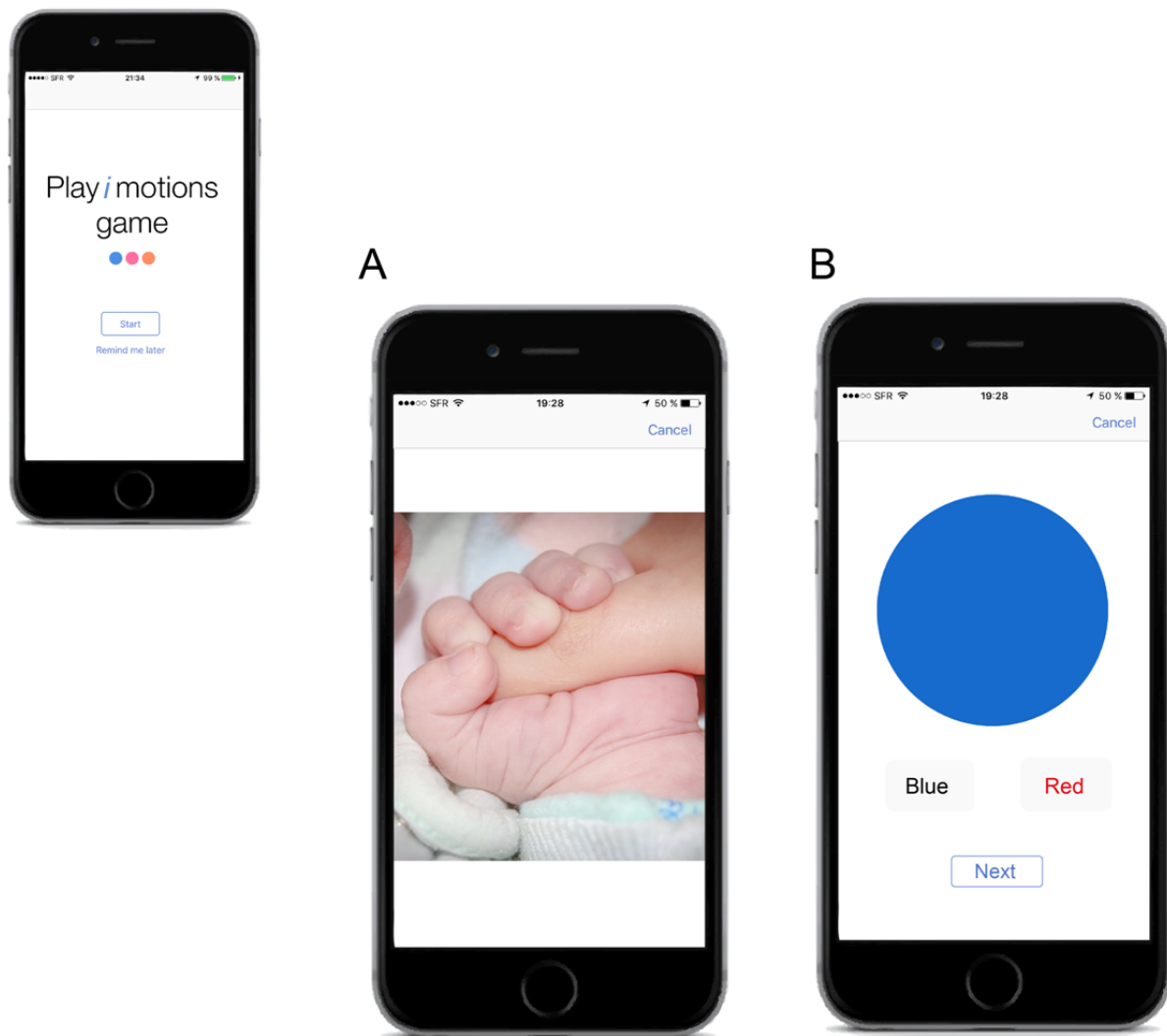
Figure 3. Example of the *Toi Même* app dashboard.

Outcome Measures

Outcome measures are assessed at the baseline visit and after 2 weeks, 1 month, 2 months, and 3 months [50]. Briefly, primary outcome measures focus on changes in the severity of the depressive and manic symptoms assessed using the MADRS and YMRS. Secondary outcomes include changes in the self-rated mood/behavioral symptoms and medication adherence assessed using the self-report instruments QIDS-SR, Altman Self-Rating Mania, Multidimensional Assessment of Thymic States, and the Medication Adherence Rating Scale [51]. Functioning will be assessed using the FAST scale. Feasibility measures include the proportion of eligible participants who have consented to participate in the study, the frequency of self-assessments, and the proportion of participants who continued using *Toi Même* app during the study period. The participant's physical activity will be inferred using the number of steps and distance automatically captured by the smartphone motion sensors.

Sample Size

Considering that the focus of this pilot study is to have patients with bipolar disorder in different mood states (depression, euthymia, and hypomania), a conservative approach for calculating the sample size was adopted (ie, concordant pairs) to ensure more qualitative feedback [52]. The overall mood/behavior states assessed using the *Toi Même* app encompasses 8 dimensions of behavior (ie, mood, energy, emotion, irritability, anxiety, activity, speech, and thought speed). Each of these dimensions is rated using a score ranging from –3 to +3, yielding a total score of 24. Accordingly, a concordant pair between the app measurements and the clinical assessments of mood symptoms was defined as follows: (1) depression, a score of $<–8$ in the app assessments and scores of >15 for MADRS and <8 for YMRS; (2) euthymia, a score between –8 and +8 in the app assessments and scores of <15 for MADRS and <8 for YMRS; (3) (hypo)mania, a score of $>+8$ in the app and scores of <15 for MADRS and >8 for YMRS. Assuming that the expected proportion of the concordant pairs is 98%, with an estimated precision of 5% and a two-sided 95% CI, 31 patients will be included in each of the 3 groups to fully accomplish the study goals (N=93).

Statistical Analysis

Descriptive analyses will be conducted to characterize the sociodemographic and clinical characteristics of the initial sample as well as the retention at the end of the study. Receiver operating characteristics analysis will be applied to calculate the concordance ratio of the pairs (ie, the area under the curve) [53]. Given that patients have started using the app from the baseline visit, the clinical data collected at this time point will not be included in the concordant pairs' analysis. Compliance will be calculated as the proportion of the enrolled patients completing the first 15 and then 30 and 90 consecutive days of ratings. The app completion rate would be completing at least 70% of the momentary assessments during the time a participant has continued in the study. The average ratings of the perceived helpfulness, ease of use, and overall satisfaction would be at least 3 on the 1 to 5 rating scores. Cluster analysis will be performed using principal component analysis (PCA) to identify groupings of the daily *Toi Même* mood/behavior questions. The PCA results will be then used to obtain a single summary statistic (*TM*P1) that will account for the maximum amount of variability in the 8 daily *Toi Même* mood/behavior responses across all the subjects during the study period. The summary statistic produced from the PCA-*TM*P1 will be used as a response to test for differences between groups in daily ratings and for comparison between this app score and the clinical rating scores. To test for differences between groups over time, linear mixed regression models will be used with autoregressive covariance adjustments for repeated measurements of continuous outcomes and logistic generalized estimating equations will be used for binary outcomes. In both linear and logistic generalized estimating equation models, adjustments for sex, age, day of the week, and elapsed time in the study will be included as other covariates in the models. The regularity in the daily ratings for each subject will be estimated using the root mean squared successive differences (a measure of the variability of the changes in scores over time), the Teager-Kaiser Energy Operator, which combines amplitude and frequency, and the information entropy, which measures regularity of amplitude [37]. The within-subject sample variance will be also used as a measure of regularity for each subject's response and will estimate the distribution of the amplitudes recorded over time. Data analysis will employ the intention-to-treat principle by including all participants in the analyses, which will be conducted using the R programming language (R Core Team).

Results

The recruitment of patients started in April 2018 and the completion of the study is estimated to be in December 2021. As of April 2019, 25 participants were enrolled in the study. The first results are expected to be submitted for publication in 2020. The association between performance on both the QU*i*CKBRAIN and PLAY*i*MOTIONS and subjective cognitive/emotional functioning difficulties will be evaluated in a subsequent specific study. In the future, the transfer of technology from the academic environment to the clinics may be a strategy to invigorate efforts, making available the *Toi Même* mHealth platform for individuals at risk of developing bipolar disorder or for those experiencing bipolar disorder. This project has been funded by the Perception and Memory Unit of the Pasteur Institute (Paris) and it has received the final ethical/research approvals in April 2018 (ID-RCB: 2017-A02450-53).

Discussion

To our knowledge, this is the first study in France that has investigated correlations between clinically rated mood symptoms and mood/behavioral data automatically collected using a smartphone app specifically developed for patients with bipolar disorder through a registered clinical trial carried out in real-world bipolar disorder treatment clinics. This multidimensional digital phenotyping approach may help to improve our understanding of bipolar illness activity and potentially contribute to early detection of subtle mood/behavior changes and to objective assessment of the response to treatment and its impact on mood, cognition, emotion, and motivation in patients with bipolar disorder. In addition, the use of digital technology in bipolar disorder treatment clinics may encourage patients with bipolar disorder to monitor their health as well as reinforce the patient-clinician therapeutic alliance.

Although the *Toi Même* project is not the first to implement a smartphone-based self-monitoring tool for patients with bipolar disorder, this app was designed as an independent self-assessment tool targeting mainly the fundamental dimensions of behavior (eg, activity, energy, cognition speed, affective responses) rather than as an augmenting intervention measuring essentially mood symptoms. The *Toi Même* clinical trial has carefully followed the ethical and legal issues around providing and obtaining adequate informed content from participants, personal privacy, and safety of data collection/storage. The same clinical psychiatrist who was blinded to smartphone data collected during the study assessed the patients by using standardized rating scales. The *Toi Même* app automatically integrates behavior data collection (eg, physical activity, user's response time) and 2 gamified modules targeting cognitive speed (QU*i*CKBRAIN) and affective response to images (PLAY*i*MOTIONS).

Smartphones are able to automatically collect a large amount of complex and diverse data that are quickly generated and could represent a paradigm shift for accessing mood/behavior in patients with bipolar disorder, thereby providing opportunities for investigation and hypothesis generation [54,55] as well as for enhancing the precision of clinical algorithms, which today are essentially based on patients' subjective self-report and clinicians' observations. Promising progress in big data analytics (eg, machine learning techniques) as well as intensive multidisciplinary collaboration, including clinicians, neuroscientists, engineers, and data scientists, could further help to solve this complex puzzle, extracting meaningful indicators of bipolar disorder onset, course, and treatment response [56,57]. Future studies investigating the use of combined automatically generated smartphone data with biological and clinical measures may lead to the discovery and validation of digital markers of risk, staging, treatment response, and prognosis in patients with bipolar disorder [58].

Owing to resource constraints, this research protocol has included a *Toi Même* app version using only the iPhone operating system; hence, Google's Android users as well those using smartphones with other types of operating systems were excluded. This could represent a sampling bias since smartphone ownership could be related to income status, education levels, and gender [14]. Three months of follow-up may be a short time frame to evaluate the feasibility of a digital self-monitoring tool for patients with bipolar disorder [39]. However, to date, there is no consensus on how long these types of interventions should be offered. Moreover, there is a multitude of smartphones in the market in which are embedded diverse sensors as well as different operating systems, which have different permissions rules to capture passive information (eg, the iPhone operating system has more restrictions than the Android operating system). To overcome this issue, research groups using digital phenotyping in psychiatry should keep trying to communicate with information technology companies regarding the development of clear and ethical frameworks for obtaining access to more homogeneous automatically generated smartphone data in order to evaluate their validity, sensitivity, and specificity for monitoring bipolar illness activity.

In summary, the *Toi Même* study is an example of the use of digital phenotyping in bipolar disorder clinical practice that can provide fine-grained mood and behavioral patterns of bipolar illness activity in real time. This clinical neuroscience–based research may add to the evidence of exploring other alternatives toward a more integrated approach, including digital phenotyping, in the management of bipolar disorder to develop a clinically meaningful framework for investigating, diagnosing, and treating individuals at risk of developing bipolar disorder or currently experiencing bipolar disorder.

Authors' Contributions

AAD conceived the concept, content, and the specifications for the *Toi Même* app. AAD, CH, and PML worked with both the IT Department and the Translational Research Center at the Pasteur Institute to develop this project. AAD drafted the protocol, and all the authors revised and approved the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AMoSS: Automated Monitoring of Symptoms Severity
CTPJ-TB: Centre Thérapeutique de Jour-Troubles Bipolaires
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition
FAST: Functioning Assessment Short Test
MADRS: Montgomery-Åsberg Depression Rating Scale
mHealth: mobile health
MONARCA: MONitoring, treAtment and pRediCtion of bipolAr Disorder Episodes
PCA: principal component analysis
QIDS-SR: Quick Inventory of Depressive Symptomatology Self-Report
REDCap: Research Electronic Data Capture
YMRS: Young Mania Rating Scale

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Protocol

Individualized Apartment Accommodation for People With Intellectual Disability: Protocol for a Qualitative Study Examining the Well-Being and Support Outcomes Linking Housing and Health

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Abstract

Background: Understanding the outcomes associated with both receiving and providing support to people with intellectual disability in specific settings can facilitate the alignment of health providers, community care providers, architects, and urban planners to strengthen levels of autonomy and community participation of people with intellectual disability living in the community. This study explores the impact of providing support (available 24 hours a day) for people with intellectual disability in a high-density apartment. It seeks the perspectives of people with intellectual disability who have moved into an apartment from a group home (where 4-6 people with disability live), their families, and support staff. It will enable comparison between two models of supported accommodation, group homes and individualized apartments, in a community setting.

Objective: The aims of this study are to explore the impact of an individualized apartment model of supported accommodation in a high-density setting on the well-being, autonomy, and participation of people with intellectual disability living and receiving support; the experience of providing care or support; and how this setting impacts the logistics of how quality support is provided.

Methods: Qualitative research methods were employed as the primary means of collecting and analyzing data. There are two main sources of data in this study: (1) semistructured interviews with participants in up to 3 waves (pre, post 1, and post 2) and (2) pre- and postoccupancy evaluation data on the design, layout, and location details of the built environments. Coded interview data will be paired with pre- and postoccupancy evaluations of the two accommodation settings.

Results: As of May 2020, we have recruited 55 participants. There have been 96 interviews conducted in 2 waves with people who have moved into supported accommodation, families, and staff. Collected data are currently being analyzed. We expect the results of the trial to be published in a peer-reviewed journal in late 2020.

Conclusions: This paper sets out a study of an alternative housing and support model for people with intellectual disability. It will capture personal experiences of people with intellectual disability receiving support in an apartment compared to their experiences in a group home. It will also capture the experiences of support staff working in the new setting and reveal how this differs from a group home setting. The inclusion of pre (group home) and post (apartment integrated into a community setting) measures addresses evaluative and comparative questions around the nature and impacts of the small-scale apartment and support model for both those who live and receive support, and those who support them.

International Registered Report Identifier (IRRID):   DERR1-10.2196/18248

KEYWORDS

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Introduction

Beyond the Group Home and Into an Apartment

The introduction of consumer-led health and disability funding across the world (including the United States, the United Kingdom, parts of Europe, and Australia) has changed in how disability housing support is provided and brought with it the opportunity for individualized living plans and accommodation settings. Developments in research across health and urban planning fields recognize the ways that urbanized, high-density settings influence a population's health, well-being, and participation in growing cities [1,2]. People with intellectual disability have largely been excluded from these discussions, and community urban life in general. This exclusion can be explained to a large degree by the fact that, prior to consumer-led disability services, people with intellectual disability who received support in their daily life activities, were historically required to live in institutional care settings. In more recent years, since deinstitutionalization, people with intellectual disability have tended to live in congregate care housing such as group homes, which, because of their spatial footprint and number of bedrooms, are likely to be located in suburban settings.

People with intellectual disability have a right to equal choice, freedom, and control over their living arrangements, including where they live, who they live with, and who provides support to them. Despite the strong evidence linking housing type, design and location, support practices, and health outcomes [3-5], there is little evidence upon which community housing providers, health providers, and urban policy makers can make aligned decisions about planning, design, health, and support practices for people with intellectual disability receiving high support.

Supported accommodation performs not only as a place where people live but also as a place where personal and social support, and health care are coordinated, provided, and received. For people with intellectual disability who receive 24-hour support, group homes remain the predominant community-based, long-term accommodation option outside the family home [6,7]. A growing body of evidence has explored the outcomes of group homes as an accommodation model for people with intellectual disability and has recognized that the quality-of-life outcomes for those living and receiving support in group homes are highly variable [7,8]. Some of the expected improvements in the outcomes and lives of people with intellectual disability in the years of post-deinstitutionalization have not been realized, most notably the fact that community participation has not increased despite group homes being community based [8-10]. In addition to this, the power dynamics that the home and work duality of the group home environment brings (being both a home for a person with disability and a workplace for support staff) can result in less-than-homely environments and workplace cultures determining the household routines and activities [7,11,12]. The lack of homeliness of some group homes has also been highlighted by Robertson et al [13].

Increasing the diversity of accommodation models that benefit both the quality of life in those living and receiving support in

the community, as well as ensuring the quality and sustainability of community health care provision, is an important area of public health research. There is evidence to suggest that alternatives to group homes are limited, with many young people with disability residing in aged care facilities [14], and a lack of choice within the housing market for supported accommodation is a problem across the world [15,16].

Group Homes Versus Smaller Models of Supported Accommodation

Group homes are defined as "accommodation for between four and six people, where extensive or pervasive paid staff support is provided to the residents, both in the home and when leaving it to use community –based settings" [8]. The support is typically provided 24 hours of the day with support staff working a sleepover shift or awake shift throughout the night. Despite evidence indicating that smaller, community-based housing arrangements (1-2 people living and receiving support) result in better outcomes for people with intellectual disability, there has been comparatively little work undertaken to understand what living in, receiving support, and providing support in these smaller models in high-density settings mean. The research that has been undertaken in this area indicates that settings of 1-2 people living and receiving support result in better outcomes including more choice, self-determination, and freedom from staff [17-19].

The transition to self-directed disability funding such as the National Disability Insurance scheme in Australia and Self-Directed Support in the United Kingdom have enabled a wide variety of accommodation setting options and funding models where people with disability could live and receive high support [20]. Consistent with this trend, a not-for-profit housing and service provider in New South Wales, Australia (Provider) has implemented a model of smaller 1- or 2-bedroom apartments "salt and peppered" throughout a high-density, privately owned apartment development. The Provider case study will be the source of participants for this study. The Provider gives support to the apartments it owns and manages where people with intellectual disability live with 24-hour support. The apartments are distributed throughout a high-density apartment complex of 416 privately owned apartments.

Researchers in supported accommodation acknowledge that an array of factors including design, layout, location, size, and staffing impact the autonomy, independence, and well-being of adults with intellectual disability living in the community [10,17,21]. New housing models suitable for high-density city settings need to be evaluated to understand the health and support practice impacts of supported accommodation models at room, apartment, site, and neighborhood scales [2].

This research design will incorporate perspectives on the design of the built environment alongside perspectives of sense of home, quality of life, and participation outcomes for people with intellectual disability. Evaluating the impact of a change in dwelling location and design, such as changes to the size, density type, accessibility, community immersion, and other functional features of housing, as well as the nature of the individualized supported living plans will in turn bring about changes in outcomes for people living with disability and the

way support is provided. Better design of accommodation, in both its quality and accessibility are acknowledged as central to the efforts of supporting the health, independence, and autonomy of people with intellectual disability in the community [18].

Methods

Aim and Research Questions

The overall aim of the evaluation is to understand the impact of providing high support for people with intellectual disability in a high-density apartment from the perspectives of those who live and receive support there, their families and guardians, and the support staff who work within this model. The objectives of this study are to explore the impact of an individualized apartment model of supported accommodation in a high-density setting (including its design and location) on:

- Well-being, autonomy, and participation of people with intellectual disability living and receiving support
- The experience of providing care and support, and the logistics of how support is provided

Qualitative research methods were employed as the primary means of collecting and analyzing data to understand the impact of individualized apartments as a supported accommodation model for people with intellectual disability. There is also some quantitative analysis undertaken, including a statistical analysis of participants and quantitative data rising from postoccupancy evaluation data on the built environments.

There are two main sources of data in this study: (1) semistructured interviews will be conducted with participants in up to 3 waves (pre, post 1, and post 2) and (2) pre- and postoccupancy evaluation data [22] that captures design, layout, and location details of the built environments where support is provided or received. A summary of the data collection methods is provided in Figure 1.

For the qualitative part of the data collection, in-depth, semistructured interviews enable the researchers to explore the "deep meaning" and "inside view" that lie beneath the human behaviors and choices being explored in this research [23]. There are three main participant groups: people with intellectual disability who are living and receiving support in the accommodation, paid support staff, and families of people with intellectual disability. Up to 20 participants will be recruited from each participant group for this exploratory study, resulting in a total of up to 60 participants. The research applies a general inductive approach for analyzing the data, whereby meaning and concepts are primarily derived from the accounts of participants in the research [24-26].

As a mixed methodology, a qualitative approach coupled with postoccupancy data provides an opportunity to deepen understanding of the built environment's influence on independence participation and support practices. The study is designed to build new evidence that informs researchers across disciplines (housing, disability, and community services) and begins to "make sense" of the relationships between housing design, location, and support systems that take place in a supported accommodation setting. Most importantly, the study provides an opportunity to represent the voice of people with intellectual disability by hearing their experiences of living in and receiving support in a new environment.

Figure 1. Approach to data collection.

Ethics Approval and Consent to Participate

Ethics approval was granted by the University of Technology Sydney (UTS) Human Research Ethics Committee approval number ETH17-2032: Supported Living Accommodation: Housing, Quality of Life and Support Services for people with intellectual disability. Participants (including people with intellectual disability, their families or guardians, and support staff) are required to sign a consent form to indicate their willingness to participate. Voluntary participation and the right to ask any questions, and to decline participation at any time, will be emphasized during the data collection. Easy read versions of Project Information Statements and consent forms were developed to inform participants with intellectual disabilities of the purpose and processes involved in the research.

Setting and Participants

The Provider owns and gives supported accommodation for people with intellectual disability in 22 apartments (one or two bedroom) that are "salt-and-peppered" across a high-density, privately owned development of 416 apartments in Sydney, Australia. This apartment development has been selected as the setting for participant recruitment. Each apartment owned by the Provider has 1-2 bedrooms, providing 24-hour support to over 40 people with intellectual disability. The site has a number of apartment towers accessed by multiple lift wells and underground parking, and is secured by locked gates. The site has shared garden areas typical of a high-density development found in a larger city such as Sydney. Staff are rostered to provided 24 hour "awake" support across the 22 apartments located in all four towers on the development site. This is in contrast with the support provided previously in the group home settings, where 24-hour support was rostered with a "sleepover" shift overnight.

Self-selection sampling is to be used in this study to recruit participants living and receiving support in apartments owned by the Provider, their families, and support staff employed by the Provider. Posters explaining the research will be placed in staff quarters, and the researchers will attend family and staff meetings to explain the research aims. This study will target sampling at least 20 people with intellectual disability, 20 family carers, and 20 support staff.

The qualitative study will explore how the design of the home and accommodation setting influences the quality of life domains of the person receiving support and how it functions as a work environment for staff providing support. This will enable an understanding of different experiences and perspectives from three stakeholder groups:

1. People with intellectual disability who are living and receiving support in the new apartment, having moved from a group home
2. The families and guardians of people with intellectual disability
3. Support staff providing disability services in the supported apartment accommodation

The key elements of the qualitative design are outlined in Figure 1. Data collection methods include semistructured interviews conducted with people with intellectual disability, their families, and staff providing support. Semistructured interviews with people with disability and families will focus on understanding what aspects of the support model and environment design influence their quality of life and daily lives. The semistructured interviews with support staff will explore perspectives on how the built environment and supporting features and technologies impact their support provision, including identification of any current difficulties and perceptions of the new individualized model.

The data from this study will reveal how the different models of group home or individualized apartment living impact the lives of people with intellectual disability and the working practices of support staff. The quality of life approach will enable a comparison between the social impacts of living in a group home compared to individualized apartment accommodation models.

Analysis

The research will gather data that combines housing design and experiences of people with intellectual disability, families, and support staff. Data analysis will explore how the design of the built environment intersects with outcomes for people with intellectual disability and support delivery, and the principles underpinning quality supported accommodation. The thematic analysis of the qualitative content will be undertaken using the stages reported by Green and colleagues [27], which includes immersion in the transcripts, text coding, creation of broader categories from the coded text, and identifying themes.

The coding process will involve both open and axial coding of the data and comparison of the dwellings (both group homes and apartments), with performance criteria developed from the literature. This methodological approach is based upon foundation work undertaken by Bridge and Donelly [28].

Availability of Data and Material

Materials described in this paper pertain to the study protocol only and there are no raw data reported. The data sets are currently being collected and analyzed. The data sets generated or analyzed during this study are not publicly available due to the terms of consent that the participants agreed to but are available from the corresponding author on reasonable request.

Results

As of May 2020, we have recruited 55 participants. There have been 96 interviews conducted in two waves with people who have moved in to supported accommodation, families, and staff. Collected data are currently being analyzed. We expect the results of the trial to be published in a peer-reviewed journal in late 2020 and early 2021.

Discussion

Receiving Support in Urbanized, High-Density Settings

This research will contribute to an evaluation of community care and disability housing models. The study will increase our understanding of the experiences of people with intellectual disability to inform person-led best practices for disability support in the community for people with disability. The study will also provide a means of understanding how support is influenced by the model of housing and will contribute to the body of knowledge about how urbanized, high-density settings influence health, well-being, and participation in growing cities.

By providing a comparison of group home models with individualized apartment accommodation, it is hoped that this research will also lead to better quality and more informed housing and community support choices for people with intellectual disability.

The theoretical framework that will be generated from this study will be practical and useful in producing knowledge about factors that influence independence, autonomy, support provision, and participation for people with intellectual

disability. Pairing data with pre- and postoccupancy information about the design and location of the accommodation will enable specific environmental factors that influence support practice to be clearly identified. The framework will, therefore, be useful in guiding further support interventions and innovations that will address the needs of people with intellectual disability and the sustainability of the support workforce that underpins community-based supported accommodation models.

As housing availability and affordability is in decline in urbanized city centers around the world [29] and people with intellectual disability continue to experience layers of disadvantage [30], those with intellectual disability face limited opportunities to claim the right to make choices about where they live, who they live with, and who provides support to them and how. This research provides information upon which informed decisions can be made with and by people with intellectual disability so that they may live the life they choose to lead, participating and living in the communities of their choice.

Limitations

The limitations of this particular study design include that the research is single arm (no control) and that participants are recruited from a single site; therefore, generalizability can be considered limited. This study can be considered exploratory with the potential to be broadened in scope and size to include other sites with similar accommodation models at a later date.

Strengths

This research recognizes the role of environmental factors, including urban planning and housing design, in influencing the well-being, participation, and quality of life in people with intellectual disability. The accommodation design and setting also influences the type and quality of support provision provided to people with intellectual disability living in a community. The study will provide new insights into emerging health and well-being outcomes associated with community living for people with intellectual disability. It will also inform policies and practices for innovative, sustainable, and person-led models of high (24-hour) support provision in the community.

Despite being small in scale the study promises to lay the theoretical groundwork, produce policy learnings, and begin to build an evidence base that will be relevant for the disability sector in an area where changes to group homes as the default model have been difficult or slow to achieve. It will also establish an evidence base of associations between the design of the built environment and outcomes around support, participation, and independence for people with intellectual disability.

Conclusion

This paper sets out a study of an alternative housing and support model for people with intellectual disability. The study will capture personal experiences of people with intellectual disability receiving high levels of support in an apartment compared to their experiences in a group home. It will also capture the experiences of support staff working in the new setting and reveal how this differs from providing support in a group home. The collected data will be triangulated with data from family and guardians' perspectives.

The inclusion of pre (group home) and post (apartment integrated into a community setting) measures addresses evaluative and comparative questions around the nature and impacts of the small-scale apartment and support model for both those who live there and receive support, and those who support them.

Authors' Contributions

PC drafted the protocol. The project was conceptualized by PC, and informed and guided by industry disability support providers. The protocol incorporates peer-reviewed feedback received during the application process for the Innovation Workforce Fund.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Letter from government funder attesting to peer-reviewing of the funded project.
[PDF File (Adobe PDF File), 3948 KB - resprot_v9i8e18248_app1.pdf]

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Abbreviations

UTS: University of Technology Sydney

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Original Paper

Lung Function Variability in Children and Adolescents With and Without Asthma (LUV Study): Protocol for a Prospective, Nonrandomized, Clinical Trial

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Abstract

Background: Variability analysis of peak expiratory flow (PEF) and forced expiratory volume at 1 second (FEV1) has been used in research to predict exacerbations in adults with asthma. However, there is a paucity of data regarding PEF and FEV1 variability in healthy children and adolescents and those with asthma.

Objective: The objective of this study is the assessment of PEF and FEV1 variability in (1) healthy children and adolescents, to define the normal daily fluctuation of PEF and FEV1 and the parameters that may influence it, and (2) children and adolescents with asthma, to explore the differences from healthy subjects and reveal any specific variability changes prior to exacerbation.

Methods: The study will include 100 healthy children and adolescents aged 6-18 years (assessment of normal PEF and FEV1 variability) and 100 children and adolescents of the same age with diagnosed asthma (assessment of PEF and FEV1 variability in subjects with asthma). PEF and FEV1 measurements will be performed using an ultraportable spirometer (Spirobank Smart; MIR Medical International Research) capable of smartphone connection. Measurements will be performed twice a day between 7 AM and 9 AM and between 7 PM and 9 PM and will be dispatched via email to a central database for a period of 3 months. PEF and FEV1 variability will be assessed by detrended fluctuation and sample entropy analysis, aiming to define the normal pattern (healthy controls) and to detect and quantify any deviations among individuals with asthma. The anticipated duration of the study is 24 months.

Results: The study is funded by the "C. Caratheodory" Programme of the University of Patras, Greece (PN 47014/24.9.2018). It was approved by the Ethics Committee (decision 218/19-03-2019) and the Scientific Board (decision 329/02-04-2019) of the University Hospital of Patras, Greece. Patient recruitment started in January 2020, and as of June 2020, 100 healthy children have been enrolled (74 of them have completed the measurements). The anticipated duration of the study is 24 months. The first part of the study (assessment of lung function variability in healthy children and adolescents) will be completed in August 2020, and the results will be available for publication by October 2020.

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Conclusions: Healthy children and adolescents may present normal short- and long-term fluctuations in lung function; the pattern of this variability may be influenced by age, sex, and environmental conditions. Significant lung function variability may also be present in children and adolescents with asthma, but the patterns may differ from those observed in healthy children and adolescents. Such data would improve our understanding regarding the chronobiology of asthma and permit the development of integrated tools for assessing the level of control and risk of future exacerbations.

KEYWORDS

asthma; lung function variability; fluctuation analysis; children; adolescents

Introduction

Asthma is the most common chronic disease of childhood and represents an important cause of morbidity worldwide [1]. The disease is characterized by episodes of reversible airway obstruction (exacerbations), with specific symptoms (such as wheezing, dyspnea, coughing, chest tightness) and a decrease in peak expiratory flow (PEF) and forced expiratory volume at 1 second (FEV1) [2]. However, lung function changes occur in parallel with clinical deterioration, thus presenting limited ability to predict the exacerbation of the disease [3].

Both PEF and FEV1 demonstrate significant daily variability, in relation to circadian and day-by-day fluctuation of measured values [4,5]. In healthy individuals, the pattern of these fluctuations remains constant over long time periods (weeks or months); this contrasts with patients with asthma, for whom PEF and FEV1 variability increase with loss of disease control, especially prior to exacerbations [5,6]. Thus, lung function variability analysis has been used in research to recognize high-risk patients, predict asthma exacerbations, and evaluate the effectiveness of treatment [6-10].

In clinical practice, however, the evaluation of lung function variability requires daily measurements with portable devices, the recording of PEF and FEV1 values in specialized diaries, and periodic evaluations of the data by the attending physicians [2]. The whole process may be both complicated and time-consuming, reducing patients' adherence—especially in the cases of children and adolescents [11,12]. In addition, the periodic post hoc review of measurements may hamper the prediction of exacerbations, as the time of evaluation may not coincide with changes in the variability of lung function that characterize the loss of asthma control [12].

In recent years, technological advancements in the field of biosensors and microprocessors have permitted the development of reliable, low-cost, ultraportable spirometers, able to connect with cutting-edge mobile phones (smartphones) and monitor lung function parameters in real time and from a distance [13]. The introduction of such devices in clinical practice may overcome most of the aforementioned barriers in following up lung function parameters in the long term [13].

Currently, there is a paucity of data regarding long-term PEF and FEV1 variability in children and adolescents; this holds particularly true for children and adolescents with asthma. Such data would improve our understanding regarding the chronobiological aspects of the disease and may permit the development of integrated tools for assessing the level of asthma control and the risk of future exacerbations.

Methods

Study Objectives and Hypotheses

The first objective of the study (objective 1) is the assessment of lung function variability in healthy children and adolescents, focusing on the range and pattern of short- and long-term fluctuations of PEF and FEV1 and the parameters that may influence them. The second objective (objective 2) is the assessment of lung function variability in children and adolescents with asthma; the pattern of short- and long-term PEF and FEV$_1$ variability will be established and the differences from healthy subjects will be defined. Specific changes in the variability pattern prior to exacerbation will also be sought and described (objective 3).

We hypothesize that healthy children and adolescents present normal short- and long-term variability of PEF and FEV1, and that the pattern of variability is influenced by age, sex, and environmental stimuli (season, weather conditions, viral infections, etc). Significant lung function variability is also expected for children and adolescents with asthma; the patterns of variability in children and adolescents with asthma may differ from those observed in healthy children and adolescents, being also influenced by environmental conditions and treatment modalities (controller therapy) in a distinguishable way. Finally, we hypothesize that changes in the pattern of lung function variability occur prior to the loss of asthma control and, thus, may be used to predict the exacerbations of the disease.

Study Design

The study was designed as a nonrandomized, open-label, interventional clinical trial with single group assignment (2 study groups).

Study Population

The study will include a cohort of healthy children and adolescents (n=100) for the assessment of normal PEF and FEV1 variability (objective 1) and a cohort of children and adolescents with asthma (n=100) for the assessment of PEF and FEV1 variability in this population (objective 2), as well as an investigation of its potential clinical relevance (objective 3).

Participants will be recruited at the Pediatric Respiratory Unit and the Department of Pediatrics of the University Hospital of Patras, and at private pediatric offices in the city of Thessaloniki, Korinth, and Trikala, Greece. Each participant will receive a unique study number (comprising 2 letters and 8 numbers in random order).

Sample Size Estimation

Data regarding long-term PEF and FEV1 variability in children and adolescents (with or without asthma) are lacking. Based on lung function variability, data from adults with asthma [14], and assuming a maximum dropout rate of 10%, we estimated that a sample size of 200 children and adolescents (100 in each group) would allow us to detect a difference of at least 1% in PEF or FEV1 coefficient of variation (CV) between healthy participants and participants with asthma, with 90% power at the 0.05 level. Sample size estimation was performed using the G*Power software (version 3.1.6) [15] after assuming a nonparametric distribution of lung function parameters (Wilcoxon rank-sum test).

Inclusion and Exclusion Criteria

Inclusion criteria for both cohorts are individuals 6-18 years old; who have access to (or whose parents have access to) a smartphone with internet connection (Wi-Fi or mobile data); and who have given (or whose parents have given) informed, written consent to participate.

Inclusion criteria for the cohort of healthy children and adolescents are no asthma diagnosis or prescription of relevant medication (beta-2 agonists, anticholinergics, inhaled corticosteroids or montelukast) in the last 2 years; and normal baseline spirometry, defined as FEV1 and FEV1/FVC > 80% of predicted (Global Lung Initiative [GLI] normative data [16]) without significant reversibility (FEV1 change < 10%) after administration of 300 μg salbutamol inhaler.

Inclusion criteria for the cohort of children and adolescents with asthma are doctor-diagnosed mild or moderate asthma [2] in the last 2 years; administration of controller therapy for at least 6 months in the previous year; and at least one spirometry, with FEV1 and FEV1/FVC < 80% of predicted (GLI normative data [16]) in the previous year.

Exclusion criteria for both cohorts are major disabilities (eg, chromosome abnormalities, neurological or muscular disorders, neurodevelopmental delay) that may hamper the proper performance of lung function measurements; respiratory conditions (eg, severe respiratory infection, chest trauma) or other health-related events (eg, surgery, trauma) in the month prior to enrollment or during the 3-month period of observation; failure to complete the run-in period successfully (ie, to perform acceptable spirometries at the predetermined time frames); or inability to perform 3 consecutive measurements or 6 measurements in total (3.3% of the anticipated 180 measurements) within the 3-month period of observation.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee (decision 218/19-03-2019) and the Scientific Board (decision 329/02-04-2019) of the University Hospital of Patras, Greece.

The study was registered with ClinicalTrials.gov under the number NCT04163146 (registered on November 14, 2019). Informed consent from parents, or from parents and participants (in the case of adolescents older than 12 years of age), will be obtained at inclusion. The informed consent grants access to the participants' measurements and medical files, and permits the transmission of data through the internet, given that all conditions of anonymity and data protection are met.

Lung Function Measurements

PEF and FEV1 measurements will be performed using an FDA-approved ultraportable spirometer (Spirobank Smart; MIR Medical International Research), with a bidirectional digital turbine (flow range ± 16L/s; volume accuracy ±3% or 50 mL; flow accuracy ±5% or 200 mL/s; dynamic resistance <0.5 cm H_2O/L/s) and capable of connecting to a smartphone via Bluetooth using a dedicated freeware app (iSpirometry, MIR Medical International Research). Apart from PEF and FEV1, the device provides data on the forced expiratory capacity (FVC) and forced expiratory flow between 25% and 75% of FVC (FEF25-75). The app includes graphic incentives to assist in performing technically acceptable tests; it also includes a quality grading system that generates messages to inform whether the measurement was technically correct or, if not, the nature of the mistake (eg, "good blow" for an acceptable test, or "blow faster," "blow longer," etc, for nonacceptable maneuvers). Each participant will receive his personal spirometer, which will be paired to one or more smartphones (participant's device, parents' device, or both). In a case of two or more participants from the same family, each spirometer will be paired to a separate smartphone. Detailed information regarding use and maintenance of the device will be provided in the form of a printed brochure and online resources available on the study web site [17].

Protocol

Tests will be performed according to American Thoracic Society/European Respiratory Society (ATS/ERS) standards [18]. The technique will be demonstrated by one of the investigators at enrollment, while detailed information will also be available through the online video resources on the study web site [17]. Measurements will be performed twice a day between 7 AM and 9 AM and between 7 PM and 9 PM. Each participant must perform at least 3 technically acceptable maneuvers. Completed measurements will be dispatched by the participants or their parents to a central database via email (encrypted pdf format).

Eligible children and adolescents will initially be asked to complete a run-in period of 10 days (20 trials) to assess their ability to perform technically acceptable spirometries (daily and at predetermined time frames), dispatch the measurements to the central database, and comply to investigators instructions. Those who will demonstrate satisfactory adherence will proceed to the main study consisting of daily measurements at predetermined time frames for a period of 3 months (90 days, 180 trials).

The expected duration of the study is 24 months and it will include two phases: Phase I and Phase II. Phase I will proceed

from January 2020 to September 2020 and will consist of assessments of lung function variability in healthy children and adolescents. Phase II will proceed from October 2020 to December 2021 and will consist of assessments of lung function variability in children and adolescents with asthma.

A flow chart of the study is presented in Figure 1. The protocol is in accordance with SPIRIT (standard protocol items: recommendations for interventional trials) guidelines (Figure 2).

Figure 1. Study flow chart.
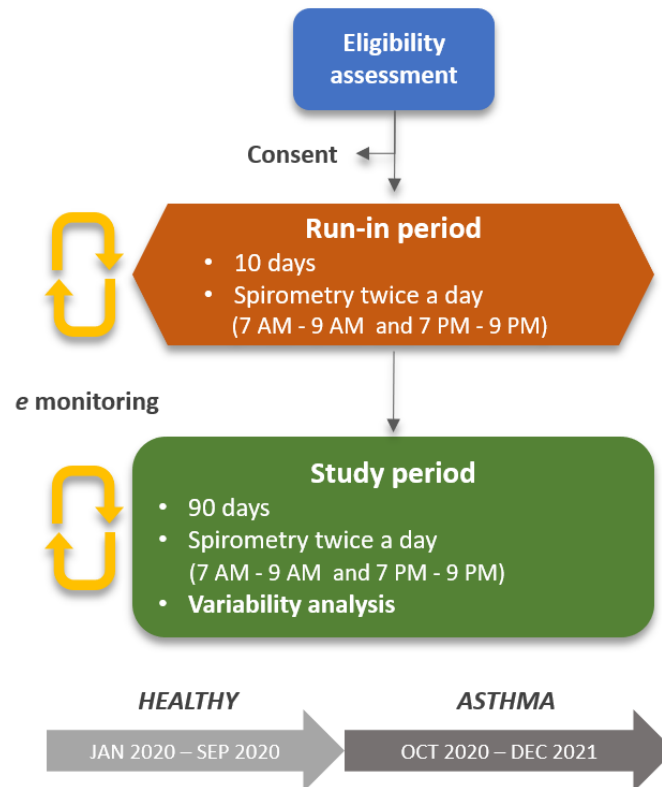
Figure 2. Standard protocol items: recommendations for interventional trials (SPIRIT) checklist.

TIMEPOINT	Enrolment JAN 2020 – SEPT 2021 *	Run-in period - 10 days	Study period JAN 2020 – DEC 2021			Close-out Day 91
			Month 1	Month 2	Month 3	
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation *	X					
INTERVENTIONS:						
Spirometry **		X	◄—————————►			
ASSESSMENTS:						
Height, weight	X			X		X
History	X					
Symptoms		X	◄—————————►			
Adherence		X	◄—————————►			X

* Phase I (January - September 2020): healthy children and adolescents; Phase II (October 2020 - December 2021): children and adolescents with asthma.
** Measurements with portable spirometers at home, twice a day, between 7 AM and 9 AM and then between 7 PM and 9 PM, dispatched to the central database via email.

Data Acquisition and Monitoring

PDF files will be downloaded and converted to text files using optical character recognition. PEF, FEV1, FVC, and FEF25-75 values, as well as quality grading of each measurement, will be recognized and introduced in a specific registry. The best PEF, FEV1, FVC, and FEF25-75 values among the technically acceptable trials for a given date and time will be identified and transferred from the registry to a participant-specific file.

Additionally, all registry data will be included in a monitoring table that presents the number of acceptable tests per day and time for each participant (Figure 3). PDF downloading and data acquisition will be performed automatically by special scripts implemented in MatLab (version R2019a; MathWorks Inc).

The monitoring table (Figure 3) will be reviewed twice a day (at 11 AM and 11 PM) and participants will be notified by direct telephone contact in case of inappropriate technique or missing measurements.

Figure 3. Example of the monitoring table presenting the number of acceptable tests per day/time point for each participant. Green cells: full adherence; orange cells: <3 acceptable measurements; red cells: missed measurements.

Participant ID	Date & Time Point							
	6/1/2020		7/1/2020		8/1/2020		9/1/2020	
	AM	PM	AM	PM	AM	PM	AM	PM
23s45f31	4	3	3	3	3	3	4	3
x124b451	3	3	2	3	4	3	4	4
3hg45679	3	3	3	4	0	4	3	3

Variability Analysis

Participant-specific files will be used for variability analysis, focusing primarily on the variability of PEF and FEV1 and secondarily on FEV1/FVC and FEF25-75. All variables will be transformed into percentage predicted values according to GLI normative data [16].

Lung function variability will be assessed in 3 ways: (1) standard variability indices, (2) detrended fluctuation analysis (DFA), and (3) sample entropy (SampEn).

Standard variability indices such as CV (defined as SD divided by the mean) will be used. To avoid any bias due to the presence of trends within the time series, CV will also be calculated as the average of 24 moving windows (length 14 measurements; step 7 measurements).

DFA is a method that has been widely used for the investigation of intrinsic correlation within time series [19]. Initially, the square root of the time series F(n) is calculated for segments of different (time) length n. A linear relationship in the logarithmic graph F(n) - log(n) indicates the existence of fractal architecture in the scaling of the specific data, while the slope a of the line describes the pattern of long-term fluctuations [19]. A change in daily variability of PEF or FEV1 results in a simultaneous deviation from the predetermined a value [6]. This deviation can easily be detected and quantified. It has been shown that the magnitude of a deviation reflects the likelihood of asthma exacerbation within the next month [6].

SampEn is a measure of increased irregularity or complexity, which relies on the identification of recurrent patterns within a nonstationary time series (ie, the probability that a series of points within the signal will repeat themselves at a subsequent time-point) [20]. Within a regular and less complex system, the frequency of sequence matches is high; therefore, the entropy is low. SampEn has emerged as a more reliable index of dynamic variability, mainly because it is relatively independent of the length of the time series [20].

Variability analysis will be performed in the MatLab environment.

Additional Data

Patients' characteristics (age, sex, place of residence, baseline lung function, allergies, comorbidities, type of medication, etc) will be recorded. The effect of these parameters on the pattern of lung function variability will also be explored.

Statistics

Normally distributed data will be presented as means (SD) and compared with Student's t test, while nonparametric data will be presented as medians with ranges and compared with the Mann-Whitney U test. A chi-square or Fisher exact test will be applied to compare different frequencies between the study groups. Multivariable linear regression analyses will be used to explore the effect of various parameters on lung function variability. All analyses will be performed with MatLab and SPSS software (version 25.0; IBM Corp).

Results

The study is funded by the "C. Caratheodory" Programme of the University of Patras, Greece (PN 47014/24.9.2018). It was approved by the Ethics Committee (decision 218/19-03-2019) and the Scientific Board (decision 329/02-04-2019) of the University Hospital of Patras, Greece.

Patient recruitment commenced in January 2020, and the trial is scheduled to end in January 2022. As of June 2020, 100 healthy children have been enrolled (74 of them have completed the measurements). The anticipated duration of the study is 24 months. The first part of the study, the assessment of lung function variability in healthy children and adolescents, will be completed in August 2020, and the results will be available for publication by October 2020.

Access to the study dataset will be limited to the investigators. After the analysis and publication of the results, the study database will be made available by the corresponding author upon reasonable request. Results will be published in peer-reviewed journals and will be presented in relevant conferences. Authorships will follow the Vancouver declaration.

Discussion

Increased lung function variability correlates with the frequency of respiratory symptoms in the general population [21] and is indicative of poor asthma control in patients with asthma [7-9,14].

Frey et al [6] applied DFA on 300 consecutive PEF values from a cohort of adults with asthma treated in a crossover manner with regular short-acting beta-2 agonists (SABA), regular long-acting beta-2 agonists (LABA), or placebo. They showed that long-term PEF variability was increased in the SABA phase, which meant that there were several periods of decreased lung function (increased vulnerability and high probability of exacerbation). Conversely, PEF variability was decreased during the LABA phase, signifying that lung function remained persistently within normal limits (decreased vulnerability and low probability of exacerbation). Thamrin et al [8] showed that the self-similarity of PEF values over time correlates well with the loss of asthma control within two weeks following the withdrawal of inhaled corticosteroids. Their findings were later corroborated by Kaminsky et al [14] in a large clinical trial of adults with asthma under controller therapy. Thamrin et al [22] have also demonstrated that the probability of asthma exacerbation at the individual level can be estimated by combining the autocorrelation properties of PEF over time with the absolute PEF value at a specific time point, indicating that both are significant for predicting a loss of disease control in the near future.

Regarding SampEn, Veiga et al [23] found that the entropy of airflow time series was reduced in subjects with asthma compared to healthy controls; lower entropy was associated with more severe airflow obstruction (forced oscillations technique) in that study. More recently, Dames et al [24] investigated the entropy of airflow in patients with chronic obstructive pulmonary disease (COPD) and reported that the

SampEn of airflow during resting breathing decreased in proportion to the degree of airway obstruction. Similar data in children and adolescents with or without asthma are lacking.

To remain stable yet adaptable to change, any physiological system needs to balance between order and chaos [25]. Asthma appears to be associated with increased order (reduced complexity) and increased variability of lung function, resulting in wide fluctuations that may lead to periods of increased vulnerability and reduced adaptability to a changing environment [26]. From a clinical standpoint, these features translate into more frequent exacerbations and poor control of the disease.

Thus, when properly quantified, changes in lung function over time may reflect both past and future control of asthma [26].

Healthy children and adolescents may present normal short- and long-term fluctuations in lung function; the pattern of this variability may be influenced by age, sex, and environmental conditions. Significant lung function variability may also be present in children and adolescents with asthma, but the patterns may differ from those observed in healthy children and adolescents. Such data would improve our understanding regarding the chronobiology of asthma and may permit the development of integrated tools for assessing the level of control and risk of future exacerbations.

Acknowledgments

Authors' Contributions

SF and MBA designed this protocol and revised the manuscript. ESF and IT drafted the manuscript and participated in the design of the study. DG, NK, GC, and PP helped with manuscript drafting and revision. ESF, DG, NK, and GC will enroll participants and assign participants to the interventions. ESF, IT, and PP will be involved in data collection and study monitoring. SF and MBA act as study supervisors. All authors read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Funding Approval.
[PDF File (Adobe PDF File), 1775 KB - resprot_v9i8e20350_app1.pdf]

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Abbreviations

COPD: chronic obstructive pulmonary disease
CV: coefficient of variation
DFA: Detrended Fluctuation Analysis
FEF25-75: forced expiratory flow between 25% and 75% of FVC
FEV1: forced expiratory volume at 1 second
FVC: forced expiratory capacity
GLI: Global Lung Initiative
LABA: long-acting beta-2 agonists
PEF: peak expiratory flowSampEn: Sample entropy
SABA: short-acting beta-2 agonists

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Evaluation of the Universal Prevention Program Klasse2000 in Fourth Grade Primary School Children: Protocol for a Propensity Score-Matching Approach

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Abstract

Background: Klasse2000 is the most widely adopted school-based prevention program in Germany. It addresses health promotion, addiction, and violence prevention in primary schools. As a universal prevention program, it has reached more than 1.4 million German children in the past 25 years.

Objective: The effectiveness of Klasse2000 will be evaluated with a large representative survey among students. Students who have participated in the prevention program (intervention group) will be compared with students who did not participate (control group). The comparison will cover the following outcome domains: well-being, self-esteem, emotion regulation, food habits, behavioral problems, and school and classroom atmosphere. Furthermore, victimization and perpetration regarding bullying, alcohol consumption, smoking, and media consumption are assessed.

Methods: To control for potential group differences, treatment effects will be estimated using propensity score-matching, which matches students from the intervention and control groups based on an identical propensity score or a propensity score that does not differ by more than a previously defined distance. The treatment effect will then be estimated in the matched sample taking the matching process into account.

Results: Enrollment of schools began in March 2017. A total of 6376 students participated in the survey (n=4005 in control group; n=2371 in Klasse2000). The parent survey was returned by 52.13% (3324/6376) of parents. Results are expected in mid-2020.

Conclusions: The results on the effectiveness of the Klasse2000 prevention program will form an empirical basis for legitimizing universal prevention programs and for planning future prevention approaches.

Trial Registration: German Clinical Trials Register DRKS00014332; https://tinyurl.com/y2trvq4p

International Registered Report Identifier (IRRID): DERR1-10.2196/14371

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Introduction

Health Risks of Children and Adolescents

Although most children in Germany can be regarded as physically and mentally healthy, there are numerous studies that report alarming findings regarding pediatric health risks. The study of the health of children and adolescents in Germany (KiGGS), for example, reports that 15.0% of all primary school children are overweight. Among these, 6.4% require treatment due to obesity [1]. According to a Bundeszentrale für Gesundheitliche Aufklärung (BZgA) study, 10.6% of adolescents aged 12 to 17 years consume alcohol at least once per week, and 14.1% drink excessively at least once per month (equaling four glasses of liquor per occasion in girls and five glasses in boys) [2]. Furthermore, 9.7% of adolescents aged 12 to 17 years smoke [2]. Over 20% of children and adolescents aged 7 to 17 years suffer from mental health issues, the most prevalent being behavioral problems, anxiety, and depression [1]. An increase in mental health issues in children and adolescents has been associated with a decreased health-related quality of life [3]. Children with behavioral problems such as noteworthy results on the Strength and Difficulties Questionnaire (SDQ) [4,5] show a lower quality of life compared with children who score within the normal range [3].

Another important health-related aspect is bullying and school-based violence. A German representative survey among students from the years 2007 and 2008 showed that a significant number of 15-year-olds had been violent offenders in the previous school year. For example, 24.2% of students had hit or kicked fellow students, 34.3% had purposefully ignored others, and 51% had more than once picked on another student or said mean things [6]. Another study on violence among 9th graders in the German federal state of Lower Saxony revealed that in 2015, 17.2% of students had suffered from physical violence in the previous school year, 45.0% had been the victim of bullying, and 11.4% had encountered vandalism [7]. In a survey among 4th graders in Berlin, 33.0% of boys and 13.0% of girls showed aggressive behavior, indicating they had either hurt or threatened fellow students, committed vandalism, or played with fire [8].

According to the life skills approach [9], problematic behaviors in different domains are related and have a common cause. Life skills can be defined as skills that enable appropriate behavior in interactions with others and the ability to handle problems and stressful situations [10]. Prevention measures that are based on the life skills approach thus focus on health promotion and on strengthening the children's social and personal resources in order to prevent addiction and violent behavior.

Klasse2000 Program

The primary goal of the Klasse2000 program is the promotion of a healthy lifestyle in parents, children, and teachers as well as other youth workers involved in leisure activities [11]. Klasse2000 has reached over 1.4 million children in the past decades and can therefore be regarded as the most widely adapted school-based prevention program for the promotion of health and the prevention of addiction and violent behavior in German primary schools [11]. In Lower Saxony (a state in northwestern Germany with a population of about 8 million), about 2800 primary school classes with 60,000 students participated in the school year 2015-2016. This corresponds to 19.4% of the Lower Saxony student population [11,12]. The program was developed in 1991 at the Klinikum Nuremberg by an interdisciplinary workgroup around Dr Pál Bölcskei [11]. The program is sponsored by a nonprofit organization funded by donations [11].

Domains Addressed in the Klasse2000 Intervention

For the promotion of general health and life skills, Klasse2000 addresses the following domains:

- Healthy food and beverage choices
- Exercise and relaxation
- Positive self-image and friendships
- Solving problems and conflicts
- Critical thinking and saying no (especially to alcohol and tobacco)

Specially trained Klasse2000 health promoters (with backgrounds in health care and/or education) visit the classrooms and introduce new focus areas to the lesson plan (1st grade: 2 visits; 2nd to 4th grade: 3 visits per school year). After these visits, the teacher further discusses these topics and includes them in the regular curriculum (10 to 12 units per school year) using detailed aids such as lesson guides, student worksheets, posters, CDs, and parent information material, etc.

Furthermore, Klasse2000 includes various interactive components such as games, visits by the health promoter, visits from the mascot, KLARO (Figure 1), and special material such as a breathing coach, stethoscopes, and feeling diaries. Klasse2000 targets all students hence no special registration is required. Participation is free for schools, children, and their parents. This approach ensures that children from families at risk who have a particular high need for prevention (such as children from families with a low socioeconomic or migration background) are equally reached [12].

Figure 1. Mascot KLARO.

The parents are included using a parent newspaper, information meetings, and a yearly information letter (available in several languages). Of special importance are research tasks for the children that are accompanied by take-home material. These reinforce the topics addressed at school in the home environment. To account for individual differences, especially regarding special needs children or classes spanning varying grade levels, all student material is available for various levels of ability. The aim is to provide each child with appropriate worksheets that are neither too boring nor beyond the student's capabilities [12]. The contents of the program are explained using the symbol figure, KLARO (Figure 1). The program developers outline the chain of the effects of the program as shown in Multimedia Appendix 1 and mention the following intended intervention effects:

- Children know their body and know what they can do to promote health and well-being, for example, regarding nutrition, exercise, and relaxation
- Children perceive health as important and are confident that they can contribute to their own health
- Children possess important life skills such as handling emotions and stress, communicating and cooperating with others, solving conflicts and saying no (eg, to alcohol and tobacco)

Current Research Results From the Klasse2000 Prevention Program

The Klasse2000 program has previously been evaluated by the University of Bielefeld and the Institute for Therapy and Health Research (IFT-Nord). The University of Bielefeld conducted four consecutive surveys in primary school children. In their evaluation study with a randomized waiting control group design, they concluded that the dietary behavior has worsened considerably less in the intervention group. Regarding exercise, they could merely conclude that the commute to school became more passive in control group children. Furthermore, it became apparent that baseline well-being had been very high, not allowing for the detection of any differential effects. According to the parents' perspective, the children in the intervention group had less frequently become victims of violence [13].

A study by IFT-Nord compared Klasse2000 participants to a control group of nonparticipating students in a nonrandomized control group design. Assessment took place during primary school years as well as 16 months and 3 years after the intervention. A positive effect of the Klasse2000 program on the incidence and life-time prevalence of smoking could be observed in the first and second follow-up [14,15]. A reduction in alcohol consumption was only observed immediately after the intervention and in the first follow-up. Nevertheless, the intensity of alcohol consumption among those children with previous alcohol exposure was lower in the intervention group [16]. Furthermore, health-related knowledge and classroom atmosphere were rated higher in the intervention group [17]. During primary school years, internalizing and externalizing behavioral problems were significantly reduced in classrooms participating in the Klasse2000 intervention [17]. Students participating in the intervention could be characterized as more frequently seeking social support when dealing with stress and attempting to resolve unpleasant emotions by cognitively addressing the potential root of the problem. Intervention and control groups did not differ on other health-related behavior, health-related attitudes, and life skills in the 3-year follow-up [15].

Aim of the Evaluation

This study protocol outlines an evaluation study of the Klasse2000 intervention. Short-term effects on all four target areas are investigated via a survey among 4th grade primary students, their parents, teachers, and school principals. The evaluation of the prevention program Klasse2000 in Lower Saxony (official study title: Evaluation des Präventionsprogrammes Klasse2000 in Niedersachsen) is funded by the BZgA.

Role of Study Sponsors

The evaluation study can be subdivided into 6 domains: (1) training of test administrators, (2) correspondence with school principals, (3) school survey, (4) data preparation and integration, (5) data analysis, and (6) dissemination of results. The sponsoring institution Kriminologisches Forschungsinstitut Niedersachsen (KFN, Criminological Research Institute of

Lower Saxony) is involved in all domains, and the State Police College of Baden-Wuerttemberg is involved in domain 1. An overview of the evaluation schedule can be found in Multimedia Appendix 2. The protocol is furthermore documented according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT; Multimedia Appendix 3).

Methods

Sample and Sampling

In this evaluation study, 4th graders were assessed on the classroom level. Since 19.4% of students in Lower Saxony participate in the Klasse2000 program, it seemed feasible to base group comparisons on a sufficiently high number of students [11]. For this evaluation, a random representative sample of 600 classes was drawn out of a total of about 4000. Based on the current implementation rate of the Klasse2000 program, it was expected that around 120 of the 600 randomly selected schools were participating in the program. To ensure a sufficient rate of participating primary Klasse2000 classrooms, 140 additional classrooms known to have participated in the program were randomly selected and added to the sample (oversampling). In addition to surveying the 4th grade students of participating and nonparticipating classes, parents, teachers, and school principals were assessed. Overall, we aimed for the total sample to consist of 8000 students and their parents.

Ethical Approval and Consent to Participate

The evaluation as described in this protocol has been approved by the ethics committee of the Georg Elias Müller Institute for Psychology at the Georg August University Göttingen (Multimedia Appendix 4). Furthermore, the survey was approved by the regional school authorities (Landesschulbehörde Niedersachsen H1Rb-81402-09-2017; Multimedia Appendix 5). Participation is entirely voluntary among principals, teachers, parents, and children, and nonparticipation does not lead to any negative consequences. Children whose parents have not provided written informed consent are not surveyed. Teachers administered the written informed consent forms, did not forward them to the researchers, and destroyed them 2 weeks after the survey was conducted. Since the study design provides for complete anonymization, no signature of the participating adults could be obtained for their own participation. There was no intermediary person like a teacher who could have managed the written informed consent forms, since the adult questionnaires were sent directly to the KFN. The adults gave approval for the participation in the study by sending the completed questionnaire to the institute. If a participant demands the deletion of their answers, this can be achieved up until the point the personal code (see heading Parent survey) is deleted. From then on, the data are completely anonymous and cannot be traced to an individual.

The study was registered March 22, 2018, with the German Clinical Trials Register [DRKS00014332]. The main sponsor of the study is the KFN (primary investigator SK). Furthermore, the KFN cooperates with TM of the State Police College of Baden-Wuerttemberg.

Selection Criteria

All primary schools located in Lower Saxony and providing general education were part of the sample population. A complete list for sampling was obtained from the national office for statistics of Lower Saxony. It was not assessed whether the schools participated in any other prevention programs apart from Klasse2000. Any other prevention measures of a general or specific nature were regarded as the standard the Klasse2000 prevention program should be contrasted with. The adherence to the Klasse2000 protocol was also not essential for eligibility as this evaluation is explicitly interested in assessing the treatment effect on an intention-to-treat basis.

Procedure

Administrator Training

Test administrators underwent several hours of training by the project staff of the Klasse2000 evaluation at the KFN. The training covered general information on the study, survey contents, coordination of scheduling the individual survey appointments, and professional behavior toward teachers and students. Test administrators received detailed instructions on the survey tools to ensure a standardized procedure. All test administrators were blinded regarding intervention versus control group membership of the relevant classrooms.

Enrollment

The schools of the selected classes were contacted by postal mail addressed to the school principal (Multimedia Appendix 6). In this initial letter, the principals were informed about the survey's contents, potential scheduling, and which classes had been selected for participation in the evaluation study.

Student Survey

The student survey was conducted in a classroom context in the presence of the teacher using standardized questionnaires. A trained test administrator guided the children through the questions with the help of a fully standardized testing manual (about 28 pages). At the beginning of the survey, the children were informed of the content and nature of the questions. They were told that their participation is entirely voluntary and anonymous and that nonparticipation would not yield any negative consequences. The majority of questions and possible answers were read aloud and explained by the test administrator. Additionally, the corresponding pages were shown on a screen using an overhead or video projector. After the survey, the questionnaires were collected by the test administrator. To ensure anonymity, student and teacher questionnaires were sealed in an envelope on site and sent to the KFN by mail. Details on the assessment tools can be found in Multimedia Appendix 7.

In accordance with the World Medical Association Declaration of Helsinki, the parents and children who took part in the study were informed about our institution, the voluntary nature, aims, methods, and financing of the study by means of a parent information letter prior to the survey being conducted (Multimedia Appendix 8). The information letter stated they had the right not to take part in the survey and that there were no disadvantages if they did not participate. The same

information was provided to teachers and headmasters in the letter to the principal (Multimedia Appendix 6).

Parent Survey

After the student survey was conducted, the children were asked to give an envelope with the parent questionnaire and a return envelope with prepaid postage to their parents. The parents could return the completed questionnaire directly to the KFN by mail. Due to the study design that provides for complete anonymization and therefore no collection of real names, no signature of the participating adults could be obtained. Parents, teachers, and principals decided on their own participation by sending the completed questionnaire to the institute. To match the children's and the parents' questionnaires, the children wrote a code on their parents' questionnaire. This code is only used for matching and does not include any identifiable information. After the matching has been performed, this code will be deleted, rendering the final data completely anonymous. Due to anonymity, parents cannot be reminded to return the questionnaires nor are any incentives offered for participation.

Data Handling and Monitoring

Data assessment and management is completed by the KFN data protection official. The data protection official is employed directly by the KFN and has neither monetary nor scientific involvement in the project. All project staff members were obliged to uphold data protection rules and regulations. Participants do not reveal their names at any point in the study. The students provide their month of birth, age, and gender. The parents provide the same information, which will be used for matching should matching via the matching code not be possible. Children and their parents can be matched to a school by a field code. This field code is necessary to determine whether a school participates in the Klasse2000 program without endangering the blinding of the test administrators. After successful matching of parents, children, principals, and schools, all corresponding field codes are deleted. The data are then fully anonymous (ie, the school name can no longer be inferred from the cases).

Evaluation of Effectiveness

It is of special interest whether the underlying constructs are based on the direct efficiency hypothesis of the Klasse2000 program (primary outcome) or based on an efficiency hypothesis but one that must be regarded as less probable than the primary outcome (ie, secondary outcome). For some outcomes (such as alcohol and tobacco consumption), the expected prevalence is generally low.

The evaluation focuses on the following research questions:

- Research question 1 (well-being; primary outcome domain): How does participation in the Klasse2000 prevention program influence children's well-being?
  - Hypothesis 1.1: The prevention program Klasse2000 has a positive influence on the children's well-being.
  - Hypothesis 1.2: The prevention program Klasse2000 has a positive influence on the children's self-esteem.

- Hypothesis 1.3: The prevention program Klasse2000 has a positive influence on the children's emotion regulation.
- Hypothesis 1.4: The prevention program Klasse2000 reduces the severity of behavioral problems.

- Research question 2 (health-related behavior; primary outcome domain): How does participation in the Klasse2000 prevention program influence children's health-related behavior?
  - Hypothesis 2.1: The prevention program Klasse2000 increases fruit and vegetable consumption.
  - Hypothesis 2.2: The prevention program Klasse2000 increases the consumption of water and unsweetened tea.
  - Hypothesis 2.3: The prevention program Klasse2000 decreases the consumption of sweets, salty snacks (eg, chips, pretzels), and sweetened beverages.
  - Hypothesis 2.4: The prevention program Klasse2000 increases the time children spend exercising.

- Research question 3 (school and classroom atmosphere, school-based conflicts, and violence; primary outcome): How does participation in the Klasse2000 prevention program influence the school and classroom atmosphere and school-based violence?
  - Hypothesis 3.1: The prevention program Klasse2000 has a positive influence on the school and classroom atmosphere.
  - Hypothesis 3.2: The prevention program Klasse2000 decreases the probability of engaging in bullying.
  - Hypothesis 3.3: The prevention program Klasse2000 decreases the probability of becoming a victim of bullying.

- Research question 4 (media use; secondary outcome): How does participation in the Klasse2000 prevention program influence media use?
  - Hypothesis 4.1: The prevention program Klasse2000 decreases the time spent on media.
  - Hypothesis 4.2: The prevention program Klasse2000 decreases the probability of watching movies with an age rating of 16 or 18.
  - Hypothesis 4.3: The prevention program Klasse2000 decreases the frequency of watching movies with an age rating of 16 or 18.
  - Hypothesis 4.4: The prevention program Klasse2000 decreases the probability of playing video games with an age rating of 16 or 18.
  - Hypothesis 4.5: The prevention program Klasse2000 decreases the frequency of playing video games with an age rating of 16 or 18.

- Research question 5 (alcohol and tobacco consumption; secondary outcome): How does participation in the Klasse2000 prevention program influence the children's alcohol and tobacco consumption?
  - Hypothesis 5.1: The prevention program Klasse2000 decreases the probability of drinking alcohol.
  - Hypothesis 5.2: The prevention program Klasse2000 decreases the frequency of alcohol consumption.

- Hypothesis 5.3: The prevention program Klasse2000 decreases the probability of smoking cigarettes.
- Hypothesis 5.4: The prevention program Klasse2000 decreases the smoking frequency.

Details on the assessment tools can be found in Multimedia Appendix 7.

Data Analysis

The decision to participate in the Klasse2000 program is made at the school level. Hence, schools self-select for implementing the intervention. This selection bias must be controlled for when comparing the outcomes of children participating in the Klasse2000 and those who did not. The gold standard for preventing selection bias is randomization. There are three major factors that made a randomized trial highly infeasible for this evaluation: (1) as a general intervention, the Klasse2000 targets a high number of outcomes, (2) effect sizes in universal prevention programs can be expected to be rather small, (3) the intervention is implemented during the entire primary school time (ie, over a time span of 4 years). Hence, a very high number of schools would need to be randomized to participate in an intervention over several years. An attractive alternative to an randomized controlled trial is a natural experiment. However, the Klasse2000 is implemented all over Germany, and there are no immediately comparable intervention programs. Hence, neither regional implementation nor the comparison of a comparable program lend themselves for overcoming selection bias. Given these circumstances, a propensity score-matching approach will be implemented as a feasible alternative. The basic idea of a matching approach is as follows: for each student who is currently participating in the Klasse2000 program, a control student will be selected who matches the treatment group participant as closely as possible regarding criteria that are relevant yet unrelated to the participation in the prevention program (ie, gender, socioeconomic status). The matching will be performed with a matching algorithm that assigns weights to each individual in the control group (ie, inverse probability weighting). The estimation of treatment effects will be completed using regression-based analyses that take these weights into account. Simulation studies show that the propensity score-matching approach enables an unbiased estimation of intervention effects [18].

Prior to analysis, data will be checked for outliers, inconsistencies, and possible transformation. We predict that our sample size will be large enough for our statistical tests to be robust regarding nonnormally distributed variables. Power analyses (ie, a priori) based on a type I error rate (false positive) of $\alpha=.05$, statistical power of $1-\beta=.80$, and a minimum detectable effect size of ES=0.2 resulted in a required sample size of n=310 (1-tailed) students in each group (intervention and control).

Missing data will be handled using state-of-the-art imputation techniques (multiple imputation in missing non-at-random scenarios [ie, by parametric recursive partitioning] [19,20]). Wherever earlier findings suggest differential effects (ie, regarding gender), subgroup analyses of the above-mentioned hypotheses will be performed. Furthermore, post hoc analyses of different implementation factors potentially contributing to positive treatment effects over time will be conducted.

Dissemination

Study results will be disseminated in a final report for the funder (BZgA), who will further disseminate the findings in their own publications. In addition, findings will be submitted to suitable peer-reviewed journals.

Results

Trial Status Upon Initial Protocol Submission

Schools were first contacted in March 2017. Between April and June 2017, students and teachers were surveyed. Teachers and principals returned their questionnaires by mail resulting in questionnaires being returned by mail until November 2017. Data entry and cleansing began in May 2018 and was estimated to take until mid-2019.

Trial Status Upon Submission of Protocol Revision

During the period this protocol was under revision, data integration was completed. Data integration included linking the child and parent data. Matching was performed with the help of the codes. Figure 2 presents the final number of participants and details on nonparticipation. All 6376 participating children were supplied with a questionnaire for their parents. We received 3324 completed questionnaires which corresponds to a response rate of 52.13%. Of the control group, 52.91% (2119/4005) of parents participated in the survey, whereas 50.82% (1205/2371) of parents of the Klasse2000 group returned the questionnaire. Data analysis is ongoing with only descriptive statistics extracted so far. Beyond the descriptives regarding participation, we analyzed the feedback from the test administrators to confirm data quality. Furthermore, the following demographics were obtained: 50.57% (3140/6352) of the children were female. The average age was 10 (SD 0.62) years. The parent survey was mostly completed by a female parent (2899/3259, 88.95%). The parents completing the survey were on average 42.6 years old. Hypothesis-related results are neither obtained nor published upon resubmission of the protocol to ensure transparent reporting and analyses practices.

Figure 2. Sampling procedure, participation, and nonparticipation in the Klasse2000 evaluation study.
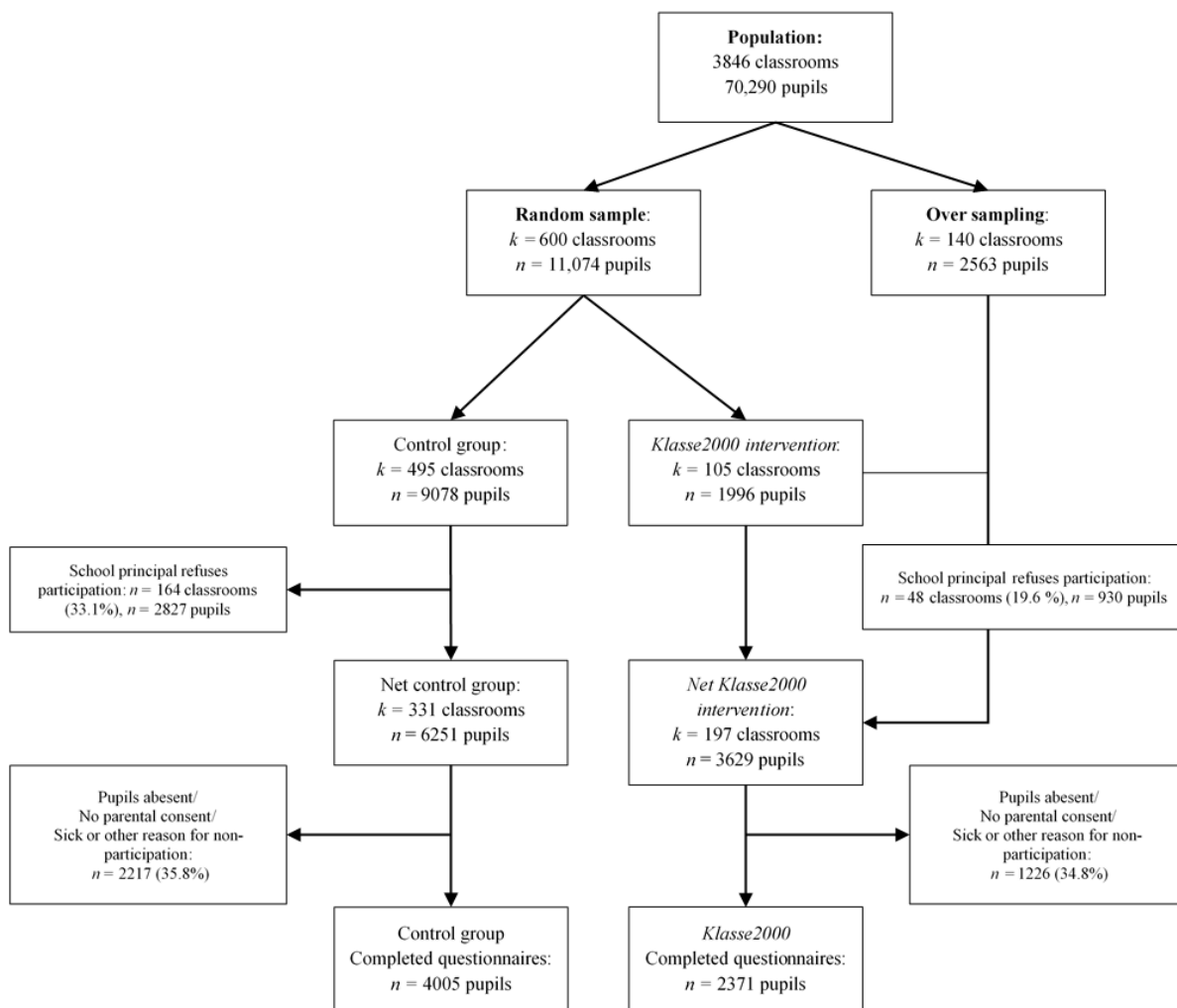
Discussion

Summary

The aim of the study is a large-scale evaluation of the effectiveness of the Klasse2000 prevention program. The effects of the program as implemented in the field shall be evaluated using a representative sample. As a randomized design was not feasible within the framework of this evaluation, a propensity score-matching approach is used to control for potential selection bias.

Intervention effects in the following domains are assessed: well-being, health-related behavior, classroom atmosphere, school violence, alcohol and tobacco consumption, and media use. These domains are investigated from the perspective of the students and their parents. Klasse2000 is a large universal prevention program. It is financially supported with donations from well-known institutions such as health care providers and banks and endorsed by experts of national recognition [21]. The program has received the highest possible rating category from the green list prevention provided by the Crime Prevention Council of Lower Saxony. Furthermore, it has received several

awards [21]. Given this high status, the results of this study potentially have far-reaching consequences not only for the program at hand but, depending on the nature of results, on other preventions with similar target areas. It is likely that this evaluation will not confirm all hypotheses stated in this protocol. The failure to find and intended intervention effect might be due to a lack of effect or the presence of a meaningful but undetectable effect. Should the intervention fail to produce some of the desired effects, it might warrant improvement. The materials of the Klasse2000 intervention are regularly updated. These updates attempt to improve support for teachers in the implementation, communication with parents, and communication of teaching content to the students. Recent updates include, for example, content for DigiBoards (Digi International) and an interactive website for the students; further digitalization and extension of online health-related content is planned [21]. Depending on the areas that might warrant improvement, successful concepts from eHealth interventions might provide fruitful starting points. Through the wide implementation of the Klasse2000 program, even small effects might be of value from a public health perspective. Future evaluation studies might want to address this issue using assessment tools that assess the targeted health-related behaviors

more reliably. Expertise with mobile assessment from the eHealth domain could help future evaluations to quantify small effects.

As outlined in the introduction, this evaluation is part of an ongoing evaluation effort of the Klasse2000 intervention. With the timepoint of evaluation in the 4th grade, this evaluation addresses short-term effects. To tentatively quantify medium-term effects, results from a student survey among 9th grade students will be used. The study among 9th grade students did not specifically focus on the target areas but assessed similar domains relating to criminal and health-related behavior. Students from the 9th grade survey indicated whether they had participated in the Klasse2000 prevention program when they attended primary school.

Limitations

The main limitation of the study is the missing randomization. The main problems of missing randomization are potential selection effects at the school level. Schools that are problem-prone might be more likely to participate in the Klasse2000 program, hoping that participation might reduce prevailing problems. On the other hand, the exact opposite might also be the case. Schools that can be characterized as especially committed and dedicated might decide to participate in the Klasse2000 program. Such selection effects might be counterbalanced with the propensity score-matching approach. It should also be noted that the study design does not include any measurement prior to the intervention. This is a cross-sectional survey that can identify correlations but cannot map causal relationships. The results should be checked within the framework of a longitudinal study design and a preliminary survey and offer necessary space for future research projects.

Authors' Contributions

SK and YK drafted the protocol. AL and TM revised the draft critically for important intellectual content. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Chain of effects of Klasse2000.
[DOCX File , 28 KB - resprot_v9i8e14371_app1.docx]

Multimedia Appendix 2
Schedule of enrollment and assessments.
[DOCX File , 19 KB - resprot_v9i8e14371_app2.docx]

Multimedia Appendix 3
Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist.
[DOCX File , 38 KB - resprot_v9i8e14371_app3.docx]

Multimedia Appendix 4
Ethics approval.
[PDF File (Adobe PDF File), 271 KB - resprot_v9i8e14371_app4.pdf]

Multimedia Appendix 5
Approval of the state school authority.
[DOCX File , 21 KB - resprot_v9i8e14371_app5.docx]

Multimedia Appendix 6
Letter to the school principal.
[DOCX File , 128 KB - resprot_v9i8e14371_app6.docx]

Multimedia Appendix 7

Assessment tools.
[[DOCX File , 37 KB](#) - [resprot_v9i8e14371_app7.docx](#)]

Multimedia Appendix 8
Parent information letter.
[[DOC File , 75 KB](#) - [resprot_v9i8e14371_app8.doc](#)]

Multimedia Appendix 9
Grant letter.
[[DOCX File , 13 KB](#) - [resprot_v9i8e14371_app9.docx](#)]

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Abbreviations

BZgA: Bundeszentrale für Gesundheitliche Aufklärung (Federal Center for Health Education)
IFT-Nord: Institut für Therapie- und Gesundheitsforschung (Institute for Therapy and Health Research)
KFN: Kriminologisches Forschungsinstitut Niedersachsen (Criminological Research Institute of Lower Saxony)
KiGGS: Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland (Study of the Health of Children and Adolescents in Germany)
SDQ: Strength and Difficulties Questionnaire (German version)
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

Protocol

Aftercare of Childhood Cancer Survivors in Switzerland: Protocol for a Prospective Multicenter Observational Study

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Abstract

Background: Most children and adolescents diagnosed with cancer become long-term survivors. For most of them, regular follow-up examinations to detect and treat late effects are necessary, especially in adulthood. The transition from pediatric to adult-focused follow-up care is a critical moment for childhood cancer survivors (CCSs); a substantial proportion of CCSs are lost to follow-up in this transition process and do not attend follow-up care in adulthood. This can have serious effects on survivors' health if late effects are not discovered in a timely fashion.

Objective: In this study, we primarily assess the current follow-up situation, related needs, and knowledge of adolescent and young adult CCSs who have transitioned from pediatric to adult-focused follow-up care. As secondary objectives, we evaluate transition readiness, identify facilitating factors of transition and adherence to long-term follow-up (LTFU) care, and compare three different transition models.

Methods: The Aftercare of Childhood Cancer Survivors (ACCS) Switzerland study is a prospective, multicenter, observational study that was approved by the ethics committee in February 2019. We are recruiting CCSs from three pediatric oncology centers and using questionnaires to answer the study questions.

Results: To date, we have recruited 58 participants. The study is ongoing, and recruitment of participants will continue until January 2021.

Conclusions: The ACCS study will provide information on CCSs' preferences and expectations for follow-up care and their transition into the adult setting. The results will help improve the LTFU care and cancer knowledge of CCSs and subsequently enhance adherence to follow-up care and reduce loss to follow-up in adulthood.

Trial Registration: ClinicalTrials.gov NCT04284189; https://clinicaltrials.gov/ct2/show/NCT04284189?id=NCT04284189

International Registered Report Identifier (IRRID): PRR1-10.2196/18898

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Introduction

Background

Most children and adolescents diagnosed with cancer become long-term survivors and need lifelong follow-up care [1]. Childhood cancer survivors (CCSs) are vulnerable to physical and psychosocial chronic medical conditions, so-called late effects. Some late effects are characteristic of CCSs, while most of them are also associated with aging in the general population but develop earlier in CCSs. Three out of four 5-year CCSs treated between 1966 and 1996 with a median follow-up time of 17 years experienced at least one late effect, 37% of which may be life threatening [2]. The goal of follow-up care is to detect late effects early and to intervene, treat, or slow their progression. Finally, follow-up care aims to reduce the burden of late effects and improve CCSs' quality of life. Studies show that long-term follow-up (LTFU) care improves the detection of late effects and survivors' health behavior and knowledge, encourages health care use, and decreases survivors' distress levels [3].

As CCSs reach adulthood, questions and issues arise that pediatric oncologists are no longer expert in addressing and, therefore, adult physicians are needed. This process of change in health and follow-up care is known as transition. Transition has been described as the planned movement of adolescent and young adult (AYA) patients with chronic health conditions from child-centered to adult-oriented health care systems. The preparation of adolescents for transition should start several years before the actual transition occurs. Adolescents need to acquire the knowledge and skills to assume independent responsibility for their health care in the adult system. The process of transition ideally should address medical, psychosocial, and vocational needs. During transition, care shifts from family-centered pediatric to independent patient-centered health care as survivors enter adulthood. The transition of CCSs is a critical moment in LTFU care that may affect survivors' LTFU clinic attendance and may cause loss to follow-up [4-7]. There is a clear and steady decrease in the proportion of CCSs who attend a clinic visit as time since treatment completion increases [4]. This is particularly concerning since CCSs are at greater risk of late effects as time passes [8,9]. One reason for loss to follow-up seems to be CCSs' lack of knowledge regarding their diagnosis, treatment, and risk of developing late effects [10,11]. This factor can be influenced by educating CCSs. Another reason is the lack of knowledge about late effects and the need for further follow-up examinations with adult physicians who should provide this care [12].

To date, it is not clear which transition and LTFU care model is the best based on the existing health care system. Many different models of LTFU care exist: (1) models calling for transition to primary care physicians, (2) shared-care models with LTFU care provided by the primary care physician in collaboration with the oncology team, (3) models suggesting transition from pediatric to adult oncologists, or (4) models proposing transition to specialized LTFU clinics, which provide LTFU care in multidisciplinary teams [13,14]. In addition to the debate surrounding the model of LTFU care, there is debate on the right time point of transition. Some study groups have developed and used scores to assess the transition readiness of AYA patients with chronic diseases, such as inflammatory bowel disease [15], cystic fibrosis [16], or congenital heart disease [17]. Klassen et al developed tools to assess CCSs' readiness for transition [18], and Schwartz et al are currently developing a Transition Readiness Inventory Item Pool, which measures socioecological components relevant for successful transition [19]. However, evidence collected prospectively during the transition process addressing the needs of young adult CCSs during their transition into adult LTFU care in different settings is limited.

Nine pediatric oncology centers treat children and adolescents up to the age of 18 years diagnosed with cancer in Switzerland. Like the initial treatment, follow-up care is provided in these nine centers until at least the age of 18 years and usually for longer. A recent survey including the division head or the responsible staff physician for follow-up care of each of the nine centers showed differences in follow-up care between centers, especially concerning transition [20]. These differences were also noted in the current position statement from the Pediatric Swiss Long-Term Follow-Up Working Group [21]. This working group aims to achieve harmonization between the centers. Both publications reflect the current situation of physicians in Switzerland, but the needs of Swiss CCSs are still unknown.

Objectives

The primary objectives of the Aftercare of Childhood Cancer Survivors (ACCS) Switzerland study are to assess the current follow-up situation, related needs, and knowledge of AYA survivors of childhood cancer undergoing LTFU care transitions from pediatric to adult-focused follow-up care. By including three pediatric oncology centers with different transition and LTFU care models, we aim to investigate which model or which parts of the models have the best fit for Swiss CCSs. As secondary objectives, we aim to evaluate the transition readiness of CCSs, identify facilitating factors for transition and adherence to LTFU care, and compare the transition models of the three participating centers. The results of this study are intended to serve as a basis to improve transition and LTFU care in Switzerland and could be transferrable to countries with similar health care systems.

Methods

Study Design

The ACCS study is a prospective, multicenter, observational study and is registered at ClinicalTrials.gov (NCT04284189).

Setting: Transition and LTFU Care Models in Participating Clinics

We included three pediatric oncology centers with different transition and LTFU care models—Center 1: Department of Pediatrics, Kantonsspital Luzern; Center 2: University Children's Hospital Basel; and Center 3: Department of Pediatrics, Kantonsspital Aarau. All three centers are very similar in terms of the geographical catchment area, number of

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new diagnoses per year, and location of the adult hospital on the same campus. Center 1 refers most CCSs to the primary care physician but does not systematically make these referrals when CCSs reach a certain age or time since the completion of treatment. Some CCSs with already symptomatic late effects are transitioned to adult oncology. Center 2 transitions all CCSs to adult oncology and has done so since 2014. Their model includes one joint visit at the age of 18 years during which the adult oncologist or hematologist attends part of the pediatric clinic visit. The following visit takes place in the adult hospital with the adult oncologist or hematologist only. The transition model of Center 3 involves a transition process over a minimum of two clinical visits. The transition team, consisting of a designated pediatric oncologist and adult oncologist or hematologist, attends both appointments for the whole consultation time. The first visit takes place in the pediatric hospital, and the second visit takes place in the adult hospital. If the CCS feels comfortable, the third appointment is attended by the adult oncologist or hematologist only, but the pediatric oncologist is still available in case of specific questions.

Eligibility Criteria and Group Assignment

CCSs are eligible to participate in the ACCS study if it has been at least 5 years since completion of their treatment, either first-line treatment or treatment for relapsed disease; if they were diagnosed with cancer according to the International Childhood Cancer Classification, third edition (ICCC3); if they were less than 18 years of age at cancer diagnosis; and if they are 16 years of age or older at the time of inclusion in the ACCS study. In addition, CCSs have to either be ready to transition from pediatric to adult-focused LTFU care (group 1) or already have been transitioned since 2014 (group 2). We chose the year 2014 because the standardized transition into adult oncology in Center 2 was established in that year. We exclude CCSs treated with surgery only and with no increased risk for late effects (eg, teratoma), those with ongoing cancer treatment or in a palliative situation, those with cognitive disabilities that would prevent the CCS from completing a questionnaire, and those not fluent in speaking and reading German.

Recruitment Overview

We received approval from the cantonal ethics committee (Ethikkommission Nordwest- und Zentralschweiz) that is responsible for all three participating centers in February 2019 and started patient recruitment at all three study centers immediately following the approval. We plan to recruit participants over a period of 2 years, and we expect to have the results of the analyses of the questionnaires by autumn 2021.

The local investigator at each of the three sites is responsible for patient recruitment. After study initiation, each local investigator prepared a list with all eligible survivors for group 1 and group 2. During the recruitment period, each local investigator will include additional CCSs who meet the eligibility criteria.

Recruitment and Study Time Points for Group 1 Childhood Cancer Survivors

Group 1 CCSs receive the study material by mail before their next scheduled visit at the pediatric LTFU clinic. The study material consists of an information letter, the informed consent form, the baseline questionnaire, a reply sheet to return if they do not want to participate, and a prepaid envelope to return the study documents before the next visit if they do want to participate. If an eligible CCS does not reply before the visit, the local investigator reminds him or her before the LTFU visit, and he or she still has the opportunity to participate. All group 1 CCSs receive the baseline questionnaire before the LTFU visit and the follow-up questionnaire 3 months after the LTFU visit. Group 1a consists of CCSs who decide to transition into adult care (see Figure 1). They receive a second follow-up questionnaire approximately 15 months after the first visit. An interval of 15 months was chosen because most survivors have roughly one LTFU visit per year. Therefore, with an interval of 15 months, the follow-up questionnaire is sent 3 months after the first visit in an adult setting. Whenever possible, we adapt the time at which the second follow-up questionnaire is sent according to the actual date of the follow-up visit in the adult setting. Group 1b consists of CCSs who decide during the LTFU visit to stay in pediatric follow-up care for another year (see Figure 2). They receive only the baseline questionnaire and first follow-up questionnaire after 3 months, which provide us with important information on transition readiness, related needs, and cancer knowledge.

The local investigators send one reminder only if the CCS does not respond within 4 weeks to the first and second follow-up questionnaires.

Figure 1. Timeline of the Aftercare of Childhood Cancer Survivors (ACCS) study and time points where group 1a participants answer questionnaires; questionnaire sections are numbered and identical numbers correspond to identical content.

Figure 2. Timeline of the Aftercare of Childhood Cancer Survivors (ACCS) study and time points where group 1b participants answer questionnaires; questionnaire sections are numbered and identical numbers correspond to identical content.
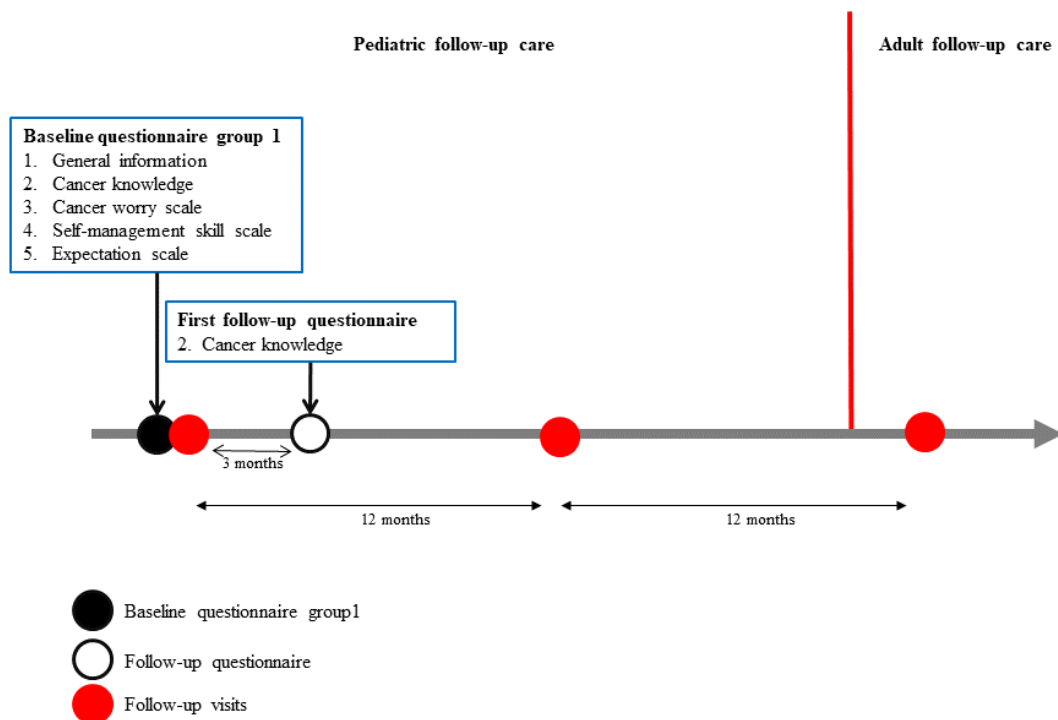
Recruitment of Group 2 Childhood Cancer Survivors

The local investigators contact group 2 CCSs who have already left pediatric follow-up care at the start of the study. The time since transition might range from 3 months to 6 years (see Figure 3). These CCSs receive the study material by mail and a maximum of one reminder if they do not reply within 4 weeks.

Group 2 CCSs receive only one baseline questionnaire. The information provided by group 2 CCSs is crucial to assess cancer knowledge and needs related to transition and LTFU care in adult CCSs. In addition, comparing the answers of former and currently transitioned CCSs will enable us to evaluate whether transition practices in each participating center improved over time from the CCS point of view.
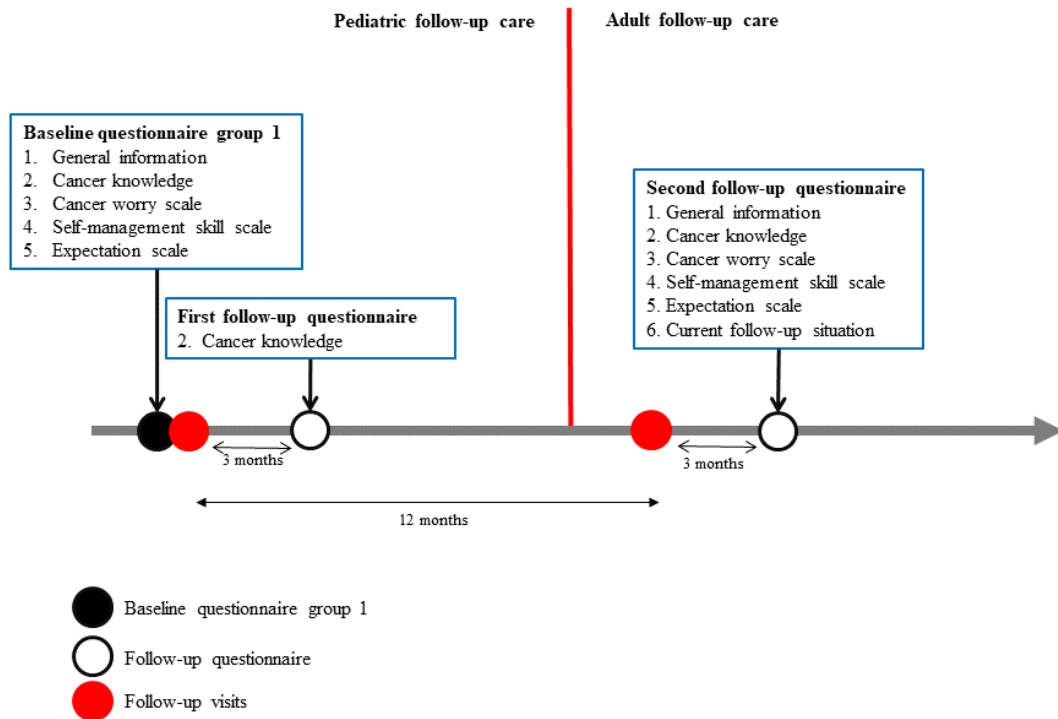
Figure 3. Timeline of the Aftercare of Childhood Cancer Survivors (ACCS) study and time point where group 2 participants answer the questionnaire.
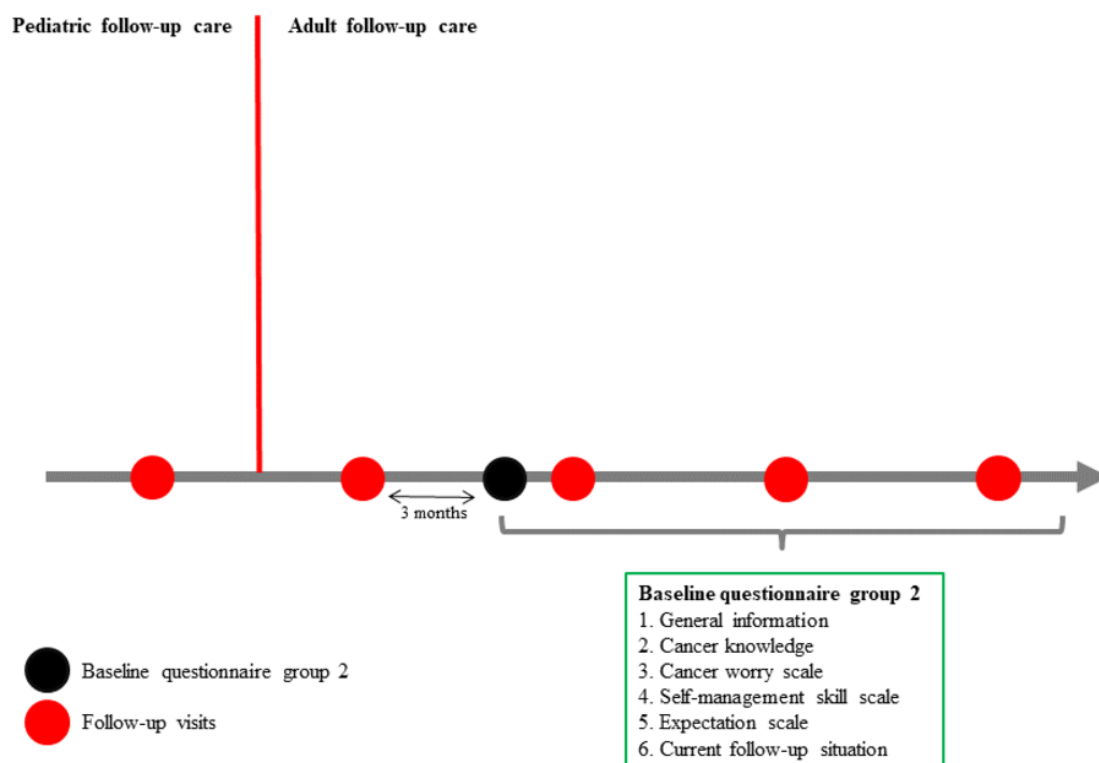
Data Collection and Questionnaire Content

Baseline Questionnaires for Childhood Cancer Survivors

All participants receive a baseline questionnaire, which is largely identical for survivors in group 1 and group 2: Baseline questionnaire group 1 and Baseline questionnaire group 2. The baseline questionnaires provide us with information on CCSs' cancer knowledge, current follow-up situation, and needs. In both groups, we collect data on CSSs' current age, sex, highest completed or ongoing education level, and the subjective assessment of current health status. We assess CCSs' knowledge on their cancer diagnosis, treatment modalities received, and potential late effects using questions with the answer options "yes," "no," and "unsure." Subsequently, we assess cancer worry, self-management skills, and expectations for follow-up care using validated scales. The Cancer Worry Scale consists of six questions on how much CCSs worry about their cancer history, relapse, fertility, late effects, and secondary malignancy [18]. The Self-Management Skill Scale consists of 15 questions, which cover factors important for evaluating CCSs' independence and personal responsibility [18]. The 12 questions of the Expectations Scale cover a broad spectrum of expectations concerning the treatment team and organizational or structural processes in the clinics [18]. For all three scales, the questions use Likert response scales with the following options: "strongly disagree," "disagree," "agree," and "strongly agree."

The baseline questionnaire of group 2 CCSs contains one additional question that the group 1 baseline questionnaire does not contain, which asks about the current follow-up situation. The response indicates whether the CCS is continuing with follow-up care and either where the follow-up care takes place or why the CCS discontinued follow-up care.

Follow-Up Questionnaires for Childhood Cancer Survivors

The first follow-up questionnaire for group 1 CCSs, including groups 1a and 1b, only asks about cancer knowledge. The content of the second follow-up questionnaire is identical to that of the baseline questionnaire of group 2 CCSs.

Collection of Medical Data

We collect medical data using a questionnaire completed by the local investigators. The local investigators answer five questions regarding tumor diagnosis: main category of cancer diagnosis (eg, leukemia), diagnosis according to the ICCC3, tumor location, whether the patient has suffered from a relapse, and patient's age at diagnosis. In addition, the local investigators indicate CCSs' treatment exposure and organ-specific risks for late effects. The local investigators extract these data from medical records.

Data Management

For electronic acquisition of the paper-based questionnaires, we use the software Remark Office OMR (Gravic, Inc). After each questionnaire version has been edited with the software, the software recognizes the selected answers on the completed documents and saves the answers electronically. The software traces changes in the database via an audit trail. The data stored in Remark Office OMR can be exported as Excel documents, which allows further processing of the data by statistical software, such as Stata (StataCorp LLC) and R (The R Foundation).

Statistical Analysis

The ACCS study has two analytical approaches: a cross-sectional approach and a longitudinal approach. The

cross-sectional approach includes analysis of the baseline questionnaire from group 2 CCSs and the second follow-up questionnaire from group 1 CCSs. Both questionnaires contain the same questions and answer options, with the exception of the "Current follow-up situation" question, which is asked only for group 2 CCSs. For the cross-sectional approach, we will present the results mainly descriptively (ie, mean and median with an appropriate measure of spread as well as summary tables and graphs), for example, the distribution of the four answer options for the questions on cancer worries. Additionally, we will quantify the associations between survivors' worries or expectations regarding follow-up care and diagnosis, treatment exposure, or the risk of developing late effects based on specific parameters such as odds ratio with respective measures of distribution.

The longitudinal approach includes the analysis of questionnaires from group 1 CCSs who answer at least one follow-up questionnaire. The answers from the group 1a and 1b CCSs can be used to determine whether follow-up consultation improves cancer knowledge. For the analysis of CCSs' satisfaction and expectations over time, we will use data from group 1b CCSs who answer the baseline and second follow-up questionnaire. In addition to using descriptive analysis as in the cross-sectional approach, we will use analysis of covariance in the longitudinal approach, whereby the result of the baseline questionnaire will serve as a covariate in the model for the result of the second follow-up questionnaire. In addition, we will analyze and discuss the different transition models taking into account the follow-up situation of each center when the project started. We will use the statistical software programs Stata and R.

Results

To date, we have recruited 58 CCSs in total, with 33 participants from the Division of Oncology-Hematology at Kantonsspital Aarau. We use this center to provide a practical illustration of the recruitment process and the current status. The center invited 72 CCSs to participate in the study in the first year. A total of 33 CCSs (46%) have confirmed their participation and completed the baseline questionnaire. A total of 19 of these CCSs are in group 1 and have already completed the first follow-up questionnaire, and 14 CCSs belong to group 2. Of the remaining 39 CCSs, 10 were recently contacted for the first time, whose responses are still pending, and 16 did not respond; of these 16 nonresponders, 5 stated no interest in the study, 2 could not be included due to medical reasons, 2 did not show up for the visit, and 1 stated insufficient time for participation. The recruitment will continue until January 2021.

Discussion

Overview

In this study, we will assess the follow-up situation, related needs, and knowledge of AYA cancer survivors who transition from pediatric to adult-focused follow-up care. We will evaluate their transition readiness, identify facilitators for transition and adherence to LTFU care, and compare the transition models of the three participating centers.

Strength and Limitations

This is the first study in Switzerland assessing CCSs' needs and perceptions of transition and LTFU care using a prospective, multicenter, observational approach. The survivors' feedback on the study has been mostly positive. At this preliminary state, we assume that the questionnaires are understandable and easy to complete, as most participants have completed all questions, and no questions regarding content have arisen during the clinic visits. Remark Office OMR is an easy-to-use tool for scanning and analyzing questionnaires, as it eliminates the need to manually transcribe the original questionnaires.

The questionnaire-based design might introduce selection bias, as CCSs who are interested in LTFU care are potentially more willing to participate than those who are not interested. For CCSs who are still in follow-up care, social desirability bias might positively influence their answers and prevent them from being critical. The interval between the last LTFU care visit to the completion of the questionnaire among the group 2 CCSs is variable and ranges theoretically from 3 months to 6 years (inclusion starts from 2014 onward).

Lessons Learned

Setting up and participating in a prospective study requires the willingness of all local investigators to continuously work on the project. For the ACCS study, this means always thinking about CCSs who are potentially eligible to participate in the study and sending them the documents, reminders, and follow-up questionnaires. Close collaboration and site visits by the primary investigator are essential. Regarding patient recruitment, we have learned that some CCSs prefer oral information to written information. We noticed this during the clinical visits when we asked survivors eligible for group 1 who had not returned the documents beforehand why they had not returned them. By providing oral information, we could recruit more participants. It is, therefore, worthwhile to talk to the survivors personally about the planned study.

Conclusions

The ACCS study collects detailed information on CCSs' preferences and expectations regarding LTFU care and the transition into the adult setting. We need these results to adapt LTFU care to CCSs' needs and to identify areas where targeted interventions are possible, such as patient education. Through this approach and a subsequent well-structured, standardized transition focused on the survivor's needs, adherence to LTFU care can be improved and loss to follow-up can be reduced.

Acknowledgments

Authors' Contributions

KS is the primary investigator of the ACCS study. SD and MO wrote the manuscript, which was reviewed and adapted by KS.

Conflicts of Interest

None declared.

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Abbreviations

ACCS: Aftercare of Childhood Cancer Survivors
AYA: adolescent and young adult
CCS: childhood cancer survivor
ICCC3: International Childhood Cancer Classification, third edition
LTFU: long-term follow-up

Protocol

A Digital Substance-Use Harm Reduction Intervention for Students in Higher Education (MyUSE): Protocol for Project Development

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Abstract

Background: Digital interventions have been identified as a possible tool for reducing the harm caused by illicit drug use among students attending higher education (ie, college students). However, the success of interventions in this area has been hampered by a lack of user involvement and behavior change theory in their design. The My Understanding of Substance use Experiences (MyUSE) project combines a rigorous user-centered design (UCD) methodology and a robust behavioral change framework to develop a digitally delivered harm reduction intervention for illicit drug use among students in higher education.

Objective: This project aims to design and develop a digital intervention that targets drug use–related harm among students in higher education.

Methods: The MyUSE project will take place over 3 phases. The first phase was exploratory in nature, involving 3 systematic reviews, a large survey, and student workshops to gather a comprehensive evidence base to guide the project. The second phase is the development stage of the project, involving the use of the Behavior Change Wheel theoretical framework to determine the behavior change techniques of the intervention and the use of the UCD methodology to guide the development of the digital intervention. The third phase is the evaluation stage, whereby the intervention will undergo a 5-stage evaluation process to comprehensively evaluate its impacts.

Results: The exploratory phase 1 of the MyUSE project was completed in December 2018. Phase 2 is currently underway, and phase 3 is due to begin in September 2020.

Conclusions: Higher education institutions (HEIs) are ideally placed to intervene and support students in the area of illicit drug use but are constrained by limited resources. Current digital interventions in this area are sparse and have several weaknesses. The MyUSE project combines a UCD approach with a robust behavior change framework to develop a digitally delivered intervention that is economically viable, effective in changing behavior, usable and acceptable to students, and able to sustain long-term implementation in HEIs.

International Registered Report Identifier (IRRID): DERR1-10.2196/17829

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Introduction

Background

The use of illicit drugs among students in higher education is a growing public health issue, with the annual prevalence of illicit drug use among students increasing gradually over the past 10 years [1]. Approximately one-fourth of higher education students report current use of an illicit drug [1-4], placing them at high risk of experiencing a myriad of academic, social, physical, and mental harms [3,5-16], with the risks particularly high for first-year students [5,17,18]. In particular, a recent study in Ireland found that 50% of young adults present with at least a low level of problems resulting from drug use [19]. As a result, higher education institutions (HEIs), such as universities, institutions of technology, or colleges of higher education, are ideally placed to intervene to reduce harm from drug use among student populations. However, student support services are limited in their capacity to deliver face-to-face interventions to large student bodies [20]. Students may be unlikely to recognize a need for, or be reluctant to seek help or support [21,22]; thus, alternative delivery methods should be considered. Digital interventions have been developed that target a range of potentially harmful behaviors, including alcohol consumption [23-27], smoking [20,28], and illicit drug use [29-35]. Despite the initial optimism surrounding the effectiveness of such interventions, many have failed to achieve positive results [26,27,32-34]. Two of the potential reasons for this are a lack of user involvement in the development of such interventions and a lack of a theory-driven behavior change framework to inform their design and development.

The development of digital interventions should explore the needs of end users in their context [36]; involve those users throughout the process of designing, developing, and evaluating a new intervention; and use a systematic approach to synthesize the available evidence to select the most precise behavioral change components to maximize intervention outcomes [37]. The user-centered design (UCD) methodology is an iterative process that requires the early and active engagement of the target user through a number of activities including the development of user profiles and early prototyping and evaluation of the intervention [38]. The implementation of the UCD process is critical to ensuring user engagement with the intervention and subsequently enhancing the effectiveness of the behavior change techniques (BCTs) employed [39]. In addition, digital interventions are more likely to be effective if their active components employ relevant mechanisms of action, such as a theoretically informed understanding of the motivations for change in their target population [40]. Digital interventions focused on enhancing health behaviors, such as harm reduction practices or substance use cessation, highlight that user involvement plays a key role in achieving the objectives of the intervention [41-43]. At present, few of the existing digital harm reduction interventions describe the process involved in their content development and feature selection. This narrows the opportunity to replicate effective interventions, synthesize evidence based on theoretical premises, or understand the causal mechanisms that facilitate behavior change [44]. The intention of this project is to employ a UCD approach and to incorporate behavioral theory processes in the design and development of a digital intervention that targets drug use–related harm among students in higher education. Mummah et al [45] outlined the Integrate, Design, Assess, and Share (IDEAS) framework, a comprehensive 4-stage process to guide the development and evaluation of digital interventions, incorporating behavioral theory, design thinking, and evaluation. Utilizing the IDEAS framework, this project will incorporate the UCD methodology as a core research toolkit along with the Behavior Change Wheel (BCW) framework [46], embedded in an interdisciplinary design approach, to develop and evaluate a digital intervention. This study outlines the protocol for the development of a digital harm reduction intervention for illicit drug use specifically designed for students in higher education.

The My Understanding of Substance Use Experiences Project

The Irish Government has published an 8-year strategy to address the harms caused by alcohol and drug use in Irish society. The strategy, "Reducing Harm, Supporting Recovery, a health led response to drug and alcohol use in Ireland 2017-2025," identifies "the development of IT/web-based drug education, harm reduction and brief advice tools targeted at higher education students" as a key element of the prevention strategy. The strategy further states that "the engagement of people who use drugs and/or services in the development and roll-out of any awareness campaigns is particularly important to ensure relevance and accuracy" [47].

The increasing prevalence of drug use among higher education students in Ireland highlights the need for a theoretically robust, specifically developed program to support students to enjoy well-being and minimize the harms associated with drug use, using both prevention and intervention approaches. In response to this growing student health issue, University College Cork (UCC) established an interdisciplinary team and developed a proposal for the "My Understanding of Substance use Experiences" (MyUSE) project. The project aims to develop, implement, and evaluate a digitally delivered harm reduction intervention targeting both those who use illicit drugs and those who do not in the higher education setting. For the purpose of this project, we define illicit drug use as "the use of substances which have not been prescribed, with the exception of alcohol and tobacco, or the use of prescription medication not as prescribed." This project is fully supported by a grant from UCC, Ireland, emphasizing the university's commitment to the welfare of its students. This study presents the research phases, methods, and processes utilized in the MyUSE project.

Methods

Overview

The MyUSE project will be undertaken over 36 months in 3 phases, combining UCD and BCW methodologies, guided by the IDEAS framework. The first phase focuses on establishing the evidence base around digital interventions for drug use, drug use and nonuse trends, and behaviors, through systematic literature reviews and surveys and gathering a deep understanding of the target population through qualitative focus

groups. The second phase focuses on the design and development of the intervention, involving the identification of the behavioral change components, and the development of the digital intervention, involving the users at each phase as part of an iterative design process. The final phase will consist of a comprehensive, stepwise evaluation. Learnings from each phase of the project will be shared to inform future intervention development in this area. The project will contribute to the broader seminal body of research for both researchers and practitioners, including health care professionals, student health services, and software developers, by producing academic outputs and disseminating findings at national and international

conferences to ensure that all results and learnings from this project are shared widely. This project will be developed in accordance with the 10 principles of the code of conduct for data-driven health and care technology, as outlined by the UK Department of Health and Social Care [48]. These principles were implemented to enable the development and adoption of safe, ethical, and effective data-driven health and care technologies and to incorporate principles such as understanding user needs and defining outcomes, transparency, and accountability. An overview of the 3 phases of the MyUSE project is outlined in Figure 1, along with the specific objectives for each phase.

Figure 1. Objectives of the MyUSE (My Understanding of Substance use Experiences) project.
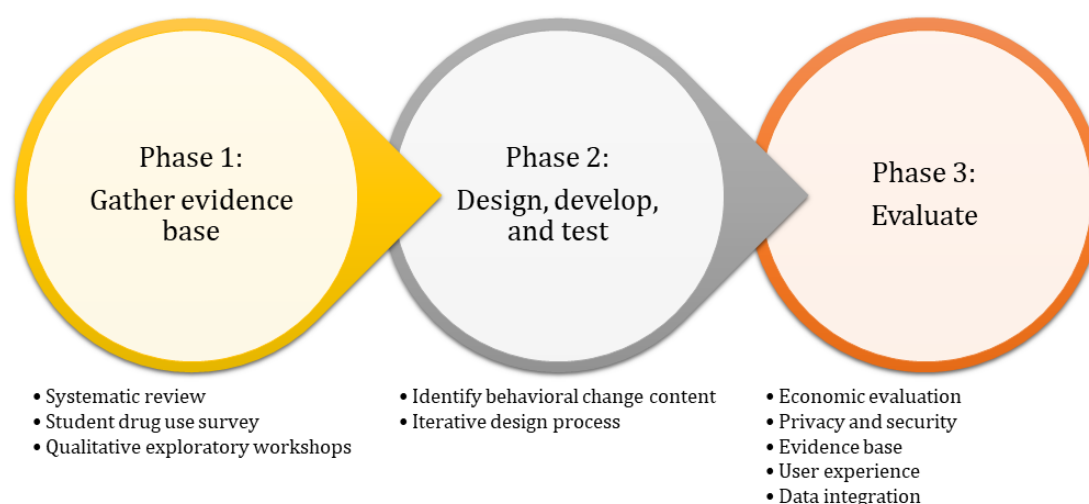
Project Objectives

The MyUSE project objectives are as follows:

1. To systematically review the relevant literature across 3 areas: (1) the use of UCD practices in similar interventions, (2) the effectiveness of similar interventions, and (3) the motivations for changing drug use in a higher education population (phase 1).
2. To design a survey instrument that will capture the drug use patterns of students and identify their capabilities, opportunities, and motivations for change (phase 1).
3. To conduct qualitative exploratory workshops with students to gain a deep understanding of the characteristics of end users and scenarios within which a student may decide to engage with an intervention of this nature (phase 1).
4. To develop intervention content by identifying the capabilities, opportunities, and motivations for changing (or in the case of nonusers, reinforcing) the targeted behaviors and by employing the BCW framework [46],

which addresses the specific characteristics, needs, and behaviors of students in higher education (phase 2).
5. To develop the digital intervention through an iterative design, development, and test process, involving the end user (ie, students in higher education) in each stage of development and decision making (phase 2).
6. To conduct a comprehensive evaluation of the MyUSE intervention following a stepwise approach (phase 3).

Phase 1: Gather the Evidence Base

The first phase of the MyUSE project was carried out over a 15-month period from October 2017 to December 2018. This phase included a systematic interrogation of the literature in the area of digital interventions and student drug use in higher education settings; qualitative exploratory workshops with higher education students to identify characteristics, needs, goals, and values of target users; and the design of a survey to assess baseline drug use behaviors and trends. At the outset of the project, a public and patient involvement group of student partners was assembled based on guidance from the National

Institute for Health Research [49]. The *Student Advisory Group* (SAG) will inform and guide project development from the student perspective as the key stakeholders in the intervention.

The first recruitment of the SAG took place in January 2018. Academic leads on the MyUSE project provided information about the opportunity to join the SAG through class email lists. A total of 10 undergraduate students from 3 disciplines (Public Health, Applied Psychology, and Information Systems) signed up to the group. Members of the group are never asked to disclose their personal experiences with drug use. To date, 10 meetings have been held with the SAG. The meetings follow an informal discussion style format; members of the MyUSE team present a particular piece of work (eg, survey questions, design idea, etc); and the group engages in discussion around the student's perception and areas of improvement. Brief notes are recorded throughout the meeting. The MyUSE team holds a debriefing session following each meeting to discuss key points arising from the meetings. A second round of recruitment took place in January 2020 as a number of SAG members had recently completed their studies or decided to leave the group.

Systematic Reviews

At the outset of the MyUSE project, 3 systematic reviews were conducted with the aim to identify, gather, synthesize, and analyze all relevant research to, first, assess the potential effectiveness of digital behavioral change interventions in this area and, second, to guide the project methodology.

The first review, "A systematic review of the effectiveness of digital interventions for illicit drug misuse harm" (n=8 studies, reported elsewhere [50]), was conducted to assess the effectiveness of digital interventions for drug use harm reduction in student populations. Modest success has been reported for alcohol and tobacco harm reduction interventions [23-25,28], but the differences between legal and illegal drug use with regard to the user's related behavior may limit the extrapolation of those results to illicit drug users. Therefore, it was important to carry out a review specifically targeting digital interventions for illicit drug use to assess their overall effectiveness. The review reported modest positive outcomes for harm reduction in 5 of the 8 included studies. However, the overall quality of the included studies was weak, and few studies focused solely on illicit drug use (including smoking and/or alcohol use) and those that did focused only on marijuana [29-31]. In addition, there was very little information provided on the involvement of users in the design of the interventions included in this review.

The second review, "A systematic review of user-centered design practices in illicit drug use interventions for higher education students" (n=7 studies, reported elsewhere [51]), was conducted to investigate the previous interaction with UCD practices in the development of similar interventions to guide the development of the MyUSE intervention and our adoption of the UCD methodology. The review revealed that limited consideration had been given to the end user experience (UX), and there had been minimal engagement with UCD practices. Failure to engage users in the design and evaluation of digital interventions would have a significant influence on their effectiveness and sustainability in normal user conditions [39].

This review highlighted a gap in the current processes for intervention design in this area.

The third review, "Motivational factors related to higher education student's decision to decrease or cease drug use: A scoping review" (n=3 studies, manuscript in preparation), was conducted to explore students' motivations to change their drug use. A considerable amount of research has been conducted to explore the motivations for beginning or continuing drug use, but a scant number of studies have examined the motivations to reduce or stop drug use behaviors. This review reported that the sole identification of the adverse consequences of drug use is not sufficient to prompt students to change their current pattern of use. The findings also indicate that a motivation to reduce or stop drug use behavior may emerge from multiple cumulative and/or interactive factors [52], and the identification of consistent negative effects across several life domains may be necessary as a precedent for change. Findings from this review highlight how motives relating to the perceived social acceptability of various behaviors can facilitate behavior changes and how increasing awareness of individual decision making regarding drug use can also motivate changes in the use of illicit drugs.

Qualitative Exploratory Workshops

During this phase of the project, 8 exploratory workshops were conducted with 31 undergraduate students between December 2017 and February 2018. The workshops utilized a UCD methodology known as persona building. Persona building attempts to capture the user's expectations, prior experiences, and anticipated behaviors, allowing developers to identify with and meaningfully communicate with the target user [53]. The workshops invited the participants to create detailed personas based on their own understanding of nonuse, moderate use, and heavy use of drugs and to identify conflicts between drug use behavior and students' values and interests.

1. Understanding the service user: The participants were presented with fictional end users and asked to build a persona for each user based on (1) demographic information, (2) personality, (3) relationships, (4) interests, (5) behavioral patterns, (6) goals, (7) challenges, (8) annoyances, (9) fears, and (10) social routine. Participants developed personas for characters with no use, moderate use, or heavy use of drugs.
2. Motivation for service use: The participants were asked to describe how their persona's relationship with drugs may interfere with various aspects of their life, including mental and physical health, relationships, and work or study.
3. Understanding service interaction scenarios: The participants were asked to write a short story about the personas they had developed, describing the series of events that led to their recognition of a need or concern.

These exploratory workshops assisted in identifying and characterizing the types of users who will engage with this intervention and how the intervention can be tailored toward their needs, values, and goals. Finally, a large mapping exercise was undertaken by the project team to synthesize the information from previous research. Participants identified 5 distinct drug use archetypes: (1) the social butterfly, (2) the high achiever,

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(3) the pleasure seeker, (4) the approval seeker, and (5) the health enthusiast. Full details of the workshops are presented elsewhere [54].

Drug Use Behavior Survey

The drug use behavior survey was developed by undertaking an iterative process over 12 months. The SAG was consulted on several aspects of the survey design, including its length, language style, mode of delivery, and the content of the questions. Survey questions were developed under 6 sections to collect information on (1) demographics, (2) student life, (3) drug use, (4) the decision-making process, (5) motivations for use, and (6) behavior change. Sections 1 to 3 of the survey assessed illicit drug use trends using items from a number of validated questionnaires, including the Core Alcohol and Drug Survey [55], the Alcohol Smoking and Substance Involvement Screening Test V3 [56], and the European School Survey Project on Alcohol and Other Drugs [57]. Sections 4 to 6 were constructed to assess students' capabilities, opportunities, and motivations relevant to drug use behaviors. An overview of the survey content is included in Multimedia Appendix 1.

The survey was distributed via email to a randomly selected, representative sample of UCC students at the beginning of the 2018-2019 academic year. Proportional sample sizes were calculated from each year group of students (undergraduate years 1-5 and all postgraduates) to ensure that samples were representative of each year of study. The sampling framework was then utilized by the Information Technology Department to select and distribute the survey to a single mailing list of 3770 students.

The results of this survey will provide baseline information on drug use and nonuse trends among university students and assist in the process of identifying effective BCTs through a synthesis analysis, following the BCW framework. Following this, the survey will be optimized for delivery on an annual basis to facilitate longitudinal data collection on the drug use trends and behaviors among higher education students. The survey will be offered to other Irish HEIs in an effort to create a national data set that can be used to inform policies and practices within HEIs.

Phase 2: Intervention Design, Development, and Testing

This phase of the project was carried out over an 18-month period, from January 2019 to June 2020 and included the systematic identification of the BCTs that will be implemented in the intervention and the iterative design and testing of the intervention with a small sample of higher education students.

Behavioral Content Development

The BCW is a theoretical framework for designing interventions, developed by synthesizing 19 existing behavior change theories

[46]. It encapsulates the Capabilities, Opportunities, Motivations, and Behavior (COM-B) model, which states that for a behavior change to occur, individuals should change one or more components of physical or psychological capacity, social or physical opportunity, and automatic or reflective motivation [44]. The COM-B model is grounded by the Theoretical Domain Framework [58], a separate tool that includes a taxonomy of BCTs [58], which facilitates decision making from a pool of 93 different BCTs.

The BCW has been used in many digital interventions [59-63]. The BCW provides a framework to link intervention outcomes with the mechanisms of action, which enables an evaluation of the intervention and mechanism. The BCT taxonomy component of the BCW allows for the identification of the *active ingredients*, the observable, replicable, and irreducible components of the intervention. There are several applications of the BCW in the substance use domain: StopAdvisor, a smoking cessation program uses 33 BCTs from the taxonomy in its digital intervention, including "identifying reasons for not wanting to smoke" and "providing information on consequences of smoking" [61]. Similarly, Breaking Free Online, a computer-assisted therapy for substance use disorders, uses 6 BCTs, including the *framing*, *reframing,* and *goal setting* techniques [60]. To our knowledge, the BCW framework has not previously been applied to drug use in higher education populations.

Following the BCW framework, the evidence from the exploratory workshops, scoping review, and the survey will be synthesized to fully understand the motivations to change drug use behavior in higher education students. The evidence synthesis will determine which of the 9 intervention functions and 7 policy categories from the BCW will be considered as potential means by which the intervention can facilitate behavior change or behavioral reinforcement in the target population. Finally, the selected intervention functions and policies will guide the identification of the most relevant BCTs, which will then be translated into digital components.

Iterative Design Process

The iterative design process consists of 3 types of workshops: (1) an exploratory co-design workshop, (2) concept evaluation workshop, and (3) UX evaluation workshop, as illustrated in Figure 2. Recruitment for the workshops will follow a similar format to the phase 1 workshops. A call for participants will be periodically advertised through the Student's Union social media platforms to create a *pool* of interested participants. Workshops will be advertised to the participant pool 2 weeks in advance. Participants will be able to participate in each type of workshop if they wish.

Figure 2. Iterative design process.
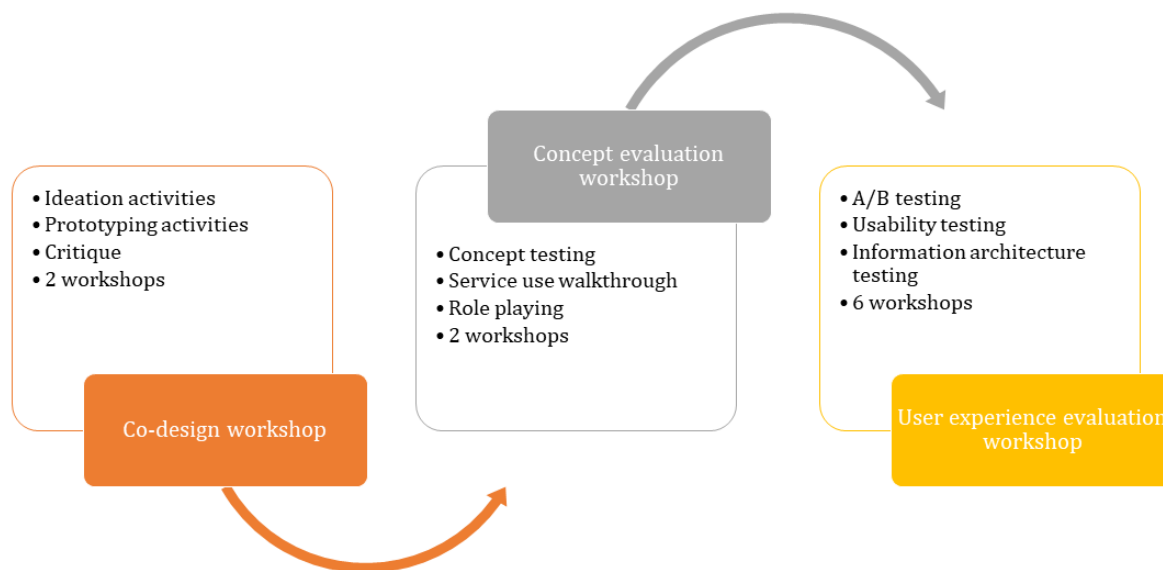
The co-design workshops will focus on the collaborative design of specific elements of the intervention. At this stage of the process, the project team would have determined (based on phase 1 evidence) which specific BCTs need to be included in the intervention. The co-design workshops are a process for deciding how to implement those specific BCTs in the intervention in a manner that is engaging and meaningful for participants. It is intended that at least two co-design workshops with groups of 6 to 8 participants each take place. The workshops consist of 3 steps: (1) ideation activities, (2) prototyping activities, and (3) critique.

1. Ideation activities: This involves a process similar to brainstorming, in which all stakeholders contribute their ideas to the various intervention BCTs. Participants will be presented with a specified activity that will be included in the intervention and will be asked to use flashcards, each containing a different element of delivery (eg, tone: funny, emotional, and trendy; mode: animated, pictures and text, and interactive visualization; and framing: mental health, well-being, and drug use, etc) to create a number of combinations of the delivery methods for the specified activity.
2. Prototyping activities: Having identified a number of ways in which each element of the intervention can be implemented, stakeholders will be asked to design low-fidelity prototypes, suggesting how these ideas could be implemented in the system, using paper, cards, pens, and post-its, to visualize their prototypes.
3. Critique: The facilitator will present a summary of the outcomes from the previous 2 exercises, and participants will engage in group discussion and critique of the ideas generated.

A small number of low-fidelity, digitalized intervention prototypes will be developed using Sketch prototyping software [64]. These will be based on the evidence gathered in phase 1 and the exploratory workshops and presented to students in a series of evaluative workshops. The concept evaluation workshops will consist of 3 parts: (1) concept testing, (2) service use walkthroughs, and (3) role playing.

1. Concept testing: During this workshop, a series of design components will be provided to the participants, supported by visual aids. Participants will be asked to provide feedback on these concepts [65].
2. Service use walkthroughs: Interface mockups will be used to guide participants through the task flow of the intervention. Participants will be asked to think aloud as they interact with each screen, verbalizing their actions, thoughts, and feelings as they attempt to achieve defined objectives. Participants will be asked to score the intervention across several criteria upon completion, such as functionality, ease of use, interactivity, clarity, and satisfaction [66].
3. Role playing: Using a UX analysis approach, participants will be presented with role scripts of a typical service use interaction and of the fictional personas developed in the exploratory workshops in phase 1. The scripts will describe a scene, plot motivations, and goals for each role. As participants act out the interaction scene, they will be asked to highlight areas where the experience with the intervention could be improved. The user will be asked to score the experience against defined criteria, and observers will also be asked to comment on the interaction scene [66].

It is expected that at least two concept evaluation workshops will take place with groups of 6 to 8 participants each before

the project team reaches a decision on the final prototype to be employed for the MyUSE intervention to ensure that the final prototype adequately fulfills the needs of the student users. Each student workshop will be followed by a qualitative analysis of the students' narratives and a half-day working meeting with the project team to discuss findings from the student workshops and incorporate changes accordingly.

The final task of the digital design and evaluation process will be iterative in nature, taking place over 12 months during which time the project team will work closely with students, allowing for further evaluation of the intervention to take place. Approximately 6 UX evaluation workshops will be held one-on-one with 3 to 5 students each, focusing on (1) A/B testing, (2) usability testing, and (3) information architecture testing The one-to-one nature of the final workshop will allow the facilitator to closely observe the participants as they interact with the intervention.

1. A/B testing: Pre-prepared sets of service interfaces will be provided to the participants, each representing 2 different design formats for task flow, interactive experience, or screen layout. The participants will be able to indicate which designs they prefer [65].

2. Usability testing: Participants will be provided with a general goal to achieve with the service. Using the think-aloud methodology, participants will be observed as they attempt to achieve the goal. Participants will be asked to assess the service in terms of its features and functionality, ease of use, navigation flow logic, and gestural design [67].

3. Information architecture testing: Participants will be asked to assess the ease of locating certain information and the intuitiveness of the structure of the information presented by the intervention. Participants will be provided with a series of cards representative of items in the navigation menu, and they will be asked to indicate which card they expect the information to be found under. Participants will be provided with cards that represent page headings and content sections. They will be asked to structure the pages and content in a manner that seems most logical to them [65].

Phase 3: Evaluate and Disseminate

The final phase of the project will take place over 6 months, beginning in late 2020. The MyUSE project will follow a holistic approach to evaluation, following the stepwise framework proposed by Henson et al [68], modified for the needs of the MyUSE intervention. The framework comprises 5 ascending levels of evaluation, emphasizing the need to adequately assess the intervention at each level before proceeding to the next level. In keeping with the code of conduct for data-driven health and care technology [48], data security and privacy will form a core part of the intervention design. A secure, anonymous log-in feature will be developed, and a comprehensive data management plan will be established before the commencement of phase 3.

Level 1—Economic Evaluation

Reliable evidence of the economic effectiveness associated with eHealth remains to be limited [69]. We will undertake an analysis of the cost-effectiveness and budget impact associated with the MyUSE digital intervention. This will include understanding the benefits accrued by making this new student health intervention available, investigating value for money in the digital delivery model compared with traditional face-to-face interventions and establishing the quality of this digital health intervention. Furthermore, we need to develop an evidence base that will inform the business case for the potential delivery of MyUSE as an integral part of student health services in higher education.

Level 2—Privacy and Security

A Data Protection Impact Assessment will be carried out to assess the data protection risks associated with the MyUSE intervention. This will allow for the identification and mitigation of any data protection risks and assess the viability of the intervention [70]. Furthermore, the development of the intervention will implement the principles of *Privacy by Design* following a practical approach, with the inclusion of transparent, clear, and honest user agreements, terms and conditions, and consent process [71].

Level 3—Evidence Base

In September 2020, the finalized MyUSE intervention will be pilot tested in the UCC student population. A proportionally representative sample of UCC students will be invited to participate in the MyUSE pilot intervention during the registration period of semester 1, 2020-2021. A mixed methods approach will be used to evaluate the impact of the MyUSE intervention and to assess the UX. A pretest and posttest control group study will be conducted. Students will be randomly assigned to receive either the MyUSE intervention or an education-only control. This study will incorporate measures assessing the process of change variables, including the degree to which the intervention reduces the harm associated with drug use. The primary outcome measure will be the level of drug use problems, measured using the Drug Abuse Screening Test 10-item (DAST-10) questionnaire [72]. The DAST-10 is a brief screening tool suitable for self-administration that has been validated in college students [73].

The intervention and control groups will be assessed at 2 time points: T1 (semester 1), before the rollout of the MyUSE intervention, and T2 (semester 2), 3 months after the rollout of the MyUSE intervention. A sample of participants in the intervention (MyUSE) arm will be invited to focus groups to assess the UX and perceptions of the usefulness of the intervention at T2.

In addition, the baseline and subsequent cross-sectional survey of drug use trends collected in UCC (and other institutions in March 2020) will be used to map trends and will serve as an indicator of the long-term impacts of the MyUSE intervention within and across the student cohorts.

Level 4—Usability and Experience

The evaluation of usability and UX will begin during phase 2 of the project and will be achieved through a series of evaluative workshops. Following an agile approach, development in phase 2 will be conducted in 3 sprints, with the release of an updated prototype version at the end of each sprint. At least one evaluative workshop with 5 participants will take place following the release of each new version to inform further development. Furthermore, participants who receive the MyUSE intervention in the pilot evaluation will be invited to participate in focus groups and interviews to assess the usability and UX of the intervention.

Level 5—Data Integration

The final level of evaluation is complex and involves assessing the long-term clinical impact and sustainability of the intervention. A three-arm, clustered, controlled trial will be conducted with a number of institutions within Ireland to assess the behavioral impact and long-term scalability of MyUSE. All Irish HEIs will be invited to take part in the trial, and institutions will be allocated to receive the MyUSE intervention, an education-only control, or no intervention.

Primary outcome measures will assess the level of drug use risk (using the DAST-10 as outlined previously) and changes in targeted behaviors, such as decision making, behavioral awareness, and value progress using the Generalized Pliance Questionnaire [74], the Comprehensive assessment of Acceptance and Commitment Therapy processes questionnaire [75], and the Valuing Questionnaire [76]. Secondary outcome measures will assess user engagement using the analytics function built into the intervention (ie, number of clicks, time spent on each page, dropout point, etc). The trial will begin at the beginning of the academic year, with follow-ups after 3 months (end of semester 1) and again at 6 months (end of semester 2) to assess the longer-term impact of the intervention.

Interviews will be conducted with key stakeholders (ie, those responsible for the implementation, such as Student Health Department leads, Student Experience leads, and Student's Union representatives) from institutions in the intervention arm to assess the barriers and facilitators of long-term implementation and scalability in the higher education setting.

Dissemination

The MyUSE project will publish the results of the 3 systematic reviews, a process article describing the procedures of mapping harm reduction practices to the BCW, and findings from the iterative UCD workshops. The survey results and intervention evaluation will also be published. Furthermore, abstract and poster submissions will be shared at local, national, and international conferences to ensure that the findings and learnings from the MyUSE project are disseminated as widely as possible to contribute to the literature on intervention development. Furthermore, the MyUSE project will contribute to a much-needed national evidence base on the drug use trends and behaviors of higher education students. This will enable the development of evidence-based harm reduction policies and interventions at a national level.

Results

Phase 1 of the MyUSE project was completed in October 2018, and phase 2 is currently underway. This project received funding for phase 1 in January 2017 and funding for phases 2 and 3 in May 2018. The project has received ethical approval from the Social Research Ethics Committee at UCC. Ethical approval for the student workshops was granted on November 17, 2017, and for the student survey on May 3, 2018.

In total, 3 systematic reviews were completed in phase 1. Two have been published [50,51]. A total of 8 persona building workshops with 31 students were conducted in phase 1. The findings from these workshops have been published elsewhere [54]. The student survey was distributed to 3770 UCC students in October 2018. The survey achieved a 30% response rate and a 20% completion rate.

Discussion

Summary

Students' health and well-being services in HEIs are ideally placed to intervene and reduce the harm from drug use, yet they are limited in their capacity to reach large student populations [20]. In today's increasingly connected society, digital devices provide the ideal platform to reach large student populations. However, previous digital interventions for illicit drug use in higher education students have seen only modest reductions in drug use–related harms [50], and many have suffered from problems with user engagement or lacked a strong theory-based framework as a foundation for BCTs [39]. Subsequently, there is little evidence to suggest that student populations had any role in the design, development, and evaluation of these interventions [51], despite the literature consistently identifying the importance of end user involvement [77-79].

There is currently very limited guidance available to research teams in the development of digital behavior change interventions [45]. The IDEAS framework [45] is one of the first to provide a systematic guide to intervention development, incorporating the essential components of behavioral theory, design thinking, and evaluation and dissemination. The MyUSE project aspires to avoid previous methodological caveats and aims to facilitate better exploration of the topic by adopting a mixed-method design, with the aim of maximizing the formation of a user-friendly, acceptable digital behavior change intervention. By applying UCD and BCW, formed under the umbrella of the IDEAS framework, we support the development of a context-driven design approach.

Integrate

The first phase of IDEAS involves empathizing with target users, specifying the target behavior, and grounding in behavioral theory [46]. Our inclusion of a rigorous UCD process including persona building and user stories, in the design of this intervention, allows for a comprehensive understanding of the needs of the target population to be gained and will be used to inform the intervention design by identifying specific characteristics, needs, goals, and values of target users.

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The use of the BCW framework allows us to specify the problem in behavioral terms (identify the specific components of drug use–related behaviors occurring within a higher education context) and to identify key sources of those behaviors (eg, habitual use of drugs among higher education students) that, when matched with specific intervention functions, can lead to the highly sensitive selection of BCTs holding the potential to maximize effective harm reduction practices. To the best of our knowledge, this is the first study in the area of drug use and experimentation within the university context that formulates the BCW as a primary framework for guiding the development of the content of a digital harm reduction intervention.

Design

The second phase of the IDEAS framework involves ideating creative implementation strategies, prototyping potential products, gathering user feedback, and building a minimum viable product. The MyUSE intervention design will be undertaken in an iterative process, with several early prototypes introduced in succession to users for evaluation and feedback at each stage through evaluative workshops. The final design phase will take place over a 12-month period, again incorporating user feedback at each iteration. The inclusion of users throughout the intervention design, development, and evaluation will contribute to an intervention that is acceptable, user-friendly, and relatable to higher education students.

Assess and Share

The final 2 phases of IDEAS include pilot testing, evaluation of efficacy, and sharing widely. The MyUSE intervention will be pilot tested with higher education students from the university before being rolled out on a larger scale. Finally, the systematic approach of researching and identifying effective components via the application of the BCW framework can be a useful working example for other researchers in the area and can contribute to the dearth of scientific knowledge on how implementation interventions are delivered in educational settings. The development of a survey that can be delivered on a national scale will provide a rationale for investment and opportunities for evidence-based policy and intervention development. Furthermore, the MyUSE intervention will be made available for HEIs across Ireland, with expansion to institutions in the United Kingdom and Europe a future possibility.

Strengths and Limitations

This project combines 2 well-established and rigorous context-driven design methodologies in a systematic and transparent manner. Using UCD methodologies, this project aspires to circumvent barriers related to the use of technology,

contributing to an optimal use of the digital intervention. Consequently, the MyUSE project maximizes the chances for intervention effectiveness. This project contributes to the advancement of digital intervention development, detailing the multidisciplinary approach in a manner that future research teams can draw on and replicate. Furthermore, this intervention provides a blueprint for intervention designers and software developers undertaking this type of project in the future.

This project has several limitations. The intervention focuses exclusively on students in higher education declaring use, past use, or nonuse of drugs. However, students with drug use–related disorders, as clinically defined in the Diagnostic and Statistical Manual of Mental Disorders [80], and individuals with comorbid mental health problems or other psychosocial and behavioral problems are not targeted, as they traditionally need a more intensive level of health care.

Conclusions

To reach the overarching goal of delivering a web-based harm reduction intervention for illicit drug use in higher education student populations, this project combines a rigorous UCD methodology and a multiphase process-based BCW framework. Both procedures are employed to tailor the intervention to the unique needs of a higher education student population and to be attractive, usable, and acceptable to this population. Students attending higher education will be included as participants in exploratory and evaluative workshops as well as partners in our SAG, involved in decision making throughout the design, development, and evaluation. By incorporating all the involved stakeholders, the project ensures that the design is calibrated to the needs of the users, addressing a growing, yet unmet need of higher education health care policies to provide an evidence-based public health intervention targeting at-risk student populations [81].

This project has several research and public health implications. First, the digital intervention has the potential to protect students in higher education from the harm caused by drug use. Second, the agile digital delivery of the intervention will allow policy makers and health practitioners to communicate and promote effective behavior change practices via a wide range of channels (eg, web-based and smartphone-adapted technologies, social media campaigns, etc) and in different settings where drug use occurs (eg, music festivals, universities' events, clubs, etc). Finally, given that students declaring drug use rarely visit traditional university health centers [21,22], this intervention has the capacity to deliver support to those students who may use illegal drugs to a degree that may cause them harm but are not motivated enough or lack the awareness required to seek help and support.

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Authors' Contributions

All authors conceived the manuscript and participated in the planning of the project. S Dick led the writing and revision of the manuscript. VV assisted in the writing of the manuscript and reviewed and edited the manuscript. MD reviewed and edited the manuscript. S Dockray reviewed and edited the manuscript. CH reviewed and edited the manuscript. CL reviewed and edited the manuscript. MB edited and reviewed the manuscript and provided overall supervision of the project. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
MyUSE drug use survey overview. My Understanding of Substance use Experiences.
[DOCX File , 20 KB - resprot_v9i8e17829_app1.docx]

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Abbreviations

BCT: behavior change technique
BCW: Behavior Change Wheel
COM-B: Capabilities, Opportunities, Motivations, and Behavior
DAST-10: Drug Abuse Screening Test 10-item

HEI: higher education institution
IDEAS: Integrate, Design, Assess, and Share
MyUSE: My Understanding of Substance use Experiences
SAG: Student Advisory Group
UCC: University College Cork
UCD: user-centered design
UX: user experience

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Protocol

Systemic Sentinel Lymph Node Detection Using Fluorescence Imaging After Indocyanine Green Intravenous Injection in Colorectal Cancer: Protocol for a Feasibility Study

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Abstract

Background: Nodal staging is a major concern in colorectal cancer as it is an important prognostic factor. Several techniques that could potentially improve patient treatment and prognosis have been developed to increase the accuracy of nodal staging. Sentinel lymph node detection has been shown to accurately reflect nodal status in various tumors and has become the standard procedure in nodal staging of breast cancer and melanoma. However, in colorectal cancer, sentinel lymph node detection techniques are still controversial as the sensitivity reported in the literature varies from one study to another. Recently, indocyanine green fluorescence–guided surgery has been reported to be a useful technique for detection of macroscopic and microscopic metastatic deposits in lymph nodes after intravenous administration of indocyanine green dye. However, no studies have focused on the potential role of sentinel lymph node detection after systemic administration of indocyanine green dye, so-called systemic sentinel lymph nodes, or on the correspondence between the identification of the sentinel lymph node by standard local injection techniques and the detection of fluorescent lymph nodes with this new approach.

Objective: The aim of this protocol is to validate the concept of sentinel lymph nodes identified by fluorescence imaging after intravenous injection of indocyanine green dye and to compare the sentinel lymph nodes identified by fluorescence imaging with sentinel lymph nodes detected by the standard blue dye technique.

Methods: This study (SeLyNoFI; Sentinel Lymph Nodes Fluorescence Imaging) is a diagnostic, single-arm, open-label feasibility study, including patients with colorectal adenocarcinoma with or without metastatic disease who are admitted for elective colorectal resection of the primary tumor. This study evaluates the feasibility of a new approach for improving the accuracy of nodal staging using fluorescence imaging after intravenous administration of indocyanine green dye. Sensitivity, positive predictive value, and accuracy of the classical blue dye technique and of the investigatory fluorescence imaging technique will be calculated. Translational research will be proposed, if applicable.

Results: As of June 2020, this study has been registered. Submission for ethical review is planned for September 2020.

Conclusions: The potential correlation between the two different approaches to detect sentinel lymph nodes offers new strategies for improving the accuracy of nodal staging in colorectal cancer. This new concept of the systemic sentinel lymph node and a greater understanding of the interactions between systemic sentinel lymph nodes and standard sentinel lymph nodes may provide important information regarding the underlying mechanism of primary tumor lymphatic drainage. The enhanced permeability and retention effect can also play a role in the fluorescence of systemic sentinel lymph nodes, especially if these lymph nodes are inflamed. In this case, we can even imagine that this new technique will highlight more instances of lymph node–positive colorectal cancer.

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Introduction

Colorectal cancer represents a major cause of cancer-related mortality worldwide [1]. Nodal staging in colorectal cancer is of major concern as patients with stage III cancer, which is defined by nodal metastases at pathology, should receive adjuvant chemotherapy [2]. Sentinel lymph node analysis has been shown to accurately reflect nodal status in various tumors and sentinel lymph node detection techniques have become the standard of care in breast cancer and malignant melanoma where unnecessary lymphadenectomy can be avoided in patients with negative nodal status [3,4]. Sentinel lymph node detection was introduced for colorectal cancer in the early 2000s [5,6]. The aim of sentinel lymph node detection in colorectal cancer is not to identify the need for lymphadenectomy—this is already systematically performed during surgery—but to identify the first tumor draining node and focus on more advanced techniques during histopathological analysis to improve the accuracy of nodal staging. Despite some encouraging results, the technique has not been widely used. This is probably due to the fact that data reported in the literature have provided mixed results [5,7]. The poor performance of classical sentinel lymph node detection techniques using intra- or peritumoral injections in colorectal cancer could be related to two factors. The first is that, in patients with locally advanced tumors, draining lymphatic channels could be obstructed by the tumor, leading to false negative results [5]. The second is that mesenteric drainage is more heterogeneous when compared with cutaneous or subcutaneous region drainage, such as those involved in breast cancer or in melanoma, potentially leading to missed metastases [8]. For this reason, there may be discordance between the first lymph node, which anatomically drains the tumor and which is detected after peritumoral injection, defined classically as the *sentinel lymph node*, and lymph nodes invaded by cancer cells and detected after intravenous injection that we have defined as the *systemic sentinel lymph node*.

Recently, indocyanine green–fluorescence imaging has emerged as a potential technique for the detection of sentinel lymph nodes after peritumoral injection [9-11]. The preliminary results of studies [12-15] using peritumoral injection of indocyanine green dye for sentinel lymph node detection in colorectal cancer were encouraging, but we recently reported the results of a pilot study [16] which were disappointing in terms of accuracy and sensitivity.

New approaches are thus required. Recently, we published our observations on using fluorescence imaging after intravenous injection of indocyanine green dye to detect lymph node metastatic deposits both ex vivo and in vivo in colorectal cancer [17]. We confirmed these findings in a recent retrospective study [18] evaluating 12 patients who underwent colonic resection, for peritoneal metastasis detection after intravenous injection. Moreover, we observed that primary colonic tumors were more fluorescent than surrounding tissue upon fluorescence imaging after intravenous injection of indocyanine green dye.

Therefore, we hypothesized that ex vivo fluorescence imaging after intravenous injection of indocyanine green dye could represent a new approach for improving nodal staging through detection of fluorescent lymph nodes on the operative specimen. Furthermore, we hypothesized that these lymph nodes, identified after intravenous injection of indocyanine green dye and defined as systemic sentinel lymph nodes, when compared with classical anatomical tumor-draining sentinel lymph nodes, could represent a lymph node subset that is more sensitive to nodal invasion, thus serving as a more appropriate target for advanced histopathological analyses. The pathophysiological mechanism is 3-fold: first, in patients with large tumors, involved lymph nodes will be more fluorescent; second, in patients with small tumors, the fact that primary colonic tumors accumulate indocyanine green dye and that the dye is progressively cleared from the tumor by lymphatic drainage should allow the lymph node draining the tumor to be highlighted (Figure 1); and third, regarding the enhanced permeability and retention effect, we can consider that inflamed or reactive lymph nodes accumulate more indocyanine green dye and become more fluorescent [19]. This is very interesting considering that reactive lymph nodes present more risk to be invaded and are thus a key target for extensive histopathological analyses [19].

Figure 1. Illustrations of the systemic sentinel lymph node hypotheses. In patients with small tumors, we expect to find a correlation between the blue sentinel lymph node and the systemic lymph node. In patients with large tumors, we expected to have a false negative blue sentinel lymph node and a true positive systemic lymph node. FI: fluorescence imaging; ICG: indocyanine green.
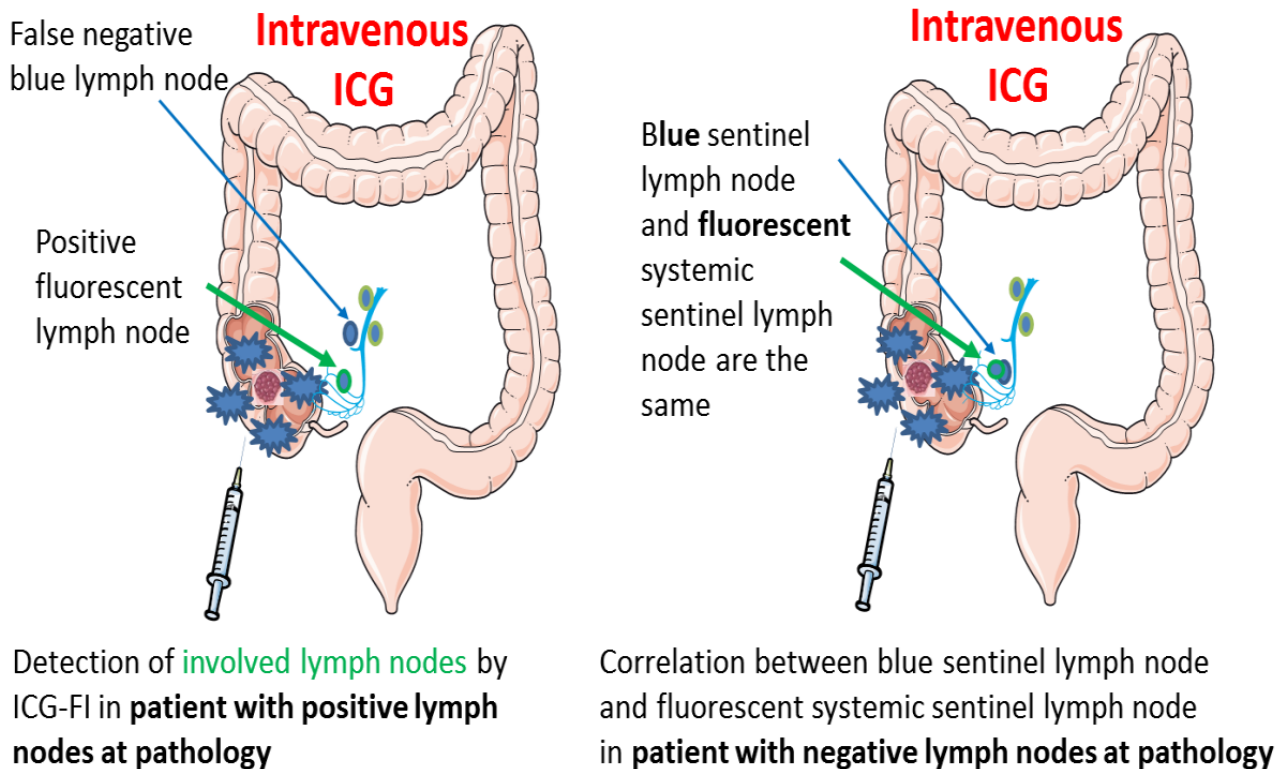
The primary objective of the SeLyNoFI study is to assess the feasibility of metastatic lymph node detection in colorectal cancer by ex vivo fluorescence imaging after intravenous administration of indocyanine green dye. In this study, we will evaluate the sensitivity, specificity, and accuracy of the technique for determining nodal status, both intraoperatively (entire fresh specimen imaging) and in the pathology department (fixed specimens).

The secondary objectives are to correlate the results of the fluorescent sentinel lymph node detection technique after intravenous injection of indocyanine green dye with sentinel lymph node detection by the standard blue dye technique, to study the link between the local lymphatic drainage pathway (classical tumor-draining sentinel lymph nodes) and the systemic pathway (systemic sentinel lymph nodes). Finally, we will evaluate the tumor-to-background fluorescence ratio of the primary colonic tumor.

Methods

Study Design

The SeLyNoFI study is designed as a single-arm, 2-step (monomulticentric), academic, prospective observational-interventional study conducted by the Department of Surgical Oncology at the Institute Jules Bordet of the *Université Libre de Bruxelles* in Brussels. It will start as a monocentric, 2-stage (Simon procedure) study and will be followed by a multicentric study (among members of the International Research Institutes network) if the null hypothesis that the sensitivity of the indocyanine green–fluorescence imaging technique is lower than 60% (p_0, sensitivity obtained by the classical blue dye technique improved by 10%) can be rejected based on the data generated in the monocentric study (p_1, power calculated in case of a true sensitivity of 90%). To assess the feasibility of this technique, all cases will be included, even under conditions in which the technique might be expected to be unreliable (eg, long delay between injection of indocyanine green dye and fluorescence assessment). However, if the null hypothesis cannot be rejected after the monocentric phase, further development will be halted (Figure 2).

Figure 2. Flowchart of the study. CAE: carcinoembryonic antigen; CT: computed tomography; FDG-PET/CT: 18-Fluoro-deoxy-glucose positron emission tomography with computed tomography; MRI: magnetic resonance imaging.
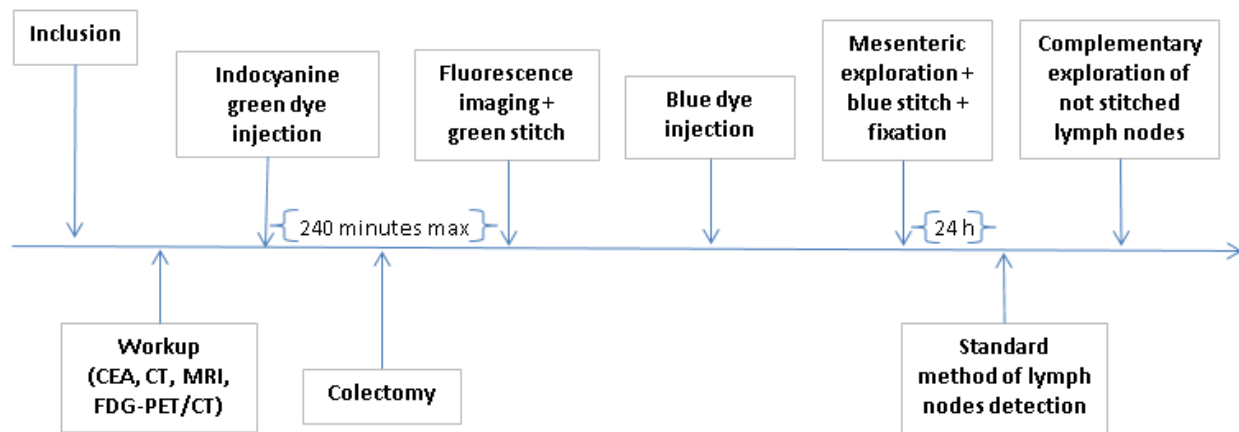
Population

First Step (Monocentric)

To determine the sample size of the study, we used the 2-stage Simon procedure (minimax design) [20]. The first stage requires a small sample size (n_1) and determines the threshold r_1 as the number of successes (ie, TP_1, the number of true positives) above which the trial's second stage can begin. If that number is not surpassed ($TP_1 < r_1$), then the trial ends at the end of the first step.

Once the second stage has begun, the total sample size, including those already enrolled in stage 1, is defined ($n_{tot} = n_1 + n_2$), and the second threshold r_{tot} for the number of successes ($TP_1 + TP_2$) is defined. If the total number of successes surpasses the threshold ($TP_1 + TP_2 > r_{tot}$), the monocentric study can terminate, and the indocyanine green dye technique will be considered worthy of further evaluation in the multicentric study. If the number of successes is not surpassed after ($TP_1 + TP_2 < r_{tot}$ for n_{tot} cases), then the trial will terminate, and the technique will be considered inadequate and abandoned.

With $p_0 = 60\%$ and a $p_1 = 90\%$, the sample size needed in the first stage is $n_1 = 8$ (lymph node–positive N1 or N2) and the number of successes (true positive) to surpass is $r_1 = 5$. The total sample

size needed is $n_{tot} = 17$ (lymph node–positive patients) with a total number of successes $r_{tot} = 14$ (with $\alpha = .05$ and $\beta = .10$). As the prevalence of patients with N1, N2, or N3 is estimated to be 50%, the number of patients needed for enrollment in stage 1 and 2 are about 16 and 34, respectively.

Based on the number of patients treated at the Institute Jules Bordet, the time necessary to execute this step is estimated to be 1 year.

Second Step (Multicentric)

As the primary aim of this study is not to prove a hypothesis but to estimate parameters (sensitivity and ratio of fluorescent to nonfluorescent lymph nodes), sample size planning may be based upon the expected width of the confidence intervals [21]. In this study, in order to estimate a sensitivity of 95% with a 5% precision, we need a total sample size of 73 (lymph node–positive patients) to get a 95% confidence interval with a half-length of 5%. If the true sensitivity is 90% (ie, p_1 for our Simon design), the precision will be 7% rather than 5%. As the prevalence of patients with N1, N2, or N3 is estimated to be 50%, the total number of patients needed is about 146. At least two other centers of the *Pole Hospitalier Universitaire de Bruxelles* network will be included (Figure 3).

The general overview of the study is shown in Figure 4.

Figure 3. Decision diagram for 2-step study plan. True-positive patients required in stage 1 and stage 2 of the monocentric study to proceed to the multicentric study (step 2). P: patients; TP: true positive.
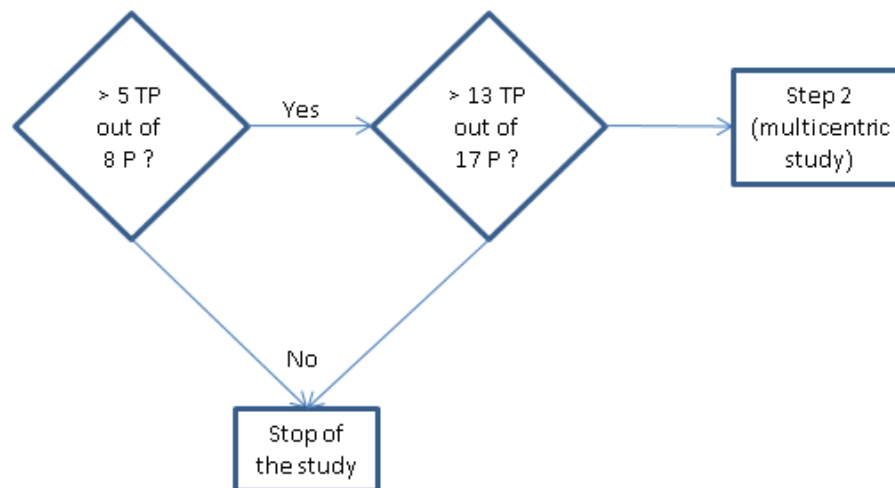
Figure 4. Flow of samples through the study. After indocyanine green and blue dye injection, all lymph nodes removed during colectomy will be analysed for indocyanine green fluorescence and blue dye positivity, followed by pathologic analysis. Lymph nodes that are negative by initial pathology will be further examined by serial sectioning. ICG: indocyanine green; IHC: immunohistochemistry; LN: lymph node.
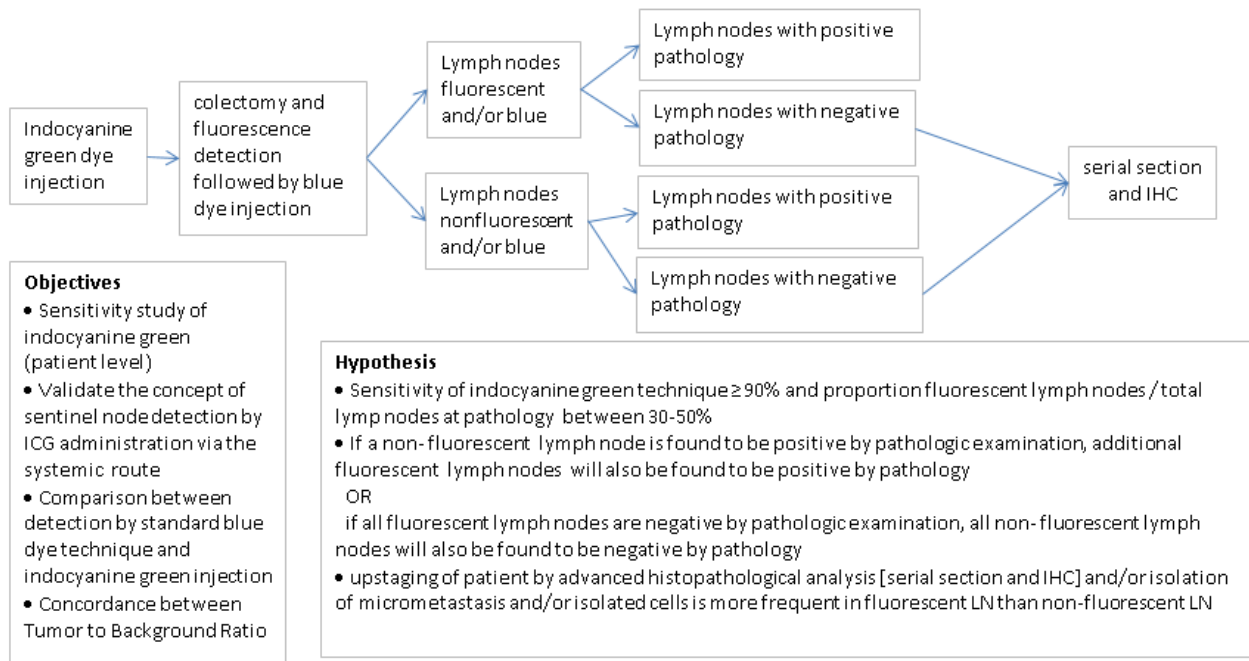
Inclusion Criteria

Patients with biopsy-proven primary or metastatic colorectal cancer admitted for elective surgery of the primary colorectal tumor and who provide written informed consent will be included.

Exclusion Criteria

Patients who are younger than 18 years old; are unable to give informed consent; have a history of allergy or hypersensitivity to investigational product (active substance or ingredients), to iodine, or to shellfish; have apparent hyperthyroidism, autonomous thyroid adenoma, unifocal, multifocal, or disseminated autonomy of the thyroid gland; have documented coronary disease or advanced renal insufficiency (creatinine >1.5 mg/dL); are on concurrent medication which reduces or increases the elimination of indocyanine green dye (ie, anticonvulsants, haloperidol, and heparin) during the 2 weeks before the expected operation; are pregnant; or are breastfeeding will be excluded.

Preoperative Work-up and Surgery

All patients will undergo standard work-up including laboratory testing for tumoral carcinoembryonic antigen, thoraco-abdominopelvic computed tomography (CT), and abdominal magnetic resonance imaging (MRI), as necessary (eg, in patients with renal insufficiency). Patients with suspected metastases will undergo 18F-fluorodeoxyglucose positron emission tomography with computed tomography (FDG-PET/CT). Patients will undergo laparoscopy or laparotomy following the standard procedures for colectomy.

Tracer Preparation

Indocyanine green dye (Pulsion Medical Systems SE) will be diluted with 10 mL of sterile water (2 mg/mL), and a dose of 0.25 mg/kg will be administrated by slow intravenous injection by central venous catheter at the beginning of the surgical procedure.

In the Operating Room

Fluorescence Imaging

After colonic and rectal resection (as necessary), the operative specimen will be placed on a back table and the mesentery exposed. Fluorescence imaging is carried out with a dedicated near-infrared camera system. A light-emitting diode light source set to a wavelength of 760 nm is used, and the detector is a charge-coupled device (CCD) camera with a filter set to detect light with a wavelength of <820 nm. The fluorescent signal is sent to a digital video processor to be displayed on a monitor in real time. Videos will be recorded on a personal computer using a standard high-definition video program. The camera will be held directly by the surgeon at a distance of approximately 20 cm from the operative specimen. During fluorescence imaging exploration, hyperfluorescent lymph nodes will be marked with a green stitch. Thereafter, the colon will be opened, and primary tumors will be imaged for their fluorescence.

Time From Injection to Fluorescence Imaging

The time from injection of indocyanine green dye to fluorescence imaging will be recorded. We predict that there will be a minimum of two groups of patients for analysis of the results of fluorescence imaging in view of the variability of operation durations associated with the procedure (eg, <180 minutes versus >180 minutes). Patients with prolonged operative procedures and complete clearance of indocyanine green dye from the operative specimen will be excluded from further analysis. The limit of the timing for fluorescence imaging after indocyanine green injection has yet to be determined.

Standard Sentinel Lymph Node Detection (Blue Dye Technique)

After fluorescence imaging in the operating room, a submucosal injection of 0.5 mL of patent blue dye will be injected at the 4 cardinal points around the primary tumor, and the injected area will be gently massaged to increase diffusion of the blue dye. After a few minutes, the mesentery will be explored for blue sentinel lymph nodes. Sentinel lymph nodes will be marked with a blue stitch.

In the Pathology Department

Fluorescence Imaging

The operative specimen will be fixed and will be examined 24 hours later using standard methods for lymph node detection. Lymph nodes marked with a blue (blue sentinel lymph node) or green (fluorescent lymph node) stitch in the operating room will be examined separately and noted as blue or fluorescent lymph nodes. Concomitant blue and fluorescent lymph nodes will be noted as concordant sentinel lymph nodes for the two techniques.

Thereafter, nonstitch sentinel lymph nodes will be placed into cassettes and systematically examined for their blue or fluorescent staining and noted as fluorescent, blue, or neither blue nor fluorescent. Importantly, those stained lymph nodes found to be blue or fluorescent afterwards will not be classified as sentinel lymph nodes.

Finally, the operative specimen will be examined with the camera for complementary exploration and to evaluate whether fluorescence imaging is able to detect more lymph nodes than classical analyses can detect. Those lymph nodes will be categorized as *clinically unfound lymph nodes*.

Pathology Examination

All lymph nodes will be placed into cassettes. Nonsentinel lymph nodes (including blue stained lymph nodes found afterwards) will undergo classic pathologic analysis (longitudinal bivalve section). If lymph nodes have a size of less than 4 mm, they will be loaded unsectioned into the cassette. Conversely, blue sentinel lymph nodes and all fluorescent lymph nodes (found to be fluorescent in the operating room and in the pathology department) will be sectioned into multiple slices at 2 mm to 3 mm intervals along their longest axis. Thereafter, all cassettes will be paraffin embedded. All lymph nodes will be analyzed after standard staining with hematoxylin and eosin.

Negative sentinel lymph nodes and fluorescent lymph nodes will be examined with further serial sectioning at 150 μm intervals and evaluated by standard hematoxylin and eosin staining.

To avoid the risk of bias with micrometastases being detected more frequently in fluorescent lymph nodes related to the higher number of examined fluorescent lymph nodes in comparison with nonfluorescent lymph nodes, a similar number of negative lymph nodes (nonstained or blue found afterward at pathology) will be examined in the same way as the fluorescent lymph nodes by serial section with standard hematoxylin and eosin staining.

Semiquantitative Image Analysis of Fluorescence

Recorded videos will be used to calculate the fluorescence intensity of all primary tumors and analyzed lymph nodes. Regions of interest will be drawn over the primary tumor and lymph nodes and over the adjacent background tissue. Fluorescence intensity, expressed in arbitrary units of lymph nodes and tumor background, will be measured with the IC-Calc (version 2.0, Pulsion Medical Systems SE). Finally, tumor-to-background fluorescence ratios will be calculated for each lymph node and for the primary tumor. Fluorescence imaging videos of fresh (nonfixed) and fixed lymph nodes in cassettes will be used for tumor-to-background fluorescence ratio calculations. For primary colon calculations, tumor-to-background fluorescence ratio will be calculated using intraoperative videos on the entire fresh operative specimen after exposure of the colon.

All specimens will be imaged under standard conditions with the near-infrared camera by the same person. The findings of these images will be correlated with definitive pathological reports of the lymph nodes.

Statistical Analyses

The sensitivity of the first step (monocentric study) will be evaluated for patients where the fluorescence evaluation has been performed just after the colectomy in the operating room and also afterward in the pathology department.

Sensitivity and positive predictive value will be computed at the patient level, on the total, and in different subgroups based on histology of the tumor (nonmucinous versus mucinous adenocarcinoma) or delay between injection of indocyanine green dye and fluorescence examination.

Upgrading percentage will be calculated on fluorescent lymph nodes with negative pathological examination. Concordance between visual scale and tumor-to-background fluorescence ratio will be evaluated with the kappa statistic.

Ethical Considerations

The study will be submitted by the principal investigator, the national coordinator, or the sponsor (or its legal representative), in accordance with local regulations, to and approved by an appropriate independent ethical review committee or institutional review board and a regulatory authority if required by the national laws of the countries where the study will be conducted. Local regulatory approval may also be required.

The study will not start at a participating site before written approval by the corresponding ethics committee has been obtained and the local regulatory requirements have been complied with.

The principal investigator and the sponsor will ensure that the study is conducted in full conformance with the principles of the Declaration of Helsinki 1964, as revised from time to time and with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in Guideline for Good Clinical Practice ICH-E6 Tripartite Guideline and with national laws.

For studies conducted in European Union or European Economic Area countries, the principal investigator will ensure compliance with the EU Clinical Trial Directive (2001/20/EC) and with the EU Data Protection Directive (95/46/EC).

In other countries where guidelines for good clinical practice exist, the sponsor and the principal investigators will strictly ensure adherence to the stated provisions.

Results

The study was registered in the European Union Drug Regulating Authorities Clinical Trials Database (Eudract number 2020-002521-29) in June 2020. Submission for ethical review is planned for September 2020.

Discussion

Accurate nodal staging is crucial in colorectal cancer as a prognostic factor and to determine the need for adjuvant treatment. In patients with nodal invasion (stage III), adjuvant chemotherapy is required, while the benefit of adjuvant chemotherapy in stage II remains controversial [2]. Notably, 20% of patients identified as stage II colorectal cancer will experience recurrence, potentially due to missed lymph node metastases [2], justifying efforts to increase the accuracy of nodal staging. It has been clearly demonstrated that one of the most important prognostic factors associated with the accuracy of nodal staging is the number of lymph nodes analyzed from the operative specimen [22], and the Union for International Cancer Control recommends that at least 12 lymph nodes should be resected and analyzed [23]. In the early 2000s, sentinel lymph node detection in colorectal cancer emerged as a promising technique for increasing the accuracy of nodal staging, focusing pathological analyses on detection of micrometastases in a limited number of lymph nodes using advanced techniques such as serial section, immunochemistry, and reverse transcription polymerase chain reaction techniques [6]. Currently, however, the contribution of classical sentinel lymph node detection with blue dye in colorectal cancer remains a subject of debate [5,7,8]. One of the major limitations of this technique that uses intra- or peritumoral marker injection is that it may result in false negatives due to the fact that lymphatic drainage can be impaired by tumor compression in large tumors (pT3 and pT4) [5]. Therefore, the technique is mostly used for staging smaller tumors. This is inconsistent with the higher risk for nodal dissemination associated with large tumors compared to small tumors. Recently, the use of fluorescence imaging in the detection of sentinel lymph nodes has emerged as a promising technique in several cancers [9,11-16], but the sensitivity of the blue dye method in patients with stage pT3 or pT4 tumors remains disappointing [16]. This provides the rationale for finding a solution that overcomes this problem, such as using intravenous injection as we recently reported in a proof-of-concept study in metastatic colorectal cancer [17,18].

The purpose of this study is to evaluate a new technical approach using fluorescence imaging after systemic administration of indocyanine green dye in order to increase nodal staging accuracy in colorectal cancer. Our working hypotheses are that fluorescence imaging may be able to detect metastatic lymph nodes and that hyperfluorescent lymph nodes detected after intravenous administration of the dye (systemic sentinel lymph nodes) will be more representative of cancer invasion than the classical sentinel lymph nodes detected after local peritumoral injection. In that sense, we will correlate the lymph nodes identified using fluorescence techniques with lymph nodes found by the classical blue dye sentinel lymph node detection technique.

We expect that more fluorescent lymph nodes will be found than sentinel lymph nodes, but based on current experience in breast cancer, this number is still largely inferior to the total number of lymph nodes resected and analyzed on the operative specimen, allowing advanced histopathological analyses on only a limited number of lymph nodes. In this study, we propose to include both metastatic and nonmetastatic colorectal patients as the principal objective is to demonstrate the feasibility of the concept.

This observational study was designed to evaluate the feasibility of a new concept that aims to increase the accuracy of nodal staging using fluorescence imaging after intravenous

administration of indocyanine green dye in colorectal cancer patients. Furthermore, this study will serve to evaluate the validity of the concept of the systemic sentinel lymph node compared to the classical anatomical sentinel lymph node, draining directly from the primary tumor site, in the context of colorectal cancer.

Authors' Contributions

PB, DL, MGC, VD, IE, and RB revised the protocol. GL is the principal and coordinating investigator of the SeLyNoFI trial. GL drafted the study protocol and revised the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CT: computed tomography
FDG-PET/CT: 18-Fluoro-deoxy-glucose positron emission tomography with computed tomography
MRI: magnetic resonance imaging
PET: positron emission tomography

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<u>Protocol</u>

Personalized Approach Bias Modification Smartphone App ("SWIPE") to Reduce Alcohol Use Among People Drinking at Hazardous or Harmful Levels: Protocol for an Open-Label Feasibility Study

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Abstract

Background: Alcohol accounts for 5.1% of the global burden of disease and injury, and approximately 1 in 10 people worldwide develop an alcohol use disorder. Approach bias modification (ABM) is a computerized cognitive training intervention in which patients are trained to "avoid" alcohol-related images and "approach" neutral or positive images. ABM has been shown to reduce alcohol relapse rates when delivered in residential settings (eg, withdrawal management or rehabilitation). However, many people who drink at hazardous or harmful levels do not require residential treatment or choose not to access it (eg, owing to its cost, duration, inconvenience, or concerns about privacy). Smartphone app–delivered ABM could offer a free, convenient intervention to reduce cravings and consumption that is accessible regardless of time and place, and during periods when support is most needed. Importantly, an ABM app could also easily be personalized (eg, allowing participants to select personally relevant images as training stimuli) and gamified (eg, by rewarding participants for the speed and accuracy of responses) to encourage engagement and training completion.

Objective: We aim to test the feasibility and acceptability of "SWIPE," a gamified, personalized alcohol ABM smartphone app, assess its preliminary effectiveness, and explore in which populations the app shows the strongest indicators of effectiveness.

Methods: We aim to recruit 500 people who drink alcohol at hazardous or harmful levels (Alcohol Use Disorders Identification Test score≥8) and who wish to reduce their drinking. Recruitment will be conducted through social media and websites. The participants' intended alcohol use goal (reduction or abstinence), motivation to change their consumption, and confidence to change their consumption will be measured prior to training. Participants will be instructed to download the SWIPE app and complete at least 2 ABM sessions per week for 4 weeks. Recruitment and completion rates will be used to assess feasibility. Four weeks after downloading SWIPE, participants will be asked to rate SWIPE's functionality, esthetics, and quality to assess acceptability. Alcohol consumption, craving, and dependence will be measured prior to commencing the first session of ABM and 4 weeks later to assess whether these variables change significantly over the course of ABM.

Results: We expect to commence recruitment in August 2020 and complete data collection in March 2021.

Conclusions: This will be the first study to test the feasibility, acceptability, and preliminary effectiveness of a personalized, gamified ABM intervention smartphone app for hazardous or harmful drinkers. Results will inform further improvements to the app, as well as the design of a statistically powered randomized controlled trial to test its efficacy relative to a control condition.

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Ultimately, we hope that SWIPE will extend the benefits of ABM to the millions of individuals who consume alcohol at hazardous levels and wish to reduce their use but cannot or choose not to access treatment.

Introduction

Globally, alcohol is estimated to account for 5.1% of the burden of disease and injury, and is associated with health, social, and economic harms that not only impact the drinker but also those around them, including their family, work colleagues, and the broader community [1]. Approximately 1 in 10 adults worldwide have had an alcohol use disorder (AUD) during their lifetime, and it is estimated that 1 in 5 adults in Australia have met the criteria for AUD [2]. Unfortunately, even among those individuals who seek treatment, relapse rates typically range from 55% to 85%, depending on the population being studied, the type of treatment administered, and the definition of relapse used [3-5].

There are numerous factors that may make it difficult for people to reduce or cease their drinking, and recent research suggests that these include learned associations between alcohol and related stimuli, which have a strong influence on behavior at a subconscious level. According to the highly influential incentive-sensitization model [6], repeated use of addictive drugs sensitizes the neural reward system, thereby strengthening the attention-grabbing and motivational properties of drugs and their associated cues [7]. Stimuli associated with drug use (such as physical and social contexts, sights, sounds, and scents) increasingly capture attention (ie, developing an "attentional bias" [8]), resulting in cue-induced cravings [9]. This incentive sensitization process is also purported to lead to the development of "approach bias" (ie, an automatic, impulsive action tendency to approach drug-related cues) [8]. Berridge and Robinson [10] posit that the subconscious aspects of incentive salience may influence behavior in the absence of conscious "wanting," or even in the presence of a conscious desire to *not* use the drug. Thus, while there is some evidence that alcohol cognitive biases are associated with craving [11], cognitive biases may also influence alcohol consumption even when a drinker does not consciously "want" alcohol. Craving [12,13], approach bias [14], and attention bias [15] have all been found to predict heavy alcohol use and relapse. Since alcohol-related cues are ubiquitous in Western societies, and nearly impossible to avoid, the craving and cognitive biases that can be elicited by these cues pose a serious challenge for people seeking to reduce or cease their drinking.

Research has shown that alcohol approach biases can be reduced, or even reversed, through a form of computerized "brain training" known as approach bias modification (ABM)

[16]. ABM works by repeatedly presenting individuals with alcohol-related pictures to which they must make an "avoidance" movement (eg, by pushing away images of alcoholic beverages using a joystick) and nonalcoholic beverage images to which they must make an "approach movement" (by pulling on the joystick). Over time, individuals learn to automatically avoid alcohol-related cues. In one study, completing only six 15-minute ABM training sessions reduced cue-induced neural activity in the amygdala in male patients with AUD, and this reduction in neural activation was associated with reduced self-reported alcohol cravings [17]. Importantly, several randomized controlled trials (RCTs) have shown that when delivered as an adjunctive intervention during residential AUD treatment, 4-6 sessions of ABM can reduce the likelihood of posttreatment relapse [5,16,18,19].

Residential treatment is appropriate for people with severe AUD [20]. However, there is a much larger population of people with less severe alcohol use problems that do not warrant residential treatment, although their alcohol use still poses risks to health and quality of life [21,22]. Thus, expanding the application and availability of ABM beyond the residential settings where its efficacy has been demonstrated could have a more widespread benefit, provided it can be shown to be feasible and effective in these other settings or modes of delivery. One way in which this can be achieved is through the development of smartphone apps, which have several advantages, including the ease of use of smartphones, their wide availability, and the fact that they are already owned by a large number of people [23-25]. By delivering ABM remotely via smartphone, people can complete training sessions at times that are most convenient for them (which could increase the acceptability of ABM) and in any location (where contextual generalization of training effects may be increased by completing ABM in more naturalistic environments rather than in clinical settings). Smartphone ABM would therefore allow people to freely access ABM training, including those who have difficulty accessing, or who are reluctant to access, traditional addiction treatment services.

Thus far, we are aware of only two studies examining ABM smartphone apps, both of which had promising findings. In the United Kingdom, Crane et al [26] tested apps containing various combinations of 5 different modules (including an ABM module) among people drinking at hazardous levels, and found that combinations in which both ABM and normative feedback were included reduced participants' weekly alcohol consumption. In Germany, Laurens et al [27] piloted an ABM app in people who were concerned about, or wished to reduce,

their drinking. Participants were encouraged to complete at least 2 ABM sessions per week over a 3-week period. Although the majority of those who enrolled failed to complete the 3-week posttraining questionnaire, the majority of those who submitted the questionnaire had completed the recommended 6 sessions. Weekly alcohol consumption declined over this 3-week period, and even further at a 3-month follow up (although there was no control group with whom to compare these outcomes, which may have been biased by the high dropout rate). Participants were asked to provide feedback regarding the app, and although the feedback was generally positive, the participants criticized the lack of personalization, as well as the monotony and repetitiveness of the ABM training, suggesting that game-like features could make it more engaging [27].

Participants' criticism of the lack of personalization of Laurens et al's [27] app is unsurprising, given that all participants were trained using the same standardized set of beverage images. In our research on AUD treatment-seekers [19,28], we have observed that participants tend to drink a limited range of beverages. Thus, when ABM programs use a standard picture set of beverages for all participants, many images may have little relevance to most individuals (eg, being repeatedly trained to avoid images of beer may have little impact for someone who only drinks wine). Since approach bias is the product of repeated associative conditioning experiences [29], it is likely to be specific to stimuli resembling the drinks frequently consumed by an individual. Designing ABM tasks where individuals can use their own "personalized" images is therefore likely to be more engaging (as previously suggested [27,30]), as well as potentially more "potent" at reducing approach bias. Smartphones can facilitate this personalization by allowing participants to incorporate their own photos of the beverages they most wish to avoid.

In addition to personalizing the "avoidance" stimuli, "approach" stimuli could also be personalized. In almost all alcohol ABM research conducted to date [5,16,18,19,26-28,31], participants have been systematically trained to approach nonalcoholic beverages. These serve as relatively neutral stimuli, well-matched to alcohol-related stimuli in terms of content, and are therefore ideal for laboratory studies examining the psychological mechanisms of ABM. However, they are likely to be monotonous and of relatively little personal relevance to patients [27], and thus may not be ideal for clinical application. Recently, we have begun exploring the use of images representing positive, personal goals (eg, images symbolizing friends, family, social connection, pets, exercise, financial gain) as the "approach" stimuli in ABM training for other substance use disorders [32]. In this way, personalized ABM can simultaneously be used to weaken the motivation to drink while increasing the motivation toward positive goals, which may further increase its overall therapeutic benefit. Indeed, one recent study supports this possibility. In students with a recent history of both risky alcohol use and unprotected casual sex, Hahn et al [33] showed that by training participants to avoid alcohol images and approach condom images, approach bias was both reduced toward alcohol and increased toward condoms. In a smartphone app, people could use their own photographs of friends, family, hobbies, and similar as approach stimuli, making

the training task highly tailored to the individual. Including gamified aspects in the task may also improve engagement even further, enhance completion rates, and thereby further enhance efficacy.

We aim to test the feasibility and acceptability of SWIPE, a novel smartphone-delivered personalized ABM app to help reduce alcohol consumption and cravings, in a sample of people reporting hazardous alcohol use (ie, a score of 8 or more on the Alcohol Use Disorders Identification Test (AUDIT), a commonly used AUD screening tool [34]) recruited from the general community. In addition, we aim to gather preliminary data on drinking, alcohol craving, and alcohol dependence severity outcomes following training, and to test whether these outcomes vary according to participants' demographic and preintervention alcohol use characteristics. This will allow for assessment of whether there are grounds to proceed to an RCT for testing its effectiveness, and identify which population would be best for such an RCT to target.

We have established the following 5 hypotheses. First, we expect to recruit at least 500 participants within 6 months of launching the app, and estimate that at least 60% of participants will complete 8 sessions of ABM, supporting its feasibility. Second, the mean ratings of the app will be greater than 3 on the "functionality," "esthetics," and "app subjective quality" subscales of the Mobile Application Rating Scale (MARS) [35], demonstrating adequate acceptability. Third, there will be statistically significant decreases in the number of standard drinks per week, number of days in which alcohol was used in the past 7 days, alcohol craving, and Severity of Dependence Scale (SDS) [36] scores at the end of the 4-week intervention, relative to pretraining scores, suggesting its potential effectiveness. Fourth, there will be dose-response relationships, whereby the degree of reduction between the pretraining and 4-week assessments in measures of alcohol drinking, craving, and dependence severity will be related to the number of ABM sessions completed over this period (ie, more sessions will be associated with larger reductions). Finally, we hypothesize that the reduction of drinking over the intervention period will be larger in those with more severe baseline alcohol use or problems, and will also be larger in those with greater motivation and confidence to reduce alcohol use.

We also intend to explore participants' reaction time and error rate data from their ABM sessions as this will inform further refinement of the technical parameters of the app after this study is complete.

Methods

Design

This is a single-group, open-label feasibility study. Analyses of drinking, craving, and dependence severity will use a repeated-measures design.

Participants

We aim to recruit a minimum of 500 participants reporting hazardous alcohol use through social media and other online advertising. Participants must be aged 18 years or older, have an AUDIT score of at least 8, own a recently updated (ie, within

the past year) Android or Apple iOS smartphone with an Australian phone number, and wish to reduce their drinking.

Measures

Demographic Information

Participants will be asked to enter their age, gender, and postal code of residence in an online survey hosted on Qualtrics [37].

Alcohol Problem Severity

The AUDIT [34] will be used at baseline to measure the severity of alcohol use and related problems during the past year. The SDS [36] will be used to measure the severity of psychological dependence on alcohol in the past month. Since the SDS was initially developed to measure dependence on heroin, cocaine, and amphetamines, the wording of some items will be slightly modified to enhance its relevance to alcohol, similar to the wording used by Gossop et al [38].

Motivation and Confidence to Change

The "Readiness Rulers" [39] will be used to measure how important participants feel it is to change their drinking (ie, motivation to change) and how confident they feel in their ability to change. Both motivation and confidence are measured on a 1-10 scale.

Alcohol Craving

The frequency scale of the Craving Experience Questionnaire (CEQ) [40] will be used to measure the frequency of alcohol cravings over the past week. This scale consists of 10 items, with each item rated on a scale of 0 (not at all) to 10 (constantly). This scale can further be broken down into 3 factors: "intensity," "imagery," and "intrusiveness" [40].

In addition to the CEQ, we will also utilize a single-item visual analog scale (VAS) to measure the current intensity of alcohol craving immediately before and after each ABM session. Participants will be asked "How strongly are you craving alcohol right now?" with a line displayed below the question and a slider that they can place between ends anchored with the words "not at all" on the left end and "extremely" on the right. A participant's placement of the slider will be converted to a number ranging from 0 to 100.

Alcohol Consumption

At baseline, participants will be asked to estimate the number of days on which they consumed alcohol out of the past 28 days. In addition, they will be asked to use a calendar chart to enter the number of standard drinks consumed on each of the past 7 days so that the total amount of alcohol consumed in the past week can be calculated. To improve accuracy of the self-report, an infographic showing how much wine, beer, or spirits corresponds to one standard drink will be displayed with the calendar chart, and this infographic will also contain a link to the Australian Government's Department of Health standard drinks guide [41]. This 7-day drinking assessment will be repeated at weekly intervals over the course of the intervention. Twenty-eight days after completing the intervention, participants will again be required to complete the alcohol consumption calendar chart, where they will estimate the number of days on which they consumed alcohol out of the past 28 days, and the number of standard drinks consumed on each day in the past week.

App Acceptability

At the end of the 4-week intervention, participants will be asked to complete the "functionality," "esthetics," and "app subjective quality" subscales of the user version of the MARS (uMARS) [35]. Additionally, participants have the option to enter free text in response to 3 open-ended questions: "What did you like about this app?" "What did you not like about the app?" and "Any further comments about the app?"

Intervention

Prior to commencing the intervention, participants will be prompted to select 6 alcohol-related pictures that represent the drinks they most frequently consume. Participants can either take photographs using their phone or select pictures from a library of 72 alcohol-related images chosen to represent a broad range of alcoholic beverages and brands commonly consumed in Australia. Participants will then be prompted to select 6 pictures that "represent your goals and motivations." Again, participants can either use photographs from their phone or select pictures from a library of 72 pictures representing a range of healthy activities or positive goals and sources of pleasure (including family or friends enjoying time together; financial success; employment; exercise, sports, and recreational activities; healthy foods; pets; travel and holidays) that do not contain any depiction of alcohol. Images included in the alcohol and positive image libraries were selected in consultation with a focus group of people (N=5) with lived experience of treatment for alcohol use problems (see further details below). It should be noted that if participants use their own photographs, these images are not uploaded to a SWIPE server. To maintain their privacy, images remain stored only on the participant's phone, and the SWIPE app only uses these files locally while the participant is completing a training session.

Once the participant selects their 12 pictures, they will be presented with instructions for the ABM task. Pictures will be displayed with a white frame around them, which will be in either landscape or portrait orientation. When the frame is in landscape orientation, the participant is required to swipe downward (ie, toward themselves), which causes the picture to expand, as if the participant has pulled the picture toward themselves. When the frame is in portrait orientation, the participant is instructed to swipe upward (ie, away from themselves), which causes the picture to shrink until it disappears, as if they have pushed it away. If the participant swipes in the wrong direction, a red "X" is displayed to inform them that they made an error. Additional technical details regarding image display (including image size, swipe movement criterion, rate of image size change after a swipe response, and interstimulus interval) are reported in the Australian New Zealand Clinical Trials Registry [42].

Following the display of the instructions, participants complete 10 practice trials (including 5 images in portrait frames and 5 in landscape frames, in random order) to familiarize them with the task before commencing the first session of ABM. Each session consists of 156 trials, comprising 13 presentations of

each picture. For alcohol pictures, 12 of the 13 presentations are framed in portrait orientation and one is framed in landscape orientation. This is reversed for positive pictures, whereby 12 of the 13 presentations of each positive picture are framed in landscape orientation and one is framed in portrait orientation. Thus, participants should push away 92.3% of alcohol images and pull 92.3% of positive images toward themselves. If participants make the incorrect movement, they are informed that it was an error, but the trial is not repeated.

To increase engagement and encourage participants to respond both quickly and accurately, the task is gamified with a scoring system. Each time the participant swipes an image in the correct direction, they are awarded 10 points. Additionally, they score bonus points for correct responses if their response is fast enough. They will receive 30 bonus points (yielding a total of 40 points for that trial) If they swipe correctly and within 500 milliseconds of picture onset, 20 bonus points (ie, 30 points total) if they swipe correctly within 500-1000 milliseconds, and 10 bonus points (ie, 20 points total) if they respond correctly within 1000-1500 milliseconds. Correct responses that are slower than 1500 milliseconds following picture onset earn only 10 points. If they swipe an image incorrectly (ie, swipe down for portrait or swipe up for landscape), they lose 100 points, regardless of their reaction time.

Participants' scores will be displayed on the screen as they perform the task. Upon completion of the task, the final score is displayed. On the second and subsequent sessions, participants' previous session score and the score of their highest-scoring session will be displayed after completing the task so they can compare their performance to previous sessions.

Consumer Input

Prior to finalizing the app for this trial, we conducted two rounds of consumer consultation with different groups of people who have lived experience of alcohol use problems. The first was a focus group of people with a lived experience of AUD treatment (N=5). This group assisted us in finalizing the alcohol and positive image libraries by reviewing images we were considering including, providing feedback regarding their relevance and appropriateness, and suggesting other imagery to include. This focus group study was approved by the Monash University Human Research Ethics Committee (MUHREC; project 23287). When an initial version of the app was then developed, we pilot tested it with a group of people (N=7) who identified themselves as having unsuccessfully tried to control or reduce their drinking, who were recruited from the general community via social media advertising. We conducted one-on-one interviews with these participants, seeking feedback

regarding the functionality and acceptability of the app. Several changes were then made in response to their feedback to make the user interface more convenient and to improve the app's wording. This pilot testing was approved by the MUHREC (project 23022).

Procedure

Individuals interested in participating in the study will be directed by social media and online advertising to an online survey hosted by Qualtrics. Participant information will be displayed along with the option to provide consent to participate. The intended schedule of assessments and intervention for those who provide consent is shown in Table 1. Those who agree to participate then proceed to a survey that will screen for eligibility and collect information regarding alcohol problem severity and craving (ie, demographic questionnaire, a question asking them to confirm that they wish to reduce or cease drinking, AUDIT, Readiness Rulers, SDS, and CEQ). If a participant's total score on the "dependence" items of the AUDIT (ie, items 4, 5, and 6) is at least 4, contact details for a national addiction telephone helpline service will be displayed. Those screened as eligible will be required to provide their mobile phone number in order to receive a link via SMS text message to download the SWIPE app from the Apple or Google Play Store. Upon first opening SWIPE, they will be prompted to provide information about their past-month and past-week alcohol use. Participants are then prompted to upload or select their alcohol-related and positive pictures and will proceed to the first session of ABM. Each session of ABM is immediately preceded and followed by a VAS craving rating. If a participant's postsession VAS score is 90 or above after any session, contact details for a national addiction helpline service will be displayed.

Participants will be prompted by app notifications to complete a minimum of two ABM sessions each week for 4 weeks. In addition, every 7 days, participants will be prompted to report the number of standard drinks consumed on each day of the past week. At the end of the 4-week training protocol, participants will be prompted to complete a second Qualtrics survey, which will include the CEQ, SDS, and uMARS. Participants who complete this posttraining survey will be given the option to provide their contact details to be in a draw to win one of 10 US $70 (AUD 100) gift vouchers. Four weeks after completing training, participants will be prompted to complete a final 1-month follow-up questionnaire that will assess past-month and past-week alcohol consumption. This study has been reviewed and approved by the MUHREC (project number: 21393).

Table 1. Overview of SWIPE app study measures and schedule.

Assessment	Study period						
	Baseline	Week 1	Week 2	Week 3	Week 4	Posttest	Follow up
Demographics	X						
AUDIT[a]	X						
Readiness Rulers	X						
SDS[b]	X					X	
CEQ[c]	X					X	
uMARS[d]						X	
28-day TLFB[e] (drinking days)	X						X
7-day TLFB (standard drinks)	X	X	X	X	X		X
ABM[f] intervention		X X	X X	X X	X X		

[a]AUDIT: Alcohol Use Disorders Identification Test.

[b]SDS: Severity of Dependence Scale.

[c]CEQ: Craving Experience Questionnaire.

[d]uMARS: User version of the Mobile Acceptability Rating Scale.

[e]TLFB: timeline followback.

[f]ABM: approach bias modification.

Primary Outcomes

The primary outcomes will be the number of sessions completed, the proportion of participants who complete 8 sessions of ABM, and the number of days of alcohol use in the past 7 days. The primary time point for all 3 of these outcomes is 4 weeks after a participant commences using the app. Secondary time points for past-week alcohol use will be 1, 2, and 3 weeks since commencing app use and at the 1-month follow up.

Secondary Outcomes

uMARS subscale scores will serve as a secondary measure of acceptability, and will be measured at the posttest (ie, 4 weeks after commencing the app). An additional secondary outcome to measure feasibility will be the number of participants recruited within 6 months of launching the app. Secondary outcomes pertaining to alcohol use, dependence, and craving will include: (1) number of days of alcohol use in the past 28 days (primary time point at posttest, secondary time point at the 1-month follow up); (2) total standard drinks consumed in the past 7 days (primary time point at posttest, secondary time points 1, 2, and 3 weeks since commencing the app and at the 1-month follow up); (3) SDS score (primary time point at posttest); (4) CEQ score (primary time point at posttest); (5) craving VAS score (primary time point immediately after the final session of ABM).

Additional secondary outcomes will include trial error rates, reaction times, and session durations over the course of all ABM sessions.

Data Management

Demographic, AUDIT, Readiness Rulers, SDS, CEQ, and uMARS data will be stored in a password-protected online Qualtrics database, from where it will be downloaded for storage and analysis on a password-protected shared drive controlled by Turning Point, an addiction treatment, research, and workforce training organization run by Eastern Health (a public health service in Melbourne, Australia). At posttest, participants will be asked to provide the mobile phone number used to sign up to the app to allow for matching of pretest and posttest responses at the individual level. Alcohol use data and backend user metrics (number of sessions commenced, number completed, session duration, session total score, trial reaction time, and error data) will be stored on a secure Google Firebase server, which will be downloaded for storage and analysis on a password-protected shared drive controlled by Turning Point at the end of the study.

Statistical Analysis

Feasibility and acceptability will be assessed using descriptive data, including the number of participants recruited, number of sessions commenced, number of sessions completed, and means and distributions of uMARS scores (for each uMARS subscale). Changes in alcohol consumption, craving, and SDS scores will be analyzed using linear mixed modeling. To analyze whether there is a dose-response relationship between the number of ABM sessions completed and these outcomes, we will examine a model including the interaction term between number of sessions and time, which tests whether the number of sessions moderates the effect of time on these outcomes. Similarly, we will examine models containing interaction terms between time and other potential moderators of interest (baseline AUDIT, SDS, CEQ, or Readiness Ruler scores; baseline alcohol use days or standard drinks; whether participants wanted to completely cease vs only reduce alcohol use; demographic variables) to examine whether changes in alcohol consumption, craving, or dependence severity are dependent on any of these factors. To inform refinement of task and scoring parameters

for future versions of the app, we will examine rates of errors and distributions of reaction times for each image type. We will also examine the mean and distribution of session durations.

Statistical Power for Analyses of Alcohol Outcomes

We are likely to have very high power to detect main effects of time on alcohol-related outcomes. A similar study by Laurens et al [27] found that that participants' weekly consumption of alcohol declined by 0.36 standard deviations postintervention relative to their baseline levels (baseline mean standard drinks per week 33.3, SD 21.8, and mean decline of 7.8 standard drinks per week at posttest). Changes of approximately this effect size (ie, 0.3-0.4) on alcohol-related measures (eg, days of use, number of standard drinks, SDS, CEQ) would be of modest clinical significance. A sample of only 119 would provide 90% power to detect changes of this magnitude using $\alpha=.05$. We anticipate that at least 300 (ie, 60% of 500) participants will complete the posttest, but even if we achieve the much lower posttest completion rate (37.89%) reported by Laurens et al [27], in a sample of 500, equivalent to 189 participants, we will have 98% power to avoid type 2 errors if the effect size is only 0.3.

It is more difficult to estimate power for the interaction effects we intend to examine in moderation analyses. We conducted 500 simulations, optimistically assuming an overall average effect size of 0.4, but which ranged from 0.1 to 0.7 at the lowest and highest level (respectively) of a uniformly distributed continuous moderator. We also assumed a 0.5 correlation between pre and postintervention values. Under these optimistic assumptions, a posttest sample of 300 would provide approximately 75% power to detect the interaction between the moderator and the effect of time. Thus, moderation analyses are likely to be underpowered if we only recruit 500 participants. Therefore, if we reach our recruitment target early, we will still leave recruitment open until the planned recruitment end date (start of February 2021) to seek a larger sample size for these analyses.

Results

This project was funded on March 30, 2020 and received approval from the MUHREC on May 29, 2020. As of July 30, 2020, we expect to commence recruitment in mid-August 2020, complete data collection in March 2021, and publish results by the end of 2021.

Discussion

This study will be a world-first examination of personalized alcohol ABM delivered via a smartphone app. The application of ABM is still in its infancy, despite strong evidence of its efficacy in residential AUD treatment settings [5,16,18,19]. The advantage of smartphone technology is that it allows individuals to engage in neurocognitive training that is designed to dampen impulsive, automatic responding to cues, regardless of time and place. This is the first alcohol ABM study to personalize "avoid" images by using those representing participants' preferred alcoholic beverages and brands. It is also the first to personalize the "approach" images, following recommendations that these should align with patients' goals for behavioral change or offer alternative strategies to manage stress (eg, personal health, reconnecting with family and friends, exercise) [30,43-45]. Indeed, this tailored "dual-target" approach (ie, dampening alcohol associations and reinforcing positive motivations) holds promise in light of preliminary evidence that ABM can simultaneously reduce approach bias to an unhealthy behavior (alcohol) and increase approach bias toward a healthy behavior (condom use) in a student sample [33].

There are several practical and logistical issues that may pose potential challenges to successful completion of this study. One limitation is the reliance on self-reported consumption data, including the potential impact of poor recall. We believe the impact of poor recall on reliability of consumption data will be minimized by requiring participants to only recall and report standard drinks in the past week, and that including the standard drink conversion infographic will increase reporting accuracy. Whilst in-person biometric measures to confirm self-reporting are beyond the scope of the current study, we have modeled the assessments closely on the computerized 7-day timeline followback assessment used by Simons et al [46], which showed good concordance with other measures of alcohol use. Nevertheless, some degree of inaccuracy of self-reported data is almost certain despite our measures to minimize it.

It is possible that overall recruitment will be lower than expected, limiting the power of our planned analyses of alcohol use, craving, and dependence outcomes even if completion rates are good. However, we consider this to be unlikely, given that Laurens et al [27] managed to recruit 1082 participants in only 13 days using a similar social media recruitment strategy. However, if recruitment is much slower than expected, we have several additional strategies we can employ. Turning Point, the addiction treatment and research center at which we are based, has a media department that can assist with further promotion of the trial by seeking coverage in other media (eg, radio, newspaper, online news sites). We will also use the professional networks of the authors to enable publicizing the study to more than 3000 alcohol and drug clinicians and other service workers if we need to increase recruitment rates.

Even if the recruitment target is reached, a low rate of completion of postbaseline assessments could still limit our statistical power to analyze alcohol-related outcomes, as well as increase the likely bias of these outcomes. Previous studies of smartphone apps have had very low rates of participants who completed the primary outcome assessment (eg, 27% in Crane et al [26] and 38% in Laurens et al [27]). We hope that offering participants a personalized intervention and incentivizing the posttest questionnaire by offering the opportunity to win a prize will enhance completion rates. Furthermore, to mitigate the risk of poor posttraining assessment completion rates, the app has been designed to include prompts (app notifications) to remind participants to complete assessments. Even if recruitment is faster than anticipated, we will keep recruitment open for the planned 6-month recruitment period to hopefully recruit more than 500 participants, since exploration of potential moderation effects is likely to require larger sample sizes to achieve adequate statistical power.

Nonetheless, even with a majority completing these assessments, outcomes related to craving, alcohol consumption, and app acceptability may be biased by loss of participants; for example, if those who drink more are less likely to complete these measures. We will examine baseline differences between those who complete assessments and those who do not to examine if they differ in terms of alcohol use, AUD severity (ie, AUDIT and SDS scores), and demographic characteristics. However, our main aim in this trial is to test feasibility, and recruitment and completion rates (whether good or poor) will inform assessment of this outcome. Moreover, our findings regarding feasibility, including any problems encountered in this trial, will inform the design of subsequent RCTs aimed at testing the efficacy of this intervention relative to a control condition. Drinking, craving, and dependence outcomes will also inform the design of RCTs by indicating whether certain subpopulations show stronger evidence of effectiveness.

There is a risk that the ABM training, which involves repeatedly responding to alcohol-related images, will have the opposite effect to that intended (ie, triggering cravings [9], potentially leading to increased alcohol consumption). However, in our experience conducting trials of ABM in clinical samples (with much more severe substance use disorder than we anticipate in this trial), rates of withdrawal from participation due to triggering of cravings or distress have been low [19,47]. Moreover, the two previous trials of alcohol ABM smartphone apps found reductions, not increases, in alcohol use, further suggesting that the risk of this unintended, counterproductive outcome is low [26,27]. Nevertheless, as noted above, if participants rate their alcohol craving as very high after a session, the app will display the details of a free 24/7 alcohol and drug counseling telehealth service.

If we find that this intervention is feasible and acceptable, with preliminary evidence of reduced craving or consumption, the findings will inform the design of a large, statistically powered RCT in which its efficacy could be established (eg, with a sham-training or other control condition). This will be a critical next step as its low cost, easy implementation, and wide accessibility means that SWIPE could address the significant gap between the demand for treatment and availability of addiction treatment services [48]. Importantly, this project extends addiction neuroscience-informed interventions beyond the lab and clinic, and translates them into an accessible, easy-to-use tool for the broader community. SWIPE has the potential to deliver a just-in-time intervention during periods of heightened vulnerability (ie, events, days, and times associated with drinking). Although several smartphone apps exist to help individuals reduce their drinking, they predominantly focus on monitoring alcohol consumption and providing normative feedback, while a few also aim to ameliorate psychological processes impaired by heavy alcohol use (eg, long-term planning, decision making) [49]. Because ABM dampens activity in distinct neural pathways that become overactive through heavy alcohol use [17], SWIPE may be a particularly advantageous intervention that is able to benefit heavy drinkers beyond what is afforded by currently available smartphone apps. Additionally, because the training operates by using images of one's drug of choice (in this case, alcohol), this app could in the future be easily adapted for use with other substances or behaviors that individuals may wish to cut down on (eg, smoking, use of illicit drugs, gambling, gaming).

Conflicts of Interest

DL has provided consultancy advice to Lundbeck and Indivior, and has received travel support and speaker honoraria from Astra Zeneca, Camurus, Indivior, Janssen, Lundbeck, Shire, and Servier. These organizations do not stand to benefit from this project. DL has been an investigator on an untied education grant from Sequirus, unrelated to the current work. The other authors have no conflicts of interest to declare.

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Abbreviations

ABM: approach bias modification
AUD: alcohol use disorder
AUDIT: Alcohol Use Disorders Identification Test
CEQ: Craving Experience Questionnaire
MARS: Mobile Application Rating Scale
MUHREC: Monash University Human Research Ethics Committee
SDS: Severity of Dependence Scale
RCT: randomized controlled trial
uMARS: user version of the Mobile Application Rating Scale
VAS: visual analog scale

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Protocol

Improving Airways Patency and Ventilation Through Optimal Positive Pressure Identified by Noninvasive Mechanical Ventilation Titration in Mounier-Kuhn Syndrome: Protocol for an Interventional, Open-Label, Single-Arm Clinical Trial

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Abstract

Background: Mounier-Kuhn syndrome or congenital tracheobronchomegaly is a rare disease characterized by dilation of the trachea and the main bronchi within the thoracic cavity. The predominant signs and symptoms of the disease include coughing, purulent and abundant expectoration, dyspnea, snoring, wheezing, and recurrent respiratory infection. Symptoms of the disease in some patients are believed to be pathological manifestations arising due to resident tracheobronchomalacia. Although treatment options used for the management of this disease include inhaled bronchodilators, corticosteroids, and hypertonic solution, there is no consensus on the treatment. The use of continuous positive airway pressure (CPAP) has been reported as a potential therapeutic option for tracheobronchomalacia, but no prospective studies have demonstrated its efficacy in this condition.

Objective: The purpose of this is to identify the presence of tracheobronchomalacia and an optimal CPAP pressure that reduces the tracheobronchial collapse in patients with Mounier-Kuhn syndrome and to analyze the repercussion in pulmonary ventilation. In parallel, we aim to evaluate the prevalence of obstructive sleep apnea/hypopnea syndrome.

Methods: This interventional, open-label, single-arm clinical trial will enroll patients who are diagnosed Mounier-Kuhn syndrome. Patient evaluation will be conducted in an outpatient clinic and involve 3 visits. Visit 1 will involve the collection and registration of social demographic, clinical, and functional data. Visit 2 will entail polysomnography, bronchoscopy for the evaluation of tracheobronchomalacia, titration of the optimal pressure that reduces the degree of collapse of the airway, and electrical impedance tomography. In visit 3, patients exhibiting a reduction in collapse areas will be requested to undergo chest computed tomography during inspiration and forced expiration with and without positive pressure (titrated to determine optimal CPAP pressure).

Results: This protocol is a doctorate project. The project was submitted to the institutional review board on January 24, 2017, and approval was granted on February 2, 2017 (Brazilian Research database number CAAE 64001317.4.000.0068). Patient evaluations started in April 2018. Planned recruitment is based on volunteers' availability and clinical stability, and interventions will be conducted at least once a month to finish the project at the end of 2020. A preliminary analysis of each case will be performed after each intervention, but detailed results are expected to be reported in the first quarter of 2021.

Conclusions: There is no consensus on the best treatment options for managing Mounier-Kuhn syndrome. The use of positive pressure could maintain patency of the collapsed airways, functioning as a "pneumatic stent" to reduce the degree of airflow obstruction. This, in turn, could promote mobilization of thoracic secretion and improve pulmonary ventilation.

Trial Registration: ClinicalTrails.gov NCT03101059; https://clinicaltrials.gov/ct2/show/NCT03101059.

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Introduction

Mounier-Kuhn syndrome (MKS) or congenital tracheobronchomegaly is a chronic and rare airway morbidity associated with recurrent respiratory infections and characterized by dilation of the trachea and the main bronchi [1]. This disease was first clinically described by Mounier-Kuhn in 1932 [2]. The estimated prevalence of this syndrome in patients with pulmonary symptoms is between 0.4% and 1.6%, and it mostly affects the male gender [1,3-5]. Diagnosis of the MKS is frequently made in the third or fourth decade of life when the symptoms are more exuberant [6]. Histological alterations seen in the disease can be used to explain structural defects such as tracheobronchomalacia (TBM), saccular diverticula between cartilages, and bulging and dilation of the trachea and bronchi [1,7].

The predominant signs and symptoms of the disease include coughing, purulent and abundant expectoration, digital clubbing, dyspnea, snoring, wheezing, and recurrent respiratory infection [1]. The disease could be associated with other comorbidities such as gastroesophageal reflux disease, chronic obstructive pulmonary disease, bronchiectasis, and obstructive sleep apnea/hypopnea syndrome (OSAHS) [1,8-12].

Some of the observed symptoms could be a consequence of TBM occurrence in some patients, which is defined by more than 50% collapse of the intrathoracic trachea and bronchi [13-16]. The main clinical consequences of TBM are obstruction to expiratory airflow; secondary air trapping; decrease in the effectiveness of cough and bronchial hygiene; and facilitation of conditions that promote microorganism colonization, leading to recurrent respiratory infection [4,13].

Despite the patient's normal pulmonary function, the occurrence of obstructive ventilatory disorder is not uncommon [1,17-19]. Thorax computed tomography (CT) shows dilatation of the trachea and the right and left main bronchi [4,20,21]. Tracheobronchial diverticula, bronchiectasis, air trapping, and emphysema are common findings, suggesting involvement of the small airways [1,7,10,11,22-26]. Bronchoscopy is the gold standard examination for TBM diagnosis [12,14-16,26].

Since TBM is a rare and poorly studied disease, there is no consensus on a specific therapy. Therapeutic management includes inhaled bronchodilators, corticosteroids, hypertonic solution, and mucolytic agents. Some complementary tools used for disease management include noninvasive positive respiratory pressure, vaccination, respiratory physiotherapy, and pulmonary rehabilitation [1,27-29]. Continuous positive airways pressure (CPAP) support has been reported as an option for the treatment of tracheomalacia [5,15,30]. The rationale for using positive pressure in TBM is to recover the patency of the collapsed airways, thereby reducing airflow obstruction and promoting sputum clearance.

Previous experience has shown that CPAP can reduce symptoms, infections, and morbidity/mortality caused by TBM [5,15,31-33]. Additionally, it is an effective therapy in patients diagnosed with concomitant OSAHS [34-36]. This study has two main objectives. First, we aim to confirm the presence of tracheal collapse and the main bronchi of patients with MKS through respiratory endoscopy. Second, we will attempt to optimize the pressure with the CPAP approach to reduce or reverse the pathological consequences of the syndrome on the ventilatory pattern. We also will investigate the prevalence of OSAHS in this population. We hypothesize that maintenance of greater patency of airways could improve pulmonary ventilation for a longer time, reduce symptoms, and improve the quality of life of these patients.

Methods

Overview

This is an interventional, open-label, single-arm clinical trial to be conducted on patients diagnosed with MKS, who are followed up in the outpatient clinic from a tertiary university hospital. Eligible patients diagnosed with MKS who are followed up and agree to participate in the study will be requested to sign an informed consent form after verbal explanation and clarification of the study are provided by the investigator.

The following patients will be excluded from the study: those who are contraindicated for bronchoscopy (with thrombocytopenia, incorrigible coagulopathies, refractory hypoxemia, recent acute myocardial infarction, unstable angina, acute cardiac arrhythmias, and refractory bronchospasm), pregnant women under the age of 18 years, and those suspected of having or diagnosed with mycobacteriosis or other related risk factors by the clinical investigator. The study is approved by the institution's ethical review board and funded by the Division of Pulmonology Obstruction Group.

Study Design

The study will be conducted in three steps including three patient visits. During visit 1 (day 1), sociodemographic information, modified Medical Research Council dyspnea questionnaire measures [37-39], the Saint Georges Respiratory questionnaire measures [40,41] for health-related quality of life, and most recent spirometry values will be recorded. In addition, all eligible patients will receive 40 mg/day oral prednisone for 7 days before endoscopy, to reduce pulmonary secretion and possible airways hyperreactivity. If the patient presents signs or symptoms that characterize an acute pulmonary infection,

the inclusion will be postponed, and specific treatment will be prescribed to reschedule the inclusion.

During visit 2 (day 7 ± 3 days from visit 1), polysomnography and respiratory endoscopy will be performed. Full-night polysomnography will be performed in accordance with the recommendations of the American Academy of Sleep Medicine [42,43].

After polysomnography, a strap of 32 self-adhesive electrodes strap will be attached at the level of fourth intercostal space around the chest, and patients' electrical impedance tomography data will be recorded concomitantly with bronchoscopy. Bronchoscopy will be performed in two stages: (1) sedation, analgesia, and evaluation of the presence of TBM followed by bronchial hygiene and (2) optimal pressure titrations to decrease airway collapse and EIT performance. The procedure sequence will be conducted in two stages, as described below.

Stage 1

The patient will be placed in a dorsal position for cardiac monitoring, noninvasive blood pressure measurement, and pulse oximetry. The nasal fossae will be lubricated with 2% topical lidocaine gel, followed by the introduction of nasopharyngeal catheter number 08 to provide supplemental oxygen. Fentanyl (0.5-2 μg/kg) and midazolam (0.03-0.05 μg/kg) will be administered intravenously to achieve light sedation. Propofol

bolus (20-40 mg/dose) may be used to achieve the desired sedation. Next, the custom nasal mask of CPAP will be attached to the patient's face, allowing the passage of the video-bronchoscope (Standard Q180 Olympus) with an external diameter of 4.9 mm and a working channel of 2.0 mm. Topical lidocaine at a dose of 1% without a vasoconstrictor (maximum dose of 7 mg/kg) will be instilled in the larynx and tracheobronchial tree. This will be followed by secretion aspiration. Subsequently, the presence of fixed or dynamic tracheal and bronchial collapse during the respiratory cycle will be analyzed and recorded. Direct observational assessment will be defined at the site with the greatest tracheal collapse and main bronchi during inspiratory and expiratory normal ventilation. Patients who do not present significant airway collapse will be excluded from the next step.

Stage 2

To evaluate the reduction of airway collapse, the bronchoscope will be fixed with the aid of a customized catheter in the tracheal region at least 2 cm before the area of the greatest collapse, previously defined by three bronchoscopists present in the examination room. The CPAP titration will start with a pressure of 0 cm H_2O and be gradually increased in steps by 2 cm H_2O every 10 complete respiratory cycles until a pressure of 18 cm H_2O is reached (Figure 1).

Figure 1. Bronchoscopic view of the trachea and the catheter (blue). Trachea during 0 cm H_2O pressure during inspiration (A) and during expiration (B). Trachea in 18 cm H_2O pressure during inspiration (C) and expiration (D)
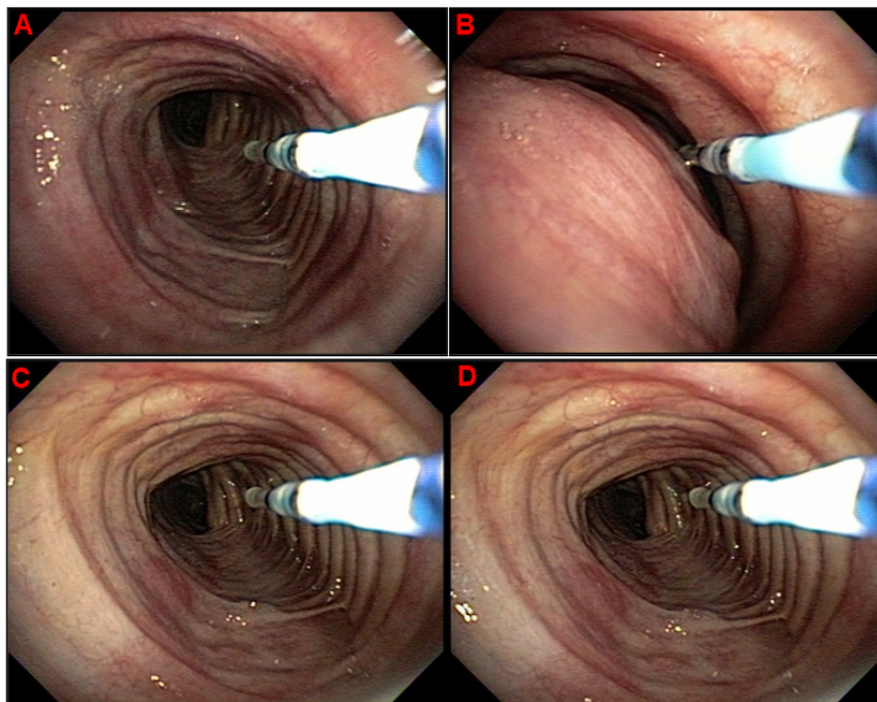
Through observational analysis and after a complete consensus among the bronchoscopists is reached, the minor pressure capable of reducing the degree of collapse in the trachea will be defined (P1). This procedure will be repeated in the main bronchus presenting major collapse. The entire procedure will be documented through video recording, and the images will be analyzed with software assistance (Image Processing

Toolbox, Matlab). Measures in the airway variation area will be analyzed by comparing the area of collapse at 0 cm H_2O pressure with the corresponding measurements at different applied pressures titrated during the procedure. This analysis will allow us to find the pressure that reduces the degree of airway collapse (P2) [42,43]. EIT will be used for impact analysis of different pressures on pulmonary ventilation (distal

airways), a functional imaging method that uses low-intensity electric currents. EIT can dynamically evaluate regional pulmonary ventilation by analyzing impedance variations and minimum impedance in a given thoracic segment by reproducing them in two-dimensional images. It is a noninvasive method that does not use ionizing radiation [44-47].

The EIT data will be acquired using ENLIGHT (Timpel), which produces 50 images per second, sampled in real time [44-47]. Distribution of ventilation will be analyzed at each CPAP level during the positive and expiratory pressure (PEEP) titration maneuver by dividing the EIT image into 4 quadrants (regions of interest, ROI), 2 of which will be gravity dependent (lower lobes) and 2 will be gravity independent (upper lobes). In patients who present tracheomalacia during bronchoscopy, a chest CT will be performed at visit 3 during inspiration and forced expiration in the presence or absence of CPAP. The ideal pressure for this will be obtained during bronchoscopy with an aim to evaluate and document the reduction of tracheal collapse. The images will be obtained by multislice tomography. No intravenous contrast will be administered.

Statistical Analysis

Because MKS is a rare disease, there will be no sample size calculation. It will be a convenience sample including all eligible patients from Mounier-Kuhn reference centers in Brazil. As of July 2020, we are following at least 15 patients with MKS.

We will perform five main types of descriptive analysis on the data: (1) sociodemographic data of all MKS populations included in the study; (2) comparative analysis of the clinical-functional data of patients with and without collapse; (3) prevalence of sleep apnea/hypopnea syndrome; (4) repeated measurement techniques (bidirectional analysis of variance and Tukey or Sidak post hoc test when there is a difference) correlating the pressure that reverses the collapse (P1 and P2), to analyze the difference between airway collapse that occurs with and without PEEP; and (5) comparisons in the distribution of EIT ventilation with and without PEEP. Statistical analysis will be performed with statistical packages Sigma Stat V3 or SPSS V22, and an α level $\leq.05$ will be considered significant for all tests.

Results

The project was submitted to the institutional review board on January 24, 2017, and approved on February 2, 2017 (Brazilian Research database number CAAE 64001317.4.000.0068). The project was registered in ClinicalTrails.gov (NCT03101059) on March 23, 2017. This protocol is a doctorate project. Patient evaluations started in April 2018. Planned recruitment is based on volunteers' availability and clinical stability, and the interventions will be conducted at least once a month and completed at the end of 2020. A preliminary analysis of each case will be performed after each intervention, but detailed results are expected to be closed in the first quarter of 2021. We plan to publish 3 papers on this project. The proposed schedule for publication of the papers is as follows: the intervention protocol in 2019-2020; literature review about the concept of tracheobronchomalacia and airway collapse according to diverse uses ways to measure them and their definition in 2020; and results of the presence of tracheal collapse and the main bronchi of patients with MKS, through respiratory endoscopy and optimum positive pressure with CPAP that reduces or reverse it, in 2021.

Discussion

Thus far, the main finding of this study is the identification of the progressive increase in the degree of pressure that can reverse the collapse of the trachea and bronchi and stabilize the airway.

MKS or congenital TBM is a rare and poorly studied disease. It has a wide spectrum of signs and symptoms and can have a great impact on the quality of life. Dyspnea, accumulation of secretions in the airways, bronchiectasis, and recurrent respiratory infections increase the morbimortality of the disease.

There is no consensus on the best treatment. In general, measures extrapolated from other pulmonary pathologies, such as those employed in chronic obstructive pulmonary disease and bronchiectasis, are used for therapeutic management. Among the specific treatments currently available, we want to highlight the endotracheal and endobronchial prosthesis and tracheobroncoplasty surgery. However, both approaches have limited results and are associated with frequent complications.

There is a rationale for the use of positive pressure. The use of positive pressure could maintain the patency of the collapsed airways, thereby providing a "pneumatic stent," which in turn could reduce airflow obstruction and promote mobilization of secretions within the airways. However, no study protocol has been performed to test this hypothesis.

The goal of this study is to assess if positive pressure with CPAP can be applied to reduce the extent of airway collapse and improve ventilation in MKS patients with tracheobronchomalacia. At the same time, we will evaluate the prevalence of OSAHS, a related and frequently occurring comorbidity that contributes to the worsening quality of life of patients with MKS.

Conflicts of Interest

None declared.

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Abbreviations

CPAP: continuous positive airway pressure
CT: computed tomography
EIT: electrical impedance tomography
MKS: Mounier-Kuhn syndrome
OSAHS: obstructive sleep apnea-hypopnea syndrome
TBM: tracheobronchomalacia

Protocol

Development of an International, Multicenter, Hyperbaric Oxygen Treatment Registry and Research Consortium: Protocol for Outcome Data Collection and Analysis

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Abstract

Background: Hyperbaric oxygen (HBO_2)—oxygen at pressures higher than atmospheric—is approved for 14 indications by the Undersea and Hyperbaric Medical Society. HBO_2's main effect is to increase oxygen content in plasma and body tissues, which can counteract hypoxia or ischemia. Laboratory studies show that HBO_2 has effects beyond relieving hypoxia (eg, promoting angiogenesis in irradiated tissue, anti-inflammatory effects, radiosensitization of tumors, hypoxia preconditioning, and fungal growth inhibition) and has potential to treat conditions such as inflammatory bowel disease and pyoderma gangrenosum. Lack of consistently collected outcome data on a large cohort of individuals receiving HBO_2 therapy limits its use for both established and new indications. A course of therapy often involves 30-40 visits to a hyperbaric chamber, so the number of patients seen at any given center is constrained by chamber capacity. As a result, published HBO_2 outcome data tend to be from small case series because few patients with a particular condition are treated at a given center. To solve this problem, a registry that collects and pools data systematically from multiple institutions has been established.

Objective: The aim of this study is to collect consistent outcome data across multiple hyperbaric centers to assess treatment effectiveness and establish a research consortium.

Methods: A consortium of hyperbaric centers who have agreed to collect consistent outcome data on all patients seen has been assembled. Data are collected at each participating center using Research Electronic Data Capture (REDCap), a web-based, data collection system used frequently for research. Standard outcome measures have been defined for each condition, which are programmed into the REDCap data collection templates. Governance is through a consortium agreement that defines data security, data sharing, publications, liability, and other issues. Centers obtain Institutional Review Board (IRB) and ethics approval to participate, either from their own institutions or by relying on the IRB at the coordinating center at Dartmouth College. Dissemination will occur through a yearly report and by publications based on the data in the registry.

Results: Early results from some common indications show significant pretreatment to posttreatment changes. Additional indications and outcome measures are being added using the procedures outlined in the consortium agreement.

Conclusions: The registry collects consistent outcome information for a therapy that needs further study and a stronger evidence base. It also overcomes the challenge of collecting data from an adequate number of patients for both established and emerging indications by combining data collection from multiple centers. The data entry requirements should be within the capabilities of existing staff at any given hyperbaric center. By using REDCap, the registry can be expanded to include detailed information on particular indications and long-term follow-up on selected patients without significantly increasing the basic data entry requirements.

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Through the registry, a network of enrolled hyperbaric centers has been established that provides the basis for a clinical trial network.

Introduction

Hyperbaric oxygen (HBO_2) treatment, defined as breathing 100% oxygen at pressures greater than 1.4 atmospheres absolute, is used for 14 indications approved by the Undersea and Hyperbaric Medical Society (UHMS), such as soft tissue radiation injury and enhancement of healing in selected problem wounds (see Table 1) [1]. HBO_2 greatly increases the amount of oxygen dissolved in plasma and is effective at relieving hypoxia. This effect is useful in conditions such as ischemic wounds or compromised flaps or grafts, where inadequate oxygenation is a factor. Laboratory studies also suggest HBO_2 has actions beyond the relief of hypoxia (eg, promoting angiogenesis in irradiated tissue, anti-inflammatory effects, radiosensitization of tumors, hypoxia preconditioning, and fungal growth inhibition) and has potential to treat other currently unapproved conditions, such as inflammatory bowel disease and pyoderma gangrenosum [2-4]. Approximately 1350 hyperbaric chamber facilities exist in the United States, and outpatient facility claims for hyperbaric services to Medicare alone totaled US $178 million in 2015. Although HBO_2 treatment is used for a variety of indications, much of the evidence to support its use is based on small trials, case series, and retrospective studies (see Table 1) [2,5-11].

This inconsistent evidence base has led to a range of opinions about when and how HBO_2 should be used. For example, a common application of HBO_2 is in treating radiation cystitis, which is supported by most insurance policies in the United States [12,13]. The evidence base and practice patterns are strong enough that when a randomized trial of HBO_2 for radiation cystitis was attempted (ie, ClinicalTrials.gov Identifier: NCT00134628), the trial had to be closed due to poor recruitment. It was difficult to find patients who were willing to be randomized to placebo treatment and providers who were willing to refer them. In one review describing the many treatment options for radiation cystitis, the authors concluded "there are currently no adequate treatment options." They cited HBO_2 response rates between 27% and 92%, and recurrence rates after treatment from 8% to 63% [14]. The lower end of this response rate range suggests HBO_2 should only be tried occasionally for selected patients, while the higher end argues that HBO_2 should be the treatment of choice. The largest prospective study of HBO_2 treatment for radiation cystitis included in that review was based on 40 patients [12]. Since that review, five Nordic university hospitals were able to complete a randomized trial for radiation cystitis, although they excluded from enrollment patients with severe ongoing bleeding (ie, the patients where the impact from HBO_2 treatment would be most meaningful). The trial showed benefit from HBO_2 [15].

This diversity of opinion and practice creates a difficult situation where the published evidence base is small, but advancing to large-scale clinical trials has been difficult. Also, hyperbaric centers worldwide are being asked to provide a stronger level of evidence to support the treatments they deliver. For example, the National Health Service (NHS) England will now support the routine use of HBO_2 treatment only for decompression illness and gas embolism [16]. Conditions reviewed and not recommended for routine hyperbaric therapy because of the perceived lack of reliable outcome data include the UHMS-approved indications of carbon monoxide poisoning, soft tissue radiation damage, and necrotizing soft tissue infections. A new approach is needed to collect outcome data for HBO_2 treatments.

The study of HBO_2 treatment presents unique challenges. Because HBO_2 treatment usually requires daily treatments over the course of 1-2 months in a hyperbaric chamber, single hyperbaric centers typically do not treat large numbers of patients and cannot accrue sufficient numbers to conduct credible studies. Furthermore, because patients are referred for treatment from other specialties, follow-up tends to be conducted by the referring specialist, and outcome data are not available to the hyperbaric program beyond the treatment period. Obtaining meaningful data on HBO_2 outcomes requires pooling of data from multiple centers and establishing an infrastructure of centers motivated to conduct research and initiate long-term follow-up. The HBO_2 Registry Consortium described here will provide this framework for urgently needed evaluative observational studies, with the potential to improve the clinical application of HBO_2 dramatically. In addition, the consortium will provide an efficient platform for conducting trials on a wide range of HBO_2 indications, as well as studies of the molecular underpinnings of the treatment itself. This consortium infrastructure could be used to develop the platform from which multiple studies could be conducted at much lower cost.

Table 1. Indications for hyperbaric oxygen (HBO$_2$) therapy with Undersea and Hyperbaric Medical Society (UHMS) assessment of the quality and strength of evidence from the UHMS Indications report [1].

Indication[a]	UHMS assessment of evidence:quality[b], strength[c]	Notes relevant to the registry
UHMS-approved indications		
Acute thermal burn injury	A, IIa	Used only at certain centers; need to combine data from centers
Air or gas embolism	C-LD, I	Individual centers likely to see indication only occasionally
Carbon monoxide	A, IIa	Sporadic cases at multiple centers
Central retinal artery occlusion	C-LD, IIb	Sporadic cases at multiple centers
Compromised grafts and flaps	C-LD, IIa	Diverse presentations; registry good for retrospective as well as prospective analysis
Crush injury and compartment syndrome	B-R, I	Used at some centers and not others
Decompression sickness	C-LD, I	Use is concentrated at certain centers
Delayed radiation injury	B-R to C-LD depending on site, I to IIb depending on site	Registry can offer consistent outcome tracking across centers
Enhancement of healing in selected problem wounds	A, I for diabetic foot ulcers B-NR, IIb for others	Common use of HBO$_2$; registry can offer consistent outcome measures needed across sites
Gas gangrene	B-NR, I	Sporadic cases at multiple centers
Idiopathic sudden sensorineural hearing loss	A, IIa	Used regularly at some centers and not at others
Intracranial abscess	C-LD, IIb	Sporadic cases at multiple centers
Necrotizing soft tissue infections	B-NR, IIa	Sporadic cases at multiple centers
Chronic refractory osteomyelitis	B-NR, IIa to IIb depending on site	Sporadic cases at multiple centers
Severe anemia	C-LD, IIb	Individual centers likely to see indication only occasionally
Non-UHMS-approved indications		
Calciphylaxis	Not rated	No randomized controlled trials for any treatment modality; recommended as second-line therapy [5]
COVID-19[d]	Not rated	Case series show benefit [6,7]
Crohn disease	Not rated	Benefit seen in case reports and case series [8]
Frostbite	Not rated	Multiple case reports show benefit; often classified as part of *acute traumatic ischemia*, like crush injury
Otitis externa	Not rated	Case reports show benefit; Cochrane report recommends further research [9]
Peripheral vascular disease–related ulcer	Not rated	HBO$_2$ may be beneficial in selected cases
Pneumatosis intestinalis	Not rated	Multiple case reports show benefit [10]
Pyoderma gangrenosum	Not rated	Multiple case reports show benefit
Raynaud syndrome	Not rated	Case reports and case series show benefit [11]
Ulcerative colitis	Not rated	Recent randomized trial shows benefit for acute flares [2]

[a]Many of these indications are only seen episodically at any given center, so a registry is important for aggregating a sufficient number of cases to draw conclusions.

[b]Quality of evidence has five levels—Level A: highest quality, where evidence comes from more than one randomized controlled trial, a meta-analysis of high-quality randomized controlled trials, or one or more randomized controlled trials corroborated by high-quality registry studies; Level B-R: evidence comes from randomized trials; Level B-NR: evidence comes from nonrandomized trials; Level C-LD: evidence comes from limited data; and Level C-EO: evidence comes from expert opinion.

[c]Strength of evidence is classified as Class I: Strong; Class IIa: Moderate; Class IIb: Weak; Class III: No benefit; and Class III: Harm.

[d]COVID-19: coronavirus disease 2019.

Beyond the fundamental question of whether HBO$_2$ treatment should be recommended for given indications, the HBO$_2$ community needs data to answer more detailed questions, such as: Are some forms of radiation injury (eg, brain radionecrosis) more or less responsive than others to HBO$_2$ treatment? Are some patients more likely than others to benefit from HBO$_2$ for a given indication, and can those patients be identified? Having identified the patients most likely to benefit from treatment, can trials be designed more effectively to test HBO$_2$ treatment (eg, crossover trials)? A well-designed registry can provide the data required to answer these questions.

Methods

Overview

This paper outlines the development of an international, multicenter, prospective registry consortium. A center joins the consortium by signing the consortium agreement. This agreement covers membership, governance, data sharing requirements, use of member data, publications, intellectual property, liability, confidentiality, and insurance. Data are collected using Research Electronic Data Capture (REDCap), a widely available, easily accessible, Health Insurance Portability and Accountability Act (HIPAA)-compliant, web-based data collection system [17]. Each participating center determines its own start date for data collection (ie, *reference date*) and records baseline data for every patient referred to the treatment center, whether or not treatment is indicated for, or accepted by, the patient after that start date. Patients included in the registry are those patients who have been evaluated for possible treatment of any UHMS-approved condition, or any non-UHMS-approved condition, including those who are part of research studies or trials. The registry gathers data on whether the evaluation determined that treatment was contraindicated, indicated and scheduled, or indicated but declined by the patient.

Each center's participation is overseen by its own US Institutional Review Board (IRB) or the country-specific equivalent, or a center can opt to rely on the Dartmouth Committee for the Protection of Human Subjects (ie, the Dartmouth IRB). The REDCap-based data collection template is the same at all centers, so all centers collect the same outcome measures. Quarterly, each center performs a deidentified data download from their REDCap database to the coordinating center's REDCap database at Dartmouth College. These deidentified data from each center are combined into a single REDCap database, which is the multicenter data registry. Optional consent for longer-term follow-up is being pilot tested at one center.

Data Collected

The design approach to the registry is to create a system that can be used at any hyperbaric center. This means the system must be low cost and not require excessive staff effort. Although gathering data from electronic medical record systems is desirable to avoid repeated data entry, this is not practical for this project due to the diversity of medical record systems and the level of effort and funding required to standardize and update outcome measures and procedures among them. To minimize staff effort, data entry needs to be minimal, which means extensive data on comorbid conditions, medications, and medical history cannot be collected. Instead, the registry has to focus on a few key outcome measures whose data any center can collect and enter reliably. For studies using registry data where more information on the individual patients is needed, an interested investigator can obtain IRB or ethics approval to work with more detailed data at the individual centers using procedures outlined in the consortium agreement.

The registry database was initially designed by a consensus of founding members of the HBO$_2$ research consortium—the Geisel School of Medicine at Dartmouth in Hanover, New Hampshire, and the Dartmouth-Hitchcock Medical Center in Lebanon, New Hampshire—and core data are collected for UHMS-approved and some nonapproved conditions. Data are collected using four main data collection instruments (see Table 2). The Demographics instrument collects demographic information as well as information on insurance and distance traveled. The Pre Treatment Information instrument collects information on the condition being treated, treatments prescribed and administered, and subjective and objective measurements of the patient's status at treatment start. A quality-of-life measure—the EuroQol, 5-dimension, 5-level (EQ-5D-5L)—is also administered at baseline on all patients [18,19] as part of the Pre Treatment Information instrument. The Pre Surgical Information instrument collects subjective and objective measures of the patient's status prior to a surgical intervention (eg, tooth extraction) if one is performed. The Treatment and Outcomes instrument repeats information collection of the Pre Treatment Information outcome measures, records the actual treatment given, asks about complications, and repeats the quality-of-life questionnaire.

Both indication-specific outcomes and general outcomes are collected, including HBO$_2$ treatment complications (eg, changes in refraction, seizures, pneumothorax, confinement anxiety, barotrauma, and placement of pressure-equalization tubes in the ear). Wherever possible, common objective outcome measures are used. The registry uses validated questionnaires that have supporting evidence in the literature (eg, the Common Terminology Criteria for Adverse Events [CTCAE] hematuria grading scale for radiation cystitis and the European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire Head and Neck [QLQ-H&N35] for head and neck symptoms) [20,21] as well as some questionnaires that were custom developed for the registry (see Table 2) [22-24]. Factors that might affect the effectiveness of the therapy are also collected (eg, diabetes, smoking, and other nicotine use). Future plans, including long-term follow-up and linkage to cancer registries and vital status data, depend on future funding. Table 3 lists the parameters measured [25,26].

Table 2. Data collection instruments and questionnaires used in the registry. Patient-reported outcomes are used in the registry whenever possible.

Instruments and questionnaires	Details[a]
Data collection instruments	
Demographics	Age, race, ethnicity, biological sex, insurance, and driving distance; personal health information is only kept at individual centers
Pre Treatment Information	Referral reason, urgency, diabetes, smoking, nicotine, indication, baseline questionnaires and outcome information, EQ-5D-5L[b], and prescribed treatment
Pre Surgical Information	Outcome measures prior to intervention if one is performed (eg, tooth extraction, mandibular reconstruction, etc)
Treatment and Outcomes	Treatment given, complications experienced, and outcome measures
Questionnaires used in the registry	
Bladder Questionnaire (radiation cystitis)	Seven questions from the Urinary Distress Inventory 6 plus one custom registry question on urinary bleeding [24]
Bowel Symptoms Questionnaire	Nine questions custom developed for the registry
Head and Neck Questionnaire	37 questions selected from the EORTC[c] QLQ-H&N35[d] [23] and the GRIX[e] questionnaire [22]
Laryngeal Soft Tissue Radionecrosis Questionnaire	Two questions based on the Chandler [20] and RTOG[f] scales [21]
Perianal Crohn's Symptom Index	11 questions custom developed for the registry

[a]Details of data collection instruments include the types of data collected; details of questionnaires used in the study; and the sources used to develop the questionnaires.

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

[c]EORTC: European Organisation for Research and Treatment of Cancer.

[d]QLQ-H&N35: Quality of Life Questionnaire Head and Neck.

[e]GRIX: Groningen Radiotherapy-Induced Xerostomia.

[f]RTOG: Radiation Therapy Oncology Group.

Table 3. Indications for hyperbaric oxygen (HBO_2) treatment and outcomes measured for the registry.

Condition	Pre- and posttreatment outcome measurements[a]
Undersea and Hyperbaric Medical Society (UHMS)-approved conditions	
Acute ischemia (not crush injury or compartment syndrome)	Assessment of cyanosis in affected areas pre- and posttreatment and amputations post-treatment
Acute thermal burn injury	Number of wounds and wound measurements
Air or gas embolism	Glasgow Coma Scale score for brain events, troponin for cardiac events, and six-level outcome measure for all
Carbon monoxide	Narrative on treatment and outcome
Central retinal artery occlusion	Visual acuity (right and left)
Compromised grafts and flaps	Graft and flap assessment (necrosis and color), number of wounds, and wound measurements
Crush injury and compartment syndrome	Location, number of wounds, and wound measurements
Decompression sickness	Six-level patient outcome measure
Delayed radiation injury	
Brain	Nine-Hole Peg Test and Trail-Making Test
Larynx	Laryngeal Soft Tissue Radionecrosis Questionnaire and Head and Neck Questionnaire
Bladder	Hematuria grade and Bladder Questionnaire
Bowel	Bowel Questionnaire
Jaw	Exposed bone percentage coverage if exposed bone present, osteoradionecrosis grade [25], tooth complications after extraction, and Head and Neck Questionnaire
Enhancement of healing in selected problem wounds	Number of wounds, wound measurements, Wagner grade, and Strauss score [26]
Gas gangrene	White blood cell count, number of wounds, wound measurements, and number of surgical interventions
Idiopathic sudden sensorineural hearing loss	Four-frequency pure-tone average and word recognition score
Intracranial abscess	Number of surgical interventions
Necrotizing soft tissue infections	White blood cell count, number of wounds, wound measurements, and number of surgical interventions
Chronic refractory osteomyelitis	White blood cell count, C-reactive protein, and number of surgical interventions
Severe anemia	Hemoglobin; markers of end-organ damage; and narrative on treatment, complications, and outcome
Conditions not currently UHMS approved	
Calciphylaxis	Location, number of wounds, wound measurements, number of surgical interventions, and subjective assessment at end of treatment
COVID-19[b]	Pulse oximetry pre- and posttreatment, respiratory rate pre- and posttreatment, and pre-treatment oxygen
Crohn disease	Perianal Crohn's Symptom Index and Bowel Questionnaire
Frostbite	Number of wounds, wound measurements, and number of surgical interventions
Malignant otitis externa	Narrative on treatment and outcome
Peripheral vascular disease–related ulcer	Number of wounds, wound measurements, and number of surgical interventions
Pneumatosis intestinalis	Narrative on treatment and outcome
Pyoderma gangrenosum	Number of wounds, wound measurements, and number of surgical interventions
Raynaud syndrome	Number of wounds, wound measurements, and number of surgical interventions
Ulcerative colitis	Bowel Questionnaire

[a]All patients will complete a quality-of-life questionnaire—the EuroQol, 5-dimension, 5-level (EQ-5D-5L) [19]—at the start and end of treatment. Text entries are available for all indications to provide more detail about the cases.

[b]COVID-19: coronavirus disease 2019.

Governance

The HBO$_2$ Registry Consortium includes member institutions fulfilling the requirements as shown in Textbox 1. A steering committee is responsible for the governance of the registry. The Geisel School of Medicine at Dartmouth and the Dartmouth-Hitchcock Medical Center are the founding members of the consortium and each have representatives on the steering committee. The steering committee also includes a representative from each participating center. By a majority vote, with affirmative votes from the founding members, the steering committee has the authority to set the strategic direction for the registry, admit or remove members, set membership fees, establish policies, and relocate the registry. Member-initiated research protocols are approved by a majority vote of the steering committee. The committee also votes on any changes to the REDCap data collection instruments. The steering committee meets annually at the UHMS annual meeting, where changes and modifications to the registry are discussed and voted upon. Template IRB application materials are freely shared between participating centers.

Textbox 1. Requirements and activities of participating centers of the HBO2 Registry Consortium.

Center characteristic:

- Hyperbaric oxygen (HBO$_2$) treatment program

Administrative requirements:

- Ethics Committee approval, either by relying on Dartmouth or at own center

- Execution of consortium agreement, which includes agreement to share deidentified data with coordinating center and willingness to have data used for registry purposes

- Installation of, or access to, Research Electronic Data Capture (REDCap) database at the center or establishment of procedures and authorization to enter patient data securely into REDCap database hosted by another participating center

Data collection activities:

- Patient informed consent or waived consent, depending on Ethics Committee requirement

- Prospective data entry for all patients evaluated at the center; if consent is not waived, need to have 95% or greater participation over a year

- Administration of indication-specific questionnaires and/or collection of outcome measurement data before and after treatment

- Completion of annual audit and quality assurance processes; responsiveness to feedback on data quality and attainment of defined minimum data-quality standards

- Quarterly submission of deidentified patient data to coordinating center at Dartmouth College

- Option to participate in research studies, grant writing, or fundraising efforts

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Statistical Analysis

Descriptive analyses will be conducted to describe the baseline characteristics and outcomes of patients with each indication, overall and by center, including the numbers, proportions, and confidence intervals for the following: patients with each indication for treatment; those evaluated who were not treated or who were partially treated and the reasons why; baseline characteristics, including referral information and baseline outcome measures; treatments given; occurrence of each type of side effect; and outcome measures at the end of treatment with change scores and relative change scores, as appropriate. For measures with numerical scores, we will assess absolute and relative changes; for other measures, we will report outcomes in terms of the proportions with symptom resolution, improvement, no change, or deterioration. Factors associated with key outcomes will be explored using multifactorial analyses where sample size is sufficient for models to be stable. All results will be presented and discussed in terms of estimates and 95% confidence intervals to avoid focusing on *P* values alone.

Results

Data collection started within the registry at the Dartmouth-Hitchcock Medical Center as a pilot project in 2012. During this time, the consortium agreement was developed and processes were established to enroll other centers. In 2019, four additional centers began entering patient data. Currently, the registry has 919 individual patient entries from four centers, with the majority from the Dartmouth-Hitchcock Medical Center (n=621). Over time, the registry is gradually collecting sufficient data to robustly explore changes before and after HBO$_2$ treatment. Figure 1, for example, shows the results for the Head and Neck Questionnaire before and after HBO$_2$ treatment. Figure 2 shows changes in patient-reported symptoms of xerostomia (ie, dry mouth) after receiving HBO$_2$ treatment. These responses are important because whether HBO$_2$ treatment has an effect on xerostomia has been a longstanding question in the HBO$_2$ field [27]. Figure 3 shows changes in the hematuria score for those patients undergoing treatment with HBO$_2$ for radiation cystitis. Figure 4 shows the experience to date for patients treated for idiopathic sudden sensorineural hearing loss. These preliminary results show that the registry is useful for tracking trends in outcomes and patient-reported symptoms after HBO$_2$

treatment. As further patient experiences are collected, these data will also be used in retrospective analyses to determine the characteristics of those patients who responded well and of those who did not.

Figure 1. Delayed radiation injury. Scores on the Head and Neck Questionnaire before and after hyperbaric oxygen (HBO$_2$) are shown: lower scores indicate fewer symptoms. This questionnaire is administered to any patient who had experienced head and neck radiation and is being treated for radiation injury in the head and neck region. Although responses vary between patients, results show lower scores posttreatment (16.9 pretreatment to 14.3 posttreatment, P=.03, Wilcoxon signed-rank test). By identifying patients who did not respond or who worsened, these data can guide further analyses.
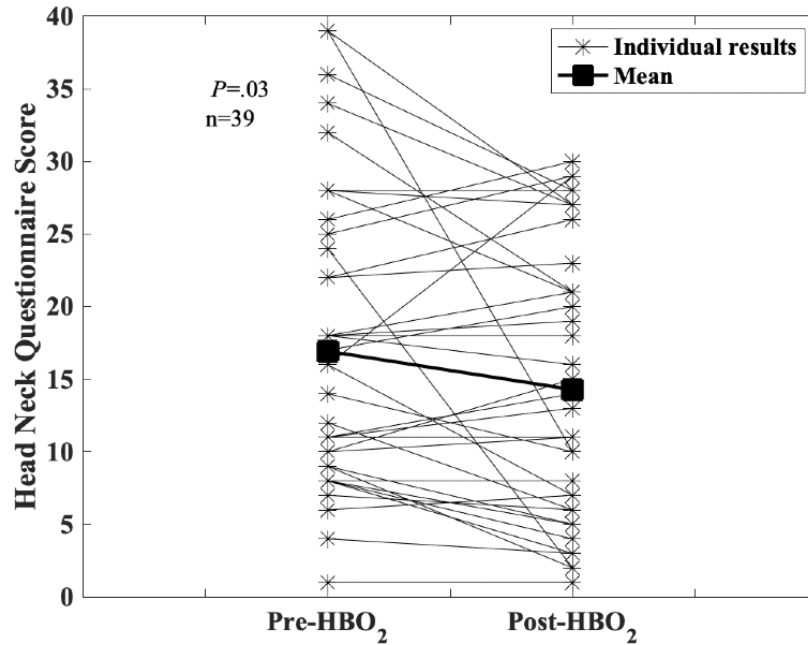
Figure 2. Delayed radiation injury. Scores on the xerostomia (ie, dry mouth) questions within the Head and Neck Questionnaire are shown: lower scores indicate fewer symptoms. Dry mouth is a common complication of head and neck radiation, and whether hyperbaric oxygen (HBO$_2$) helps with this symptom is an open question. Early results from the registry suggest improvement (11.9 pretreatment to 8.9 posttreatment, P=.01, Wilcoxon signed-rank test).
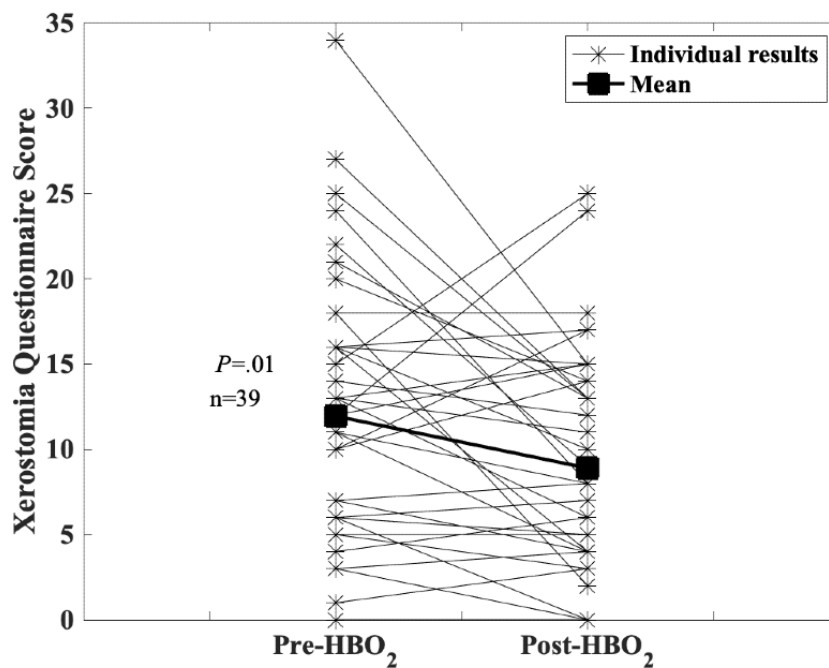
Figure 3. Delayed radiation injury, radiation cystitis. Scores on the hematuria scale before and after hyperbaric oxygen (HBO_2) treatment are shown: 0=no hematuria, 1=microscopic hematuria, 2=occasional macroscopic hematuria, 3=frequent macroscopic hematuria, and 4=severe hemorrhagic cystitis. Most patients see an improvement in hematuria score (2.5 pretreatment to 1.0 posttreatment, $P<.001$, Wilcoxon signed-rank test). As the number of entries in the registry grows, these data may be useful for assessing the number of treatments needed for successful outcomes.
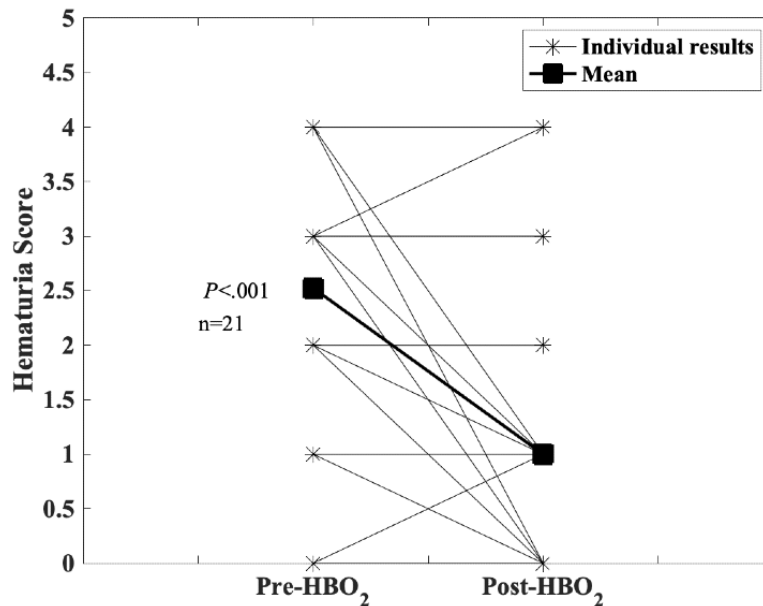
Figure 4. Idiopathic sudden sensorineural hearing loss. Four-frequency pure-tone averages on audiometry before and after hyperbaric oxygen treatment (HBO_2) are shown: a lower number indicates an improvement in hearing. Most patients are experiencing an improvement in audiometric thresholds (89.9 dB hearing loss [HL] pretreatment to 72.3 dB HL posttreatment, $P=.03$, Wilcoxon signed-rank test). As the number of cases in the registry grows, these data could be used to assess how long after the hearing loss HBO_2 may be useful.
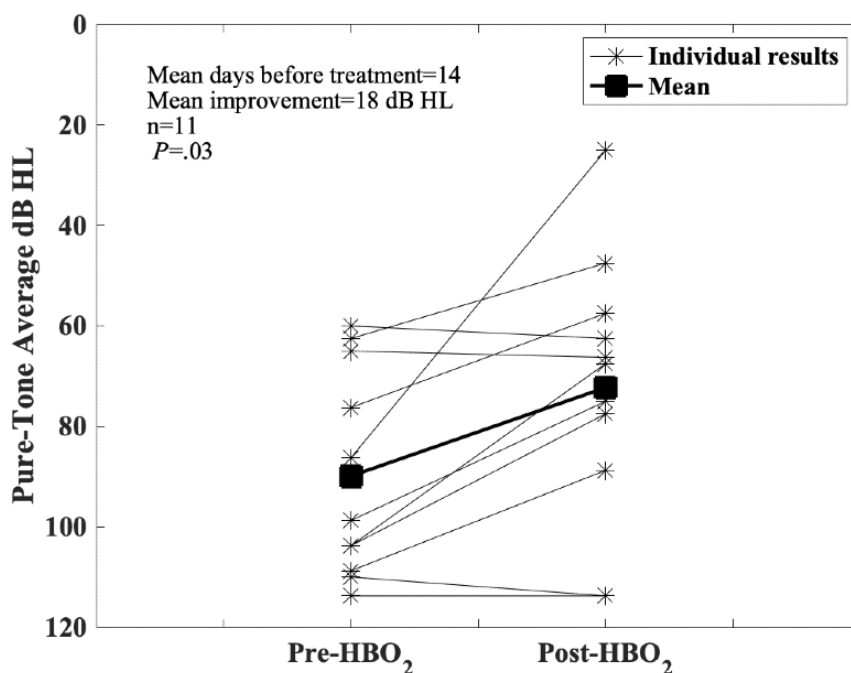
Discussion

Principal Findings

An HBO_2 treatment outcomes registry is feasible and can provide consistently recorded outcomes from HBO_2 treatments at multiple centers. Initial analyses of some of the outcome data are already showing significant changes after HBO_2 treatment.

Strengths of the Registry

A key strength of the registry is its use of REDCap [17], a free, secure, web-based, data collection system used to build and manage online surveys and databases in more than 3964 centers worldwide. The HBO_2 REDCap database has been pilot tested and revised at the coordinating center for 6 years, and core variables have been collected on UHMS-approved indications for HBO_2 treatment, as well as some non-UHMS-approved

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indications. The database includes 1996 variables, many of which are disease specific and are programmed to appear only for particular indications or situations (ie, during data entry, a staff member will only be entering data on a small subset of the variables available). Data entry takes an average of 15 minutes per case, distributed over several clinical visits. The template for the database can be exported to Excel, emailed to another center, and easily uploaded to create an identical registry that is ready for data entry. REDCap provides the ability to perform a deidentified data export from each participating center. This is sent to a central, pooled REDCap database at the Geisel School of Medicine at Dartmouth. Because of the simplicity of the software and the relatively low burden of data entry, the registry is relatively inexpensive for new centers to install and maintain. Because only deidentified data are pooled, the risk to participants is minimal.

Limitations of the Registry

At present, the registry is following individuals who receive HBO_2 treatment, and a registry of similar patients with similar conditions who are not receiving HBO_2 treatment does not exist.

Therefore, there is no way to compare outcomes from HBO_2 treatment directly with outcomes from similar patients who did not receive the treatment. As the registry grows, an additional limitation will be funding, which will be needed to maintain a system of data-quality oversight, analysis, longer-term follow-up, and other registry-related activities.

Conclusions

An outcome-focused registry for HBO_2 treatment is needed urgently to provide both patients and providers with the information they need to decide whether and how to use HBO_2 treatment. To be successful, this registry must be practical, easy to use, and easily expandable. The registry described here meets these requirements. The data entry requirements are not excessive and should be within the capabilities of existing staff at any given hyperbaric center. Also, by using REDCap, the registry can be expanded to include detailed information on particular indications and long-term follow-up on selected patients without significantly increasing the basic data entry requirements.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Presentation of the study.
[PPTX File , 2418 KB - resprot_v9i8e18857_app1.pptx]

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Abbreviations

CTCAE: Common Terminology Criteria for Adverse Events
EORTC: European Organisation for Research and Treatment of Cancer
EQ-5D-5L: EuroQol, 5-dimension, 5-level

HBO$_2$: hyperbaric oxygen
HIPAA: Health Insurance Portability and Accountability Act
IRB: Institutional Review Board
NHS: National Health Service
QLQ-H&N35: Quality of Life Questionnaire Head and Neck
REDCap: Research Electronic Data Capture
SEAM: Scholarship Enhancement in Academic Medicine
UHMS: Undersea and Hyperbaric Medical Society

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Protocol

Long-Term Opioid Therapy in Spine Center Outpatients: Protocol for the Spinal Pain Opioid Cohort (SPOC) Study

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Abstract

Background: Spinal pain is the leading cause of patient-years lived with chronic pain and disability worldwide. Although opioids are well documented as an effective short-term pain-relieving medication, more than a few weeks of treatment may result in a diminishing clinical effect as well as the development of addictive behavior. Despite recognition of opioid addiction in pain patients as a major problem commonly experienced in the clinic, no reference material exists on the scope of long-term problems in novel opioid users and the link to clinical outcomes.

Objective: The main aims of this study are to describe baseline and follow-up characteristics of the Spinal Pain Opioid Cohort (SPOC), to evaluate the general use of opioids in spinal pain when an acute pain episode occurs, and to demonstrate the prevalence of long-term opioid therapy (LTOT).

Methods: Prospective clinical registry data were collected from an outpatient spine center setting during 2012-2013 including patients with a new spinal pain episode lasting for more than 2 months, aged between 18 and 65 years who had their first outpatient visit in the center. Variables include demographics, clinical data collected in SpineData, the Danish National Patient Register, and The Danish National Prescription Registry. The primary outcome parameter is long-term prescription opioid use registered from 4 years before the first spine center visit to 5 years after.

Results: This is an ongoing survey. It is estimated that more than 8000 patients fulfill the SPOC inclusion criteria. In 2019, we began the intellectual process of identifying the most relevant supplementary data available from the wide range of existing national registries available in Denmark. We have now begun merging SpineData with relevant opioid data from Danish national registers and will continue to extract data up to 2021-2022. We will also be looking at data regarding somatic or psychiatric hospitalization patterns, patient usage of health care resources, as well as their working status and disability pensions.

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Conclusions: To our knowledge, this survey will be the first to document the scope of long-term problems regarding LTOT and opioid addiction following new spinal pain episodes and comparing descriptive follow-up data between substance users and nonusers.

Introduction

Spinal pain is the leading worldwide cause of patient-years lived with chronic pain and disability [1,2]. The impact on resources related to diagnostic procedures and treatment, including rehabilitative activities, is enormous [3,4]. Despite all of the resources allocated to the management of patients with spinal pain, the incidence of disability problems is projected to increase over the coming decades [5]. One of the most widely prescribed treatment forms is medical analgesics [6]. Opioids are well documented as an effective short-term pain-relieving medication [7,8] and are frequently prescribed in North America and most European countries [8-12]. However, more than a few weeks of treatment may well result in a diminishing clinical effect, risk of opioid-generated hyperalgesia that worsens the pain, as well as the development of addictive behavior [8]. Additionally, long-term opioid therapy (LTOT) may also result in a long series of somatic and psychological side effects such as depression, anxiety, and pain catastrophizing, as well as generally reduced physical activity [13-16]. Moreover, long-term usage of opioids is associated with lower rates of return to work in injured workers and the risk of social isolation issues [8]. Adding to the general health risk of prescribing opioids is the possible harm of adverse selection [15] and the fact that personal premorbid psychological disorders may impact the individual prognostic course following the first spinal pain episode [17].

Despite the increasing long-term dependence risk of change in addictive behavior associated with opioid treatment [18], most published spinal pain cohorts do not include follow-up data beyond 1 year [19]. Additionally, only a few studies have focused on spinal pain patients [8]. Thus, long-term studies are necessary to develop benchmark reference material documenting the scope of potential problems of opioid addiction to target preventive strategies more effectively.

The aim of this prospective Spinal Pain Opioid Cohort (SPOC) research program is to collate relevant individual patient data over a decade to illuminate both the overall group data developments as well as developments relating to individual usage of different opioids during this period, and to correlate these findings with the individual patient's physical, psychological, and social data over 10 years. In Denmark, a large number of different national registers are available, and the present data will provide the opportunity to assess different long-term effects of opioid use.

Methods

Study Design

This is a longitudinal cohort study based on prospectively collected data as part of routine daily clinical practice in The Spine Center of Southern Denmark during 2012-2013. This outpatient secondary care department is a unit in a public hospital with a geographic catchment area of approximately 1.2 million inhabitants [20]. The department applies multidisciplinary assessments of patients with spinal pain after a referral from general practitioners, chiropractors, and medical specialists in primary care.

Initial data are collected in the Spine Center's electronic clinical registry, named the SpineData database, at the date of the first visit (Regional Ethics Committee Project ID: S-200112000-29) [20]. Patients answered a comprehensive self-reported baseline questionnaire on a touch screen in the waiting area before their first consultation. The patient could identify the area of pain on the screen and choose between neck pain, midback pain, and lower back pain. The patient's initial choice of which area of the spine was giving them the most trouble determined which anatomical subgroup they were enrolled in. All follow-up data have been gathered using an internet-based version of the SpineData database and patients are enrolled in the analyses by linking data from the SPOC with data from the Danish national registers. An overview of the data collection and subgroups for the SPOC is provided in Figure 1.

Figure 1. Spinal Pain Opioid Cohort (SPOC) flowchart.
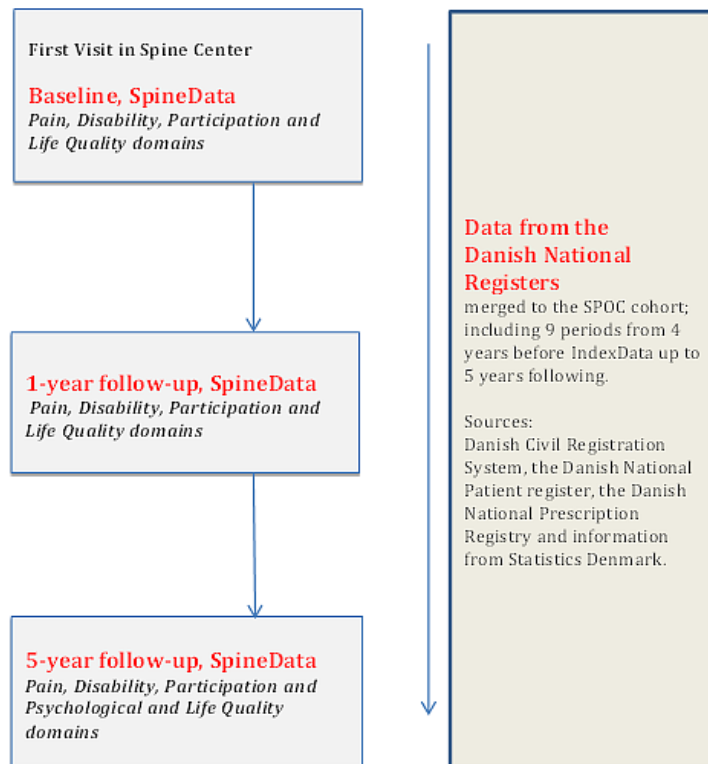
Study Population

Patients aged between 18 and 65 years who had a new pain episode for more than 2 months and had their first outpatient visit at the Spine Center between November 1, 2012 and December 31, 2013, with no indications for acute spinal surgery intervention, are enrolled in the SPOC. Patient symptoms indicating serious systemic diseases such as cancer, infections, or inflammatory spondylopathies are excluded a priori. An individual patient is included in the SPOC if the baseline questionnaires has no missing data related to pain intensity.

Variables and Domains

In accordance with the biopsychosocial model of health, information is collected across a set of broad health domains of pain, activity limitation, work participation, psychological factors, physical impairment, and contextual factors. Wherever possible, the choice of questions and questionnaires is based on evidence of their role in the diagnosis, prognosis, or treatment of spinal pain. The questions vary across the three spinal regions of principal complaint: neck pain, midback pain, and lower back pain [20].

Pain Domain

Patient-reported questions include a main pain chart (current pain) and other pain charts (any additional areas of pain during the previous 2 weeks), the onset date of pain, any previous lower back pain or radiating episodes, pain intensity (current, typical, and worst in last 14 days), extremity pain intensity (current, typical, and worst in last 14 days), number of days per week with pain, cause of or reason for onset, morning stiffness, diurnal variation, movement-related pain, activity-related pain, the

effect of physical rest on pain, and pain easily aggravated by movement [21].

Activity Limitation Domain

Patient-reported questions include the 23-item Roland-Morris Disability Questionnaire for lower back pain [22,23] and the Neck Disability Index for midback or neck pain [24].

Participation Domain

Patient-reported questions include type of employment, whether on sick leave due to back pain at any time in the last 3 months and for how long, expectation of working in 6 months, physically strenuous work, monotonous work, and work satisfaction [20].

Psychological Domain

Levels of depressive symptoms and anxiety are measured with the Hospital Anxiety and Depression Scale (HADS) [25]. The HADS was originally constructed to detect anxiety and depression in nonpsychiatric medical patients. It was subsequently shown to be useful as a "case finder" in other populations, and it is a well-validated questionnaire with good psychometric properties [25]. The depression subscale consists of 7 items related to depression and the anxiety subscale consists of 7 items related to anxiety [25]. Symptom levels on both subscales are measured on a 4-point Likert scale for each item, resulting in symptoms ranging from 0 to 21 for each subscale, with a high score indicating high levels of depression and anxiety.

Exposure to traumatic events is assessed by a modified version of the Life Events Checklist-5 (LEC-5) [26]. Among a list of a large number of possible traumatic events, patients are asked whether they have witnessed or been directly exposed to any

of the events. Examples of traumatic events listed are natural disasters, accidents, assaults, or life-threatening illnesses. Results are reported as exposure to the number of trauma types.

The International Trauma Questionnaire (ITQ) [27] can be used to assess symptoms of posttraumatic stress disorder (PTSD) related to the index trauma as identified on the LEC-5. The ITQ is a 6-item questionnaire assessing PTSD symptoms according to the International Classification of Diseases (ICD)-11 criteria on three clusters of reexperiencing, avoidance, and hyperarousal. Each item is rated on a 5-point Likert scale ranging from 0 (not at all) to 4 (extremely) indicating how much each symptom has bothered the respondent in the past month. A probable PTSD diagnosis can be calculated according to the ICD-11 criteria if the respondent endorses at least one symptom on each PTSD cluster, as indicated by a score2.

Attachment security is measured on the Experiences in Close Relationship Scale-Short Form (ECR-S) [28]. The ECR-S is a 12-item self-report instrument that measures attachment-related anxiety and avoidance. Participants are asked to think about how they generally experience close relationships and to rate the extent to which each item accurately describes their feelings in such relationships using a 7-point Likert scale ranging from 1 (not at all) to 7 (very much). Six items measure attachment-related anxiety (eg, "I need a lot of reassurance that I am loved by my partner") and 6 items measure avoidance (eg, "I try to avoid getting too close to my partner").

Contextual Factors Domain

Patient-reported questions include height, weight, previous back surgery, prolonged corticosteroid use, exposure to prolonged mechanical vibration, handedness, level of recreational physical activity, allergies, cigarette use, alcohol consumption, serious lung disease, heart disease, or cancer, which are generated from SpineData [20].

Quality of Life

Quality of life is measured using a validated and recognized Danish self-perceived general health scale inspired by the EuroQoL Health Measure Thermometer (0-100) [20,29].

Follow-Up Questionnaires

All patients are invited to complete two electronically provided follow-up questionnaires that contain representative questions from the baseline patient questionnaires. The first email follow-up questionnaire takes place 12 months after the date of the initial consultation. The second email-based follow-up questionnaires are sent to the patient as a 5-year follow up. All of the patients received an electronic questionnaire and have been asked to complete the questionnaire and return it via email. If a patient did not respond, they were contacted 2 more times after the first email communication.

Data From National Registers

Linking data from the SPOC with data from the Danish national registers is possible using the Danish Identity Number (known as the CPR number) assigned to all citizens in Denmark at birth or immigration. We link the SPOC with information from the Danish Civil Registration System (CRS) [30], Danish National

Patient Register (DNPR) [31], Danish National Prescription Registry (NPR), [32] and information from Statistics Denmark.

The DNPR contains information on all inpatient and outpatient visits as well as emergency room visits in Denmark. From the DNPR we extract information on the patient's comorbidities including 5 years ending on the date of the first visit in the Spine Center and using the diagnostic codes according to the disease-specific ICD-10 [33]. Data in the NPR [32] are collected on an individual level and include all drugs dispensed by prescription at community pharmacies. For this study, information on prescribed drugs is available from 2007 to June 30, 2018.

The study also provides an opportunity to link the data to the many different national registers available in Denmark [34], and therefore provides the opportunity for further national and international collaboration on the long-term effects of opioid use (Figure 1).

Comorbidity

Based on the diagnostic codes (ICD-10) from DNPR, we calculate comorbidity among the individuals at their first visit to the Spine Center. We use the Charlson Comorbidity Index to classify comorbidity among the individuals, which is based on 19 comorbid conditions [33,35].

Opioid-Related Variables

Classification of Opioids

The prescribed and dispensed medications from the NPR are classified according to the Anatomical Therapeutic Chemical (ATC) classification system [36]. We extract dispensed opioids from the NPR using the following ATC codes: morphine (N02AA01), hydromorphone (N02AA03), oxycodone (N02AA05), oxycodone combination (N02AA55), ketobemidone (N02AB01), pethidine (N02AB02), fentanyl (N02AB03), dextropropoxyphene (N02AC04), buprenorphine (N02AE01), ketobemidone (N02AG02), tramadol (N02AX02), tapentadol (N02AX06), codeine with paracetamol (N02AJ06), codeine with acetylsalicylic acid (N02AJ07), codeine with ibuprofen (N02AJ08), and codeine (N02AJ09).

Time Intervals for Prescribed Opioids

The Spine Center referral guidelines generally state that patients should not be referred to the center before having experienced pain for at least 2 months (mean 4.5 months) and for no longer than 12 months since symptom onset. As a consequence, for the present survey, we presume that the most intense pain period in the referred patients typically will begin and be concluded in the 364-day period minus 182 days (IndexDate) and up to 182 days following the day of the first visit in the Spine Center. In other words, the definition of the IndexDate is the date of the first visit to the Spine Center minus 182 days.

From the IndexDate, we define a total of 9 observation intervals for a single patient, including 4 intervals before and 5 intervals after the IndexDate. Each interval consists of a period of 364 days. The numbers of dispensed prescriptions are counted in each interval.

Definition of Subgroups

For most of the analyses, patients in the SPOC will be separated into the following 3 subgroups: (1) patients who do not receive any opioid prescriptions at any observation point (nonopioid users); (2) patients who have their very first opioid prescription following IndexDate (NaiveStarters); and patients who had one or more opioid prescriptions in the intervals before IndexDate (PreStarters). The separation between PreStarters and NaiveStarters allows us to differentiate patients with former spine pain episodes and related use of opioids before the IndexDate (Figure 2).

Figure 2. Spinal Pain Opioid Cohort subgroups receiving opioid prescriptions.
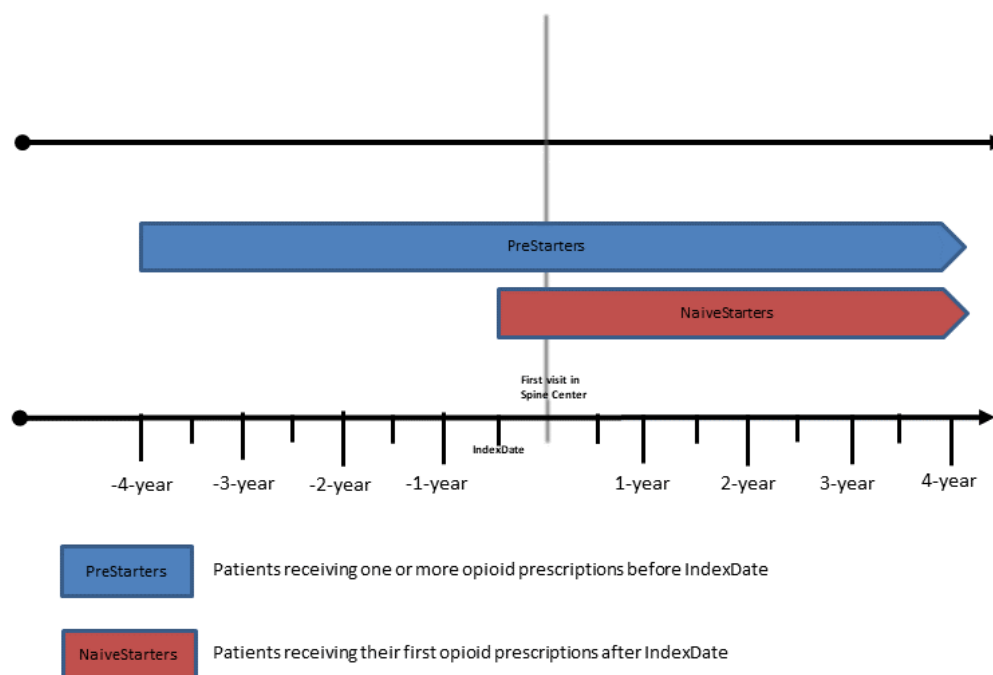
Primary Outcome Parameter: LTOT

This study's primary outcome parameter was inspired by "The Copenhagen Criteria" definitions and methods to register LTOT [11]. In our study, 6 or more opioid prescriptions in a single 1-year interval fulfill the LTOT criteria in that interval. The prevalence for patients fulfilling LTOT in the respective subgroups is calculated for all 9 364-day intervals. Additionally, the prevalence of receiving at least one prescription in a single interval will be evaluated.

Statistical Modeling

Baseline, and 1- and 5-year follow-up characteristics of the SPOC will be reported either as proportions or median values with IQR. We use the median and IQR for continuous variables that are not normally distributed. Differences between the level of comorbidity according to the Charlson comorbidity index [33,35] are also calculated. Possible statistically significant differences between the subgroups will be calculated using the Chi-square test. Differences are considered to be statistically significant at $P<.05$. Analyses are performed using STATA version 14.2 (StataCorp, College Station, TX, USA).

Ethics

Ethics approval for the collection and use of these data for quality assurance and research purposes has been provided by the Scientific Ethics Committee of the Region of Southern Denmark (project ID S-200112000-29). The database is also registered with the Danish Data Protection Agency (2008-58-0035). All patients have been invited to give two types of written informed consent. The first is for their patient data to be used for quality assurance and research purposes, including publications of anonymized group-level data, and the second is for the Spine Center to contact them requesting the completion of follow-up questionnaires.

Results

The project is ongoing. The gathering of questionnaire data among SPOC patients began in 2012. From 2013 to 2019, 1-year and 5-year follow-up data were collected and stored in the Spine

Center's SpineData database. It is estimated that more than 8000 patients fulfill the SPOC inclusion criteria. In 2019, we began the intellectual process of identifying the most relevant supplementary data available from the wide range of existing national registries available in Denmark. We have now begun merging SpineData with relevant opioid data from the NPR and will continue to extract data from this register as well as other relevant Danish national registers up to 2021-2022. We will be looking at data regarding somatic or psychiatric hospitalization patterns, patient usage of health care resources, as well as their working status and disability pensions. We have plans to run a 10-year follow-up study.

Discussion

This survey will be the first to document the scope of long-term problems regarding LTOT and opioid addiction following new spinal pain episodes and comparing opioid usage in PreStarters and NaiveStarters. Usage will be registered from 4 years before the new pain episode and for 5 years afterward. In parallel, we will be able to present continuously descriptive follow-up data from the SPOC.

Previously published data indicate that Danes have relatively high utilization of opioids in patient groups experiencing benign pain in the musculoskeletal system [8,11]. A reasonable prediction of the study results is that a relatively high percentage of SPOC patients will continue to use opioids for several years, including the last follow-up period and probably for the rest of their lives for some patients. It will be interesting to carry out a subgroup analysis between NaiveStarters and PreStarters. Reasonably more individuals in the latter group are at risk to have LTOT status compared to NaiveStarters. In addition, it

will be relevant to carry out future analyses of the impact of social and psychological elements on the SPOC general prognosis and LTOT prevalence [8,15,17].

The structure of this study involves both methodological strengths and limitations. One of the absolute strengths in this study is the possible high number of included patients, all of whom experience pain from the same anatomical structures. Additionally, by using the links to national databases during the entire study period, we will be able to obtain a complete dataset for all of the patients regarding their ongoing use of opioids. All of the patients are included from the same regional health system and only one health care entity; in other words, a relatively homogeneous group of patients will be included in the study. A limitation is that we will not be able to gather general data regarding the stoppage of opioid utilization due to side effects or the frequency of side effects.

From the long-term collection of relevant individual patient data, it will be possible to illuminate both the overall group data developments as well as long-term developments relating to individual usage of different opioids and to correlate these findings with the individual patient's physical, psychological, and social data. Results obtained in this study may help to identify a subset of patients with chronic pain for whom long-term opioid use is both safe and effective [8,37,38].

We expect that SPOC data in the future will contribute research information qualifying the debate about the importance of the clinician undertaking a very thorough patient selection process before prescribing the very first opioid prescription and to provide patients with a solid understanding of the risks of developing addictive behavior and other potential side effects related to LTOT.

Authors' Contributions

All authors (CM, LS, SR, TA, LB, KR, BC, LA, and SS) have contributed equally in designing the study and in formulating the hypothesis and commenting on the manuscript draft. CM and LS and drafted the full manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ATC: Anatomical Therapeutic Chemical classification system
CRS: Danish Civil Registration System
DNPR: Danish National Patient register
ECR-S: Experiences in Close Relationship Scale-Short Form
HADS: Hospital Anxiety and Depression Scale
ICD: International Classification of Diseases
ITQ: International Trauma Questionnaire
LEC-5: Life Events Checklist-5
LTOT: Long-Term Opioid Therapy
NPR: Danish National Prescription Registry
PTSD: posttraumatic stress disorder
SPOC: Spinal Pain Opioid Cohort

Bridging the Gap in Community Care for Patients With Borderline Personality Disorder: Protocol for Qualitative Inquiry Into Patient, Caregiver, and Clinician Perspectives on Service Gaps and Potential Solutions for Severe Emotion Dysregulation

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Abstract

Background: Borderline personality disorder (BPD) is characterized by severe emotion dysregulation that is often complicated by comorbid diagnoses, deliberate self-harm, and chronic suicidal ideation. Unfortunately, current care pathways for individuals with BPD are strained by limited resources, inadequate training, and an overuse of emergency departments and crisis teams. Such barriers result in delayed access to effective treatment, which increases risk of deterioration, disability, and morbidity. A first step toward addressing these limitations of the current care pathway is to understand key stakeholders' lived experiences in this pathway and their perspectives on potential solutions.

Objective: The purpose of this paper is to present a protocol for a study that explores the lived experiences of the current care pathway from the perspectives of patients with BPD, as well as their caregivers and clinicians.

Methods: A qualitative approach is most appropriate for the exploratory nature of the research objective. Accordingly, 3 to 6 patients with a diagnosis of BPD, 3 caregivers of individuals with BPD, and 3 clinicians of patients diagnosed with BPD will be invited to participate in individual, semistructured interviews that focus on service experiences.

Results: It is anticipated that results will yield insight into the lived experiences of patients with BPD, caregivers, and clinicians and provide a better understanding of the perceived gaps in services and potential solutions. Results are expected to be available in 12 months.

Conclusions: This paper describes a protocol for a qualitative study that seeks to understand the lived experiences and perspectives of key stakeholders (patients, caregivers, and clinicians) on the current care pathway for BPD. Results will provide a basis for future research in this area and will have the potential to inform training, practice, and policy.

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Introduction

Borderline Personality Disorder

Severe and pervasive emotion dysregulation is central to borderline personality disorder (BPD). This core trait, along with proclivity for high impulsivity, can increase the risk of engaging in emotionally driven or risky behaviors (eg, unsafe sex, self-harm, problematic relationships) and experiencing adverse events [1,2]. Left untreated, BPD is often accompanied by maladaptive behaviors that can lead to increased risk of suicide and comorbid psychological problems [3-6]. In 2006, an estimated 38% to 73% of individuals with BPD attempted suicide, with approximately 10% of individuals with BPD completing suicide [7]. Now, barely a decade later, estimates of patients with BPD who attempted suicide at least once have increased from 46% to 92% [8]. While rates of suicide are high for this population, not all deaths among individuals diagnosed with BPD are due to suicide. An estimated 14% of patients with BPD die due to causes other than suicide, including cardiovascular disease, substance use, cancer, and accidental reasons [8].

Compounding the risk of suicide is the fact that individuals diagnosed with BPD rarely present with a sole issue or concern. Instead, it is typical for individuals to present with comorbid mental and physical health disorders as well as psychosocial problems [9]. More specifically, individuals diagnosed with BPD can be at a higher risk for depression and anxiety [10], posttraumatic stress disorder, antisocial or criminal behavior [11], homelessness [12], substance use [13], and poor physical health [14]. A further challenge for effective care is that these individuals often present with fluctuating levels of readiness to engage in treatment [15,16]. The complexity of BPD results in high utilization of crisis supports [9] and patterns of inefficient resource utilization [17-19]. Disengagement from services as well as the mismatch between care and patient needs are linked to poorer patient outcomes [20]. The severity of risk, comorbidity, and compounding features associated with BPD have led to a surge of efforts to develop specialized treatments for BPD.

Treatment for Borderline Personality Disorder

Psychopharmacological treatments for BPD continue to be poorly understood [21], with inconsistent results; therefore, there is no medication that has been officially recognized as effective [22,23]. However, several evidence-based psychological treatments have been developed [24,25]. Arguably the most widely known and empirically tested psychosocial treatment for BPD [24-27] is dialectical behavioral therapy (DBT) [28]; stemming from the cognitive behavioral model, DBT combines cognitive behavioral techniques with principles from eastern philosophy, such as mindfulness to equip individuals with the skills they need to regulate emotions. Another approach, mentalization-based therapy [29,30], draws on psychodynamic principles and attachment theory to help individuals to better understand (ie, mentalize) both their own and others' thoughts, desires, and intentions and in turn, improve their interpersonal and intrapersonal functioning. Schema-focused therapy [31] integrates cognitive, gestalt, and psychodynamic models of psychotherapy to help identify and change maladaptive frameworks of understanding, or schemas. Evidence suggest that these various approaches to treating BPD result in significant decreases in self-harm, anxiety, depression, and interpersonal problems [32-34].

Gaps in the Availability of Treatment

While these approaches may be effective in the treatment of BPD, some, like DBT, are resource-intensive and require extensive patient engagement and clinician training. For example, DBT involves weekly individual therapy (typically 1 hour), weekly group skills training (typically 2-2.5 hours), access to telephone coaching of behavioral skills in-between sessions, and weekly therapist consultation team meetings that are designed to support and motivate therapists [28,35]. DBT requires highly trained therapists and many resources to fully operate, which is not always feasible in health care systems that are already facing shortages in staff and resources [36,37]. In turn, wait times for fully adherent DBT programs can range from months to years. Moreover, these programs have eligibility requirements that exclude some individuals with significant barriers to participation, such as low readiness for treatment or significant instability in their social environment.

Due to the extensive resources and training involved in delivering longer-term psychotherapies such as fully adherent DBT, there are alternative approaches used to provide care for individuals with BPD. In particular, many health care systems have DBT-informed groups and shorter-term psychoeducation or skills training groups focused on emotion regulation [38]; however, these services still require patients to be ready for therapy, able to manage treatment interfering behaviors (ie, active self-harm, poor attendance), and participate effectively in group therapy programs. Due to the volatile behaviors and affect that are central to BPD, it is estimated that 46% to 67% of BPD outpatients disengage from these alternative services [39,40]. Therefore, similar to DBT, a substantial number of individuals with the most severe BPD struggle to meet eligibility requirements. Consequently, these individuals tend to become frequent users of crisis teams and emergency departments or get "lost to the system" and otherwise do not receive appropriate care [16,41,42].

Patients with BPD require services that are more accessible, engaging, and stable and that keep them safe and help set goals for their future — regardless of ability or willingness to participate in more structured therapy approaches. One potential solution to this problem is the implementation of stepped care [43-45], a care pathway that matches intervention intensity to patients' severity and needs [46,47]. A small but growing body of literature suggests that stepped care results in more timely and accessible care and may provide effective treatment for emotion dysregulation [48].

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The limited availability of specialized, stepped care undermines the overall effectiveness of health care systems. Perhaps one way to address this problem is to understand the experiences of individuals who have lived experiences in the current care pathway for BPD. The exploratory nature of qualitative research is a viable way to shed light on these experiences. Previous qualitative research demonstrates that patients often feel neglected and stigmatized by health care providers [3,49,50], caregivers feel overlooked by mental health services [50], and providers hold negative attitudes towards individuals with BPD [19,41,51]. While existing data support the frustration experienced by stakeholders, there are no studies that explore these various stakeholder perspectives on the current care pathway in Canada.

Purpose

The purpose of the present paper is to describe a protocol of a qualitative study that seeks to understand key stakeholders' (ie, patients with severe BPD, caregivers, and clinicians) experiences with, expectations of, and suggestions for the current care pathway. The protocol is designed to explore two main research questions. First, how do patients with BPD, caregivers, and clinicians experience the health care system during times of severe emotion dysregulation? Second, how do patients with BPD, caregivers, and clinicians think the gaps in care could be addressed?

Methods

Design

A qualitative approach and phenomenological method known as interpretative phenomenological analysis (IPA) [52] will be used, wherein researchers use broad and open-ended interviews to explore individuals' experiences [52,53]. This approach is flexible and non-prescriptive, allowing for the generation of rich information about the experiences of interest [54]. Another method that has frequently been used in interpretive research and that will be employed in this study is the use of pre-interview activities. Pre-interview activities provide prompts for interview topics, aid in memory recall about events, and, therefore, enhance qualitative interviews by holistically exploring a participant's understanding of their history, context, and the phenomenon of interest [55,56].

Setting

This study will take place in Edmonton, Alberta under the Addiction and Mental Health program of Alberta Health Services (AHS), the province's integrated health care system [57,58]. AHS encompass many public health care services, including Emergency Departments, inpatient and outpatient services, and the Family Connections program (which aims to support caregivers of individuals with mental health concerns). Participants will be recruited from a variety of these services.

While there are private psychologists in Edmonton who provide psychotherapy to patients with BPD and could be used as recruitment sites, these services typically charge CAD $200 per hour (the recommended fee by the Psychologists' Association of Alberta [59]) and are often unaffordable for individuals with severe mental health problems. Moreover, given the high risk

of suicidality and high needs common to BPD populations, private psychologists may be likely to refer their patients to emergency departments within the public health care systems or crisis teams when the patient is in acute phases of the illness. Therefore, we will recruit participants from only the public health care system.

Instrumentation

This study protocol uses pre-interview activities and interview schedules, which are supplemented with audio-recording and field note forms (researcher memos of interviews).

Pre-Interview Activities

Pre-interview activities often include lists, diagrams, timelines, drawings, or schedules; this study will use pre-interview activity templates that have been developed by an expert in the field for adaptation to research inquiries [56]. Participants will be sent the pre-interview activity instructions in advance and will be asked to complete at least 4 activities of their choice in the week leading up to the in-person interview. For a full description of the use of the pre-interview activities, the reader is referred to the work by Ellis et al [56].

Interview Schedule

The authors of this protocol developed a set of questions through team consultation and based on clinical expertise and methodological literature on the development of IPA interview questions. More specifically, a method called the "funneling technique" guided the development of the interview schedule. This method arranges the topics to be covered from general to more specific or emotionally charged themes [53]. General areas covered in these one-on-one semistructured interviews with participants mirror the research questions about participants' experiences with, and perceived gaps in, the current care pathway. The interview schedules provide structure and flexibility that allows for the emergence of rich data generation but still maintains a level of consistency across participants [52]. Accordingly, as per the nature of an exploratory study that uses IPA, interviews may not cover all questions and may overlap in the same topic more than once, with all experiences and perspectives being important to the study. The semistructured interview schedules (see Multimedia Appendices 1-3) for each group ensure that the research question(s) are significant and relevant for each individual [53].

Participants

Patients with BPD, caregivers of patients with BPD, and clinicians of patients with BPD will be invited to participate. Note that it is possible for individuals to present in dyads or triads (eg, patient with BPD, the mother of that patient, and the clinician currently treating that patient); however, this is not expected, simply due to the variability of programs and sites from which participants will be being recruited.

Inclusion Criteria

Patients must be current patients at the Edmonton Community Mental Health Clinic, diagnosed with BPD, and aged 18 years or older. Caregivers can be a parent, grandparent, sibling, partner, or close friend and must be a key support in the lives and care of patients diagnosed with BPD and current participants

in the Family Connections program [60]. Closeness will be defined as a family, partner, or friend who had direct contact with or key roles in the care of the patient. Clinicians must be mental health therapists, be currently working at Edmonton Community Mental Health Clinic, and work directly with individuals diagnosed with BPD.

Exclusion Criteria

Patients cannot participate if they are in an active psychosis state, currently suicidal or homicidal, at high risk of acute decompensation, cognitively unable to participate due to drug-related or alcohol-related activities, or determined by Edmonton Community Mental Health Clinic staff as having a cognitive capacity that is too low to participate. Caregivers cannot participate if they are not in close contact or involved in care in some way of an individual who is diagnosed with BPD. Clinicians cannot participate if they are not currently and directly working with or managing cases of individuals with BPD or have less than 1 year of work experience with patients diagnosed with BPD.

Sample Size

In accordance with IPA research guidelines [52], this protocol is designed to include a total of 9 to 12 participants who will be recruited through purposive sampling [61]. Of these 9 to 12 participants, between 3 and 6 current patients with a diagnosis of BPD, 3 caregivers of individuals with BPD, and 3 clinicians working with this population will be invited to participate. The variability in the number of participants in the patient group accounts for the variability in how BPD can present, as suggested by the Health Research Ethics Board, University of Alberta.

Procedure

Recruitment

The research team will communicate with representatives and key decision-makers of the public health care sites mentioned and inform clinicians about the study. Clinicians may be invited as potential participants and/or clinicians may have a role in recruiting potential patient participants. Clinicians who agree to partake in the recruitment phase will be informed of inclusion and exclusion criteria to consider when recruiting potential participants. Inclusion criteria will also be stated explicitly in the recruitment posters, recruitment emails, letters of information, and consent forms.

For patients, recruiters from the Edmonton Community Mental Health Clinic will approach individuals who fit the inclusion criteria. The recruiter will inform patients of the study and will provide the patient with a recruitment poster that directs patients to contact the research team for more information. The recruiter will clearly state that patients' participation in the study will not, in any way, impact their therapy or mental health services, regardless of whether they choose to participate. Recruiters will not be made aware of which patients have chosen to participate in the study.

For caregivers, recruiters from the Family Connections program in Edmonton will introduce the study to caregivers who are attending the program's group sessions. At the beginning and

end of group sessions, recruiters will inform caregivers of the study and pass out copies of the recruitment poster that directs caregivers to contact the research team for more information. The recruiter will clearly state that caregivers' participation in the study will not, in any way, impact their therapy or mental health services, regardless of whether they choose to participate. Recruiters will not be made aware of which caregivers have chosen to participate in the study.

For clinicians, researchers will use a list-serve email, recruitment posters, and word of mouth to recruit clinicians from the Edmonton Mental Health Clinic. Clinicians will be informed that they are permitted to participate in the interview during work hours and do not need to notify nor request permission to participate from their managers. Clinicians who are interested in participating are directed to use the provided contact information to contact the research team.

Data Collection

Pre-Interview Activities

Approximately one week prior to the interview, the researchers will mail a letter of information, along with a number of pre-interview activities, to participants. Once participants have read the letter of information and confirm to the researcher over phone or email that they are interested in completing the study, the researcher will ask participants to complete the pre-interview activities in the week prior to the interview date. Note that informed consent (written and oral) for official participation in the study happens on the interview date. Pre-interview activity data will not be collected prior to informed consent. Just as with the interview schedules, pre-interview activities are adapted to each participant group, to explore their perspectives. Participants will be asked to complete at least 4 pre-interview activities of their own choice from the options provided; pre-interview activities generally take from 5 to 30 minutes each to complete but participants can take as much time as they wish on these. Participants will be asked to bring the completed pre-interview activities to the interview to discuss prior to the open-ended questions.

Interview Schedules

Interviews will be conducted by one of our research team members (LF) who is trained in qualitative inquiry research, has experience using IPA in exploratory studies, and has published original IPA research findings. Upon meeting the participant, the interviewer will carefully review the information and consent form with each participant (see Ethical Considerations for details on informed consent process), which includes informing the participant of the presence of the audio-recording and the procedures used to protect their anonymity. Participants who agree to participate will be asked to sign the information and consent form.

The interview portion of the study will take 1 to 1.5 hours, starting with a discussion of completed pre-interview activities. Interviews will be conducted in person to monitor participant reactions and to effectively use the pre-interview activities (the interviewer needs to be able to see the completed pre-interview activities). Interviews will occur at one of three AHS community clinic locations for participant convenience.

Data Analysis

Expected data analysis will be guided by the step-by-step guide to conducting IPA research by Smith et al [52], which involves 6 steps.

Reading and Re-Reading

Researchers become familiar with the transcribed interviews by reading and re-reading the transcripts several times.

Coding

The researcher begins to consider possible themes that seem to be emerging; this method is called "preliminary exploratory analysis" [62]. Researchers will code the data in sections of text.

Clustering

Higher levels of abstraction will occur when codes are grouped into common themes; this method has been called "clustering" [53]. The researcher codes data into themes and subthemes while continuously seeing the data as a whole [52].

Iteration

Researchers begin an iterative process that may have many revisions during which the meaning of participants' small stories fit into the context within the narrative [52]. Researchers constantly check back to ensure that the themes cohere to the raw transcription data. The themes will be organized in an analysis table to track the themes, subthemes, and direct quotes from transcriptions that support the themes.

Narration

The researcher will develop a narrative of the findings, describing relevant themes and using direct quotations to support the interpretations that have been made.

Contextualization

Researchers will further interpret the findings in view of existing literature on the topic.

Ethical Considerations

The current study has received ethical clearance from the University of Alberta's Health Ethics Research Board (Ref. # Pro00086416). The regional health authority, AHS, has provided operational approval for the research sites (AHS #45583; #45585) and Edmonton Zone Administrative Approval (AHS #36068). Issues surrounding privacy, confidentiality, and data retention that are particularly pertinent to the present protocol are discussed in the next sections.

Evaluation of the Research

Given that qualitative research is inherently interpretive, it is understood that the researchers are as much a part of the study — including the data analysis process — as the participants [62]. The interpretive and potentially subjective nature of this research makes it important that interpretation of data and findings are verified by a source outside of the principal researcher to ensure trustworthiness and confidence in the results. Therefore, the present protocol involves member checking and external audits to enhance trustworthiness and confidence. Member checking requires the researcher to check with participants regarding the preliminary findings by asking clarifying questions used to enhance and deepen the interpretations, as they arise in the interview with the participant. External auditing considers the opinions of another person such as a co-researcher or research supervisor who reviews the codes and themes in search of continuity and validity [62]. The research findings will also be thoroughly and carefully evaluated by the research team for coherence, persuasiveness, comprehension, and usefulness [63,64].

Voluntary Participation

All participants will be informed that participation is completely voluntary. Even after participants have provided informed consent to participate in the pre-interview activities and interviews, participants will be free to exit or end their participation in the interview at any time. Participants will be free to ask to withdraw any of their comments. Participants will be given a 4-week time frame after their individual interviews to withdraw their data. These rights are outlined in the information letter and consent form, and participants will be reminded of these rights when they complete the informed consent form and at the beginning and end of the interview.

Privacy of Information

Only the research team will have access to research data. All identifying information will be removed from any materials produced by participants (ie, pre-interview activities and transcribed interviews). All participants must provide informed consent to use the pre-interview activities in the research process, including publication. Images of pre-interview activities will not be disseminated without the consent of the participants. Identifying information in pre-interview activities, if present, will be "blacked out." If this is not possible, the pre-interview activity image itself will not be published but will only be described in research documents. Finally, the participant's name will not be attached to the pre-interview activities, and a pseudonym or number will be used when describing the conversation that comes from the material created. After the completion of the study, participants' information (eg, name, phone number, and email) will be destroyed.

Confidentiality

The list of the participant names and their respective contact numbers will be confidential and securely stored separately from the data. The data and participant names will be kept in a locked filing cabinet in the research office and will only be available to the research team. All computer files (eg, transcriptions of the data) will be kept in a password-protected file that will only be accessed by the research team. Files will be kept on the secure AHS shared drive. Audio-recorders equipped with USBs will be used and will be stored in a secure location. Recordings will be deleted off the audio recorders after the audio file has been transferred to a secure research file on the researchers' secure AHS computer. Any internal communication between team members is done in-person or within the secured AHS network.

Record Retention

All data pertaining to the study will be kept for a minimum of 5 years and will be securely stored in a locked filing cabinet in

the secure research office. All computer files (eg, transcriptions of the data, analysis documents, memos) will be kept in a password-protected file that will be stored on the secure AHS network.

Results

Using the presented protocol, it is expected that themes will emerge for each participant, then within the groups (patient, caregiver, and clinician), and finally, across all groups. The main goal of this qualitative analysis is to allow for the emergence of themes that illuminate the perspectives on the current care pathway for patients with BPD, perceived gaps, and potential solutions. Recruitment will commence February 2019, and the findings of the study are expected to be available in 12 months following the publication of this protocol. The findings may be used for the development or modifications of programs for patients of AHS. In addition, articles will be written for peer-reviewed journals and dissemination at conferences.

IPA does not predetermine hypotheses but instead, all and any results are welcome. Based on existing theoretical knowledge and clinical experiences, it is foreseeable that patients with BPD will be able to describe the strengths and weaknesses of the current care pathway and will provide the most critical insights into needs and potential service solutions. It is also foreseeable that caregivers will be able to provide important information on how natural supports are challenged by shortcomings in the system and how to address those gaps. It is predicted that clinicians are aware of the existing gaps in services and clinical training and will have valuable and practical solutions to overcoming these gaps.

Discussion

Overview

The present paper describes a protocol for a qualitative study that seeks to understand the experiences, perceived gaps in services, and potential solutions in health care services for individuals with BPD from these 3 stakeholder groups: patients with BPD, caregivers, and clinicians. The interviews will have certain commonalities in terms of structure and topics covered across the 3 groups of participants. We hope to learn about the unique aspects of each perspective as well and the practical implications for the health care system.

Patient perspectives are invaluable in a health care system that strives to be patient-centered [58]. It is our hope to better understand, from a patient's perspective, what it is like to live with BPD and navigate the health care system. For example, we hope to learn more about patients' interactions with providers in the health care system, their process in accessing and accepting help, factors of care that helped or hindered their recovery, and suggestions on how to improve services for this population from their own perspectives. From caregivers, we hope to learn what it is like to care for someone who is diagnosed with BPD, to learn about the needs of the caregivers in the caring process, and what caregivers think patients with BPD need. This information can help to inform program planning and caregiver involvement in treatment and determine the need for more or different types of support required by caregivers. From clinicians, we hope to understand if, how, when, and why clinicians' experiences working with this population have changed over time. Accordingly, we hope to learn about what clinicians need to effectively work with this population and about the outcomes they have seen in their treatment of this population. We also hope to understand what the clinicians believe the patients need as well as the strengths that clinicians perceive in this population. This information can help inform processes and procedures within the system.

Limitations

Provided the small sample size inherent to this methodology, findings are not generalizable in the traditional, quantitative sense. This is a consideration of the current protocol when using the results to determine systemwide changes. Instead, this protocol provides an in-depth analysis of a small population of participants with shared experiences, which can guide future research. Still, consumers of qualitative research can take the findings and apply the new understandings to their own context, leading to helpful action in environments, populations, or scenarios that may differ from the cases presented in the research of interest [65].

Conclusion

This study will enhance our understanding of an important gap in our current health care system by exploring multiple perspectives on the care pathway for those with BPD. The findings of the study have the potential to inform training, practice, policy, and future research in this area. The aim of this exploratory research is to develop better understandings that can lead to helpful action with this population [56]. Accordingly, results can be used to inform addiction and mental health program planning within Edmonton and to disseminate the learnings to other jurisdictions.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview schedule for patients.
[DOCX File , 15 KB - resprot_v9i8e14885_app1.docx]

Multimedia Appendix 2
Interview schedule for caregivers.
[DOCX File , 15 KB - resprot_v9i8e14885_app2.docx]

Multimedia Appendix 3
Interview schedule for clinicians.
[DOCX File , 15 KB - resprot_v9i8e14885_app3.docx]

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Abbreviations

AHS: Alberta Health Services
BPD: borderline personality disorder
DBT: dialectical behavioral therapy
IPA: interpretative phenomenological analysis

Protocol

Mother and Infant Nutrition Investigation in New Zealand (MINI Project): Protocol for an Observational Longitudinal Cohort Study

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Abstract

Background: Thyroid dysfunction is associated with cognitive impairment, mood disturbance, and postnatal depression. Sufficient thyroid hormone synthesis requires adequate intake of iodine, selenium, and iron. Iodine deficiency was historically a problem for New Zealand, and initiatives were introduced to overcome the problem: (1) mandatory fortification of all bread (except organic) with iodized salt (2009) and (2) provision of subsidized iodine supplements for pregnant and breastfeeding women (2010). Subsequent to these initiatives, most adults and children have adequate iodine status; however, status among breastfeeding women and their infants remains unclear. This paper outlines the methodology of the Mother and Infant Nutrition Investigation (MINI) study: an observational longitudinal cohort study of breastfeeding women and their infants.

Objective: This study will determine (1) women's iodine intake and status among supplement users and nonusers; (2) women's intake and status of iodine, selenium, and iron relating to thyroid function; (3) associations between women's selenium status, thyroid function, and postnatal depression; (4) infants' iodine and selenium status relating to first year neurodevelopment.

Methods: Breastfeeding women aged over 16 years with a healthy term singleton infant were recruited from Manawatu, New Zealand. Participants attended study visits 3, 6, and 12 months postpartum. Maternal questionnaires investigated supplement use before and after birth, iodine knowledge, and demographic information. Dietary assessment and urine, blood, and breast milk samples were taken to measure iodine, selenium, and iron intake/status. The Edinburgh Postnatal Depression Scale was used repeatedly to screen for postnatal depression. Thyroid hormones (free triiodothyronine, free thyroxine, thyroid stimulating hormone, thyroglobulin, antithyroglobulin antibodies, and antithyroid peroxidase) were measured in blood samples, and thyroid gland volume was measured by ultrasound at 6 months postpartum. Infant iodine and selenium concentrations were determined in urine. The Ages and Stages Questionnaire was used to assess infant development at 4, 8, and 12 months.

Results: Data collection was completed. Biological samples analysis, excluding nail clippings, is complete. Data analysis and presentation of the results will be available after 2020.

Conclusions: This study will provide data on the current iodine status of breastfeeding women. It will also provide a greater understanding of the three essential minerals required for optimal thyroid function among breastfeeding women. The prospective

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longitudinal design allows opportunities to examine women's mental health and infant neurodevelopment throughout the first year, a crucial time for both mothers and their infants.

Introduction

Background

Postpartum women experience abnormalities in thyroid function at twice the prevalence of the general population [1]. Thyroid hormone is essential in maintaining the human body's metabolism, temperature (thermoregulation), and psychological mood [2]. In a developing brain, thyroid hormone is responsible for adequate myelination, neuron cell maturation, and central nervous system development [3]. Optimal thyroid function relies on adequate biosynthesis of thyroid hormones, which depends on three dietary minerals: iodine, selenium, and iron [4,5]. Pregnancy increases thyroid hormone turnover; thus, women with limited thyroidal reserve or marginal iodine deficiency are at increased risk to develop thyroid dysfunction after birth [6]. This is one of the most common endocrine disorders that postpartum women experience [7].

Iodine is the major component of thyroid hormones, but it is also a regulator for the synthesis and secretion of the thyroid hormones triiodothyronine (T3) and thyroxine (T4). Selenium, as a component of the selenocysteine-containing proteins glutathione peroxidase, protects the thyroid gland from oxidative damage [5]. Selenoproteins are required to convert T4 to T3, the active form of thyroid hormone. Iron is required for heme-dependent thyroperoxidase activity, which is required for the synthesis of adequate thyroid hormone. Selenium deficiency and iron deficiency anemia may negatively affect thyroid hormone synthesis by impairing selenium- and iron-dependent enzyme activities, even if iodine status is adequate [5]. Most previous research has investigated iodine, selenium, and iron intake/status separately or a combination of any two of them among women of childbearing age [8] and postmenopausal women [9]. However, further research is needed to explore all three micronutrients together, acknowledging their close relationship in thyroid hormone synthesis.

Thyroid dysfunction is a significant health issue in New Zealand, with women diagnosed at 5 times the prevalence in men [10,11]. Concerning adequate thyroid function, iodine, selenium, and iron play important roles. In New Zealand, soils provide low levels of available iodine and selenium, resulting in low concentrations in the food supply [12], hence in the diet [13]. Iodine deficiency in early life is associated with impaired neurodevelopment [14]. Iodine deficiency was a concern in New Zealand in the early years of the 20th century, but its prevalence was mostly reduced through the introduction of iodized salt in the 1930s. However, since the 1990s, a number of studies in New Zealand have shown iodine deficiency has reemerged in adults [15], pregnant and breastfeeding women [16,17], school children [18] and breastfed infants and toddlers [19]. To improve iodine status in New Zealand, two government initiatives were introduced: mandatory iodized salt in commercially made bread products from September 2009 and the provision of iodine supplementation for all pregnant and lactating women in 2010 [20]. Although recent studies suggested that adults [21,22] and children [23] in New Zealand may now have adequate iodine intake/status, both pregnant and breastfeeding women remain deficient. A pilot study of a small sample of self-selected highly educated pregnant and breastfeeding women assessed urinary iodine excretion, breast milk iodine concentration, and blood thyroglobulin and suggested iodine deficiency [24]. There is a need for a more robust investigation into the iodine status of postpartum women and their infants from a wide range of socioeconomic backgrounds.

Low selenium status in New Zealand has been partially reversed by increased consumption of imported flour from Australia (which generally has higher selenium concentrations than flour produced in New Zealand) [25,26]. In addition, both pregnant and breastfeeding women have an increased requirement for dietary selenium due to the demands from the fetus and breastfed infants. Previous research, which investigated selenium status among postpartum women and their infants in New Zealand 20 years ago [27], measured urinary selenium excretion and plasma selenium and indicated that such women were at risk of selenium deficiency. To our knowledge only one small study of breastfeeding women, by our research group, assessed dietary selenium, urinary selenium excretion, and breast milk selenium concentration and suggested selenium inadequacy was still a concern [28]. There remains a lack of research investigating selenium status among postpartum women and their infants.

Health professionals closely monitor the iron status of women during pregnancy. However, after birth, management of iron status can be inconsistent. Results from a UK multicenter study reported only 50% of postpartum women had hemoglobin levels checked after delivery (with 30% of those women confirmed as anemic), while the overall iron stores of participating women remained unexamined [29]. Generally, postpartum women's iron status recovers as a consequence of cessation of menstrual bleeding since conception or a minimal secretion of iron via breast milk if breastfeeding [30]. However, if women have suffered iron deficiency before and/or during pregnancy and/or

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have experienced significant blood loss during the birth, their iron status may not reach optimal levels even if an intervention subsequently occurs. A New Zealand study of 186 women found 77% of women were not tested for hemoglobin levels after birth. Further, out of those most at risk (with low iron status during late pregnancy and high blood loss, exceeding 500 mL, during birth), few women were then retested for their iron status after 10 days postpartum [31]. Iron status of postpartum women remains largely underreported.

Moreover, low serum selenium has been identified as an independent risk factor for depression, [32] and selenium supplementation has been observed to reduce postnatal depression [33]. Postnatal depression is one of the main disorders women experience postnatally, its onset being timed at 6 weeks to 6 months after birth. Most women will recover from postpartum depression, though approximately one-quarter of affected women report being depressed when their infant reaches their first birthday [34]. Using the measured criteria of postnatal depression on the Edinburgh Postnatal Depression Scale (EPDS), the prevalence of postnatal depression in New Zealand was about 8% in 1994 and 16% in 2006. In the 2015 New Mothers' Mental Health Survey [35], the prevalence was 14% and is now recorded as the most common disorder for mothers in their first year after childbirth [36].

Of additional concern, mothers are often reluctant or unable to seek help when they experience symptoms of postnatal depression [35]. Such underdiagnosed and untreated mental health conditions affect both the mother and their children's ongoing cognitive, emotional, and behavioral development [37]. Despite other social and psychological etiology of depression, potential links between micronutrient status, thyroid hormone, and the risk of postpartum depression need to be further explored. This may help develop new preventive approaches to lowering the risks of postpartum depression.

Study Objectives

The study's primary outcomes include (1) investigating breastfeeding women's iodine intake and status among supplement users and nonusers following the implementation of two government initiatives to improve iodine status; (2) examining maternal iodine, selenium, and iron intake status; and (3) exploring iodine, selenium, and iron status in maternal thyroid function.

In addition, the study provides preliminary data on possible associations between women's selenium status, thyroid function, and postnatal depression over a 1-year period and infants' iodine and selenium status in relation to neurodevelopment during their first year of life. Ultimately, this research will inform a future larger study of potential variables impacting maternal thyroid function and the risk of postnatal depression, together with early infant neurodevelopment.

Methods

Study Design and Overview

The Mother and Infant Nutrition Investigation (MINI) study is an observational longitudinal cohort study spanning the first year postpartum. It was approved by the Health and Disability Ethics Committee (15/NTA/172) in December 2015. The study's ethics approval was registered with the Royal New Zealand Plunket Ethics Committee in June 2016. The MidCentral District Health Board in New Zealand also approved the study. The study was registered with the Australian New Zealand Clinical Trials Registry [ACTRN12615001028594].

The study is being conducted in the Human Nutrition Research Unit at Massey University, Palmerston North, New Zealand. The first study visit for participants is at approximately 3 months postpartum, and follow-up assessments take place at 6 months and 12 months postpartum (Multimedia Appendix 1).

Selection Criteria

The target population for the study was healthy breastfeeding women aged over 16 years who had birthed a healthy term singleton infant 3 months prior. Women were excluded if they developed significant health problems, such as metabolic disease or cancer. Women were excluded if they had been diagnosed or treated at any time for hyperthyroidism or hypothyroidism. Participants were required to live within or near the local Palmerston North area and be able to attend Massey University for scheduled study visits. Women of any ethnic and socioeconomic status were eligible.

Recruitment and Participation

Posters to promote the study were placed at selected sites (general practitioner surgeries, midwifery clinics, pharmacies, antenatal classes, ultrasound clinics, maternal wards in hospitals, local community playgroups, and early childhood centers, etc). Local newspapers and social media sites were used to publicize the study. Local midwives, childbirth educators, and lactation consultants were asked to raise awareness of the MINI study to their clients. An effort was made to recruit women from a wide range of socioeconomic backgrounds and ethnic groups, including Maori, Pacific Islanders, and Asian women. Potential participants responded by recording an expression of interest online or via telephone or email. Prospective participants were provided with a study information sheet. Interested participants then completed a screening questionnaire to ensure eligibility. Written informed consent was obtained from all participants before their enrollment in the study. Mothers also gave written consent to their infants' participation in the study. After providing informed consent, participants were assigned a unique identifier code and scheduled for their first study visit.

Sample Size Calculation

The main outcome measure was iodine excreted per day, and the sample size was calculated using G*Power 3.1 (Heinrich Heine University) based on data (mean and standard deviation) from a preliminary study of breastfeeding women [24]. Calculation used 1-way analysis of variance with two groups (95% power, =.05, 2-tailed) and three repeat measures; 80 participants were needed, using expected mean daily urine iodine concentrations of 140 and 100 µg/d for iodine supplement users and nonusers, respectively, and a standard deviation of 60.

Outcome Measures

Questionnaires

At the initial visit, general baseline questions were asked about salt and supplements use, nutrition knowledge of iodine, tobacco and alcohol use, breastfeeding patterns, general health, and demographic information (including age, ethnicity, educational attainment, household size, and income). Potential changeable information including tobacco and alcohol use, breastfeeding patterns, and general health was also sought at the second and third visits.

Participants were assessed about their general health and that of their infants by online questionnaire when infants reached 6 months and 12 months of age. During the postpartum period, stress may negatively affect immunity, and the occurrence of infection symptoms can be an estimated measurement of postpartum immune function. The Carr Infection Symptom Checklist, which has been validated for use with postpartum women [38], was used to measure the symptoms of infection experienced by the mother since the birth. The Infant Symptom Checklist (which reports the frequency of symptoms of common illnesses in young infants) was used to measure the health of infants [38].

The 10-item EPDS was completed online by participating women to assess any symptoms of depression and anxiety over the previous 7 days. Women recorded severity of symptoms on a 4-point scale [39]. Specified anxiety disorders were evaluated using the EPDS-3A, a cluster of selected question items numbered 3, 4, and 5 from the original EPDS [40]. This is a validated tool to screen for probable anxiety and depression during the postpartum period. A cutoff point of 13 or above was used to define high levels of depressive symptoms [35]. Any woman whose score equaled 13 or above was advised to see her general practitioner for further evaluation as well as being provided with an information sheet containing postnatal depression services in New Zealand. Only study participants with the correct link supplied via emails could complete these questionnaires. All questions were answered in the same order. Participants could not go back to change their answers once the questionnaire was completed. Answers from incomplete questionnaires may be used for analysis.

The first year of infant neurodevelopment was assessed using a parent-completed Ages and Stages Questionnaire (ASQ) when the infant was aged 4, 8, and 12 months [41]. These questionnaires were self-administered and completed in hard copies. This screening tool uses parent observation to assess child development and behavior and records results in 5 developmental domains: communication, gross motor, fine motor, problem solving, and personal-social. There are 6 questions in each domain, with answers of yes, sometimes, or not yet. A yes indicates reaching the achievement with 10 points awarded, a sometimes indicates partial achievement with 5 points awarded, and a not yet indicates not achieved with 0 points awarded. The sum score of each domain was calculated and compared with the cutoff scores reached, which were derived empirically by subtracting 2 standard deviations from the mean for each area of development [41]. A score below the cutoff point indicates a fail on the ASQ. The questionnaires were used to assess the relationship between maternal and infant iodine and selenium status, maternal iron status, and recorded early child neurodevelopment.

Dietary Intake

To assess participant dietary intake including nutrients that may be associated with mental health and child development including iodine, selenium, and iron intake, participants were asked to complete a weighed 4-day diet diary within 2 weeks of the initial study visit. All 4 days were consecutive and included one weekend day. Each participant was requested to record food items, brands, amount consumed, and the content of the nutritional information panel if applicable. All food and beverage items consumed were weighed and measured with a QM-7288 electronic kitchen scale (Digitech), and household measurement cups and spoons were provided. The Digitech scale can weigh up to 5 kilograms with an accuracy to 1 gram; all women were shown how to use the scale to quantify food items. All participants received both written and oral instructions on how to complete the record, which included a written example of a 1-day food record. Women were also asked to include dietary supplements consumed. When eating or dining out, participants were asked to estimate the portion size of all food eaten. The food record and equipment were collected or return posted 2 weeks after the initial visit.

A 69-item self-administered semiquantitative iodine- and selenium-specific food frequency questionnaire, adapted from an Australian study of pregnant women [42], was used to estimate habitual maternal iodine and selenium intake at the first and third study visits. An iron-specific food frequency questionnaire, validated by other female population groups in New Zealand, was used to assess women's iron-related dietary patterns [43] at the second study visit. Within 2 weeks of this visit, participants also completed a 3-day estimated food dietary record for their infants to enable assessment of infant nutrient intakes at weaning periods.

All dietary data were entered into Foodworks 9 Professional (Xyris Pty Ltd) online and analyzed using data sets from the New Zealand Foodfiles 2016 to estimate nutrient intake. When food items were not included in Foodfiles 2016, new food items were created based on the information directly provided by participants (ie, food packages) or from appropriate international databases from Australia and the United States. Estimates for iodine concentrations of categories of bread (eg, white, fiber white, fruited, mixed grain) were based on data from the Ministry of Primary Industries [22], since iodine content has not been determined for all commercially made bread in New Zealand after the mandatory fortification of bread with iodized salt. It was difficult to quantify the amount of discretionary salt added to food. However, for women who reported using iodized salt, 48 µg of iodine (equivalent to 1 g of salt) was added to their iodine intakes [21]. Dietary supplements used by participants were entered into Foodworks as a new food item based on nutritional information obtained from the manufacturers. To ensure accuracy and completeness, a registered nutritionist (YJ) checked all dietary data and then transferred the data to SPSS Statistics (IBM Corporation) version 23 for statistical analysis.

Anthropometry

Maternal and infant anthropometry measurements were obtained at each study visit. Women's weight was measured using the same annually calibrated weighing scale with a capacity of 150 kilograms (Detecto). Before standing on the scale, participants were asked to remove their shoes and to wear minimum clothes. Body weight was recorded to the nearest 0.1 kilogram. Height was measured by using a Toledo stadiometer and recorded to the nearest millimeter [44]. Maternal body composition was determined using both bioelectrical impedance analysis (InBody230, InBody Co) and air displacement plethysmography (BodPod, COSMED SRL). Measurements were completed under the following conditions: minimal clothing, wearing swimming cap, before midday, after urination, normal room temperature (20°C to 25°C), with no exercise, eating, drinking, or bathing/showering within 2 hours prior to measurement (preferably completing the measurement after breastfeeding the baby). On the day of the test, quality control steps for BodPod were carried out by following the manufacturer's instructions, with acceptance criteria being volume ±100 mL of actual volume and standard deviation ≤75 mL.

Infant recumbent length was measured crown to heel using an infant length board and recorded to the nearest millimeter. Infant weight (without clothing and diapers) was measured using a baby weighing scale (Nagata Scale Co Ltd) and recorded to the nearest 10 grams. Infant head circumference was measured over the most prominent part on the back of the head (occiput) and just above the eyebrows (supraorbital ridges) by using a flexible, nonstretch tape [44] and recorded to the nearest even millimeter.

Ultrasound Measurement of Thyroid Gland Volume

A portable ultrasound (uSmart 3200T Ultrasound System, Teratech Corp) equipped with a linear transducer (7 to 15 mHz) was used for the thyroid measurement. Women were examined in a supine position (an adequate neck extension was achieved by placing pillows under the shoulders). Longitudinal and transverse scans were performed. Measurements of anteroposterior diameter and width (mediolateral diameter) were obtained with electronic calipers on a transverse image. The maximum lobe length was measured on a longitudinal width. The total volume of each thyroid gland was the sum of the volumes of left and right lobes, excluding the volume of the isthmus but including any nodules and/or cystic areas. The formula used to calculate the volume for each lobe is anteroposterior diameter × width × length × 0.479 [45]. A total volume greater than 18 mL was defined as thyroid enlargement based on the normative thyroid volume in iodine sufficient populations [46]. Any participant with observed abnormalities was referred to clinical health professionals for further assessment.

Biomarker Analysis

During each study visit, spot urine samples from each participating woman and her infant were collected to assess iodine, selenium, and creatinine excretion. All maternal spot urine samples were collected in the morning and immediately frozen and stored at –20°C. Infant urine was collected using a 100 mL pediatric urine bag placed inside the diaper and checked every 10 minutes. The collected urine was frozen and stored at –20°C for later analysis. Spot urine samples can be used to estimate iodine status of a population but not for individual iodine deficiency diagnosis [47]. It was not possible to estimate dietary iodine and selenium intake for lactating women via urine as we were unable to determine the daily loss of selenium from breast milk. As creatinine output is relatively constant, the adjusted iodine/creatinine ratio (μg iodine per g creatinine) can be used as a proxy measure of iodine excretion [48].

Lactating women were asked to provide a breast milk sample (approximately 30 to 50 mL) at each visit using an Allegro electric breast pump (Unimom NZ) if required. All breast milk samples were collected before noon on the study visit day, and timing of breast milk collection was not standardized. Breast milk samples were analyzed for iodine and selenium concentration, allowing for estimations of infant intake of iodine and selenium based on 750 mL/d of milk production [49].

Iodine and selenium concentration in both urine and breast milk samples were determined by an accredited commercial laboratory (Hill Laboratories) using inductively coupled plasma mass spectrometry (ICP-MS) [50]. Quality control procedures included analysis of blanks, analytical repeats, and certified reference material to ensure accuracy and precision. The Massey University Nutrition Laboratory measured creatinine using the Jaffe method in a Flexor E (Vital Scientific) biochemistry analyzer.

To assess further selenium status, toenail clippings from women and nail clippings from infants were collected. Toenail clippings have been used to determine selenium concentrations in large cohort or epidemiological studies, such as for the preeclampsia risk in pregnant women [51]. The instruction for sample collection was explained to participants during each study visit and nail clippings were self-collected by participating women at home, with the collected samples brought back by the participants at the following study visit. All toenail clippings were stored at room temperature prior to analysis. Nail clipping samples will be prepared by using the method adapted from nail zinc analysis [52]. This involves washing all nail clipping samples by using 5 minutes contact with 25 mL portions in the order of acetone, water, acetone, water, and water [53]. Selenium concentration will be measured by ICP-MS.

During the second study visit, to assess blood hemoglobin concentrations, the handheld HemoCue Hb 201+ device (HemoCue America) was used, a standard in hemoglobin point-of-care testing [35,54]. It requires a finger prick and wicking of capillary blood into a pretreated microcuvette for analysis. Quality tests using external, liquid controls were necessary for each day of instrument use prior to sample analysis.

A qualified and experienced phlebotomist collected nonfasting maternal venous blood samples (22 mL) at the second study visit. Samples were centrifuged and aliquoted into microcentrifuge tubes prelabeled with participant unique sample ID and then stored at –80°C. In conjunction with the hemoglobin results, collected maternal venous blood samples were used to determine iron status by measuring soluble transferrin receptors and serum ferritin (using the chemiluminescent microparticle

immunoassay [CMIA] method), which reflects iron storage, but if serum ferritin levels are increased during infection or inflammation, it may mask any iron deficiency results [55]. Therefore, an inflammatory marker, C-reactive protein, was measured (tested by an immunoturbidometric method analyzed on an Abbott C Series analyzer [Abbott Labs]).

Venous blood samples were assayed for hormonal biomarkers: free T3, free T4, and thyroid stimulating hormone via CMIA method; thyroglobulin (Tg, Beckman Coulter Access method); and antithyroglobulin antibodies (anti-Tg, CMIA method) at

Canterbury Health Laboratories. Serum thyroglobulin has been suggested as an alternative method to assess individual iodine status reflecting a period of months [56]; to avoid potential underestimation of thyroglobulin, anti-Tg and antithyroid peroxidase (anti-TPO) were measured. Selenium status was assessed by determining the biomarker plasma selenium via ICP-MS method [57].

Details of data and biological samples collected from both mothers and infants throughout the study period are summarized in Tables 1 and 2.

Table 1. Summary of outcome measures collected from participating women and their infants.

Outcome	Visit 1	Visit 2	Visit 3
Dietary intake			
Maternal 4-day dietary diary	x		
Maternal food frequency questionnaire–iodine/selenium	x		x
Maternal food frequency questionnaire–iron		x	
Infant 3-day dietary diary		x	
Anthropometry			
Maternal weight and height	x	x	x
Maternal body composition via BodPod and BIA[a]	x	x	x
Infant weight, height, and head circumference	x	x	x
Biochemistry			
Maternal spot urine samples	x	x	x
Maternal breast milk samples	x	x	x
Maternal toenail clipping samples	x	x	x
Maternal venous blood samples		x	
Maternal capillary blood samples		x	
Infant spot urine samples	x	x	x
Infant nail clipping samples	x	x	x
Others			
Maternal thyroid gland volume via ultrasound		x	
Maternal Edinburgh Postnatal Depression Scale results	x	x	x
Maternal self-reported health questionnaire	x	x	x
Maternal iodine nutritional knowledge questionnaire	x		
Infant health questionnaire reported by mothers	x	x	x

[a]BIA: bioelectrical impedance analysis.

Table 2. Analysis from biological data collected at each study visit for the Mother and Infant Nutrition Investigation study cohort.

Samples	Visit 1		Visit 2		Visit 3	
	Mothers	Infants	Mothers	Infants	Mothers	Infants
Spot urine						
Iodine	x	x	x	x	x	x
Selenium	x	x	x	x	x	x
Creatinine	x		x		x	
Breast milk (if available)						
Iodine	x		x		x	
Selenium	x		x		x	
Blood						
Iodine status[a]			x			
Selenium status[b]			x			
Iron status[c]			x			
Thyroid function[d]			x			
Nail clippings for selenium						
Toenails	x	x	x	x	x	x
Fingernails		x		x		x

[a]Iodine status: testing thyroglobulin and antithyroglobulin.

[b]Selenium status: testing plasma selenium.

[c]Iron status: testing hemoglobin, serum ferritin, soluble transferrin receptors, and C-reactive protein.

[d]Thyroid function: testing serum free triiodothyronine, free thyroxine, thyroid stimulating hormone, and antithyroid peroxidase.

Statistical Analysis

Statistical analysis will be performed using SPSS Statistics version 23. The Shapiro-Wilk test will be used to test for data normality. Nonparametric data will be expressed as median (25th, 75th percentile), and parametric data will be expressed as mean and standard deviation. Bivariate correlations will be tested using the nonparametric Spearman correlation coefficient. Repeated-measures analysis of variance will be used to calculate continuous variables between groups. Nonparametric Mann-Whitney U test (2-tailed) will be used to examine iodine intake and status between supplement users and nonusers. Multiple regression models analysis will be used to determine the associations between iodine, selenium, iron status, and thyroid function, as well as considering confounding factors. Multivariate analysis will be used to examine possible associations between women's selenium status, thyroid function, and postnatal depression and infant first year neurodevelopment.

Results

Recruitment traversed the 19-month period between June 2016 and December 2017, and a sample of 91 women-infant pairs was enrolled (Figure 1). Data collection has been completed. Biological samples analysis, excluding nail clippings, is complete. Data analysis and presentation of the results will be available after 2020.

Figure 1. Flow chart showing recruitment for the Mother and Infant Nutrition Investigation study.
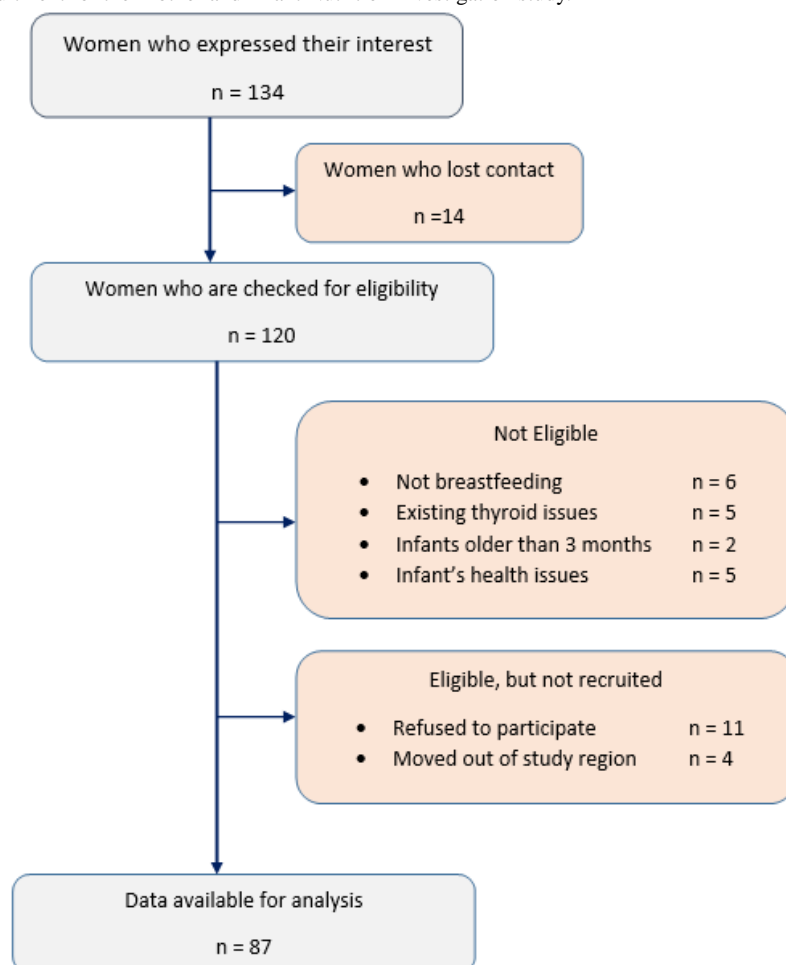
Discussion

Summary

A unique aspect of this study is that it will investigate all three micronutrients responsible for adequate thyroid hormone synthesis concurrently, rather than each separately in isolation. This observational longitudinal cohort study will measure the iodine and selenium status of women repeatedly in their first year after birth, which provides an evaluation of their nutritional status. Iodine status among supplement users and nonusers will provide up-to-date data on this postpartum group in New Zealand around 8 years after government interventions. Results will explore whether maternal iodine and selenium status could be used as a proxy measure of infant status. It provides an opportunity to examine the association of maternal iodine and selenium with infant neurodevelopment during their first year. This study explores selenium status using both short-term and long-term measures in relation to neurodevelopment at 6 months and 12 months of age, which has not been reported previously. Furthermore, the study results will add preliminary data on iron status of women at 6 months postpartum.

Importantly, the study will investigate overall thyroid function of women at 6 months postpartum with respect to the risk of postnatal depression. Measurement of thyroid hormones, thyroid stimulating hormone, anti-TPO, Tg, and anti-Tg in serum as well as measuring thyroid gland volume via ultrasound will provide an overall picture of maternal thyroid function after giving birth. This is an opportune time to check thyroid status, especially as women with limited thyroidal reserve or iodine deficiency in pregnancy may develop postpartum thyroid dysfunction, one of the most common endocrine disorders women experience [6,58].

Additionally, there will be longitudinal assessment of mothers' mental health via repeated screening by using the EPDS. The results may add to the literature in postpartum mental health status. Their offsprings' growth and neurodevelopment will be followed during the first year after birth. The findings from this study have the potential to inform future public health policy and practice regarding postpartum women's nutritional status and mental health together with infant health outcomes.

Authors' Contributions

YJ, LB, and JC conceived and designed the study and acquired funding. SJZH, SS, and RP peer-reviewed the study design. YJ drafted and wrote the manuscript. LB, JC, SJZH, SS, CB, NK, and RP critically reviewed and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Flow chart showing stages of Mother and Infant Nutrition Investigation study.
[PNG File , 52 KB - resprot_v9i8e18560_app1.PNG]

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Abbreviations

Anti-Tg: antithyroglobulin antibodies
Anti-TPO: antithyroid peroxidase
ASQ: Ages and Stages Questionnaire
CMIA: chemiluminescent microparticle immunoassay
EPDS: Edinburgh Postnatal Depression Scale
ICP-MS: inductively coupled plasma mass spectrometry
MINI: Mother and Infant Nutrition Investigation
T3: triiodothyronine

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T4: thyroxine
Tg: thyroglobulin

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Protocol

Type 1 Diabetes Mellitus Virtual Patient Network as a Peer Support Community: Protocol for Social Network Analysis and Content Analysis

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Abstract

Background: Type 1 Diabetes Mellitus Virtual Patient Network (T1DM-VPN) is a private Facebook group for youths with type 1 diabetes mellitus (T1DM) in Canada intended to facilitate peer-to-peer support. It was built on the finding that stigma is prevalent among youth with T1DM and impedes self-management.

Objective: We aim to determine if T1DM-VPN provides support as intended and to ascertain what type of members provide support. Specifically, we will (1) identify text consistent with any one of 5 social support categories, (2) describe the network by visualizing its structure and reporting basic engagement statistics, and (3) determine whether being a designated peer leader is related to a member's centrality (ie, importance in the network) and how frequently they offer social support.

Methods: We will manually extract interaction data from the Facebook group (posts, comments, likes/reactions, seen) generated from June 21, 2017 (addition of first member), to March 1, 2020. Two researchers will independently code posts and comments according to an existing framework of 5 social support categories—informational, emotional, esteem, network, and tangible—with an additional framework for nonsocial support categories. We will calculate how frequently each code is used. We will also report basic engagement statistics (eg, number of posts made per person-month) and generate a visualization of the network. We will identify stable time intervals in the history of T1DM-VPN by modeling monthly membership growth as a Poisson process. Within each interval, each member's centrality will be calculated and standardized to that of the most central member. We will use a centrality formula that considers both breadth and depth of connections (centrality = $0.8 \times$ total No. of connections + $0.2 \times$ total No. of interactions). Finally, we will construct multivariate linear regression models to assess whether peer leader status predicts member centrality and the frequency of offering social support. Other variables considered for inclusion in the models are gender and age at diagnosis.

Results: T1DM-VPN was launched in June 2017. As of March 1, 2020, it has 196 patient-members. This research protocol received ethics approval from the McGill University Health Centre Research Ethics Board on May 20, 2020. Baseline information about each group member was collected upon addition into the group, and collection of interaction data is ongoing as of May 2020.

Conclusions: This content analysis and social network analysis study of a virtual patient network applies epidemiological methods to account for dynamic growth and activity. The results will allow for an understanding of the topics of importance to youth with T1DM and how a virtual patient network evolves over time. This work is intended to serve as a foundation for future action to help youth improve their experience of living with diabetes.

International Registered Report Identifier (IRRID): PRR1-10.2196/18714

Introduction

Background

Type 1 diabetes mellitus (T1DM) is a chronic condition whereby one's immune system attacks the pancreas, rendering it unable to produce adequate insulin for glucose entry from the circulation and into the cells of the body to fuel metabolism. This differs from the general pathology in type 2 diabetes, which is one of resistance to the action of insulin, often related to low physical activity and excess adiposity. Patients with T1DM administer insulin as a medication, adjusting doses in relationship to food intake and physical activity. They are challenged by a narrow therapeutic window, navigating a tight balance between preventing low glucose levels and high glucose levels. Low levels, or hypoglycemia, can lead to confusion, loss of consciousness, and even death. Persistently high levels over time can damage blood vessels, resulting in blindness, renal injury, cardiovascular disease, stroke, and a multitude of other complications. The visibility of hypoglycemic symptoms, blood glucose testing equipment, and insulin administration, among other tasks and public misconceptions about T1DM, may lead to stigma.

Indeed, in a previous study, we determined that approximately 65% of Canadian youths (ie, aged 14 to 24 years) with T1DM experience stigma and that it is associated with greater probability of both severe hypoglycemia and high average glucose levels, specifically elevated glycated hemoglobin (HbA_{1C}) [1]. The Type 1 Diabetes Mellitus Virtual Patient Network (T1DM-VPN) is a private Facebook group launched in 2017 to help facilitate peer-to-peer support for these youths, allow youth to share experiences of living with T1DM, and perhaps mitigate stigma. We now aim to assess whether the Facebook group is providing the support it is intended to provide. We present herein a detailed protocol for this analysis.

We first provide an overview of T1DM management, existing web platforms for patients and their families, and the development of T1DM-VPN towards its current structure.

Barriers to T1DM Management

In Canada, 24,170 children and adolescents and 84,380 young adults have diabetes [2], over 90% of which is T1DM [3,4]. T1DM management requires insulin pump or injection use, finger pricks for blood glucose testing, and attention to food choices, meal timing, and physical activity levels. However, youth must also manage challenges of identity development, education and career choices, and peer pressure. Managing both sets of needs can be complicated by stigma. Stigma is defined as real or perceived negative social judgement from one's surroundings or oneself [5]. Our Canada-wide study of 380 youths determined that 65% report some degree of stigma (ie, endorsed one or more of 3 key items on a stigma subscale) [1]. Youths experiencing stigma were twice as likely to have either an HbA_{1c} above 9% or one or more severe hypoglycemic events in the prior year. HbA_{1c} is a measure of the average level of blood sugar over the past 2 to 3 months, and higher levels indicate greater risk of serious diabetes-related complications, such as cardiovascular disease and kidney, eye, and nerve damage [6]. Severe hypoglycemia may also cause distressing conditions such as confusion, loss of consciousness, and even death [7,8]. Our study also determined that stigma was associated with a reduced sense of well-being and less self-efficacy for self-management. Most participants reported that they did not personally know anyone with T1DM and desired social support specifically from peers with T1DM.

Existing Web Platforms

Web platforms for patients with T1DM vary in reach and in purpose. On Twitter, hashtags are used by people all over the world to connect on specific topics. For example, the #OpenAPS hashtag is used by patients and caregivers to vocalize their experience using do-it-yourself (DIY) innovations that bridge communication between insulin pumps and glucose monitors [9]. Meanwhile, a Facebook group numbering over 27,000 members provides practical aid in using DIY programs [10]. Some caregivers of children with T1DM publish blogs in order to publicly express their experiences and feelings, with additional caregivers commenting [11]. Some youths initiate local university-based diabetes student organizations with a respective social media platform, including in Canadian towns such as Toronto and London. Other platforms are managed professionally. For example, Beyond Type 1 is an organization that amalgamates practical resources and stories on a website, including some specific to Canada. They also have an app where registered adults and teenagers can socialize via public posts and comments. Social media groups may be generated by professionals as well; one clinical team in Australia created a

small (34 members) private Facebook group for youths with T1DM as part of a 12-week trial to support their transition to independent self-care [12].

In this landscape, T1DM-VPN is distinguished as a joint initiative between health professional researchers and youths with T1DM. It is funded by Diabetes Canada as well as the Canadian Institutes of Health Research (CIHR) grant, specifically their Strategy for Patient-Oriented Research – Patient-Oriented Research Collaboration Grants. Its core feature is a private Facebook group. Eligible members are Canadian youths (ie, aged 14-24 years) with T1DM. Many T1DM-specific groups have been initiated organically on Facebook. However, none are known to be specific to Canadian youth, who can benefit from region-specific information and from interacting almost instantly with those who face similar everyday challenges across the country. It is open only to patients, not to parents or other caregivers, at the specific request of its founding patient-partners. Its 3 goals are (1) to be a community of support, (2) to identify the issues that matter to patients, and (3) to establish a platform for action and empowerment.

Development of T1DM-VPN

We collaborated with 2 patient-partners to inform its development, 1 youth with T1DM and 1 adult with T1DM with experience as a certified peer leader for a chronic illness self-management program at the McGill University Health Centre (MUHC) called My Tool Box. My Tool Box is based on the Stanford model of chronic disease self-management, which allows individuals living with a chronic illness to engage in group discussions on self-care led by trained peer leaders who also live with chronic illness [13]. This program was

discontinued at the MUHC but our patient-partner's experience with it was important in the training of our peer leaders.

We recruited youth peer leaders for T1DM-VPN by asking our coinvestigators across Canada to approach any patients who they thought would be a champion for T1DM and by approaching patients who submitted moving testimonies from our original study on stigma and T1DM. They were told that responsibilities include starting conversations in the group and having one-on-one conversations if requested by a member.

At the 2017 Diabetes Canada conference in Edmonton, several peer leaders participated in the satellite workshop that we organized to encourage group cohesion, provide training in peer support, discuss goals, and craft community guidelines. Each peer leader receives a stipend (Can $25, or US $18.88, per month) to support involvement in T1DM-VPN. They take an active role in initiating conversations, sharing information, and answering questions. They provide input on recruitment strategy. They reach out to our team of clinicians and researchers for information.

Some regular T1DM-VPN members are recruited from among participants in our original study on stigma. Regular members are continuously recruited through the clinics of our coinvestigators and via posters displayed in clinics and posted online on diabetes-related Facebook pages and websites. Addition of members began in June 2017 and membership passed 200 on February 4, 2020 (Figure 1). Of these members, 5 are members of our research team, including an administrator account. The rest are youths with T1DM from over 20 towns and cities in all 10 Canadian provinces.

Figure 1. Number of Type 1 Diabetes Mellitus Virtual Patient Network Facebook group members from June 21, 2017, to February 4, 2020.
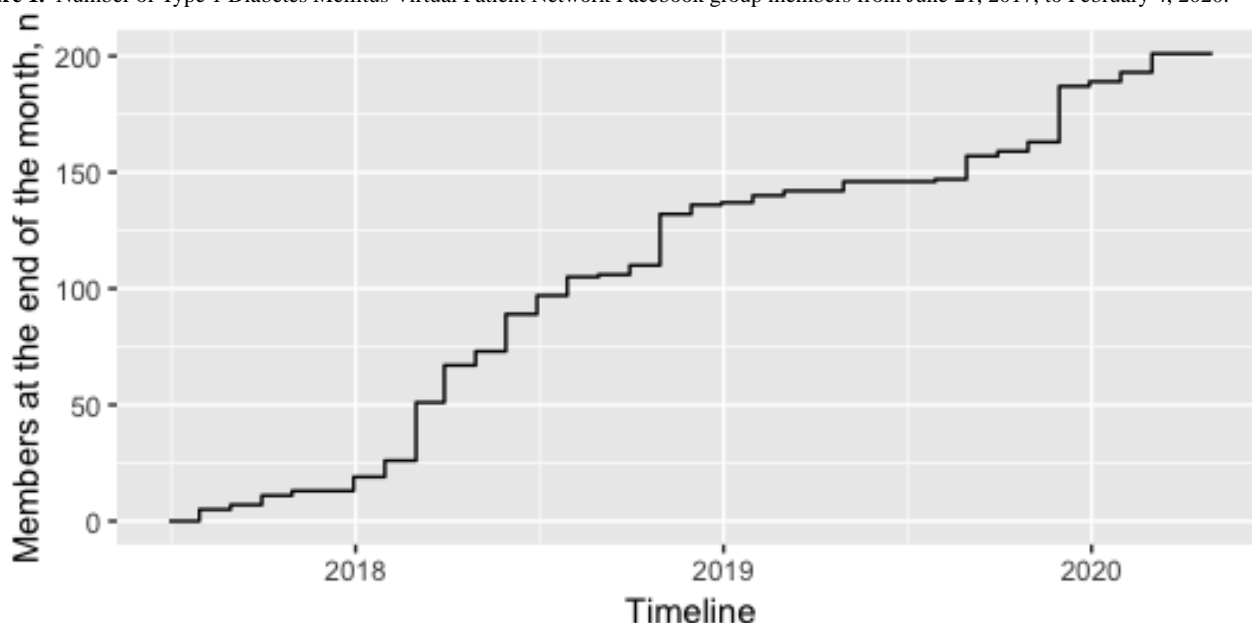
The administrator account is used by the research team to oversee the group. We add eligible members, help answer questions that may require professional input, and ensure that the code of conduct (eg, no disrespectful behavior) is followed. Fortunately, our members have only behaved in a courteous and supportive manner and we have never had to intervene. As

patient membership approaches 200, we aim to determine if the project goals are being fulfilled. This will help inform strategies to strengthen and sustain the network.

T1DM-VPN members are aware that the private Facebook group was created by researchers and trained peer leaders and that

communications are monitored. As we state on the Facebook group itself:

> The main goal of the network…is intended to be a source of support, friendship and information. It will also be used to find out what research is important to patients like you to help guide diabetes research in Canada….As we have funding from CIHR and Diabetes Canada and have health professionals and researchers on board who will help make living with T1D easier, and will be there to answer your questions!

Objectives

The goals of this analysis stem from T1DM-VPN's goals of facilitating social support and identifying the priorities of young Canadians with T1DM. This protocol is for an objectives-based program evaluation, a type of evaluation that ascertains that the intended activities are taking place [14].

Our primary analysis objective is to determine whether peer leaders are (1) more central and (2) provide more social support to the group than regular members. Through analyzing group members' exchanges, we also aim to achieve secondary objectives of (1) determining the existence and volume of 5 categories of social support and (2) identifying the issues for which informational support is requested.

Assessing the role of peer leaders has implications on the sustainability of T1DM-VPN as a program; it will help determine whether peer leaders should continue to be engaged by our team of clinicians and researchers or if regular members can rise to become "natural" peer leaders.

Previous Analyses of Web Platforms for Youths With T1DM

Researchers have previously performed content analysis on messages authored by youths with T1DM in an online context. One study amalgamated content from 8 public T1DM forums and used an inductive coding process to categorize messages. Among the 6 resulting codes were social support, factual information, and management. The forums were not age specific, but they extracted data for which the user self-reported an age between 11 and 19 years old [15]. One research group designed an app specifically for their research study, holding regularly scheduled virtual text chats with T1DM youths aged 12 to 18 years recruited from a diabetes care center in Italy [16]. Chats were actively moderated by researchers and health professionals. This study used the same social support framework that we intend to use for coding. However, the nature of T1DM-VPN bridges that of the online platforms featured in the 2 aforementioned studies—as a private Facebook group, T1DM-VPN users are enabled the spontaneity and connectivity of a public forum but offered the privacy and peer-specific audience of the chats. T1DM-VPN users may express themselves differently because they are aware that their peers, rather than our administrative team, take the lead in answering questions and moderating discussions. Furthermore, they are aware that the group is specific to Canada and that as a result, peers may be better able to answer questions related to health care and insurance. Thus, it will be interesting to compare the frequency of different kinds of support offered across these different platforms.

The study in Italy [16] also compared the frequency of social support categories from moderators versus participants. They determined that moderators were more likely to present informational support, and participants were more likely to provide emotional support. As in this study, we will be ascertaining the relationship between a designated moderator status (peer leader vs regular member) and social support behavior. However, the nature of T1DM-VPN differs in that the designated discussion moderators are peers (ie, fellow youths with T1DM). As detailed in the "Methods" section, we will ascertain this relationship by constructing multilinear regression models that consider additional variables such as gender.

Shah and colleagues [17] have previously performed social network analysis (SNA) on youths with T1DM and their parents. They mapped participants' subjective network of friends and relatives through interview and found that youths with a greater number of network members providing support reported lower anxiety. Saylor and colleagues [18] performed a descriptive correlational study that found that T1DM youths who were members of a student-led diabetes student organization were less likely to report poor mental health related to their diabetes than youths who were not [18]. We are able to similarly capture the network positions and behaviors of youths with T1DM who actively engage with the support network (T1DM-VPN) versus those who do not. However, T1DM-VPN differs in that it provides a virtual network of support to members, and to our knowledge, SNA has not been applied to virtual networks of T1DM patients. Moreover, our outcome of interest is not a self-reported health status, but a measure of importance in the network and the act of offering social support.

Overall, we are modelling T1DM-VPN as a social network for the purpose of understanding the role of different member types on this virtual platform. The interactions on a Facebook group may not reflect those that would occur between individuals outside a virtual network in their in-person social groups and settings.

Methods

Overview

Baseline information is collected upon group entry, including gender (derived from nominal information), age at diagnosis, and geographic classification (ie, large, medium, or small population centers or rural). We will manually extract interaction data from the T1DM-VPN Facebook group feed for the period between June 21, 2017 (addition of first member), and March 1, 2020. Enrollment into these groups is controlled by the researchers, and members are aware of their role in overseeing group activity. It is essential to include all members in an SNA. While we will not seek individual-level consent, we will provide a reader-friendly description of the protocol in the Facebook group and invite members to comment, as recommended by our peer leaders during a teleconference. All data will be deidentified prior to analysis by replacing names with identification numbers; the document linking these numbers to

individuals will only be available to members of the research team. This proposed analysis received ethics approval from the McGill University Health Centre Research Ethics Board on May 20, 2020.

Phase I: Directed Content Analysis

We will apply content analysis, interpreting the text and coding it into categories and then using the frequency of a category as a proxy for its importance [19]. Our content analysis will be directed, applying prior knowledge to inform coding categories. Specifically, we will apply Cutrona and Suhr's typology [20], which is used for online support group analysis by other researchers [21,22]. Its 2 overarching categories are seeking support and providing support. These in turn each have 5 subcategories: informational, emotional, esteem, network, and tangible assistance. In addition, we will code and count social support facilitators (expressions of gratitude) as well as nonsocial support exchanges (eg, administrative messages). These two frameworks — one for social support exchanges, and another for facilitators and nonsocial support exchanges — will be adapted from Gaysynsky et al's [22] directed content analysis of a private Facebook group for young clients of an HIV program. After applying these initial codes to the data, any

content deemed not adequately coded will be further examined and discussed to determine if new categories need to be added.

Two coders will review examples of how the frameworks have been applied in Gaysynsky and colleagues' study. First, a sample of data will be coded, analyzed for concordance between the 2 coders, and discussed to refine the consistency with which codes are applied. Then, all posts and comments will be reviewed to identify which code is most applicable. For a given comment, context (original post, preceding and proceeding comments) will be used to help inform coding decisions. A maximum of 2 codes may be applied to the same content. We will further examine the issues for which informational support is requested.

Phase 2: Social Network Analysis

Defining an Interaction

In T1DM-VPN, members interact via posts and comments. Members may additionally like or react to a post or comment or vote on a poll (Table 1). Following the examples of previous SNA on Facebook [23], we will define each of these as an interaction type. We will further categorize each interaction type into a high, medium, or low engagement level (Table 1). We will also take note of who has seen a post and categorize this as a low engagement level.

Table 1. Types of interactions.

| Engagement level and interaction type	Definition
High	
Post	Content posted by any member to the group feed
Comment	When a member comments on a post
Medium	
Like/react to a post	When a member likes/reacts to a post
Like/react to a comment	When a member likes/reacts to a comment
Vote in a poll	When a member votes in a poll (type of post)
Low	
Seen	When a member has seen a post (with no further interaction)

Visualizing Interactions

Based on interaction data, the social network will be visualized using programming packages specific to social network analysis, such as sna and network (R version 3.5.1 and RStudio version 1.1.456, respectively). All members (or "nodes") will be represented as dots, and any medium or high engagement level interaction between 2 nodes will be represented with a line connecting them (Figure 2, sample visualization).

For overall network visualization, each line between nodes will represent one or more interactions for the period of interest

(unweighted approach) rather than a separate line for each interaction (weighted approach). Similarly, the directionality of an interaction/line will not be indicated (undirected graph). This will render the visual representation less crowded and more interpretable. We will visualize the network both with and without peer leaders to visually appreciate their importance in driving group activity, following the example of a previous SNA evaluating the importance of a Facebook page moderator [23]. When calculating network centrality, as discussed below, we will consider both weighted and unweighted approaches.

Figure 2. Sample visualization of a social network with 9 members. Regular members are indicated as light circles, and peer leaders are indicated as dark circles. Interactions are represented by straight, connective lines.
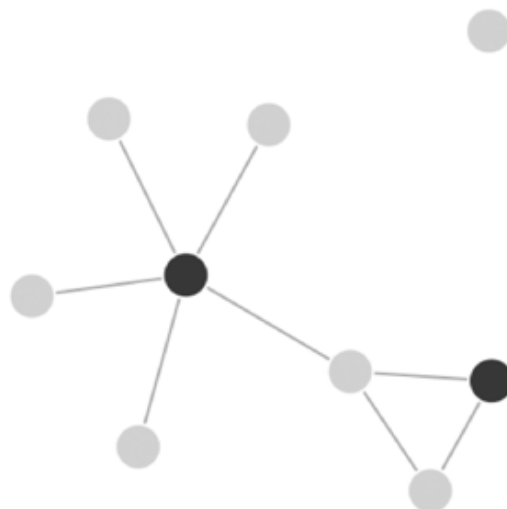
Network Dynamics and Time in SNA

We will evaluate network dynamics over approximately a 3-year period. In epidemiological terms, this is an open cohort, in that members may leave or join at different times. In prior Facebook group studies, researchers have taken a data sample from what they assumed to be a stable time frame. They then take absolute (eg, total number of posts) or per-person (eg, average number of posts per person) measurements [22,24].

Instead of making assumptions about the stability of a network, we will actually identify stable time frames by modeling monthly membership growth as a Poisson process, a process in which the average rate of events is known but the exact timing of events is random. We propose that any month for which the probability of observed growth falls below 50% (ie, is statistically unusual based on the known average rate of events) represents the end of a stable time interval and the start of a new stable interval. For several network and node attributes detailed below, we will calculate an incident measure for each time interval, then a summary measure across all intervals if applicable. These calculations are detailed below.

Network Attributes

Social networks can be characterized by measures of density, identification of cliques, and indicators of engagement [25]. Density is the total number of interactions divided by the total possible number of interactions. A clique is a subgroup of nodes that are directly connected to one another, with no node being connected to all in the subgroup. Quantifying engagement typically involves an enumeration of high engagement level interactions; we will use number of posts per person-month. These 3 attributes will be calculated for each time interval. To summarize them, the difference in density and number of cliques from the first interval to the last will be calculated, and the mean number of posts per person-month will be taken.

Node Attributes

Just as the network may be characterized by defined metrics, nodes may also be characterized in terms of their centrality and in terms of the nature of their interactions. For each node, we will calculate the proportion of all their interactions that are categorized as high, medium, or low engagement level (Table 1). This helps identify members who actively participate in discussion versus those who view others' interactions but infrequently participate themselves. We will also calculate the proportion of a user's interactions that are categorized as offering social support; this is one of the measures that will be used in the regression analysis. Because these are proportions, there is no need to additionally account for group stability.

Centrality is the other measure that will be used in the regression analysis, but it requires accounting for stability. Centrality refers to one's prominence in the network. In virtual SNA, prominence is calculated using virtual connections. In calculating degree centrality specifically [25,26], researchers may consider the total number of nodes with which a node is connected or the total number of connections, including repeated connections with the same node. We have developed a measure that incorporates both of these aspects. In ascertaining centrality, we will focus only on medium and high engagement level interactions as connections. In order to capture both breadth and depth of connection in centrality, we have adapted modeling methods from economics [27,28], creating a measure that is a convex combination of the weighted and unweighted approaches:

Centrality = $\alpha \times$ total No. of connections + $(1 - \alpha) \times$ total No. of interactions

In the above equation, we choose α to be .8. Although α is usually any number between 0 and 1, we will be testing values between .5 and 1 in a sensitivity analysis. This range ensures that breadth of connections is given equal or greater weight than depth.

The centrality of each member will be calculated for each stable time interval (ie, include interactions occurring exclusively within that interval), then standardized to that of the most central member for that interval. The resulting measures for each member will be averaged. This final mean value will be used in regression analysis.

Rather than taking a direct calculation of these attributes, as existing virtual SNAs have, we are adopting this approach because we appreciate that length of membership in T1DM-VPN is similar to exposure time. If a user has been involved in the group for a longer period of time, then their increased centrality may be a function of their increased opportunity to interact with others. We also understand that the number of possible connections exposed to a user at a given point in time differs. Network membership increases over time, and so does the number of potential connections for a user. By taking measures of centrality from smaller, stable time frames, we can better control for these two potential confounders.

Phase 3: Regression Analyses

We will evaluate the relationship between network centrality and designated peer leader status to determine whether those so designated are more likely to be central within the network. We will apply multivariate linear regression, considering inclusion of the following variables in the model: gender, age at diagnosis, and geographic classification (ie, large, medium, or small population centers or rural). Studentized residuals will be used to detect potential outliers. We will then calculate a Bayesian information criterion (BIC) for each model, where a lower BIC indicates a better model. We will also use multiple linear regression to assess whether peer leader status is correlated with the individual's proportion of interactions offering support.

Results

T1DM-VPN was launched in June 2017, and as of March 1, 2020, it has 196 patient-members. This research protocol received ethics approval from the McGill University Health Centre Research Ethics Board on May 20, 2020. Baseline information about each group member was collected upon their addition into the group. Collection of interaction data is set to be complete by fall 2020, and data analysis is set to be conducted by November 2020.

Discussion

Contribution to the Literature

Peer-led virtual networks with some professional oversight and access are promising avenues to enhance chronic disease management in general and diabetes self-management in particular. To properly understand their mechanics and impacts, traditional methods in epidemiology and social network analysis need to be adapted and applied. The proposed analytic approaches aim to do this. It will be interesting to interpret our results in the context of previous analyses of T1DM support networks that differ slightly in geographic scope, target population, and platform function. Furthermore, to our knowledge, this will be the first analysis of a virtual T1DM

patient community of this level of comprehensiveness. The findings may be of interest to professionals aiming to launch a similar virtual community in another population, country, or region.

Zhou and colleagues [29] have proposed a conceptual framework for social media–based health information management. Though commonly applied to professional-patient information exchange, it may also be used to understand peer-peer interactions; health information management refers broadly to the activities that users perform in order to process health information items to fulfill their needs. This includes needs for social support. The social media–based health information management framework outlines processes by which users aim to improve 4 outcomes, represented as the "4Cs": convenience, care, communication efficiency, and cost-effectiveness.

In their framework, Zhou and colleagues [29] focus on information processing as performed by researchers on social media data generated by users. However, we also find it useful to conceptualize T1DM-VPN members as engaging in the processes of generating and retrieving health information amongst themselves, as well as integrating and applying it in their personal lives. As a social media platform, T1DM-VPN may improve the convenience with which young Canadians living with T1DM exchange information with one another. The other *C*'s are currently less pertinent to T1DM-VPN.

Our aim is to understand if T1DM-VPN is providing support and stimulating engagement because this will inform how we will approach sustainability avenues. Thus far, our research team has actively invested time and resources to train the national panel of peer leaders and sustain their participation. Our team also recruits new T1DM-VPN members and moderates the community.

While growth of the network itself is indeed important, through the proposed analysis we will determine the degree of interaction within the network and the types of support offered. Demonstration of a high level of engagement and support would provide a strong rationale to develop a sustainability strategy. Another goal of our analyses is to determine whether central roles remain the purview of the selected peer leaders or whether regular members are naturally taking on the role of peer leaders (ie, posting often, inviting new members, offering social support). If that is the case, then there may be less need for us to recruit leaders and provide them with a stipend. The ultimate goal is for T1DM-VPN to become at least a partially self-sustaining group, with our research team transitioning from less of an active role to more of an administrative role.

We believe that our study will build evidence and provide a road map for the building and maintenance of virtual peer support networks in chronic disease.

Knowledge Dissemination

We will promote and disseminate our approach and findings via scientific manuscripts. We will also share findings through the Diabetes Canada website, social media, and professional conferences. In our consultation with the peer leaders to develop this analysis protocol, they expressed great interest in seeing

for themselves how T1DM-VPN has developed over the years. Thus, in keeping with our participatory approach, we will share and discuss our results directly with our peer leaders. Findings may also be presented to T1DM attendees of patient conferences, such as No Limits with T1D: Inspire, Empower, Connect, which is held annually in Vancouver, British Columbia, Canada.

Authors' Contributions

KD, MN, DDC, GM, DP, CP, AB, and SB conceptualized and launched the T1DM-VPN project. NW grew the network further and conceptualized the analysis protocol with guidance from KD. NW and KD drafted the manuscript. All authors provided input on the analysis, critically reviewed the manuscript, and approved the final version as submitted.

Conflicts of Interest

None declared.

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Abbreviations

BIC: Bayesian information criterion
CIHR: Canadian Institutes of Health Research
DIY: do-it-yourself
HbA$_{1C}$: glycated hemoglobin
MUHC: McGill University Health Centre
SNA: social network analysis
T1DM: type 1 diabetes mellitus
T1DM-VPN: Type 1 Diabetes Mellitus Virtual Patient Network

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Protocol

Insights From Twitter Conversations on Lupus and Reproductive Health: Protocol for a Content Analysis

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Abstract

Background: Systemic lupus erythematosus (SLE) is the most common form of lupus. It is a chronic autoimmune disease that predominantly affects women of reproductive age, impacting contraception, fertility, and pregnancy. Although clinic-based studies have contributed to an increased understanding of reproductive health care needs of patients with SLE, misinformation abounds and perspectives on reproductive health issues among patients with lupus remain poorly understood. Social networks such as Twitter may serve as a data source for exploring how lupus patients communicate about their health issues, thus adding a dimension to enrich our understanding of communication regarding reproductive health in this unique patient population.

Objective: The objective of this study is to conduct a content analysis of Twitter data published by users in English in the United States from September 1, 2017, to October 31, 2018, in order to examine people's perspectives on reproductive health among patients with lupus.

Methods: This study will analyze user-generated posts that include keywords related to lupus and reproductive health from Twitter. To access public Twitter user data, we will use Symplur Signals, a health care social media analytics platform. Text classifiers will be used to identify topics in posts. Posts will be classified manually into the a priori and emergent categories. Based on the information available in a user's Twitter profile (ie, username, description, and profile image), we will further attempt to characterize the user who generated the post. We will use descriptive statistics to analyze the data and identify the most prevalent topics in the Twitter content among patients with lupus.

Results: This study has been funded by the National Center for Advancing Translational Science (NCATS) through their Clinical and Translational Science Awards program. The Institutional Review Board at the University of Southern California approved the study (HS-18-00912). Data extraction and cleaning are complete. We obtained 47,715 Twitter posts containing terms related to "lupus" from users in the United States, published in English between September 1, 2017, and October 31, 2018. We will include 40,885 posts in the analysis, which will be completed in fall 2020. This study was supported by funds from the has been funded by the National Center for Advancing Translational Science (NCATS) through their Clinical and Translational Science Awards program.

Conclusions: The findings from this study will provide pilot data on the use of Twitter among patients with lupus. Our findings will shed light on whether Twitter is a promising data source for learning about reproductive health issues expressed among

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patients with lupus. The data will also help to determine whether Twitter can serve as a potential outreach platform for raising awareness of lupus and reproductive health and for implementing relevant health interventions.

International Registered Report Identifier (IRRID): DERR1-10.2196/15623

Introduction

Background and Rationale

Lupus is a chronic autoimmune disease that can affect any part of the body (skin, joints, or vital organs) [1,2]. Estimates from recent population-based studies in the United States report the prevalence of systemic lupus erythematosus (SLE), the most common form of lupus, to be between 60 and 80 per 100,000, although this prevalence varies greatly by age, gender, race, and ethnicity. It is generally accepted that SLE is much more prevalent in women than men (up to 9 times higher prevalence) and that people of color have both higher prevalence rates and more severe manifestations of the disease compared to White populations. Rates as high as 196 per 100,000 have been reported in African American women [3,4].

SLE predominantly impacts women during the childbearing years, affecting contraception, fertility, and pregnancy, which are matters of importance to the patients and their family members. Providing care to pregnant patients with lupus is an important challenge for their families and the health care system. Although quite a few studies in the modern era have clarified the field of reproductive health care for SLE patients [5], misinformation abounds. Perspectives on reproductive health issues, especially those regarding medication risks and benefits, among patients with lupus and their family members remain poorly understood. In this study, we define the term "perspective" as an expression of thought, viewpoint, and attitude toward the reproductive health issues that have been identified in the literature, such as pregnancy prevention, pregnancy termination, pregnancy planning, conception, and concerns and management of childbirth [6]. A better understanding of the perspectives on reproductive health issues among patients with lupus can inform and improve the advocacy and education efforts to address the gaps in care, dispel misconceptions, and more effectively assist patients in making family planning decisions.

Social Media

Social media consists of web-based and mobile technologies that allow users to view, create, and share information online and participate in social networking [7-9]. Social media provides a unique source for data mining of health conditions and concerns, serving as a massive focus group [10-12]. A total of 72% of American adults use at least some type of social media [13], which provides an unprecedented opportunity for delivering information to reach large segments of the population [14] as well as hard-to-reach subpopulations [15,16]. Data from social networks such as Twitter, Instagram, and YouTube that allow users to discuss topics of their choice "unprimed by a researcher and without instrument bias" [10] can be used to capture and describe the social and environmental context in which individuals experience and describe their health conditions and concerns [17].

Twitter

Based on Pew Research data from 2019, nearly a quarter (22%) of adults in the United States use the social network Twitter; 40% of those are daily users [13]. Twitter allows users to post "tweets", short posts that are limited to 280 characters [18]. Users can search for any public tweet and engage with it through "like," "reply," and "retweet" (repost). Twitter is primarily public. Basic account information such as profile username, description, and location remains public. However, users can choose to keep their tweets protected to make them private or visible to subsets of users such as their followers or those they decided to follow [19,20]. Due to the more public nature of Twitter, previous research suggested that Twitter provides a "rich and promising avenue for exploring how patients conceptualize and communicate about their specific health issues" [21]. The increasing use of Twitter among the members of communities with disease is further evidenced by the abundance of disease-specific and health-related hashtags used in the tweets [22-24]. A hashtag is a word or phrase preceded by a hash or pound sign (#), which is used to identify tweets on a specific topic (eg, #lupus, #spoonies). These hashtags are used by users to assign their tweets to a topic and join ongoing conversations. Users can click on a hashtag and view all of the tweets that include the same hashtag; hence, discuss the same topic. This allows users to form online communities and share their health concerns, disease experience, and questions with other users [25]. However, there is little information about the use of social media among patients with lupus.

Previous Research on Social Media and Lupus

The emergence of social media has created new sources of analyzable data [12] and led to new research fields, such as infodemiology and infoveillance [11]. The data social media users generate through their online activities is referred to as their digital footprint [26] or social mediome [27].

Previous research examined user-generated content about lupus on Facebook [28]. Hale et al [28] looked at the representation of health conditions and found that lupus-related pages ranked the highest for patient support. Additionally, a patient commentary highlighted social media use (Twitter, in particular) by patients with lupus to find rheumatologists, specialist care, and peers and to build awareness of their health needs and experiences [29]. Health surveillance researchers have used

Twitter data to gain insights into the public perspectives on a variety of diseases and health topics such as influenza, autism, schizophrenia, smoking, and HIV/AIDS [30-35]. In some cases, social media user data demonstrated a correlation between the disease prevalence and frequency with which Twitter users discussed that disease [36]. To our knowledge, there are no studies that have leveraged Twitter to gain a better understanding of the perspectives of patients with lupus on reproductive health issues.

Study Objective and Research Questions

The objective of this study is to conduct a content analysis of tweets published in English by users in the United States during the period from September 1, 2017, to October 31, 2018, and to examine the perspectives of patients with lupus on reproductive health issues. We intend to answer the following research questions outlined in Textbox 1.

Our findings will shed light on whether Twitter is a promising data source for garnering insights about reproductive health concerns among the patients with lupus. The data will also help determine whether Twitter can serve as a potential outreach platform for raising awareness of lupus and reproductive health and for implementing relevant health interventions.

Textbox 1. Research questions.

- What is the volume of Twitter users who talk about lupus and reproductive health issues such as pregnancy prevention; pregnancy termination; and planning, conception, and management of pregnancy?

- How many of these users are patients with lupus?

- What are the perspectives, issues, and concerns that the patients with lupus express regarding their reproductive health?

- What are the demographics (ie, gender, race/ethnicity) of these patients with lupus on Twitter?

Methods

Data Collection

This qualitative study will analyze user-generated posts that include keywords related to lupus and fertility from the social network Twitter.

Data Source

To access public Twitter user data, we used Symplur Signals [37], a health care social media analytics company that maintains the largest publicly available database of health care– and disease-related conversations with the globally recognized Healthcare Hashtag Project. Symplur Signals extracts data from the Twitter representational state transfer (REST) application programming interface (API) and makes those available to researchers; those data are commonly used in peer-reviewed research [22,23,38-41]. We extracted data from Twitter using Symplur Signals user interface, searching for the relevant keywords and hashtags (Multimedia Appendix 1) from September 1, 2017, to October, 31, 2018. The data were provided in a spreadsheet, which we analyzed on local computers.

Search Filters

We utilized the framework suggested by Kim et al [42] for data collection, quality assessment, and reporting of standards. Twitter posts containing lupus-related terms were obtained for the period ranging from September 1, 2017, to October 31, 2018. The list of terms we used to collect the sample of tweets is shown in Multimedia Appendix 1. These terms can appear in the post or in an accompanying hashtag, for example, lupus or #LupusChat. LupusChat is a global health organization based in New York City, founded in 2012 by Tiffany Marie Peterson, a patient advocate who was diagnosed with SLE. The biweekly Twitter chat hosted by LupusChat is popular among patients with lupus to discuss related health concerns and the impact lupus has on their lives [43]. The selected keyword and hashtags are based on expert knowledge from clinicians and social media experts as well as on a systematic search of topic-related language using the Symplur Signals database. For each term, we viewed about 50 tweets to determine inactive as well as new keywords and hashtags that were being used in the lupus-related posts, particularly by patients. We will analyze the tweets from the patients with lupus to identify the issues and concerns they express regarding their reproductive health. Previous research has identified multiple challenges experienced by patients with SLE, for example, fertility preservation, optimal care during pregnancies, risks of adverse maternal or fetal outcomes, safety of contraceptive methods for women, and effects of dermatologic medications on male fertility [44-47].

Data Cleaning

The following types of posts were excluded: (1) non-English language tweets (which were identified using the methodology by Lui and Baldwin [48] and the language detection API of detectlanguage.com), (2) retweets that were originally composed/posted by other users, and (3) tweets that originated from outside the United States. We did not include retweets in the analysis dataset, as we intend to examine the patients' original perspectives on reproductive health issues. The locations of the users were determined using a mapped location filter as defined using "Profile Geo 2.0" algorithm (Gnip Inc) [49]. The algorithm uses a number of data points to determine a user's location, including the self-reported "Location" in the user profile and geotracking data, if available.

Furthermore, we relied on machine learning to recognize tweets by social bots or marketing-oriented accounts that could possibly influence the results and introduce bias [50,51]. Automated accounts on Twitter created by industry groups and private companies contribute to the corpus of Twitter data to influence discussions and promote specific ideas or products [28]. To identify those bias accounts, we identified a user account

responsible for each tweet collected in the dataset and analyzed its recent history, interactions, and metadata to determine the account was a social bot, a computer algorithm designed to automatically produce content and engage with humans on Twitter [50]. Tweets from these accounts "pollute social and health research data sets" [52]. They were identified and excluded from the dataset of tweets from patients with lupus. Bot accounts were identified using a system that analyzes the account's network (diffusion patterns), user (metadata), friends (account's contacts), temporal pattern (tweet rate), and sentiment (content of message), as previously described. The system detects bots with a 95% success rate [50].

Data Analysis

Coding

Two independent team members will be responsible for coding based on a set of a priori classifiers listed in Multimedia Appendices 2 and 3. We will use the profile information (ie, username, description, and profile image) of a Twitter account, which generated a relevant post, to characterize its user and determine if that user is a patient with lupus (Multimedia Appendix 3). Specifically, we will check if these users self-identify as patients with lupus in their profile description.

We will then code the tweets from patients with lupus (Multimedia Appendix 2). A tweet will be classified as the one by a patient with lupus—if that user has already been identified as such through examination of their Twitter profile or if the tweet describes lupus symptoms or lupus-related events in the first person (eg, My doctor had to change my medications today to the ones that are safe in pregnancy).

Additionally, we will code the person's gender and race/ethnicity if the profile contains sufficient information to do so. Cohen's kappa will be calculated for each code category to assess interrater reliability [53,54]. Once we establish concordance in the coder's classification with $\kappa > 0.8$ for each coding category, the remaining data will be divided between the 2 coders. Principal investigators of the project will help establish consensus in instances where coders disagree.

Statistical Analysis

The analysis will rely on public, anonymized data and will adhere to the terms and conditions, terms of use, and privacy policies of Twitter. This study will be conducted under the approval from the institutional review board of the authors' university. No tweets will be reported verbatim in the findings to protect the privacy of the users. Representative examples of tweets within each category will be selected to illustrate additional themes and will be shown as paraphrased quotes.

We will use descriptive statistics to identify the most prevalent topics in the Twitter content. Units of analysis will be unique terms in tweets, number of tweets, and number of users with lupus. For each analysis, we will present the findings in a confusion matrix, where diagonal lines would indicate the prevalence of a topic and off-diagonal lines, a topic overlap. The number of posts containing 2 or more topics would be found at the intersection of the matrix for these topics. We will further describe the patient characteristics focusing on gender and race/ethnicity, as reported on Twitter.

Data Privacy and Confidentiality

Study data will be stored using the Research Electronic Data Capture (REDCap) system at the University of Southern California (USC). REDCap is a secure, web-based application designed to support data capture for research studies [55]. It provides (1) an intuitive interface for validated data entry, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages, and (4) procedures for importing data from external sources. This database system facilitates the required provision of data to the USC Institutional Review Board, National Institutes of Health (NIH), and Food and Drug Administration (FDA).

Usernames will be initially available to the coders when they are examining the profiles to record the user demographics and determine whether a user is a patient with lupus. Profile usernames will then be redacted from the data file and replaced with unique numeric code identifiers before coders start examining the tweets. The link between the unique codes and the identifiable elements will be kept in a separate file. Thus, the coders will not be able to simultaneously view the identifiable elements of a Twitter profile and tweets made by that Twitter user. Additionally, any identifying and personal health information that the coders might find in the dataset of the tweets will be redacted by the coders. We will retain the data only for use in this project and destroy the identifiable information (tweet ID, tweet URL, thumbnail/URL of profile picture, username, and display name) prior to the data analysis. Given the sensitive nature of the topic "lupus and fertility," this step will be taken to protect the privacy of pregnant women whose tweets might be included in the data sample.

Risk Analysis

This research has minimal risk. We will use publicly available data from the social network Twitter. Identifiable information such as human subjects' names and Twitter usernames will not be included in the analysis dataset. We will further abide by the USC Institutional Review Board regulations and the USC Privacy of Personal Information policy. All data will be entered into a password-protected computer database. The data will be stored using appropriate secure computer software and encrypted computers.

Dissemination of Study Findings

The authors plan to publish the study findings in a peer-reviewed journal and present those at relevant conferences (to be determined at a later date). All the listed authors and contributors comply with the guidelines of the International Committee of Medical Journal Editors on author inclusion in a published work.

Results

Study approval was obtained from the Institutional Review Board at USC (Protocol HS-18-00912) (Multimedia Appendix 4). Data extraction and cleaning are complete. We obtained 47,715 tweets containing terms related to "lupus" from users

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in the United states that were posted in English during the period September 1, 2017, to October 31, 2018. We will include 40,885 posts in the analysis. The detailed data extraction and cleaning flowchart is included in Multimedia Appendix 5. Data analysis will be completed in fall 2020.

Discussion

Limitations

This exploratory pilot study is limited to Twitter conversations from the patients of lupus who use the words lupus and SLE or the related hashtags in their tweets. As a result, tweets that share lupus-related experiences of patients without using the related terms and hashtags will be excluded from the study.

We recognize that this social media research and intervention favor those with the internet access and that this limitation could lead to potential bias in the research data. The generalizability of this study is also somewhat limited because the study excludes tweets from outside of the United States and tweets written in languages other than English. However, social media users "have grown more representative of the broader population." Twitter is used by 24% of Black Americans, 21% of White Americans, and 25% of Hispanic Americans. Twitter use is more common among younger (38% use among persons aged 18 to 29 years vs 7% use among those older than 65 years); educated (32% among college graduates vs 13% among those with a high school diploma or less); and urban (26% urban users vs 13% rural users) demographic [13].

Practical Significance

This pilot project will provide preliminary data and an insight into the application of publicly available Twitter data to gain a better understanding of the patients with lupus and their perspectives on reproductive health issues. If successful, our findings will shed light on whether Twitter provides a promising data source for garnering perspectives on reproductive health issues expressed by the patients with lupus. The data will also help to determine whether Twitter can be a potential outreach platform for raising awareness of lupus and reproductive health and for implementing the related health interventions.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Keywords and hashtags used for the Twitter search to assess Twitter conversations about lupus and reproductive health.
[PDF File (Adobe PDF File), 82 KB - resprot_v9i8e15623_app1.pdf]

Multimedia Appendix 2
Code categories to identify main themes in Twitter posts about lupus and reproductive health.
[PDF File (Adobe PDF File), 54 KB - resprot_v9i8e15623_app2.pdf]

Multimedia Appendix 3
Code categories to classify Twitter users.
[PDF File (Adobe PDF File), 43 KB - resprot_v9i8e15623_app3.pdf]

Multimedia Appendix 4
IRB approval notice.
[PDF File (Adobe PDF File), 817 KB - resprot_v9i8e15623_app4.pdf]

Multimedia Appendix 5
Data extraction and cleaning flow diagram.
[PDF File (Adobe PDF File), 54 KB - resprot_v9i8e15623_app5.pdf]

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Abbreviations

API: Application Programming Interface
FDA: Food and Drug Administration
NCATS: National Center for Advancing Translational Science
NIH: National Institutes of Health
REDCap: Research Electronic Data Capture
REST: Representational State Transfer
SLE: systemic lupus erythematosus
USC: University of Southern California

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Corrigenda and Addenda

Correction: A Novel Narrative E-Writing Intervention for Parents of Children With Chronic Life-Threatening Illnesses: Protocol for a Pilot, Open-Label Randomized Controlled Trial

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Related Article:

Correction of: https://www.researchprotocols.org/2020/7/e17561/

In "A Novel Narrative E-Writing Intervention for Parents of Children With Chronic Life-Threatening Illnesses: Protocol for a Pilot, Open-Label Randomized Controlled Trial" (JMIR Res Protoc 2020;9(7):e17561) the authors noted several errors.

In the original paper, an incorrect telephone number was provided for the corresponding author. The telephone number has been corrected to 65 63168943.

One of the author names was incorrectly displayed as "Casuarine Xinyi Low". It has now been corrected to:

Xinyi Casuarine Low

The correction will appear in the online version of the paper on the JMIR Publications website on August 18, 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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Proposal

Learning Integrated Health System to Mobilize Context-Adapted Knowledge With a Wiki Platform to Improve the Transitions of Frail Seniors From Hospitals and Emergency Departments to the Community (LEARNING WISDOM): Protocol for a Mixed-Methods Implementation Study

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Abstract

Background: Elderly patients discharged from hospital experience fragmented care, repeated and lengthy emergency department (ED) visits, relapse into their earlier condition, and rapid cognitive and functional decline. The Acute Care for Elders (ACE) program at Mount Sinai Hospital in Toronto, Canada uses innovative strategies, such as transition coaches, to improve the care transition experiences of frail elderly patients. The ACE program reduced the lengths of hospital stay and readmission for elderly patients, increased patient satisfaction, and saved the health care system over Can $4.2 million (US $2.6 million) in 2014. In 2016, a context-adapted ACE program was implemented at one hospital in the Centre intégré de santé et de services sociaux de Chaudière-Appalaches (CISSS-CA) with a focus on improving transitions between hospitals and the community. The quality improvement project used an intervention strategy based on iterative user-centered design prototyping and a "Wiki-suite" (free web-based database containing evidence-based knowledge tools) to engage multiple stakeholders.

Objective: The objectives of this study are to (1) implement a context-adapted CISSS-CA ACE program in four hospitals in the CISSS-CA and measure its impact on patient-, caregiver-, clinical-, and hospital-level outcomes; (2) identify underlying mechanisms by which our context-adapted CISSS-CA ACE program improves care transitions for the elderly; and (3) identify underlying mechanisms by which the Wiki-suite contributes to context-adaptation and local uptake of knowledge tools.

Methods: Objective 1 will involve staggered implementation of the context-adapted CISSS-CA ACE program across the four CISSS-CA sites and interrupted time series to measure the impact on hospital-, patient-, and caregiver-level outcomes. Objectives 2 and 3 will involve a parallel mixed-methods process evaluation study to understand the mechanisms by which our context-adapted CISSS-CA ACE program improves care transitions for the elderly and by which our Wiki-suite contributes to adaptation, implementation, and scaling up of geriatric knowledge tools.

Results: Data collection started in January 2019. As of January 2020, we enrolled 1635 patients and 529 caregivers from the four participating hospitals. Data collection is projected to be completed in January 2022. Data analysis has not yet begun. Results are expected to be published in 2022. Expected results will be presented to different key internal stakeholders to better support the effort and resources deployed in the transition of seniors. Through key interventions focused on seniors, we are expecting to increase patient satisfaction and quality of care and reduce readmission and ED revisit.

Conclusions: This study will provide evidence on effective knowledge translation strategies to adapt best practices to the local context in the transition of care for elderly people. The knowledge generated through this project will support future scale-up of the ACE program and our wiki methodology in other settings in Canada.

Trial Registration: ClinicalTrials.gov NCT04093245; https://clinicaltrials.gov/ct2/show/NCT04093245.

International Registered Report Identifier (IRRID): DERR1-10.2196/17363

Introduction

Background

In 2019, more than one in six Canadians were aged 65 years or older. These aging Canadians will account for 20% of the population by 2024 [1]. It is a challenge for our health care system to meet the growing needs of the aging population, whose members often have chronic conditions, take multiple medications, and receive care from multiple providers. Moreover, they are typically frequent health care users, with the system spending more on them than on any other segment of the population [2]. Seniors represent a third of all patients consulting emergency departments (EDs) [3-7]. Seniors are especially vulnerable to health system failures; one-third report experiencing care coordination problems, with the most important problems according to patients being gaps in hospital discharge planning [8,9] and long waiting lists to receive home care [10,11]. Seniors and their caregivers are obliged to manage their own care through a broken care continuum [12-14]. Discharge adverse events result in unplanned readmissions [15,16], which occur after 10%-30% of medical admissions [16-28], and loss of physical, functional, and/or cognitive capacity [29-34]. Added to poor health outcomes are patient and staff distress [35,36] and increasing lawsuits concerning inadequate discharge planning [37].

Acute Care for Elders Program: Best Practice Guidelines for Elder Care Transitions

Improving care transitions for seniors requires a multifaceted integrated approach based upon best practices [11,38], such as the Acute Care for Elders (ACE) program developed by Mount Sinai Hospital in Toronto [39-41]. Over the last decade, Mount Sinai has become Canada's most widely recognized

elder-friendly hospital, implementing evidence-informed point-of-care interventions to improve patient, provider, and system outcomes for frail older persons [2]. Supported by systematic reviews [42-48] and randomized clinical trials [49-52], the ACE care transition program is based on interprofessional interventions to enhance postdischarge care. Comparing performance in the baseline year 2009 with that in 2014, Mount Sinai reduced the total length of stay (from 12 to 8 days), reduced the alternate level of care days by 20%, reduced readmissions within 30 days (from 15% to 13%), improved the rate of patients returning home as opposed to other institutional settings (from 71% to 79%), and increased the rate of patient satisfaction (from 95% to 97%). These improvements resulted in an estimated Can $4.2 million (US $2.6 million) in savings in 2014 [53].

Unfortunately, the ACE best practice guidelines have only been implemented in a few dozen acute care organizations around the world [54]. A major barrier to their implementation is that these guidelines and tools cannot be easily transferred into different cultural, organizational, and technical contexts. Knowledge producers (researchers) and knowledge users (patients/caregivers, clinicians, and decision makers) lack effective interventions to adapt knowledge to the local context, a crucial step in the knowledge-to-action (KTA) framework [55,56]. Knowledge users lack the skills, resources, or institutional culture necessary to apply knowledge locally and support their institutions to learn new ways of operating. Researchers have been challenged to find new solutions that support the involvement of local knowledge users in adapting knowledge tools to their contexts [57-61]. Although local adaptation is a key step of the KTA framework, little is known about how to accomplish this step effectively [55,56,62,63]. New solutions are needed to support the involvement of knowledge users in adapting knowledge tools to their contexts [56-60].

Two Novel Knowledge Translation Interventions to Adapt the ACE Program to the Local Context

In 2016, the *Centre intégré de santé et de services sociaux de Chaudière-Appalaches* (CISSS-CA) was selected by the Canadian Foundation for Healthcare Improvement (CFHI), the Canadian Frailty Network, and Mount Sinai Hospital to implement and adapt the ACE program in the local context. This adaptation also had to be performed in synergy with Quebec's provincial elder-friendly best practices, the *Approche adaptée à la personne âgée en milieu hospitalier* (senior-friendly hospital care) [64].

A research team led by the first author (PA) and by the Chief Executive Officer (CEO) of the CISSS-CA (DP) has been using two novel knowledge translation (KT) interventions (WikiTrauma and Wiki101 ["the Wiki-suite"]) to engage knowledge users in adapting the ACE program in the local

context at the Hôtel-Dieu de Lévis, one of the four acute care hospitals within the CISSS-CA. WikiTrauma [65] is a knowledge-base website on which users collaboratively modify content and structure directly from the web, which contains free web-based knowledge tools. Wiki101 [66] is a web-based training course on how to use WikiTrauma. These two interventions were initially developed for trauma care [67], and our team's previous work has shown that these interventions are potentially effective KT interventions to support the implementation of best practices in other fields of health care [68-70].

Objectives

The goal of this study is to improve transition care for seniors within the CISSS-CA. Specifically, it aims to (1) implement a context-adapted CISSS-CA ACE program in its four EDs and measure the impact on patient-, caregiver-, clinical-, and hospital-level outcomes; (2) identify underlying mechanisms by which our context-adapted CISSS-CA ACE program improves care transitions for elderly people; and (3) identify underlying mechanisms by which the Wiki-suite contributes to context adaptation and local uptake of knowledge tools.

Methods

Study Design

Our study will have two main parts (Figure 1). Part 1 will involve the staggered implementation of the context-adapted CISSS-CA ACE program across four CISSS-CA sites (Hôtel-Dieu de Lévis, St-Georges, Montmagny, and Thetford Mines). We will use an interrupted time series (ITS) to measure the impact of the CISSS-CA ACE program and its context-adapted tools on all hospital-level outcomes (Table 1 and Figure 2). This design will allow us to better measure the effect of our intervention on our outcomes while controlling for secular trends in our data by comparing retrospective monthly data collected in the CISSS-CA administrative databases for 36 months before our intervention and for a maximum of 12 months after our intervention in the last targeted CISSS-CA implementation site (Hospital 4 is yet to be determined) and for up to 21 months in the first targeted CISSS-CA implementation site (Hospital 1 is the Hôtel-Dieu de Lévis). Part 2 will be a parallel mixed-methods process evaluation study to understand the underlying human, organizational, and technical factors that influence the success or failure of our intervention and, more specifically, of our Wiki-suite to facilitate it through the adaptation and uptake of geriatric knowledge tools. We will report this implementation study using the Standards for Reporting Implementation Studies (StaRI) reporting guidelines (Multimedia Appendix 1) [71]. This study has been approved by the CISSS-CA Ethics Review Committee (project #2018-462, 2018-007).

Figure 1. Study timeline. Staggered implementation of the context-adapted CISSS-CA ACE intervention across four hospitals and parallel mixed-methods process evaluation. ACE: Acute Care for Elders; CISSS-CA: Centre intégré de santé et de services sociaux de Chaudière-Appalaches (Chaudière-Appalaches Integrated Health and Social Services Centre).
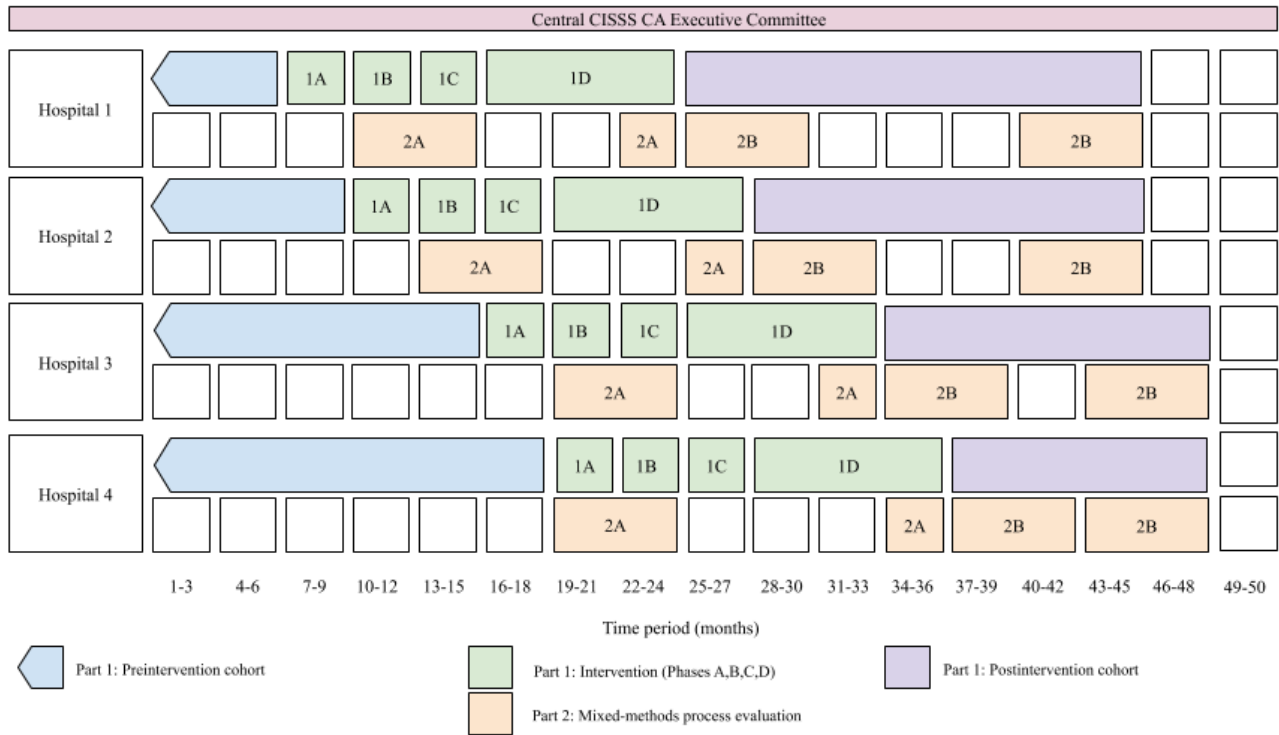

Figure 2. LEARNING WISDOM study design, data collection, indicators, and recruitment process. CLSC: Centres locaux de services communautaires (Local Community Services Centers); ED: emergency department; NHS SM: National Health Service Sustainability Model.
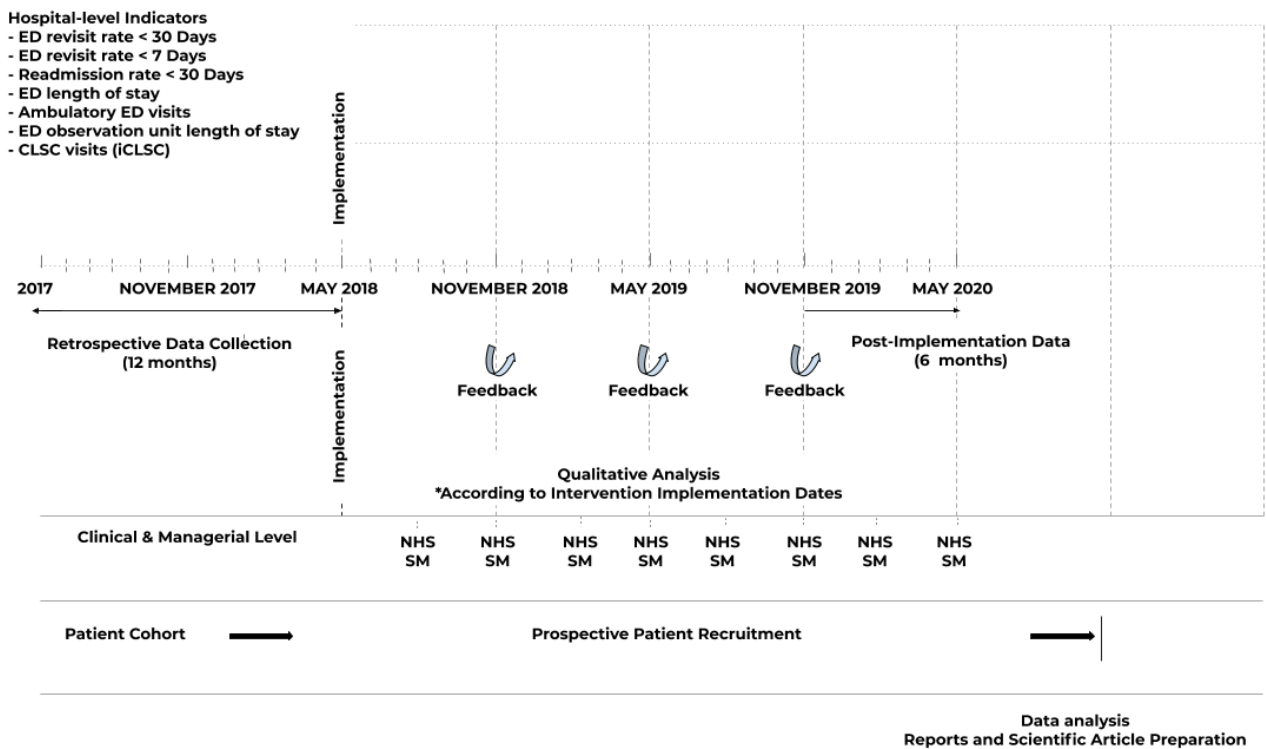
Table 1. Primary and secondary study outcomes.

Outcomes	Data source
Primary outcome	
Composite endpoint at each month (30-day hospital readmission and ED[a] visit rate)	Administrative databases (Med-GPS, RAMQ[b] billing database, and MedECHO[c])
Secondary outcomes	
Hospital level	
Hospital and ED length of stay	Administrative database (Med-GPS, RAMQ billing database, and MedECHO)
Hospital and ED admission rate	Administrative database (Med-GPS, RAMQ billing database, and MedECHO)
Alternate level of care occupation rate	Administrative database (Med-GPS, RAMQ billing database, and MedECHO)
Rate of patients returning to prehospital living situation	Administrative database (Med-GPS, RAMQ billing database, and MedECHO)
Proportion of patients with family physician appointment in the 21 days after ED discharge	RAMQ billing database
Patient/caregiver level	
Quality of care transitions	Care Transition Measure (CTM-3) (48-hour postdischarge phone questionnaire)
Functional autonomy	Chart audit to identify the PRISMA-7[d] score and Iso-SMAF[e] profile (case-mix classification profile according to patients' functional autonomy characteristics as determined by the SMAF)
Anxiety	Geriatric Anxiety Inventory-Short Form (phone questionnaire)
Living situation at 30 days after ED discharge	Chart audit
Burden of care	Zarit Brief Burden Interview with two additional open questions (phone questionnaire)
Clinical-level process	
Proportion of patients seen by a GEM[f] nurse	Chart audit
Proportion of patients/caregivers/family physicians receiving discharge summary in the 21 days following ED discharge	Postdischarge phone questionnaire and 21-day family physician follow-up phone call
Proportion of medication patients with a reconciled medication list	Chart audit
Proportion of eligible patients using telemonitoring services	TSS-CA[g] telemonitoring service database

[a]ED: emergency department.

[b]RAMQ: Régie de l'assurance maladie du Québec.

[c]MedECHO: maintenance et exploitation des données pour l'étude de la clientèle hospitalière.

[d]PRISMA-7: Program of Research to Integrate the Services for the Maintenance of Autonomy.

[e]SMAF: Système de mesure de l'autonomie fonctionnelle (Functional Autonomy Measuring System).

[f]GEM: geriatric emergency management.

[g]TSS-CA: Télé-Surveillance Santé - Chaudière-Appalaches.

Part I: Interrupted Time Series

Study Context

The four participating hospitals (Hôtel-Dieu de Lévis, St-Georges, Montmagny, and Thetford Mines) are part of the CISSS-CA, a new integrated health organization under the leadership of a single CEO and created in 2015 by a legislative health reform in the province of Quebec, Canada (Act to Modify the Organization and Governance of the Health and Social Services Network) [72]. The CISSS-CA has 318 health facilities within its large mixed rural and urban territory, including the four acute care hospitals in this study. Although this new supraregional organization now has the administrative infrastructure to offer integrated care, it still lacks the knowledge management infrastructure to mobilize knowledge within its organization that has 10,000 employees serving a population of more than 415,000 spread across a large territory (15,079 km^2) [73].

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Study Participants

Clinicians and Decision Makers

All hospital- and community-based clinicians and decision makers involved in care transitions will be eligible to participate. Hospital-based clinicians and decision-makers are CISSS-CA employees or independent professionals working at the participating hospitals (eg, managers, physicians, nurses, pharmacists, social workers, occupational therapists, and physiotherapists). Community-based clinicians and decision makers are CISSS-CA employees or independent professionals working outside of the hospital in a community setting (ie, home-care professionals).

Patients

Eligible patients will be (1) aged ≥65 years; (2) discharged from the ED; (3) able to understand and read French; and (4) able to provide informed consent.

Caregivers

Eligible caregivers will be identified by the patients themselves and approached only after patient consent is obtained. Caregivers will be (1) able to understand and read French and (2) able to provide informed consent.

Study Intervention

Our intervention is the delivery of a context-adapted CISSS-CA ACE program using a KT strategy based on our Wiki-suite. This intervention will be deployed in sequential phases.

Phase IA (Local Study Set-Up, 3 Months)

An executive committee will oversee the entire study (Figure 1). This committee, which will be led by the first author (PA) and Director of Nursing, will meet every month during this 4-year study. The other members include a community-based geriatric nurse specialist, a home care coordinator, the ED director, the ED head nurse, a geriatrician, a database and measurement specialist, an information technology analyst, our research coordinator, and a patient representative. A local implementation team for each participating hospital, including an ED physician, a hospitalist, a family physician, a home care nurse, an inpatient unit manager, a research assistant, and a local patient or caregiver, will also meet every month at each participating hospital starting 9 months before the active implementation of the ACE program (Phase ID). This team will include locally identified champions to lead the local implementation. Regular meetings will also be organized with local hospital and community-based clinicians and decision makers to gather relevant feedback.

Phase IB (Wiki101 and ACE Training, 3 Months)

All local team members and eligible health professionals or decision makers will complete the Wiki101 web-based training to learn how to navigate and edit knowledge tools in WikiTrauma. After completing Wiki101, our executive committee in collaboration with ACE experts will then offer tailored support to each local team and the local champions to implement the ACE program. The training and support aim to inform and empower the local teams by providing information on the various ACE program interventions to implement locally,

the rationale for each program intervention, and the sharing of existing knowledge tools and expertise developed in each center.

Phase IC (Local Adaptation of Knowledge Tools, 3 Months)

The context-adapted knowledge tools created at each site will be kept in WikiTrauma [74,75]. A local working group will be created in each center. All clinicians and decision makers will be encouraged to copy, edit, and update knowledge tools within WikiTrauma to create their own context-adapted tools. Our Wiki will track all changes automatically, and we will use Google Analytics to track the use of the tools. Any changes will be reviewed during our executive committee meetings and integrated after review to ensure reliability. Partners at Mount Sinai, CFHI, and *Institut national d'excellence en santé et services sociaux* (INESSS) will also have access to these web-based tools to provide expert oversight of our tool adaptation process. For any newly developed patient-centered knowledge tools (eg, self-care management guides), we will solicit in-depth feedback from a patient representative, who will lead a subcommittee of caregiver and patient representatives from the participating sites.

Phase ID (Implementation, 9 Months)

In the 9 months following training and local adaptation, we will implement the context-adapted CISSS-CA ACE program with the support of WikiTrauma and local implementation teams who will have the responsibility to roll out the different elements of our intervention within their respective hospitals. Our context-adapted CISSS-CA ACE program will include a series of systematic predischarge, postdischarge, and across transition period interventions for eligible patients as follows: (1) screening of patients in need of multidimensional evaluation of their loss of autonomy (with the *Programme de Recherche sur l'Intégration des Services de Maintien de l'Autonomie 7* [PRISMA-7] tool) [76]; (2) a geriatric emergency management (GEM) nurse; (3) geriatric training [77]; (4) communication tools for transmitting information to nursing homes and other community-based stakeholders in the health system; (5) a fall prevention program; (6) systematic medication reconciliation; (7) elder-friendly ED environment adaptation; (8) access to clinician- and patient-centered Wiki-based KT tools [78,79] (eg, standing orders for geriatric patients admitted to the ED, geriatric analgesia prescription order set, and patient communication tools and decision aids); and (9) access to a community-based telemonitoring service. This service, which is offered by *Télé-Surveillance Santé - Chaudière-Appalaches* (TSS-CA) [80], will be offered for free to all eligible patients (ie, patients aged over 65 years who have at least seven ED visits in last 12 months, where over half of these visits are triaged to the ED observation unit and where two visits are not followed by hospitalization) transitioning from the hospital or ED to their home. This service currently offers remote monitoring of patients; nurses available 24 hours a day, 7 days a week, 365 days a year; and monthly phone check-ups. It also includes a customized emergency response intervention when patients are in need and connects patients with a network of community-based volunteer caregivers who are notified to visit patients when in need or simply to conduct a routine check-up.

In parallel with these interventions, we will also offer audit and feedback for health professionals and decision-makers in order to support organizational learning that will allow for real-time adjustment of interventions that are implemented. Feedback will take the form of monthly newsletters for the CISSS-CA covering patient-, clinician-, and hospital-level quality indicators. Moreover, our research team will be embedded within the CISSS-CA elder-friendly hospital committee, which plays an active role in supporting quality improvement initiatives and program implementation. This will ensure that results generated by our research team will benefit our population and ensure timely integrated knowledge translation.

Study Comparison

Results from the centers will be compared with their own results in the preintervention period using data collected for the ITS study.

Outcomes Measured

Our primary outcome will be a hospital-level composite outcome of 30-day hospital readmission and ED visit rate. Our secondary outcomes will be hospital-, clinical-, and patient- or caregiver-level outcomes (Table 1).

Hospital-Level Outcomes

Hospital administrative databases (eg, Med-GPS, Logibec) will be used to calculate monthly hospital-level outcomes. Monthly data will then be analyzed to form points in time. Data will be extracted from the *Régie de l'assurance maladie du Québec* (RAMQ) physician billing database and Maintenance et exploitation des données pour l'étude de la clientèle hospitalière (Med-ECHO) database (containing data on hospitalizations and health professional consultations for all institutions) in addition to databases available at the INESSS in order to identify all public health services used prior to and after the implementation of the CISSS-CA ACE program.

Patient- and Caregiver-Level Sociodemographics and Outcomes

Patient and caregiver baseline sociodemographic data will include age, sex, race, language, education level, family income, prehospital living situation (eg, home, intermediate nursing homes, etc), geography of residence (rural vs urban: as defined by Statistics Canada for Rural and Small Town [81,82]), and reason for hospital admission or consultation in the ED. Patient and caregiver outcomes are presented in Table 1. The living situation will be noted in the medical file when available at 30 days after discharge. Other measures that will be collected after discharge include the Care Transitions Measure-3 (CTM-3) [17,83], the Geriatric Anxiety Inventory-Short Form (GAI-SF) [84,85], and the Zarit Burden Interview (ZBI) [86]. The CTM-3 is a three-item questionnaire that measures the perceived quality of care transition on a 0-4 scale (0, fully disagree; 4, fully agree). The French version of the tool will be used [87]. The GAI-SF measures anxiety among seniors. The short version comprises five questions. The French-Canadian version of the tool has good psychometric properties [88]. The ZBI measures the burden of caregivers. The brief French version (12 questions) of the scale has good psychometric properties and is comparable to the original version [89,90].

Clinical-Level Process Outcomes

In order to measure the change in care processes, we will measure process outcomes such as the proportion of patients seen by the GEM nurse, proportion of patients having a medication reconciliation list, and proportion of patients receiving telemonitoring services (Table 1).

Patient and Caregiver Recruitment

After receiving ethics approval, we will start recruitment for our patient-level outcomes at least 3 months before the implementation of phase 1A at each site. Due to the pragmatic nature of our study, some sites will have longer periods of patient-level outcomes collected before phase 1A than others. Patient recruitment will continue throughout our study and up to a maximum of 24 months after the intervention. We will recruit consecutive eligible ED patients aged 65 years or older, as well as one caregiver whenever possible. We will recruit 38 patients or caregivers per month for each of the four hospitals based on a precision estimate of the CTM-3 measured for the study point of each month.

With authorization from the Director of Nursing and the Professional Services Director, a member of our embedded research team will contact by telephone a randomly selected daily sample of patients who visited the ED in the last 24 hours and up to a maximum of 7 days after their ED visit. This research assistant will administer the CTM-3 questionnaire to patients for quality improvement purposes. The research assistant will then ask the patients if they agree to be contacted a second time by a member of the research team to answer additional questions for the purpose of our study. Consenting patients will then be contacted within 7 days to obtain their verbal consent to participate in the study and consent to access their medical charts. We will ensure patients' understanding by asking them to summarize in their own words the objectives of the study and what their participation involves using the Nova Scotia criteria [91]. The team member will then collect baseline sociodemographic data and administer the questionnaires for the study. The research team will then send a written consent form by mail after the interview. If a patient refuses to be contacted by our research team or to participate in this study, the CTM-3 data collected will only be available to the CISSS-CA. The research assistant will also ask permission to contact a caregiver. Identified caregivers will be contacted by telephone to complete the Zarit questionnaire. Our research assistant will first obtain the caregivers' verbal consent to participate in the study and then ensure the caregivers' understanding by asking them to summarize in their own words the objectives of the study and what their participation implies.

Sample Size and Statistical Analysis

We will use segmented regression statistics to measure the changes in the level and slope in the postintervention period compared with the preintervention period in each center for each of our primary and secondary outcomes [92]. Thus, we will present a regression model with different intercept and slope coefficients for the pre- and postintervention time periods for each center. We will compare the changes in a composite primary outcome (total 30-day hospital readmission and ED

visit rate) at our four intervention centers. We will use a Durbin-Watson test to verify the presence of autocorrelation and use an autoregressive error model to correct for this serial correlation. For an ITS, 10 measurement points before and 10 points after an intervention provide 80% power to detect a change in the level of 5 standard deviations (of the predata) only if the autocorrelation is greater than 0.4 (ie, extent to which data collected close together in time are correlated with each other) [93].

We have calculated the sample size for our patient cohort, which will be based on the smallest clinically significant difference (ie, 11%) that the CTM-3 can capture on a maximum score of 100. To detect a difference of 11% with a type I error of 5% and a type II error of 20%, 38 patients per month are needed to calculate a monthly CTM-3 estimate, based on a previous study in which CTM-3 was measured in 21 patients at Hôtel-Dieu Hospital in Lévis and showed an average of 75% and a standard deviation of 23%. Considering a call rejection rate of 70%, the number of people to be contacted in total will be 127 patients per month for each ED. We will therefore contact 5 patients per day in each of the four participating centers to obtain our targeted sample size of 38 patients at the end of the month. To ensure the creation of a random and representative sample of our population of elderly patients being discharged from the ED, a randomization table based on all patients discharged in the previous 24 hours from the ED will be provided every day to select which patients to call.

Part II: Parallel Mixed-Methods Process Evaluation

Part II aims to identify the underlying mechanisms (human, organizational, and technical) by which our context-adapted CISSS-CA ACE intervention improves care transitions for elderly people and, more specifically, how the Wiki-suite contributes to context-adaptation and local uptake of knowledge tools. Contextual elements affecting the implementation of the ACE program at the four hospital sites and use of our Wiki-suite cannot be addressed using ITS methodology, yet they can have a relevant impact on the use [94]. To scale up the CISSS-CA ACE program and Wiki-suite in multiple settings, we need to understand these contextual elements.

Approach

Phase IIA (Measurement of the Intention to Use WikiTrauma and Actual WikiTrauma Use, 9 Months)

Alongside phases IB and IC, we will conduct a theory-based process evaluation. All Wiki101 participants will be invited to answer a validated Theory of Planned Behavior questionnaire [95] at baseline before Wiki101, immediately after Wiki101, and at the end of Phase ID to measure the change in intention and the impact of Wiki101 on Theory of Planned Behavior determinants. We will also use Google Analytics to track the use of WikiTrauma tools by the participants over time. Segmented regression statistics will be used to measure the changes in the level and slope for postintervention Wiki use compared with preintervention Wiki use [92].

Phase IIB (Stakeholder Interviews, 6 Months)

We will conduct at least 32 45-minute individual interviews with purposefully selected key informants (a minimum of two

clinicians, two managers, and four patients and/or caregivers per center) to identify the contextual elements influencing the successful (or failed) implementation of the ACE program for improving care transitions and understand how our Wiki-suite facilitated this. These interviews will take place at least 9 months after first implementing the ACE program at each hospital. A pool of eligible health professionals working in the ED and administrators or decision makers will be created by direct solicitation during departmental or staff meetings (upon invitation from department chiefs) or by direct solicitation by department chiefs. Our study's goals and procedures will be briefly explained, including eventual solicitation to participate in individual interviews. All eligible and consenting individuals will be asked to provide their contact information for eventual solicitation. Participants will be identified from the pool described above, using purposeful sampling, with an emphasis on maximum variation to obtain a wide range of different points of view and opinions. Each selected individual will be solicited via the contact information provided at initial solicitation. A consent form will be completed over the internet prior to the phone interview. These interviews will be confidential, and no information allowing the identification of individuals will be provided to the administration of the CISSS-CA.

A PhD student guided by experienced qualitative researchers will perform the interviews and process evaluation of our intervention. For this analysis, we will perform a mixed inductive and deductive qualitative content analysis of the verbatim transcripts and field notes taken during these interviews, as well as key implementation project documents such as executive committee and local team meeting minutes [94,96]. The analysis will involve reading the verbatim transcripts and key project documents thoroughly and developing codes that represent the nature of the implementation, adaptation processes at each site, and barriers and facilitators to using our context-adaptation methodology. Our previous experience in conducting qualitative content analysis about Wiki use will help us understand how our Wiki-based intervention succeeded (or not) in improving care transitions [70]. We will use the Ottawa Model for Research Use [97] and the KTA framework [98] to structure our analysis.

We will also use the National Health Service (NHS) Sustainability Model to guide our process evaluation analysis [99]. The NHS Sustainability Questionnaire has been developed to support health care leaders to implement and sustain effective improvement initiatives in health care systems. The questionnaire is a diagnostic tool that identifies strengths and weaknesses in the implementation plan and predicts the likelihood of sustainability for improvement initiatives. The NHS Sustainability Questionnaire will be administered to members of the executive committee and each local implementation team at baseline before phase IA and at regular 3-month periods until 12 months after the end of phase ID.

Phase IIC (Comparative Analysis of Case Studies, 6 Months)

We will analyze the impact of our intervention within the context of Quebec's health reform aiming at better integration of care within the health system [100]. This will be accomplished by conducting a comparative case study across

the four study sites to compare the barriers, facilitators, and local solutions implemented to gain a better understanding about how our ACE program and Wiki-suite–mediated intervention could eventually be scaled up elsewhere.

Results

This study was funded by the Canadian Institutes for Health Research in May 2017. The project was approved by the CISSS-CA ethics committee in May 2018. Data collection started in January 2019. As of January 2020, we enrolled 1635 patients and 529 caregivers from the four participating hospitals. Data collection is projected to be completed in January 2022. Data analysis has not yet begun. Results are expected to be published in 2022. Expected results will be presented to different key internal stakeholders to better support efforts and resources deployed in the transitions of seniors. Through key interventions focused on seniors, we are expecting to increase patient satisfaction and quality of care and reduce readmission and ED revisit.

Discussion

Principal Findings

Our study will produce a new partnership among patients, clinicians, and decision makers, engaging and empowering them to improve care for elderly people by implementing the CISSS-CA ACE program in four hospitals within the CISSS-CA. This study will also provide qualitative and quantitative evidence on effective strategies for improved transition care for elderly people. This study specifically aims at decreasing CISSS-CA's 30-day rate of readmission for elderly patients, which has been increasing since 2014 (13% in 2014 and 16% in 2016), and its high 30-day ED visit rate (21% in 2014 and 22% in 2016). Our team will generate real-time quality improvement data that will guide decision-making by the CISSS-CA and help adjust resource allocation and policy-making that will positively influence future care transitions for elderly people.

Our study will also identify the human, organizational, and technical factors that support the local adaptation of knowledge and the scale-up of our intervention in other care settings within the CISSS-CA and elsewhere in Canada [101,102]. This will contribute to making the CISSS-CA a learning organization and to training a new cadre of clinicians, administrators, policy-makers, and scientists who will transform our health system [103]. This is also highly relevant to INESSS and CFHI, who aim to scale up innovations and best practices in the care of seniors in Quebec and Canada, respectively.

Limitations

Our study is measuring the impact of a complex intervention, which is a common problem in health services research. The ability to measure and evaluate the effect of complex interventions remains underdeveloped [104-106]. The Medical Research Council suggests evaluating complex interventions using experimental designs when possible, but quasi-experimental designs, such as prospective pre/post cohort studies [107,108] and interrupted time series [93,109,110], are acceptable when randomization is not possible, feasible, or ethical [111,112]. The highly iterative nature of our intervention made a cluster stepped wedge trial and other experimental designs unfeasible. An advantage of using an interrupted time series design is that it allows for the statistical investigation of potential biases in the estimate of the effect of the intervention. These potential biases include secular trends, seasonal variations, duration of the intervention, random fluctuations, and autocorrelation [93]. Thus, for feasibility reasons, we chose to apply an interrupted time series design for our primary outcome because we could easily access data for hospital-level outcomes using administrative databases. This interrupted time series design will be applied only if our descriptive statistics allow us to detect a clear inflection point that correlates with the implementation of our complex intervention. Our mixed-methods process evaluation will also help us understand the mechanisms in play during our study and detect any negative experiences.

Another challenge to complex interventions is the lack of local adoption. In the design of our intervention, we have incorporated best practices from the field of implementation science to design a standardized intervention comprising local barrier identification [113], multidisciplinary teamwork [114], local adaptation [115], and use of local champions [116]. We chose the ACE program because it has a strong theoretical background supporting its use and because systematic reviews support the effectiveness of its interventions [42-48]. Our strong decision- and policy-maker buy-in, frequent data collection and tracking, iterative and collaborative design, and frequent consultation with local stakeholders including patients will allow our team to identify challenges and mitigation strategies by discussing plans with team members and external partners or mentors at CFHI, INESSS, and Mount Sinai Hospital. Our budget has stipends to support the planned research activities.

Conclusion

This study will provide much needed evidence on effective KT strategies to adapt best practices to the local context in the transition of care for elderly people. It will contribute to adapting geriatric knowledge to the local context. The knowledge generated through this study will support future scale-up of ACE programs and our Wiki methodology in other settings in Canada.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Standards for reporting implementation studies (StaRI) checklist.

[DOCX File , 87 KB - resprot_v9i8e17363_app1.docx]

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Abbreviations

ACE: Acute Care for Elders
CEO: Chief Executive Officer
CFHI: Canadian Foundation for Healthcare Improvement
CISSS-CA: Centre intégré de santé et de services sociaux de Chaudière-Appalaches (Chaudière-Appalaches Integrated Health and Social Services Centre)
CTM-3: Three-item Care Transitions Measure
ED: emergency department
GAI-SF: Geriatric Anxiety Inventory-Short Form
GEM: geriatric emergency management
INESSS: Institut national d'excellence en santé et services sociaux
ITS: interrupted time series
KT: knowledge translation
KTA: knowledge-to-action
NHS: National Health Service
PRISMA: Programme de recherche sur l'intégration des services de maintien de l'autonomie (Program of Research to Integrate the Services for the Maintenance of Autonomy)
RAMQ: Régie de l'assurance maladie du Québec
TSS-CA: Télé-surveillance santé-Chaudière-Appalaches (Health telemonitoring and structured telephone support in Chaudière-Appalaches)
ZBI: Zarit Burden Interview

Proposal

Near-Infrared Cerebrovascular Reactivity for Monitoring Cerebral Autoregulation and Predicting Outcomes in Moderate to Severe Traumatic Brain Injury: Proposal for a Pilot Observational Study

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Abstract

Background: Impaired cerebrovascular reactivity after traumatic brain injury (TBI) in adults is emerging as an important prognostic factor, with strong independent association with 6-month outcomes. To date, it is unknown if impaired cerebrovascular reactivity during the acute phase is associated with ongoing impaired continuously measured cerebrovascular reactivity in the long-term, and if such measures are associated with clinical phenotype at those points in time.

Objective: We describe a prospective pilot study to assess the use of near-infrared spectroscopy (NIRS) to derive continuous measures of cerebrovascular reactivity during the acute and long-term phases of TBI in adults.

Methods: Over 2 years, we will recruit up to 80 adults with moderate/severe TBI admitted to the intensive care unit (ICU) with invasive intracranial pressure (ICP) monitoring. These patients will undergo high-frequency data capture of ICP, arterial blood pressure (ABP), and NIRS for the first 5 days of care. Patients will then have 30 minutes of noninvasive NIRS and ABP monitoring in the clinic at 3, 6, and 12 months post-injury. Outcomes will be assessed via the Glasgow Outcome Scale and Short Form-12 questionnaires. Various relationships between NIRS and ICP-derived cerebrovascular reactivity metrics and associated outcomes will be assessed using biomedical signal processing techniques and both multivariate and time-series statistical methodologies.

Results: Study recruitment began at the end of February 2020, with data collection ongoing and three patients enrolled at the time of writing. The expected duration of data collection will be from February 2020 to January 2022, as per our local research ethics board approval (B2018:103). Support for this work has been obtained through the National Institutes of Health (NIH) through the National Institute of Neurological Disorders and Stroke (NINDS) (R03NS114335), funded in January 2020.

Conclusions: With the application of NIRS technology for monitoring of patients with TBI, we expect to be able to outline core relationships between noninvasively measured aspects of cerebral physiology and invasive measures, as well as patient outcomes. Documenting these relationships carries the potential to revolutionize the way we monitor patients with TBI, moving to more noninvasive techniques.

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Introduction

Continuous measures of cerebrovascular reactivity by near-infrared spectroscopy (NIRS) provide a convenient and noninvasive method of monitoring cerebral autoregulation in adults with traumatic brain injury (TBI) [1,2]. The concept behind these indices is based on the assessment of the correlation between slow-wave (ie, 0.05 Hz to 0.005 Hz)[3,4] fluctuations in a measure of pulsatile cerebral blood volume (CBV), such as NIRS regional cerebral oxygen saturation (rSO_2), and a measure of cerebral blood flow driving pressure, such as mean arterial pressure (MAP) or cerebral perfusion pressure (CPP). These indices have been validated in experimental animal models of cerebral autoregulation, with clinical data supporting moderate associations with "gold standard" invasive measures of cerebrovascular reactivity via rough estimates [2,5-7]. However, further investigation into the value of NIRS-based cerebrovascular indices is required.

Several aspects of NIRS cerebrovascular reactivity indices require clarification before widespread clinical application. The first requirement is an in-depth assessment of the time-series relationships between gold standard ICP-derived indices such as pressure reactivity index (PRx) and indices derived from NIRS. Demonstrating strong covariance over time between PRx and NIRS indices would provide confidence in their clinical application for monitoring cerebral autoregulation in adults with TBI. Second, time-series modeling of intracranial pressure (ICP)-derived indices using noninvasively derived NIRS indices could provide a surrogate, noninvasive assessment of PRx. NIRS has never been used for this purpose, although noninvasive modeling of PRx using transcranial Doppler-derived autoregulation indices has been described [8]. Third, the association between cerebral autoregulation during the acute intensive care unit (ICU) phase and long-term follow up has never been assessed using continuous physiologic indices. Those patients with impaired cerebrovascular reactivity during the acute phase of illness may have ongoing dysfunction at 3, 6, and 12 months post-injury. Finally, the association between NIRS-based noninvasive indices of cerebral autoregulation during acute care and long-term follow-up with measures of global functional outcome and patient quality of life have never been assessed. There exists the potential for a direct association between NIRS indices in the acute phase and long-term morbidity/mortality. Furthermore, persistent symptomatology during the long-term phase may be related to ongoing autoregulatory dysfunction, as measured noninvasively through NIRS.

In this paper, we highlight a prospective pilot study that will preliminarily assess all the above questions with NIRS-derived continuous measures of cerebrovascular reactivity during the acute and long-term phases in adults with TBI. We outline the approved protocol for this National Institutes of Health (NIH)-funded study, which has just started recruitment. The specific aims/hypotheses of this project are presented below:

Aim 1

To compare spatially resolved NIRS-based continuous indices of cerebrovascular reactivity such as cerebral oxygen index (COx), the correlation between rSO_2 and CPP, and COx-a, the correlation between rSO_2 and MAP, with "gold-standard" ICP-derived continuous indices such as PRx, pulse amplitude index (PAx), the correlation between pulse amplitude of ICP (AMP) and MAP, and RAC (the correlation (R) between AMP (A) and CPP (C)), using multivariate time-series based assessments of covariance. Demonstrating strong relationships over time between NIRS- and ICP-derived indices will provide confidence in the clinical application of these measures of cerebral autoregulation in adults with TBI.

Hypothesis: NIRS based indices of cerebrovascular reactivity will closely co-vary with gold standard invasively derived ICP indices using high-frequency, high-resolution time-series data.

Aim 2

To provide models of ICP-based continuous indices (PRx, PAx, and RAC) using noninvasively derived NIRS indices, thus providing the ability to noninvasively measure "gold standard" invasive indices using NIRS in adults with TBI.

Hypothesis: Noninvasive NIRS cerebrovascular reactivity indices can accurately estimate and predict invasive ICP indices using complex time-series modeling techniques.

Aim 3

To assess cerebrovascular reactivity using noninvasive NIRS continuous indices at 3, 6, and 12 months post-TBI. We expect to demonstrate persistent impairment in vascular reactivity in the long-term phase post-TBI.

Hypothesis: NIRS-based cerebrovascular reactivity will demonstrate some features of impairment during long-term follow-up after moderate/severe TBI.

Aim 4

To compare cerebrovascular reactivity during the acute ICU phase of illness (using ICP- and NIRS-based continuous indices) and long-term follow up (using NIRS noninvasive continuous indices) at 3, 6, and 12 months post-TBI. We will demonstrate the association between impaired cerebrovascular reactivity during the acute phase, with persistent long-term dysfunction.

Hypothesis: Those with impaired cerebrovascular reactivity during the acute phase of illness will be more likely to display impaired reactivity during long-term follow-up.

Aim 5

To outline the association between impaired NIRS-based continuous cerebrovascular reactivity during the acute ICU

phase of illness with a poor global outcome and patient quality of life at 3, 6, and 12 months. This study will assess global functional outcomes via the Glasgow Outcome Score (GOS) and patient quality of life via the Short-Form 12 Health Survey (SF-12).

Hypothesis: Impaired NIRS based cerebrovascular reactivity during the acute phase of illness will be associated with poor GOS and SF-12 during long-term follow-up.

Aim 6

To outline the association between impaired NIRS-based cerebrovascular reactivity at 3, 6, and 12 months post-TBI and both poor global outcome and impaired quality of life. This study will compare long-term cerebrovascular reactivity, as assessed via continuous noninvasive NIRS indices, to both GOS and SF-12.

Hypothesis: Impaired NIRS based cerebrovascular reactivity during long-term follow-up will be associated with persistent symptomatology and poor GOS and SF-12 scores.

Methods

Patient Population

This study will be conducted at the Health Sciences Center (HSC) in Winnipeg, Manitoba, Canada. Patient recruitment will occur from January 2020 through December 2021. We will be recruiting adults (age 18 years or older) with moderate/severe TBI admitted to the surgical intensive care unit (SICU) and who require invasive ICP monitoring for clinical purposes based on Brain Trauma Foundation (BTF) guidelines [9]. Once ICP monitoring has been initiated for clinical purposes, the patient's family/legal proxy will be approached for consent for enrollment in the study. Consent will be obtained by a neurosurgical physician assistant or research assistant. Patients/families will have the opportunity to opt-out of the study at any time. Expected recruitment for this pilot prospective observational study will be ~60 to 80 patients, consistent with previously defined sample sizes for high-frequency physiology studies in TBI [10]. Patients will be followed up by the neurosurgery service at 3, 6, and 12 months according to standard post-TBI care at HSC.

All patient demographics, injury characteristics, laboratory, neuroimaging, and outcomes data will be recorded as part of another ongoing prospective moderate/severe TBI database project concurrently running at HSC in Winnipeg (HS20850; H2017:188).

Physiologic Monitoring

All moderate/severe TBI patients admitted to the SICU at HSC Winnipeg have invasive ICP monitoring initiated as part of standard clinical practice according to the BTF guidelines [9]. As part of standard monitoring within the SICU, patients also receive arterial blood pressure (ABP) monitoring for the duration of their ICU stay. Bifrontal NIRS will be employed continuously for the first 5 days in the ICU, in conjunction with ICP and ABP monitoring.

Follow-up assessment of cerebral autoregulation at 3, 6, and 12 months requires the application of bifrontal NIRS for 30 minutes. Further, in order to derive continuous indices of cerebrovascular reactivity at these follow-up visits, continuous noninvasive ABP will be simultaneously recorded with NIRS with a Finapres ABP system.

Signal Acquisition

Various signals will be obtained through a combination of invasive and noninvasive methods, with all signals recorded in high-frequency time series using ICM+ software (Cambridge Enterprise Ltd, Cambridge) connected to our SICU monitors [11]. Signals from all of the monitoring devices described below are recorded in time series using this software throughout the recording periods (ie, the first 5 days "acute phase," 3 months, 6 months, and 12 months follow up). All physiologic signals from monitoring devices within the SICU are recorded and archived as part of a separate prospective signal database study that will be ongoing at HSC (HS20840; H2017:181).

ABP will be obtained through either radial or femoral arterial lines connected to pressure transducers (Baxter Healthcare Corp CardioVascular Group). ICP will be acquired via an intraparenchymal strain gauge probe (Codman ICP MicroSensor; Codman & Shurtleff, Inc). NIRS signals will be recorded bilaterally over the frontal lobes utilizing Covidien INVOS 5100C or 7100 monitoring (Covidien Canada) [Regional cerebral oxygen saturation (rSO_2) for left and right will be recorded.

Finally, during the follow-up visits at 3, 6, and 12 months, patients will receive simultaneous bifrontal NIRS and continuous noninvasive ABP using the INVOS 5100C or 7100 and Finapres Nano-core systems (FMS, Finapres Medical Systems) [12], respectively. This technique has been previously described by our group [13].

Signal Processing

All signals will be recorded using digital data transfer or digitized via an A/D converter (DT9803 or 9826; Data Translation), where appropriate, sampled at a frequency of 100 Hertz (Hz) or higher, using ICM+ software. Signal artifacts will be removed manually before further processing or analysis.

Post-acquisition processing will be conducted using ICM+ software. CPP will be calculated using the formula CPP = MAP − ICP. Systolic ABP (ABPs) will be determined by calculating the maximum ABP over a 1.5-second window, updated every second. Similarly, diastolic ABP (ABPd) will be determined by calculating the minimum ABP over a 1.5-second window, updated every second. Pulse amplitude of ICP (AMP) will be determined by calculating the fundamental Fourier amplitude of the ICP pulse waveforms over a 10-second window, updated every 10 seconds.

Ten-second moving averages (updated every 10 seconds to avoid data overlap) will be calculated for all recorded signals: ICP, ABP (which produced MAP), ABPs, AMP, CPP and rSO_2. Ten-second moving averages will be calculated in order to focus on slow-waves of parent signals, decimating the frequency to the range associated with cerebral autoregulation.

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Cerebrovascular reactivity indices will be derived similarly across modalities (ie, ICP and NIRS); an example is provided for PRx: A moving Pearson correlation coefficient will be calculated between ICP and MAP using 30 consecutive 10-second windows (ie, five minutes of data), updated every minute. Details on each index calculation can be found in Table 1. Data for further analysis will be provided in the form of minute-by-minute time trends, output into comma-separated values (CSV) datasets.

Outcome Assessments

Patient global outcomes will be assessed via GOS at 3, 6, and 12 months post-injury within the standard scheduled clinical follow-up appointments. In addition, patient quality of life will be assessed at these time points via the SF-12 questionnaire, performed in person during the clinic visit. All outcome assessments will be performed by qualified clinic nurses or neurosurgical staff and recorded within the outpatient chart. This form will remain in the neurosurgery outpatient chart, located in GB-1 Health Sciences Center.

Table 1. Continuous cerebrovascular reactivity indices to be derived.

Index	Signals Correlated	Signal Averaging (sec)[e]	Pearson Correlation Coefficient Calculation Window (min)[d]	Index Calculation Update Frequency (sec)
PRx	ICP[b] and MAP[c]	10	5	60
PAx	AMP and MAP	10	5	60
RAC	AMP and CPP[a]	10	5	60
COx	rSO$_2$[f] and CPP	10	5	60
COx_a	rSO$_2$ and MAP	10	5	60

[a]CPP: cerebral perfusion pressure

[b]ICP: intracranial pressure

[c]MAP: mean arterial pressure

[d]min: minute

[e]sec: seconds

[f]rSO$_2$: regional oxygen saturation

Statistical Methodology

General Statistics

Statistical analysis will be performed utilizing R statistical software (R Foundation for Statistical Computing). Alpha for statistical significance will be set at 0.05, with normality for all continuous variables tested via the Shapiro-Wilks test. Basic descriptive statistics will be performed, with comparisons between groups and variables conducted via t-test, Mann-Whitney-U, chi-square, analysis of variance (ANOVA), Kruskal-Wallis, Friedman, and Joncheere-Terpstra testing, where appropriate. General correlations will be described using Pearson/Spearman coefficients, where applicable.

Multi-Variate Co-Variance Analysis

Multivariate testing for inter-index covariance between the ICP and NIRS derived indices will be performed using several methods, including principal component analysis (PCA), agglomerative hierarchal clustering (AHC), partitioning around medoid (PAM) clustering, and K-means cluster analysis (KMCA) [14,15]. A detailed explanation of these statistical techniques is beyond the scope of this section. The strength of clustering in AHC will be confirmed via cophenetic correlation coefficients [16]. KMCA clustering will be validated via the "elbow" methodology.

Time Series Techniques

All indices of cerebrovascular reactivity will be output in a minute-by-minute time-series format. Correlation between ICP- and NIRS-based indices will be evaluated in time series using cross-correlation techniques. Using Box-Jenkins time series modeling, the autoregressive integrative moving average (ARIMA) structure of each index time series will be assessed and compared [17,18]. ARIMA model accuracy for each index will be confirmed using autocorrelation function (ACF) and partial autocorrelation function (PACF) plots, augmented Dickey-Fuller (ADF) and Kwiatkowski–Phillips–Schmidt–Shin (KPSS) testing, and the presence of random normally distributed residuals. ARIMA model superiority will be confirmed via ANOVA testing and comparing Akaike information criterion (AIC), Bayesian information criterion (BIC), and log-likelihood (LL) [17-19].

Modeling of ICP-based indices using noninvasive NIRS indices (ie, COx_a) will be performed using a combination of linear mixed-effects (LME) and general linear modeling (GLM), with ARIMA structures embedded within the LME and GLM [17,20]. Model adequacy will be assessed via ACF plots, PACF plots, random, and normally distributed residuals. Model superiority will be confirmed via ANOVA, AIC, BIC, and LL.

Association Between Acute and Long-Term Cerebrovascular Reactivity

Comparison between NIRS based indices from the acute and long-term follow-up periods will be conducted, evaluating mean, the integrated area under the curve, and percent time above various thresholds. The analysis will also include comparing PCA, AHC, PMA, and KMCA between the acute and long-term follow up periods.

Association With Outcomes

ICP and NIRS indices during the acute phase will be compared with GOS and SF-12 at 3, 6, and 12 months using a variety of linear, proportional odds, and logistic regression techniques. Mean values, the integrated area under the curve, and percent time above various thresholds for the ICP and NIRS indices will be compared to GOS and SF-12 at each timepoint. A similar analysis will occur for the noninvasively derived NIRS indices from follow-up visit recordings, comparing them to GOS and SF-12 results.

Data Safety/Management

Physiologic Data

Physiologic signal data will be managed according to the approved ongoing signal database study, H2017:181. Raw physiologic signal data will be recorded and stored in time-series format by ICM+, then automatically stored on the hard drive of the recording laptops (Windows). These laptops will be password protected, with the ICM+ data files stored in an encrypted password-protected file within the laptop hard drive. ICM+ automatically splits the recording series into 370 MB files in order to reduce data loss in the event of file corruption during the recorded period. These laptops will not be connected to the internet through either hardwire or wireless systems, preventing remote access. All laptops will be stored within the neurosurgery department at HSC behind card-pass and key-protected doors.

All ICM+ datafiles from the recording laptops will be deposited on external hard drives (approximately every 2 weeks), within encrypted password-protected files. These external hard drives will not be connected to the internet, preventing remote access. All external hard drives will remain within the department of neurosurgery, behind locked doors. ICM+ data filenames will consist of unique anonymous codes (000001TBI, 000002TBI, etc), which will be assigned to each patient undergoing data recording/storage on ICM+. The master sheet of patient hospital numbers associated with the unique anonymous codes will be password-encrypted and stored on password-protected computers within the department of neurosurgery. The files are saved in a unique ICM+ file format that can only be opened in the ICM+ software (which will only be available on the laptops recording the data and those of the principal investigator). Furthermore, once the ICM+ files are opened, there is no identifiable patient information stored within, only the anonymous patient identifier and the raw signal information. Thus, there will be no direct way to link this data to any given patient.

Demographic and Outcome Data

Demographic and outcome data will be managed according to the approved ongoing database study H2017:188. Demographic and outcome (ie, GOS and SF-12) data will be stored in encrypted password-protected Excel datasheets. Outcome data will be extracted from the neurosurgery outpatient charts, stored in the Section of Neurosurgery, GF-2 Health Sciences Center. This data will be input anonymously into the encrypted Excel datasheets. Files will be stored on password-protected computers within the section of neurosurgery at HSC. All computers will

be stored behind card-pass and key-protected doors. Patient names/hospital numbers will be replaced with unique anonymous identifiers (000001TBI, 000002TBI, etc). The master sheet of patient hospital numbers associated with the unique anonymous codes will be password encrypted and stored on password-protected computers within the department of neurosurgery, separate from the Excel database files. The file containing the master sheet of hospital numbers and identifier codes will only be accessible by the principal investigator. Thus, there will be no direct way to link this data to any given patient, ensuring patient confidentiality.

Patient Safety

There will be no change in patient care. Both the INVOS 5100C/7100 and Finapres Nano-core systems are entirely noninvasive. NIRS monitoring during the first 5 days of ICU stay will not impact clinical care. Any need for transport for neuroimaging will have NIRS discontinued during that time. Follow-up visits will occur at standard intervals within the neurosurgery department for adults with TBI. No extra or additional clinic visits, outside of standard clinical follow up at our institution, will occur. During these visits, the GOS and SF-12 will be assessed. Furthermore, 30 minutes of NIRS and noninvasive ABP recordings will occur during these visits.

Ethics

Ethical approval has been obtained from the University of Manitoba Research Ethics Board (REB) for both recording and archiving of high-frequency physiologic data in adults with TBI admitted to the ICU or neurosurgical service at HSC, Winnipeg, Manitoba (HS20840; H2017:181). Furthermore, collection of patient demographics, injury characteristics, and outcomes for all adults with moderate/severe TBI admitted to HSC Winnipeg, has also received ethics board approval (HS20850; H2017:188). Approval for prospective recruitment to this study and long-term follow up assessments at 3, 6, and 12 months via NIRS, GOS, and SF-12 has been obtained from the ethics board at the University of Manitoba (HS22191; B2018:103).

Funding

Results

Recruitment began at the end of February 2020, with data collection ongoing, with three patients enrolled as of this writing. The expected duration of data collection will be from February 2020 to January 2022, as per our local research ethics board approval (B2018:103). Support for this work has been obtained through the NIH, through the National Institute of Neurological Disorders and Stroke (NINDS) (R03NS114335), funded in January 2020.

Discussion

Various important aspects of high-resolution physiologic monitoring in TBI will be assessed here, with most assessed for the first time. We hope to prove the ongoing feasibility of

bedside ICP- and NIRS-based continuous cerebrovascular reactivity monitoring in adults with moderate/severe TBI in the ICU setting. We expect to show that NIRS-based cerebrovascular reactivity indices will closely co-vary with ICP-based measures such as PRx over time. This data will support the use of NIRS indices as surrogate measures of cerebrovascular reactivity when the derivation of PRx is either not feasible or possible. Furthermore, we expect to demonstrate accurate PRx modeling using NIRS-based measures of cerebrovascular reactivity, potentially providing a noninvasive surrogate for PRx.

Second, we expect to demonstrate the feasibility of the entirely noninvasive technique for cerebrovascular reactivity monitoring in the sub-acute and long-term phases post-TBI. By demonstrating the ability to obtain continuous high-frequency monitoring of cerebrovascular reactivity in a clinic setting, we hope to expand our ability to monitor patients using high temporal resolution techniques into the follow-up phases of care.

Third, assessing the relationship between continuously measured cerebrovascular reactivity during the acute, sub-acute, and long-term phases has never been conducted before this study. We expect to show a strong correlation between vascular dysfunction during the acute phase and persistent dysfunction during follow-up. Furthermore, we expect to demonstrate a link between clinical phenotype in follow-up, and persistent dysfunction in cerebrovascular reactivity. Success here may lead to the replacement of costly and specialized functional MRI techniques in the assessment of not only moderate/severe TBI, but also mild TBI in the subacute and long-term phases post-injury, shifting the focus to clinic/bedside point-of-care monitoring methods.

Fourth, we have been able to publish our technique with NIRS and noninvasive ABP monitoring devices, for the derivation of continuous noninvasive bedside metrics of cerebrovascular reactivity [13]. Our previous work has shown that the technique is feasible and provides continuous long-duration data with limited artifacts. The technique requires only 5 minutes set-up time, most of which is for calibration of the noninvasive ABP device. We expect this exploratory study will allow us to refine the technique and provide a detailed outline of technical steps and procedures. These procedural details will enable other centers and interested parties to be able to employ this bedside technique for both inpatient and outpatient monitoring for various neuropathological states.

Finally, though not a central focus of our work, noninvasive modeling of ICP has long been of interest in the care of patients with TBI. To date, there has been no reliable noninvasive modeling technique for ICP. Our pilot data set from the above-defined protocol will be uniquely positioned to explore some of the time-series relationships between NIRS rSO_2 and NIRS-derived indices, with ICP. There is the potential that some post-hoc investigations into the NIRS/ICP relationship may provide some useful information for noninvasive modeling of ICP using NIRS.

Through the application of NIRS technology in the monitoring of TBI patients, we expect to be able to outline core relationships between noninvasively measured aspects of cerebral physiology and both invasive measures, as well as patient outcomes. Documenting these relationships carries the potential to revolutionize the way we monitor TBI patients, moving to more noninvasive techniques.

Authors' Contributions

Conceptualization, FAZ; Methodology, FAZ, AG, and LF; Software, FAZ, AG, JD, and LF; Validation, FAZ, AG, and LF; Formal Analysis, FAZ, and AG.; Investigation, FAZ, AG, LF, and JD; Resources, FAZ; Data Curation, AG, LG, and JD; Writing – Original Draft Preparation, FAZ; Writing, Review & Editing, FAZ, AG, LF, and JD; Supervision, FAZ; Project Administration, FAZ, AG, and LF; Funding Acquisition, FAZ.

Conflicts of Interest

The authors have no conflicts of interest.

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Abbreviations

ABP: arterial blood pressure
ABPd: diastolic arterial blood pressure
ABPs: systolic arterial blood pressure
ACF: autocorrelation function
ADF: augmented Dickey-Fuller
AHC: agglomerative hierarchal clustering
AIC: Akaike information criterion

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AMP: pulse amplitude
ANOVA: analysis of variance
ARIMA: autoregressive integrative moving average
BIC: Bayesian information criterion
BTF: Brain Trauma Foundation
CBV: cerebral blood volume
CPB: cerebral perfusion pressure
CSV: comma-separated values
GLM: general linear modeling
GOS: Glasgow Outcome Score
ICP: intracranial pressure
ICU: intensive care unit
KMCA: K-means cluster analysis
KPSS: Kwiatkowski–Phillips–Schmidt–Shin
LL: log-likelihood
LME: linear mixed-effects
MAP: mean arterial pressure
NIRS: near-infrared spectroscopy
PACF: partial autocorrelation function
PAM: partitioning around medoid
PCA: principal component analysis
rSO$_2$: regional cerebral oxygen saturation
SF-12: Short-Form 12 Health Survey
SICU: surgical intensive care unit
TBI: traumatic brain injury

<u>Original Paper</u>

Virtual Reality Cognitive Therapy in Inpatient Psychiatric Wards: Protocol for a Qualitative Investigation of Staff and Patient Views Across Multiple National Health Service Sites

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Abstract

Background: Patients in psychiatric wards typically have very limited access to individual psychological therapy. Inpatients often have significant time available, and an important transition back to everyday life to prepare for—but historically, there have been few trained therapists available on wards for the delivery of evidence-based therapy. Automated virtual reality (VR) therapy may be one route to increase the provision of powerful psychological treatments in psychiatric hospitals. The gameChange automated VR cognitive therapy is targeted at helping patients overcome anxious avoidance and re-engage in everyday situations (such as walking down the street, taking a bus, or going to a shop). This treatment target may fit well for many patients preparing for discharge. However, little is known about how VR therapy may be viewed in this setting.

Objective: The objectives of the study are to explore psychiatric hospital staff and patients' initial expectations of VR therapy, to gather patient and staff views of an automated VR cognitive therapy (gameChange) after briefly experiencing it, and to identify potential differences across National Health Service (NHS) mental health trusts for implementation. Guided by an implementation framework, the knowledge gained from this study will be used to assess the feasibility of VR treatment adoption into psychiatric hospitals.

Methods: Focus groups will be conducted with NHS staff and patients in acute psychiatric wards at 5 NHS mental health trusts across England. Staff and patients will be interviewed in separate groups. Individual interviews will also be conducted when preferred by a participant. Within each of the 5 trusts, 1 to 2 wards will be visited. A total of 8-15 staff and patients per ward will be recruited, with a minimum total of 50 staff and patients recruited across all sites. Focus group questions have been derived from the nonadoption, abandonment, and challenges to the scale-up, spread, and sustainability (NASSS) framework. Focus groups will discuss expectations of VR therapy before participants are given the opportunity to briefly try the gameChange VR therapy. Questions will then focus on opinions about the therapy and investigate feasibility of adoption, with particular consideration given to site specific issues. A thematic analysis will be conducted.

Results: As of May 15, 2020, 1 patient focus group has been conducted.

Conclusions: The study will provide unique insight from patients and staff into the potential for implementing automated VR therapy in psychiatric wards. Perspectives will be captured both on the use of immersive technology hardware and therapy-specific issues in such settings.

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Introduction

The Implications of Digital Technologies to Mental Health

There is a clear rise in the use of digital technologies, especially online apps, to deliver mental health treatments [1]. A second wave of digital treatments that use virtual reality (VR), increasingly being tested and shown to be effective in clinical trials, are likely to be implemented in services in the future [2]. VR therapy may be a particularly valuable tool in psychiatric wards. VR provides a safe and controlled setting for patients to practice entering, and coping with, challenging situations they may face at discharge. Therefore, it is important to assess the feasibility of implementing VR therapy in inpatient ward settings, and identify likely barriers and facilitators.

Psychiatric Wards

Over the past 60 years, there has been an increasing move away from inpatient care toward the provision of care in the community whenever possible [3]. However, inpatient admission remains an important part of the care pathway when a person's illness cannot be sufficiently managed in the community [4]. Qualitative investigations suggest that inpatient admission is needed to provide safety and protection from difficult environments, with many patients coming from places that they found to be too stressful and where they felt at risk of hurting themselves or others [5].

The shift in strategy toward community care has led to a reduction in the provision of inpatient beds. Bed numbers in England fell by 62% between 1987 and 2010, from almost 70,000 to fewer than 35,000 [4]. For adults in England, there are now just 18,000 beds, despite increases in the number of people in contact with mental health services [6]. The number of admissions to psychiatric wards has fallen accordingly, with a 19% reduction since 2012. However, bed occupancy remains high, at 95% in 2019 [6]. Average length of stay and numbers of involuntary admissions (ie, individuals detained under the mental health act) are also increasing [7]. Currently in the UK, the average length of stay in psychiatric wards is approximately 46 days. First admissions tend to be briefer, with an average length of 35 days. Length of stay is longer, with an average of 60 days, for those admitted involuntarily, compared to 37 days for those voluntarily admitted [8]. In 2019, 40% of admissions were involuntary, and the majority (62%) of all occupied bed days were by patients with psychosis [6], with these individuals also being the most likely to be detained [9]. It is clear that the need for inpatient admission remains, but with reduced capacity, the severity of illness required for admission has increased.

Inpatient wards are the most expensive form of care, with each acute adult bed costing up to GBP £180,000 (US $236,277.84) per year, the equivalent cost of supporting 44 people through a community mental health team over a year [10]. The lack of available beds and pressures to meet targets for lower bed occupancy rates [11] means ward staff are often forced to focus on achieving acute symptom reduction in patients rather than improvement in social functioning or coping ability [8]. Pressures are compounded by the limited availability of trained staff [12], a reliance on agency staff, and high levels of staff burnout [13]. Therefore, opportunities for staff-patient engagement in therapeutic relationships and collaborative care focused on recovery are limited [9,14]. Delivery of one-to-one or group psychological therapy is infrequent [15], with wards having very limited input from qualified psychologists [16] and treatment being predominantly pharmacological [12].

A further challenge to recovery is the lack of meaningful activities on wards, with patients often feeling bored and lonely [5]. Qualitative reports suggest that time is filled primarily with meals, smoking, and trying to look for someone to talk to [17], and that for some patients, the feeling of constant waiting is stressful and overwhelming [18]. One patient from a qualitative study described, "All you did was just sitting around, and there was nothing for you to do…no program to keep you busy…it's not good…I stagnate" [19]. Both staff and patients recognize that the provision of meaningful occupation is central to recovery and wellness [20,21], but pressures on staff time often prevent it.

The lack of both therapy provision and engagement in meaningful activities means that patients are often unprepared for discharge. Patients can access escorted (and eventually, unescorted) leave from the ward [22]; however, it is unclear how frequently this forms part of the therapeutic preparation for discharge, in which leave, for example, is used to practice coping with some of the difficult situations that may have led to a patient's admission in the first place. Consequently, although symptoms may be reduced upon discharge, patients can be ill-equipped with the skills needed to continue their recovery.

Leaving hospital often leads to the re-emergence of the pre-existing stressors that contributed to admission [23,24]. This may explain why the risk of relapse and rehospitalization immediately postdischarge is high [25]. Rates of suicide among patients in their first 3 months after discharge are also high, estimated at 100 times the global suicide rate, with a particular risk in the first week after discharge [23]. Significant anxiety about leaving hospital, sometimes known as "discharge grief," is common [17]. There is a clear need for greater focus on safe transition and discharge preparation. To accomplish this, it is argued that wards must shift from a predominant focus on observation and monitoring of patients for acute symptom reduction, to one of active encouragement of patients to engage in activities and their own care management [5,10].

Virtual Reality Therapy

Immersive virtual reality (VR) technology may provide a way of facilitating preparation for discharge. Difficulties interacting with the social world lie at the heart of most mental health problems [2], and it is clear that patients on wards require greater support to re-enter the external social world, which they previously found challenging [5]. In VR, it is possible to enter

computerized simulations of scenarios that an individual finds difficult, while practicing powerful psychological techniques. This enables individuals to change the way they think, react, and behave in such scenarios. Automating VR therapy means individuals can make use of the therapy even when there is a lack of highly trained staff. The potential for using VR in therapy has been well recognized over the past 25 years, but the development of consumer kits—and with it, the possibility of scaling VR therapy—has occurred only recently [2]. The hardware consists of a computer that generates an image, a display system that presents sensory information, and a tracker that feeds back the user's position and orientation to update the image.

VR has several key advantages over traditional face-to-face therapy. Patients are more willing to enter VR simulations of the situations they find anxiety-provoking because they know the simulations are not real. At the same time, individuals respond the same in VR, psychologically, emotionally, and physiologically, as they do in corresponding real-world environments [26]. Therefore, any learning that has occurred in VR transfers to the real world [27]. Consequently, VR provides a way of immersing individuals in the very environments in which they require practice when they are too fearful or, as is the case in inpatient wards, unable to do so in the real world.

The gameChange VR therapy utilizes this very concept to treat anxious social withdrawal [28]. Many individuals with mental health disorders (particularly, serious mental disorders such as psychosis) withdraw from everyday social activities due to anxiety. Two-thirds of patients with schizophrenia have levels of anxious avoidance equivalent to agoraphobia [29]. The key mechanism utilized by the gameChange therapy concerns safety-seeking behaviors, also known as defenses. Defenses are behaviors that individuals employ to help them feel safer. However, these behaviors actually serve to maintain thoughts and feelings of fear by preventing the learning of disconfirmatory evidence. Dropping defense behaviors during difficult situations allows patients to relearn concepts of safety [30]. Therefore, the gameChange therapy identifies patients' defenses and encourages them to try dropping their defenses in virtual social situations, thus helping to achieve new learning of feelings of safety and confidence. The current gameChange therapy includes 6 virtual scenarios: a street, café, pub, GP surgery, corner shop, and bus, with 5 levels of difficulty within each scenario. The user-centered design process for this therapy has been described in a recent paper [31].

Notably, the gameChange therapy is automated. A virtual coach, Nic, guides patients through each situation and suggests new behaviors to test out. Therefore, the therapy does not require a trained cognitive behavioral therapist to deliver it. While there is still someone in the room with the patient, this individual can be a peer supporter, psychology assistant, social worker, or health care assistant. This individual's role is to set up the equipment and provide support and encouragement. As such, VR delivery staff require only brief initial training and then ongoing supervision with a psychologist. The gameChange therapy is currently being tested in a multi-site randomized controlled trial [28]. Within the trial, patients are offered 6-8

weekly therapy sessions supported by a member of staff, typically an assistant psychologist, peer support worker, or clinical psychologist. Sessions take place either in the participant's home or local mental health base.

Many studies have shown the effectiveness of VR therapy for patients with a range of mental health problems [32-34]. Using these therapies on wards could provide a unique opportunity for helping patients prepare for discharge through the experiential practice of a range of everyday situations. The delivery of an automated VR therapy can be facilitated by a wider range of professionals on the ward and is not constrained to a therapist trained in one-to-one psychological therapies. Higher doses, perhaps daily, would be feasible.

If VR headsets were accessible on wards, additional, freely available VR programs such as physical activity games, relaxation, and meditation exercises could also be used by patients as therapeutic activities that lessen boredom and enhance recovery. The feasibility of this has increased greatly due to continuous hardware improvements and a reduction in costs. This means VR equipment now requires less space, is less technical, and is more user-friendly than it was previously.

Implementation Framework

Implementation frameworks provide an overview of the factors that typically shape and influence the implementation process [35]. We used the nonadoption, abandonment, and challenges to the scale-up, spread, and sustainability (NASSS) framework for health care technologies [36] to inform the study's design. The NASSS draws together a number of implementation models and theories, and covers 7 domains relating to health care technology implementation: the condition or illness, the technology, the value proposition, the adopter system, the organization, the wider context, and embedding and adaptation over time. Challenges regarding each domain are classified as simple (straightforward, predictable, few components), complicated (multiple interacting components or issues), or complex (dynamic, unpredictable, not easily disaggregated into constituent components). Staff and patients are in a position to inform 3 of these domains with regard to implementation of VR therapy: the condition and illness that the therapy is designed for, the intended adopters of VR therapy, and the organization. Other frameworks were also considered, such as the normalization process theory (NPT) [37]. However, the NASSS framework covers a wider range of potential barriers and facilitators to implementation that may be relevant at any point from design through to continued implementation, whereas NPT is more retrospective in nature.

Objectives

The study objectives are threefold: (1) to obtain initial expectations of staff and patients about VR and VR psychological therapy; (2) to gain staff and patient views of an automated VR therapy (gameChange) after trying it; (3) and to identify potential differences and requirements for implementation across health care sites.

Methods

To increase the methodological quality and reporting, the presentation of the study will follow the guidance of the 32-item consolidated criteria for reporting qualitative research (COREQ) [38].

Ethical Review

The gameChange trial received Health Research Authority (HRA) approval and Health and Care Research Wales approval (IRAS 256895, The gameChange Trial). The trial received ethical approval from the NHS South Central - Oxford B Research Ethics Committee (19/SC/0075). The trial has been registered (ISRCTN17308399) and the protocol published [28]. The present study received ethical approval as part of a substantial amendment.

Patient and Public Involvement

In line with the guidance for reporting involvement of patients and the public (short form; GRIPP2-SF [39]) we report the aims, methods, results, and reflections on patient and public involvement (PPI).

There has been considerable PPI in the development of the gameChange therapy and the running of the trial. Within this study, the aim is to ensure all study documentation (topic guide, information sheet, and consent form) is engaging and understandable, and to involve service users in the design of the study. PPI will also be used to discuss the analysis and interpretation of results. A lived experience advisory panel (LEAP), facilitated by the McPin Foundation, contributed to the development of the study. The LEAP comprises 10 individuals from across the 5 study sites. All study documentation was sent electronically to the LEAP for feedback, and an in-person discussion about the study design took place. An additional in-person session will take place to discuss the analysis and results. Many areas of the study documentation were rephrased to make them more inclusive and comprehensible, and many suggestions for how to maximize engagement in focus groups were given. These included key times on the ward to avoid (eg, visiting hours, meal and medication times), reducing the power dynamic in focus groups (eg, by emphasizing that the researchers are here to learn from participants, not the other way round), ensuring the researchers state that the focus group ground rules also apply to themselves, and asking certain questions without making people uncomfortable (eg, by offering post-it notes or asking a question before a break).

Therefore, PPI has been a helpful influence on the study. As the LEAP had been involved with the gameChange trial, they were familiar with the VR that would be demonstrated, and the LEAP was thus well placed to reflect on how this would work in the focus groups. Several members had also been inpatients themselves, allowing them to give important advice about how focus groups could best be conducted on the wards.

PPI was considerable; however, involvement could also have been further strengthened. For example, not all 10 LEAP members were able to attend the in-person meeting. If time had allowed, another in-person meeting may have enabled the incorporation of a greater number of viewpoints.

Context of Data Collection

There are likely to be a number of challenges affecting the data collection process. Wards can be chaotic environments, with unpredictable events and many patients experiencing high levels of distress, making the facilitation of focus groups difficult [16]. The staff pressures and shortages typically seen on wards may mean it is difficult for staff to schedule time for a focus group or interview in advance. For those who are able to take part, time may be limited, preventing the discussion of all relevant topics. In addition, some wards may not always have a suitable room available for conducting focus groups and interviews, so the researchers expect time constraints for when they can conduct focus groups or interviews. This will be compounded by the need to avoid key times on the ward, such as during ward rounds, medication dispensary, visiting hours, meal times, and any structured activities offered on the ward. To minimize these issues, the researchers will aim to be as flexible as possible in their approach, but challenges and disruptions to data collection are nonetheless expected.

Participants

Staff working in either the delivery or management of clinical care on the wards will be invited to take part in focus groups or individual interviews. National Health Service (NHS) patients staying on wards will be recruited according to the following inclusion criteria: (1) participants are willing and able to give informed consent for participation in the study; (2) participants are 18 years old or older; (3) participants are willing to consent to being audio-recorded; (4) participants have sufficient English language skills to participate in the focus group or interview. The exclusion criteria will include high levels of associated risk to self or others through participation in the study (eg, actively suicidal), and photosensitive epilepsy (for which use of VR is not recommended). Researchers will assess a participant's capacity to consent after the participant has read the information sheet and before they sign the consent form. Patients will receive a small payment for taking part.

Sampling and Recruitment

The gameChange trial is recruiting from 5 NHS mental health trusts across the UK: Avon and Wiltshire Mental Health Partnership NHS Trust, Greater Manchester Mental Health NHS Foundation Trust, Cumbria Northumberland Tyne and Wear NHS Foundation Trust, Nottinghamshire Healthcare NHS Foundation Trust, and Oxford Health NHS Foundation Trust. Principal investigators (PIs) and trial coordinators will be at each site. The trial is open to patients from all mental health services, but to date, almost all participants are outpatients. We will work with the PIs and trial coordinators to approach leads of psychiatric wards at each site. Only acute psychiatric wards will be visited rather than rehabilitation wards, given these are the most numerous type. We aim to visit an equal number of male and female wards.

We aim to visit 1-2 wards within each of the 5 trusts, and include 8-15 total participants (staff and patients) from each ward. A minimum total of 50 staff and patients will be recruited across

all sites. Due to the busy nature of wards and frequent lack of room availability, convenience (volunteer) sampling will be used in the first instance. Purposive sampling will then be used to ensure that a range of staff are seen (ie, those who are involved in decision-making as well as those who are more directly involved in day-to-day clinical care).

Procedure

In the weeks leading up to the site visit, staff and patients will be informed of the study and focus group dates will be arranged. Staff and patients will receive participant information sheets and be given time to discuss this with others. The researchers will predominantly rely on members of ward staff to initially introduce the study and go through the information sheet with patients, given staff will be more familiar to patients. Before taking consent, the researchers will be available to take participants through the information sheet again and answer any questions. After consenting, a demographic questionnaire will ask participants their age, gender, and ethnicity. Staff will also be asked about their job roles. Patient diagnosis will not be recorded, given that patients themselves may not be willing or able to disclose this, and we do not wish to add to staff burden by asking them to provide this patient information. The first author (PB) will lead all focus groups. There will be a cofacilitator that is likely to vary by site. A member of staff from the ward may also be present during patient focus groups and interviews. Each of the wards will be visited multiple times to ensure participation is open to as many different patients and members of staff as possible. All data collection will take place on the ward.

Focus groups and interviews will initially ask questions relating to the study's first objective (to obtain the initial expectations of staff and patients about VR and VR psychological therapy) before giving all participants the opportunity to put on a VR headset and try the therapy for a few minutes. They will meet the coach, Nic, and try out 1 level of 1 scenario. Participants will choose which scenario and level they enter, although patients will be encouraged to only try easier levels. Participants will also be observed while they try the VR therapy, and potentially videotaped if they give permission. Observations will be recorded in the researchers' field notes. Further questions will then focus on objectives 2 (to gain staff and patient views of the gameChange automated VR therapy after trying it) and 3 (to identify potential differences and requirements for implementation across health care sites). If any participants leave the focus groups before the end, we do not plan to collect data on the reasons for withdrawal. This is for two reasons: firstly, it is expected to be practically difficult to follow up with a participant who leaves; secondly, participants are told that they may withdraw from the focus groups at any point without the provision of a reason, so as not to make anyone feel obliged to stay. Any data that they have provided prior to leaving will be included in the analysis.

Focus Groups and Interviews

Focus groups were chosen as the primary mode of data collection because they allow individuals to consider ideas together while also highlighting differences in thoughts and ideas between participants [40]. They also allow participants to express ideas spontaneously, in a way that is less structured or influenced by the researchers' prejudices [41]. Given most participants are expected to be unfamiliar with VR, a group setting is likely to be helpful for allowing individuals to consider a range of viewpoints and questions raised by other group members to inform their opinions. The group setting is also likely to be most constructive for generating ideas about potential challenges around the implementation of VR therapy, as well as solutions to challenges, because individuals can build upon each other's suggestions. We aim for each focus group to contain 3-6 participants; however, this will vary depending on staff and patient availability. Wards are a challenging environment for such research, and pragmatism is needed. In particular, it is expected to be difficult to have multiple staff members available at the same time, so a number of single or joint interviews may be necessary. Individual interviews will also be conducted if a participant would prefer. For example, a number of patients might find a group setting difficult, and some members of staff may prefer to express their views privately. Focus groups are expected to last anywhere between 45 minutes to 2 hours. Individual interviews may be shorter. To limit the length of time staff are required to be available at any one time, the possibility of splitting the focus group or interview into 2 sessions will be offered.

Topic Guide

Informed by the NASSS framework, the semistructured topic guide has been created to cover all 3 objectives. PB created a first draft of the topic guide, which was then revised following feedback from FW, DF, the LEAP, 2 experts in qualitative research, and a pilot with colleagues. The topic guide will be reviewed after conducting the first focus groups, and then again at a later stage of data collection and analysis. Changes may be made in response to participant feedback (eg, if focus groups are too long for participants, or if it becomes clear that a certain topic is being under or overexplored). Significant changes to the topic guide will be reported. A copy of the topic guide can be viewed in Multimedia Appendix 1.

Analysis

Focus groups and interviews will be audio-recorded and transcribed verbatim. Field notes from each focus group or interview will also be transcribed. Field notes will record factors such as group dynamics and nonverbal cues to add context to the transcript of the audio recordings. For practical reasons, transcripts will not be returned to participants for comment or correction.

A thematic analysis will be conducted [42]. All data will be entered into NVivo (version 12.0, QSR) [43] in order to provide a transparent audit trail. PB will read and reread transcribed data to ensure familiarity before developing a preliminary coding framework. In line with recommendations [44], there will be team reviews of the coding framework, regular team consultation, and multiple coding for a number of interviews. Details regarding each code will be recorded in memos in Nvivo. Themes will be derived from the data. Data saturation will be discussed as the study progresses. Diverse cases and minor themes will be presented, as we consider breadth as important as frequency. A meeting with the LEAP will be set up in order

to discuss the thematic analysis and consider interpretations of the results.

Reflexivity

Researchers conducting the focus groups and analyzing the results will consider how their own backgrounds may impact data collection and analysis. PB will keep a reflexive log. Details of the research team and reflexivity will be reported in the full manuscript in line with COREQ guidelines [38]. However, reflexivity has also been considered at an early stage, prior to starting recruitment to the study.

All the researchers who will be conducting focus groups have been involved in the design or use of VR therapy for psychosis. Thus, existing knowledge, expectations, and hopes regarding VR therapy may impact how the focus groups are conducted. A number of groups may be cofacilitated by a clinical psychologist, and others may be cofacilitated by an assistant psychologist, which may impact the data in terms of both the cofacilitators' actions (eg, how questions are asked) and how participants respond to the different roles. To try to minimize these potential biases, PB and the cofacilitators will aim to stay close to the interview schedule, as this was created largely from the NASSS implementation framework, not just the experiences and expectations of the authors.

Results

As of May 2020, data collection for 1 patient focus group with 3 participants has been conducted, and coding is underway.

Discussion

Prospects

This protocol describes the plan for a multi-site qualitative study with patients and staff, assessing the feasibility of implementing VR therapy in inpatient psychiatric wards. As part of this process, NHS staff and patients in psychiatric wards will be able to try out and provide their feedback on the gameChange automated VR therapy. The study will provide insight into the degree to which VR therapy might be suitable for inpatient wards, and identify barriers and facilitators to implementation. Studies making use of implementation science should aim to produce generalizable knowledge [45]. As such, this study can also be contextualized as an investigation of the potential implementation of digital psychological therapies more generally in psychiatric wards.

Limitations

There are several limitations to the methodology used in the study. We will only be recruiting from acute psychiatric wards; therefore, results may not generalize to all types of wards (such as rehabilitation wards). Similarly, the wards that agree to take part may be those that are currently not experiencing significant staff shortages, which may also limit the generalizability of findings.

It has been suggested that participants in implementation studies may represent a more highly motivated group of service users who are less representative of the whole population [46]. This may be a limitation of the participant group we recruit. Patient diagnosis will also not be recorded, nor will patients be asked about their specific current experiences and difficulties. Therefore, we will not know what kinds of problems most patients are experiencing unless they discuss them in the groups. In addition, while a focus group environment has a number of benefits, a proportion of participants may not feel entirely comfortable in this setting. This could be due to low self-confidence, conflicts between individuals on the ward, or hierarchical staff roles. Consequently, a number of individuals may not fully share their views. It is hoped that offering individual interviews may help to mitigate this problem, but it is still likely to be present.

Strengths

The study methodology also has several strengths. First, multiple stakeholder involvement is considered important for implementation research [45,47]. Thus, conducting focus groups with staff of varying professional groups and patients is a particular strength of the study; a wide selection of viewpoints is likely to be gained. Second, conducting the study at 5 NHS mental health trusts across the UK will help to increase the generalizability of the results, and allow comparison between different locations. Third, the study methodology and documentation has received feedback from our LEAP, helping to ensure the study will be engaging and acceptable to patients. Fourth, the gameChange VR therapy has been designed to help with the very problem that many patients on wards are struggling with: coping with everyday environments. Therefore, it is likely to fit well with the goals of both staff and patients on wards. Finally, the majority of implementation research is retrospective [47]. This study benefits from prospectively assessing feasibility of implementation in this setting. Prospective assessment of digital interventions allows for optimization prior to implementation, in order to ensure long-term use and the meeting of clinical and scientific standards [48].

It is important to consider how health care technologies can be integrated into existing health services [49]. There have been significant recent advances in digital mental health care. This study will provide valuable insight into how one particular emerging health care technology, VR, might fare in implementation in psychiatric inpatient wards.

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Conflicts of Interest

DF is a founder and nonexecutive board director of Oxford VR, a University of Oxford spin-out company, which programed and commercializes the gameChange treatment. DF holds equity in Oxford VR.

Multimedia Appendix 1
Focus group topic guides.
[DOCX File , 20 KB - resprot_v9i8e20300_app1.docx]

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Abbreviations

GRIPP2-SF: guidance for reporting involvement of patients and the public - short form
LEAP: lived experience advisory panel
NASSS: nonadoption, abandonment, and challenges to scale-up, spread, and sustainability
NPT: normalization process theory
PI: principal investigator
PPI: patient and public involvement
VR: virtual reality

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Protocol

Closing the Gap Between Mammalian and Invertebrate Peripheral Nerve Injury: Protocol for a Novel Nerve Repair

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Abstract

Background: Outcomes after peripheral nerve injuries are poor despite current nerve repair techniques. Currently, there is no conclusive evidence that mammalian axons are capable of spontaneous fusion after transection. Notably, certain invertebrate species are able to auto-fuse after transection. Although mammalian axonal auto-fusion has not been observed experimentally, no mammalian study to date has demonstrated regenerating axolemmal membranes contacting intact distal segment axolemmal membranes to determine whether mammalian peripheral nerve axons have the intrinsic mechanisms necessary to auto-fuse after transection.

Objective: This study aims to assess fusion competence between regenerating axons and intact distal segment axons by enhancing axon regeneration, delaying Wallerian degeneration, limiting the immune response, and preventing myelin obstruction.

Methods: This study will use a rat sciatic nerve model to evaluate the effects of a novel peripheral nerve repair protocol on behavioral, electrophysiologic, and morphologic parameters. This protocol consists of a variety of preoperative, intraoperative, and postoperative interventions. Fusion will be assessed with electrophysiological conduction of action potentials across the repaired transection site. Axon-axon contact will be assessed with transmission electron microscopy. Behavioral recovery will be analyzed with the sciatic functional index. A total of 36 rats will be used for this study. The experimental group will use 24 rats and the negative control group will use 12 rats. For both the experimental and negative control groups, there will be both a behavior group and another group that will undergo electrophysiological and morphological analysis. The primary end point will be the presence or absence of action potentials across the lesion site. Secondary end points will include behavioral recovery with the sciatic functional index and morphological analysis of axon-axon contact between regenerating axons and intact distal segment axons.

Results: The author is in the process of grant funding and institutional review board approval as of March 2020. The final follow-up will be completed by December 2021.

Conclusions: In this study, the efficacy of the proposed novel peripheral nerve repair protocol will be evaluated using behavioral and electrophysiologic parameters. The author believes this study will provide information regarding whether spontaneous axon fusion is possible in mammals under the proper conditions. This information could potentially be translated to clinical trials if successful to improve outcomes after peripheral nerve injury.

International Registered Report Identifier (IRRID): PRR1-10.2196/18706

KEYWORDS

Introduction

Background

Peripheral nerve injuries (PNIs) are devastating and life-altering events that affect 20 million Americans per year and result in an annual economic cost of $150 billion [1]. Despite current nerve repair techniques, recovery from PNIs is often prolonged, incomplete, and associated with poor functional outcomes [2]. After primary repair of a peripheral nerve laceration, regenerating axons frequently contact distal nerve segments that have undergone Wallerian degeneration (WD). WD establishes the environment necessary for axon regeneration. Axons regenerate within Schwann cell tubes at approximately 1 mm per day to reach sensory or motor end organs [3].

In certain invertebrate species, WD does not occur for weeks to months after an axon is severed. The regenerating axons frequently make contact with intact distal segment axons and auto-fuse, which restores axon continuity between proximal and distal segments and enables recovery of nerve function within days [4-6]. Auto-fusion occurs with high specificity, as existing evidence suggests that regenerating axons can recognize and fuse with their original distal ends. The mechanisms underlying this specificity are still being investigated, but it is believed that there is overlap with the molecular players involved in auto-fusion. It is critical to note that membrane-bound receptors on the regenerating axolemmal membranes contact their respective ligands bound to phosphatidylserine on the axolemmal membranes of the distal segment axons. Therefore, axolemmal-axolemmal contact is required for fusion to occur [5].

There are numerous differences between the nerve structure of mammals and invertebrates. Many invertebrates have single axons that innervate a distal target, whereas mammals have nerves with highly organized motor and sensory fascicles containing many axons [3,7]. Peripheral nerves in mammals have complicated architecture consisting of multiple compartmentalized layers. Axons are compartmentalized into fascicles, which can be motor, sensory, or mixed fascicles. Mammalian peripheral nerve axons are encased by Schwann cells and produce myelin sheaths in myelinated nerves. In the nematode *Caenorhabditis elegans*, mechanosensory axons are surrounded by glial cells that do not produce myelin [8].

The most notable difference between mammalian and invertebrate species is the time for WD in the distal segment to occur. In mammals, regenerating axons contact distal segment axons that have undergone WD because of the time delay for regenerating axons to outgrow and reach the distal segment. This alone prevents axon auto-fusion in mammals, even if they do possess the intrinsic machinery necessary for fusion. Because of the delayed WD and presence of molecular fusion mechanisms observed in invertebrates, regenerating axons contact intact distal axons, which leads to auto-fusion [5,9].

Notably, in *C elegans*, reduced retraction of the severed axon ends, reduced degeneration of the distal segment, and an increased number of regenerating axons from the proximal segment strongly correlate with the success of axonal auto-fusion. These factors facilitate fusion by providing a reduction in the distance between the proximal and distal ends of the axon, maintaining an intact distal segment, and providing a greater probability of contact between the two segments [9].

In contrast to the heavily myelinated axons produced by Schwann cells in the mammalian peripheral nervous system, invertebrate axons are surrounded by glia that either do not produce myelin, such as in *C elegans* [8], crayfish [10], and leeches [11], or produce a thin layer of myelin, like earthworms [12]. This begs the question as to whether the presence of heavily myelinated axons could be one factor potentially inhibiting axon auto-fusion in mammals, as myelin is a known inhibitor of nerve regeneration [13].

Additionally, invertebrates such as *C elegans* do not have injury-induced immune responses that are present in mammals [6]. Overall, the immune response to PNI in mammals is conducive to successful nerve regeneration [3]. However, in terms of axon auto-fusion seen in certain invertebrates, the immune response is detrimental because WD must be prevented for auto-fusion to occur.

To date, there is no evidence of spontaneous axonal fusion in mammalian axons after transection. Notably, mammalian axonal fusion can be induced after transection by polyethylene glycol (PEG) fusion techniques [4,14]. PEG fusion has been shown to restore axon continuity and prevent WD. PEG fusion works by removing water molecules between two opposing plasmalemmal membranes, which allows the opposing membranes to contact and fuse [15]. However, PEG fusion techniques do not lead to rapid restoration of preinjury function, which can partly be explained by the nonspecific random fusion of axons with mixed motor and sensory end-organ targets [14]. Although there is no evidence of mammalian auto-fusion, no mammalian study has demonstrated axolemmal-axolemmal contact between regenerating peripheral nerve axons and intact distal axons. No study, to our knowledge, has simultaneously attempted to enhance axon regeneration, prevent WD, prevent myelin obstruction, and limit the immune response to establish contact between regenerating axons and intact distal segment axons to assess fusion competence. This is the aim of our novel nerve repair protocol. It is hypothesized that these conditions can be established in a rat model using a combination of pharmacological and surgical interventions aimed to (1) prevent Wallerian degeneration, (2) enhance axon regeneration, (3), prevent myelin obstruction, (4) limit the injury-induced immune response, and (5) establish contact between severed nerve ends.

Prevent Wallerian Degeneration

Numerous interventions have demonstrated the ability to delay WD in mammals when implemented prior to nerve injury or within a 4- to 6-hour critical window after the time of injury

[16]. These interventions include cryotherapy and the administration of ascorbic acid (vitamin C) [6,7,16-19].

Cryotherapy is also neuroprotective, as demonstrated by multiple studies. Within the nervous system, cryotherapy decreases oxygen demand and preserves energy stores. The net effect of cryotherapy after PNI is delayed WD, reduced membrane disruption, and decreased oxidative stress [20,21].

Marzullo et al [22] showed that rat sciatic nerves maintained electrical conduction in vitro for up to 7 days with cooling to 6-9 °C versus 36 hours at 37-38 °C. Sea et al [23] demonstrated a linear relationship between lower temperatures and delayed WD on rat models. Cooling transected nerves to 13 °C, 23 °C, and 32 °C delayed axon fragmentation up to 10, 6, and 3 days, respectively [23].

Ascorbic acid is an antioxidant that has demonstrated neuroprotective effects. Calixto et al [24] demonstrated that oral administration of ascorbic acid delayed WD up to 7 days versus 3 days in wild-type mice in a sciatic nerve transection model. In this study, ascorbic acid was given in drinking water for 10 days before nerve injury. Immunofluorescence and electron microscopy were used to confirm its protective effects on axon degeneration.

Enhance Axon Regeneration

In order to establish contact between proximal and distal axons before WD in the distal segment, regenerating axons must sprout and advance in a timely manner. The probability of axon fusion increases with a higher number of regenerating axons [9].

The L-type voltage-gated calcium channel antagonist nimodipine has demonstrated efficacy in nerve regeneration in clinical studies. After unilateral recurrent laryngeal nerve (RLN) transection in 19 patients, vocal cord motion recovered 3 times faster compared with historical controls when the RLN was repaired with adjuvant nimodipine administration [25]. Additionally, a pilot study of nimodipine treatment in patients with facial nerve paresis following maxillofacial surgery showed earlier recovery and improved facial nerve function assessed by the House-Brackmann scale after nimodipine treatment. In this study, regeneration times described in the literature were 2 or 3 times longer compared with nimodipine treatment [26].

Cyanocobalamin (vitamin B_{12}) is known to aid in the prevention of neuronal breakdown [27]. Vitamin B_{12} plays a role in various cellular processes that allow for preservation of neuronal function [27,28]. It also has the ability to promote regeneration and improve the function of damaged sciatic nerves by upregulating brain-derived neurotrophic factor expression at the mRNA and protein levels [29]. Additionally, Okada et al [30] demonstrated that high-dose vitamin B_{12} improves nerve function after PNI [30,31].

Prevent Myelin Obstruction

For many years, it has been recognized that myelin sheaths and myelin debris are present at the site of nerve transection [32,33].

More specifically, observations with electron microscopy have made it apparent that transected axonal ends are capped by collapsed myelin sheaths [34,35].

Lysophosphatidylcholine (LPC), an endogenous lysophospholipid, has been used to induce demyelination in order to study methods to enhance or promote remyelination [36-38]. LPC is commonly injected locally within myelin sheaths to induce rapid demyelination within 30 minutes [39]. Epineural injection leads to localized demyelination. From a morphological standpoint, there is no clear damage to surrounding Schwann cells or axons, which also makes it an ideal molecule to study demyelination [39].

Limit the Injury-Induced Immune Response

Corticosteroid treatment has been shown to inhibit the inflammatory response and reduce the recruitment of macrophages. Steroids such as dexamethasone act by inhibition of phospholipase A_2, a critical enzyme in the production of inflammatory cytokines [40]. Additionally, steroids are believed to inhibit lipid peroxidation after PNI and consequently enhance recovery [41].

Dexamethasone has anti-inflammatory effects and has been shown to enhance axon regeneration and functional recovery after PNI in multiple studies [29,42,43]. Using a rat sciatic nerve model, Mohammadi et al [43] demonstrated that topical application of dexamethasone to transected nerve ends placed within a silicone tube resulted in enhanced functional recovery. In another study by Sun et al [29] using a rat sciatic nerve injury model, simultaneous administration of dexamethasone and vitamin B_{12} enhanced axon regeneration of myelinated nerve fibers and improved sciatic functional index (SFI) scores and sensory nerve conduction velocity [29].

Establish Contact Between Severed Nerve Ends

Severed nerve ends must be in proximity for contact between regenerating axons and distal segment axons to occur. This will be performed with microsuture repair with a silicone tube. The proximal and distal transected nerve ends will be inserted into the silicone tube and secured to the tube with microsuture (eg, 10-0 nylon) to guide regenerating axons to the distally transected nerve end. The epineuria of the proximal and distal ends will be sutured directly to the ends of the silicone tube.

Silicone is nonabsorbable and impermeable to large molecules, which is ideal for controlling and manipulating the local microenvironment [7,44]. This controlled microenvironment has been useful to study the effects of growth factors on nerve regeneration by adding various growth factors within the tube between the transected nerve ends. For the purposes of this study, the silicone tube will surround and protect the transected nerve ends to establish a calcium-free microenvironment and minimize calcium-induced neurotoxicity.

Altogether, these medications and interventions will be used in order to prevent WD, enhance axon regeneration, prevent myelin obstruction, and limit the immune response (Table 1).

Table 1. Interventions and evidence.

Goal and intervention class	Intervention	Author	Experimental model	Dose or concentration	Route of administration	Main outcome (improvement vs control)
Prevent AAD[a] or WD[b]						
Antioxidant	Ascorbic acid (vitamin C)	Calixto et al [24]	Mouse sciatic nerve cut	2.5 mg	Oral mixed in water	Immunofluorescent neurofilament staining (WD delayed 7 days vs 3 days)
Metabolic demand	Cryotherapy	Sea et al [23]	Rat ventral tail nerves cut	13 °C	Local (water-cooled tail cuff)	Electron microscopy (intact distal axon at 10 days vs 3 days)
Enhance axon regeneration						
Calcium-dependent	Nimodipine	Scheller and Scheller [26]	Human peripheral facial nerve paresis	360 mg	Oral	Clinical evaluation (House-Brackmann 150% improvement)
Antioxidant	Cyanocobalamin (vitamin B_{12})	Sun et al [29]	Rat sciatic nerve	2 mg/kg	Injection to injury site	Sciatic functional index (recovered 48% vs 38% at 28 days vs control)
Prevent myelin obstruction	LPC[c]	Hall [39]	Mouse sciatic nerve	10 mg/mL	Perineural injection	Myelin dissolved within 30 minutes (N/A[d])
Limit the immune response						
Immunosuppressants	Dexamethasone	Feng and Yuan [42]	Rat sciatic nerve crush	1-2 mg/kg	Intraperitoneal	Gait and histology (improved ~40%)

[a]AAD: acute axon degeneration.

[b]WD: Wallerian degeneration.

[c]LPC: lysophosphatidylcholine.

[d]N/A: not applicable.

Methods

Experimental Goals and Design

The goal of this experiment is to determine if spontaneous axon fusion occurs under the proper conditions. The proposed novel nerve repair protocol will aim to promote axolemmal-axolemmal contact between regenerating axons and intact distal segment axons. Preoperative interventions include administration of multiple medications, such as nimodipine, cyanocobalamin, ascorbic acid, and dexamethasone, which have all been shown to delay WD or enhance axon regeneration. Intraoperative interventions include hypotonic calcium-free saline, ethylene glycol tetraacetic acid (EGTA), and application of a silicone tube to establish a favorable calcium-free microenvironment to delay WD and prevent formation of reactive oxygen species. In addition, LPC will be injected into the distal severed nerve end to dissolve the myelin sheaths that prevent axolemmal-axolemmal contact. Postoperatively, the drug cocktail will be continued until the end of the experiment at 42 days to allow for adequate time for regenerating axons to contact the distal segment axons. Further, cryotherapy in the form of ice packs will be applied immediately postoperatively and continued for 42 days to delay WD and increase the likelihood of axolemmal-axolemmal contact. This study will be concluded

at 42 days based on previous studies that demonstrated a plateau of SFI recovery after peripheral nerve repairs [14].

Study End Points and Modalities

Three study end points will be assessed. The primary objective will be to determine whether axon auto-fusion occurred. This will be analyzed by the electrophysiological conduction of compound action potentials (CAP) and compound muscle action potentials (CMAP). As a secondary end point, this study will assess whether axolemmal-axolemmal contact was achieved by viewing transmission electron microscopy (TEM) cross sections and sagittal sections of the distal segments of axons at different time points. Another secondary end point is the assessment of functional recovery using the SFI. SFI is a standardized gait analysis protocol frequently used to assess functional outcomes after sciatic nerve injury [14,45,46].

Study Groups and Sample Sizes

This experiment will require the use of 36 rats. The negative control group will consist of 12 rats that will undergo sciatic nerve transection and standard microsurgical nerve repair with microsutures. The experimental group will be 24 rats that will undergo standard microsurgical nerve repair of a severed sciatic nerve with the addition of the preoperative, intraoperative, and postoperative interventions outlined in the novel nerve repair

protocol. For the experimental group, 4 rats will be assigned to the behavior group for analysis and will undergo SFI testing preoperatively and postoperatively. For the negative control group, 2 rats will be assigned to the behavior group for analysis and will undergo SFI testing preoperatively and postoperatively. This makes for a total of 6 rats needed for behavioral analysis. For the experimental group, 4 rats will be assigned to electrophysiologic and morphologic analysis at each time point by re-exploring nerve repair sites on postoperative day (POD) 3, 7, 14, 21, and 42, for a total of 20 rats. The negative control group will be set up correspondingly for the electrophysiologic and morphologic analysis groups, except half as many rats will be used. This makes for a total of 10 rats needed for the negative control group and 20 rats needed for the experimental group. For the negative controls, more than one rat for each group will be used in case there are any unexpected issues that arise in one rat.

This study will not have a true control group consisting of unoperated rats. This is because this is a pilot study and axon regeneration after sciatic nerve transection has been thoroughly studied. The negative controls and experimental groups will be compared with unoperated animals in studies performed by Mikesh et al [14] and Ghergherehchi et al [45].

Rats in the negative control group will have their sciatic nerves transected and repaired with microsutures. None of the other interventions described in our protocol will be used for the negative control group. The reason for the negative control group is to compare the results of microsuture repair, the current gold standard repair in the absence of a nerve gap, with this novel repair protocol. This study will assess the outcomes of the proposed nerve repair protocol to the current gold standard microsuture repair.

For both the negative control and experimental groups, there will be two separate groups, the behavioral group and the electrophysiology and morphological analysis group. The behavioral groups will be studied using the SFI to determine functional outcomes after the standard nerve repair or the novel nerve repair protocol. The behavioral group will not be euthanized until POD 42. The electrophysiology and morphological analysis groups will be divided into 5 separate groups (POD 3, 7, 14, 21, and 42). Each group will undergo reoperation on their respective postoperative day from the initial operation in order to perform electrophysiological testing. After electrophysiology is performed, the entire sciatic nerve will be harvested for morphological analysis. Once the sciatic nerve is harvested, these rats will be euthanized. A schematic of the protocol methods is summarized in Figure 1.

Figure 1. Experimental and negative control groups. The left flowchart represents the behavioral group breakdown and the right flowchart represents the negative control group breakdown. In both experimental and negative control groups, there will be behavioral and electrophysiological/morphological groups. In the electrophysiological/morphological groups, re-exploration and analysis will be performed on postoperative days 3, 7, 14, 21, and 42. SFI: sciatic functional index.
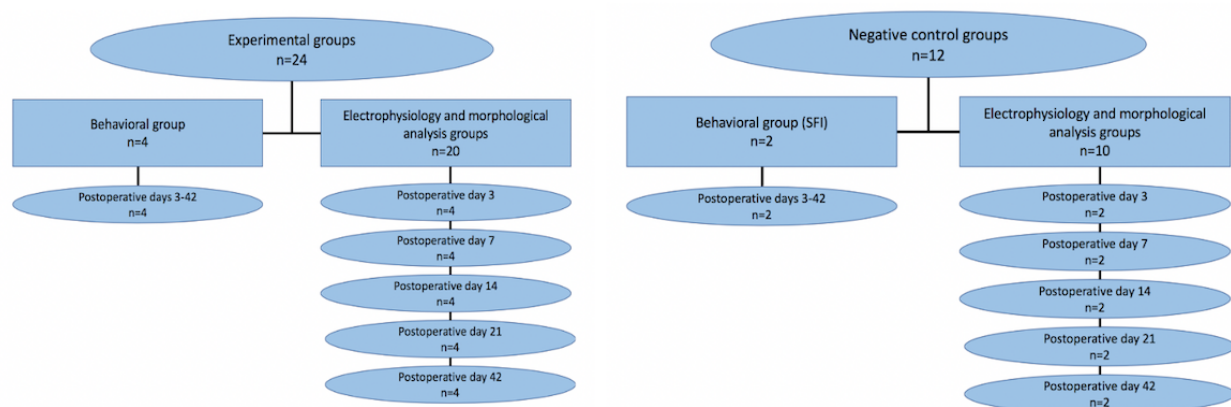
Protocol

The first part of the protocol will involve preoperative administration of medications, which will start 2 days before the surgical intervention. These medications will continue 42 days after the operation until the conclusion of the study. For the surgical protocol modified from Mikesh et al [14] and Ghergherehchi et al [45], anesthesia will be induced with intraperitoneal injection of ketamine (90 mg/kg) and xylazine (10 mg/kg) [14,45]. The lateral aspect of the left hindlimb will be trimmed and disinfected with 10% povidone-iodine. A 2- to 3-cm incision will be made above the thigh muscle in the left hindlimb of each rat. The biceps femoris muscle will be split in parallel to the muscle fibers with dissection scissors. The sciatic nerve will be trimmed with microdissection scissors to remove any connective tissue. The sciatic nerve will be

stimulated to confirm that it can conduct action potentials. The exposed sciatic nerve will be bathed with sterile Plasma-Lyte A (Baxter Healthcare Corp), a calcium-free hypotonic saline solution to prophylactically reduce calcium-induced acute axon degeneration (AAD) that occurs after cut severance. The exposed nerve ends will be bathed in 5-mmol/L EGTA in distilled water to prophylactically chelate extracellular calcium and reduce AAD that occurs after cut severance. Noncrushing double approximating Acland clamps will be applied to proximal and distal ends of the sciatic nerve prior to cut severance to prevent nerve retraction and mechanically create a complete membrane seal to prevent calcium-induced neurotoxicity. Each clamp will be applied 1 cm away from the transection site. Cut severance will be performed by completely transecting the sciatic nerve with a single stroke of dissection scissors to completely sever all the peripheral nerve axons. LPC will be

applied to the distal nerve end to dissolve the myelin sheath to allow regenerating axons to contact distal segment axons. Using a micromanipulator, the 1-μm tip of a micropipette will be introduced into the fiber bundle beneath the epineurium and the volume of solution contained within the tip will be injected (about 0.0002 mL) by applying slight positive pressure to the syringe plunger [39]. The silicone tube will be placed to protect and align the severed proximal and distal nerve ends. The ends of the nerves should be in contact within the silicone tube, and 10-0 nylon microsutures will be used to secure the silicone tube to the nerve ends. When suturing the nerve to the silicone tube, the needle will be inserted into the epineural sheath using microneedle holders to avoid axonal damage. Multiple silicone tubes will be available with the proper length and diameter to fit the rat sciatic nerve. The double approximating clamps will then be released. Throughout the procedure, the nerve ends will be moistened with calcium-free solution and EGTA. Skin over the lesion site will be closed with sutures and surgical staples.

The behaviorally studied rats will be given a 5 mg/kg subcutaneous injection of ketoprofen after surgery. Immediately after closure, continuous cryotherapy using ice packs will be applied to the left leg distal to the transection site and secured with surgical tape. A diagram of the protocol is demonstrated in Figure 2.

For rats undergoing electrophysiologic and morphological analysis, nerve repair sites will be re-explored on POD 3, 7, 14, 21, and 42. Electrophysiological tests will be performed first to assess nerve continuity (see "Electrophysiological Testing" section below). After electrophysiological recordings are performed, the entire sciatic nerve will be removed. This will be used for morphological analysis by electron microscopy (see "Morphological Analyses of Sciatic Nerves" section below). For the electrophysiologic and morphological analysis groups, postoperative euthanasia will be performed for the POD 3, 7, 14, 21, and 42 experimental group animals after reoperation and harvesting of the sciatic nerve (Textbox 1).

Figure 2. Novel nerve repair protocol. This image compares the usual course of nerve transection (on the left) with the theoretical benefits of the novel nerve repair protocol if fusion occurs (on the right). In (b), note that calcium influx after transection leads to acute axon degeneration, which is noted in (c). Also in (c), membrane seals begin to form (black circles). In (d), axon regeneration begins in the proximal segment. In (e), Wallerian degeneration occurs and regenerating axons regenerate within Schwann cell tubes. In (f), the preoperative interventions have been administered and double approximating clamps (gray vertical lines) are applied to the proximal and distal nerve ends, which will act to seal the axolemmal membranes and prevent further axon degeneration. In (g), the silicone tube is sutured in place after nerve ends have been rinsed with calcium-free saline. If mammals possess the machinery necessary for auto-fusion under the proper conditions, axon continuity could theoretically be restored with return of function, as represented by (h) and (i).
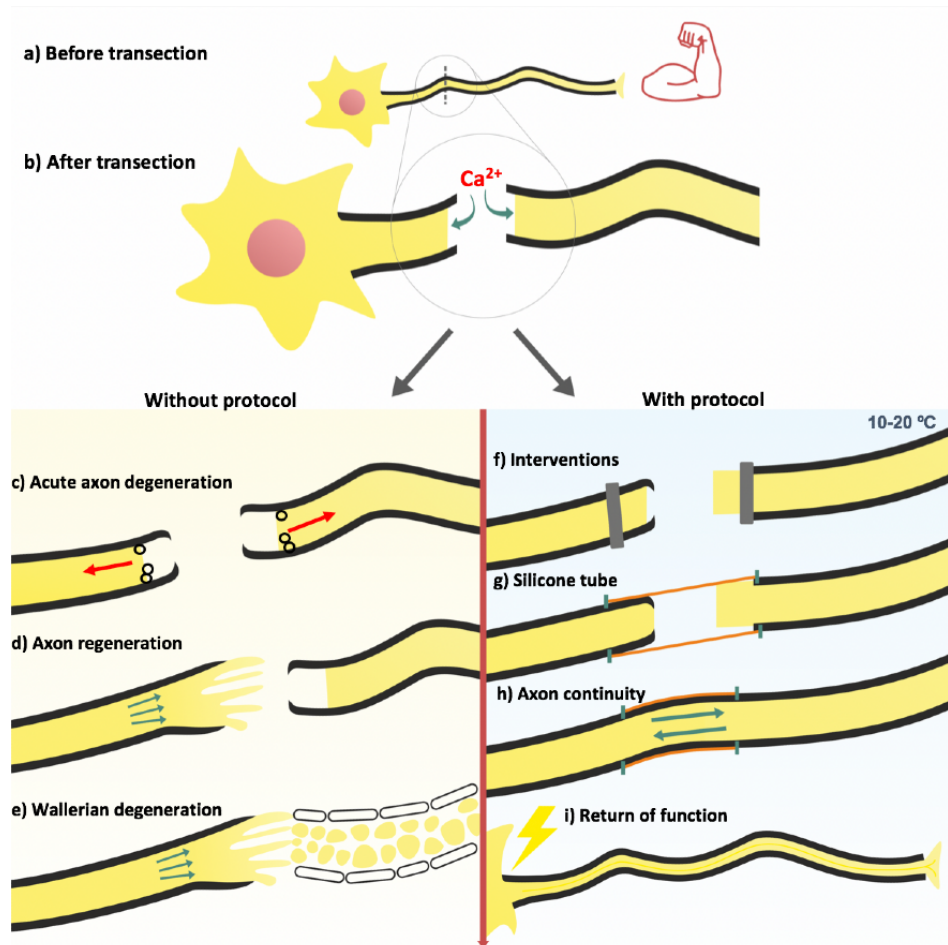
Textbox 1. Novel nerve repair protocol.

Preoperative interventions

- Administer nimodipine 6 mg/kg, gastric gavage once daily (then continue for 44 days)

- Administer cyanocobalamin 1 mg/kg, intraperitoneal injection once daily (then continue for 44 days)

- Administer ascorbic acid 2.5 mg, intraperitoneal injection once daily (then continue for 44 days)

- Administer dexamethasone 1 mg/kg, intraperitoneal injection once daily (then continue for 44 days)

Intraoperative interventions

- Expose sciatic nerve with standard microsurgical technique for primary nerve repair

- Confirm sciatic nerve can conduct action potentials by measuring the presence of compound action potentials and compound muscle action potentials

- Bathe exposed nerve in hypotonic calcium-free saline

- Apply noncrushing double approximating Acland clamps to proximal and distal end prior to cut severance

- Apply lysophosphatidylcholine to the distal nerve end using a 1-μm micropipette tip

- Apply a silicone tube and reapproximate nerve ends with 10-0 nylon microsuture

- Release double approximating clips

- Close surgical site

Postoperative interventions

- Continue medications (started preoperatively) until postoperative day 42

- Start cryotherapy (10-20 C) and continue until postoperative day 42

- Rats will undergo electrophysiological and morphological analysis by re-exploring nerve repair site on postoperative day 3, 7, 14, 21, and 42

- Behavior analyses by sciatic functional index scores will be performed until postoperative day 42

Electrophysiological Testing

Electrophysiological testing will be performed during the initial surgery before and immediately after transection. Electrophysiological testing will be identical to the protocol from Mikesh et al [14] and Ghergherehchi et al [45]. It will also be performed on reoperation for the electrophysiological and morphological analysis study groups on POD 3, 7, 14, 21, and 42 [14,45].

Morphological Analyses of Sciatic Nerves

The sciatic nerves will be removed from the electrophysiological and morphological analysis groups on POD 3, 7, 14, 21, and 42 after electrophysiological testing. Morphological analysis will be similar to the protocol from Mikesh et al [14] and Ghergherehchi et al [45]. Nerve fiber diameter and composition will be assessed in the experimental group and compared with the control group. Additionally, qualitative slide analysis will be performed to assess contact of regenerating axons with intact distal axons using TEM.

Behavior Analyses

Functional recovery of the sciatic nerve in rats will be assessed using SFI scores identical to the protocols from Mikesh et al [14] and Ghergherehchi et al [45]. SFI testing will be conducted by individuals blind to which procedure the rat has received. Animals will first be tested 3 days after surgery, then at POD 7, 14, 21, 28, 35, and 42. A successful recovery is qualified as a score of –59 or better at any time point.

Individual discrepancy can be minimized by using the behavioral analysis protocols outlined by Ghergherehchi et al [45]. This algorithm requires training the behaviorally tested animals for at least one week prior to surgery in order to acclimate the rats to the testing procedures. In practice, the left hindlimb will always be referred to as the experimental (injured) limb. Both hind paws will be dipped in blue (left) or red (right) ink. The rat will then be placed on a wooden board (100 mm in width) lined with white paper strips (100 mm in width) and permitted to run back to their home cage. A trial attempt without any stopping or hesitation during at least three consecutive footprints of both the left and right hindlimb will be considered acceptable as a preprocedure control for later comparison, and the paper strip will be collected for measurements. The normal footprint length, experimental footprint length, normal toe spread, experimental toe spread, normal intermediary toe spread, and experimental intermediary toe spread will be measured in millimeters for all footprints [14,45]. These values will be averaged among the 3 footprints for each limb. Each rat will run 2 trials, and the average will be documented as the SFI score for that rat for that day.

Cryotherapy

Immediately after surgical closure, continuous cryotherapy will be applied with ice packs and surgical tape to the left hindlimb distal to the transection site. Skin temperature will be monitored every 6 hours with a digital thermometer. The target temperature range will be between 10 and 20 °C. The ice packs will be continued for 42 days in order to maintain the target skin

temperatures. Skin checks will be performed daily to ensure that there are no freeze burns to the skin. The ice will be crushed and wrapped in plastic wrap in order to fit the operated leg.

Statistical Analysis

As outlined in Mikesh et al [14], Excel (Microsoft Corp) will be used to calculate means, linear regressions, and *t* test comparisons. A 2-tailed Student *t* test will be used to compare mean SFI scores for each treatment group on a given postoperative day. Two-way analyses of variance will be performed to analyze means and standard errors of SFI scores [14,45-47]. CAPs and CMAPs will be recorded as all or none on a binary scale to assess restoration of axon continuity. TEM will be used to demonstrate whether axolemmal-axolemmal contact has been established and will also be recorded as a binary "yes" or "no."

Data Monitoring

Dedicated staff will collect and monitor data according to the study protocol and scheduled assessments. Data queries will be addressed as needed.

Results

The author is currently in the process of obtaining institutional review board approval. After setup, the study period will take 44 days to complete. The projected completion date, including data analysis and manuscript writing, is December 2021.

Discussion

Contribution to the Literature

The use of PEG fusion has demonstrated that restoring axon continuity and preventing WD alone is not sufficient to regain preinjury function after PNI. This is likely due to the nonspecific fusion of axons that occurs with PEG fusion [4,14]. This begs the question as to whether fusion with high specificity would theoretically restore preinjury function after PNI. More studies will be needed to determine if this is the case. In our study, if fusion does occur, this would reveal that mammals do possess the molecular machinery necessary for auto-fusion and that this mechanism is only expressed under the proper conditions. If auto-fusion is possible, further experiments could be developed to address questions regarding specificity and whether there is mechanistic overlap with fusion, as is demonstrated by *C elegans*. The author believes that these important outstanding questions should be addressed experimentally before determining that mammals do not express the machinery necessary for auto-fusion, especially given the potential benefits to patients that experience PNI. Additionally, if mammalian

peripheral axon auto-fusion occurs, further studies could assess if these mechanisms are present in the central nervous system and could be directed to improve outcomes after brain and spinal cord injuries.

Potential Adverse Outcomes and Preventative Measures

There is always a potential that the protocol could worsen axon regeneration and functional outcomes compared with the standard microsuture nerve repair. One factor that may impair functional recovery is experimentally delaying WD. It is important to note that although preventing WD is necessary for auto-fusion, it is detrimental and inhibitory to axon regeneration. Therefore, if fusion does not occur, axon regeneration may be negatively impacted. This outcome will be monitored with SFI testing in the negative control group, as described earlier.

Limitations

Because there are multiple mechanisms involved in axon regeneration and WD, the author believes it is important to provide multiple medications and interventions to address the different pathways. This type of study design inherently introduces confounding variables. However, the author believes that addressing each mechanism simultaneously is essential to providing the conditions necessary to achieve the goals outlined by this protocol.

This study does not address nerve gaps. Nerve gaps are common after PNI in humans, as separated nerve ends retract after transection. These are often treated with nerve conduits, allografts, or autografts [48]. This study focuses on sharp nerve lacerations with minimal to no gap between nerve ends. Nerve gaps will need to be addressed in additional future studies.

Data are lacking in higher mammals such as primates and humans for the interventions outlined in this protocol, which is another limitation of this study. The majority of research has been performed on mice, rats, and a few invertebrate species, such as *C elegans*.

Conclusion

Outcomes after peripheral nerve injuries and nerve repair are poor. More research needs to be done to improve nerve repair protocols. In this study, the efficacy of a proposed novel peripheral nerve repair protocol will be evaluated using behavioral and electrophysiological parameters. The author believes this study will provide information regarding whether spontaneous axon fusion is possible in mammals under the proper conditions. If successful, this information could potentially be translated to clinical trials to improve outcomes after peripheral nerve injury.

Conflicts of Interest

None declared.

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Abbreviations

AAD: acute axon degeneration
CAP: compound action potential
CMAP: compound muscle action potential
EGTA: ethylene glycol tetraacetic acid
LPC: lysophosphatidylcholine
PEG: polyethylene glycol
PNI: peripheral nerve injury
POD: postoperative day
RLN: recurrent laryngeal nerve
SFI: sciatic functional index
TEM: transmission electron microscope
WD: Wallerian degeneration

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Protocol

Usability Methods and Attributes Reported in Usability Studies of Mobile Apps for Health Care Education: Protocol for a Scoping Review

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Abstract

Background: E-learning technologies, including mobile apps, are used to a large extent in health care education. Mobile apps can provide extendable learning environments and motivate students for adaptive and collaborative learning outside the classroom context. Developers should design practical, effective, and easy-to-use mobile apps. Usability testing is an important part of app development in order to understand if apps meet the needs of users.

Objective: The aim of this study is to perform a scoping review of usability methods and attributes reported in usability studies of mobile apps for health care education.

Methods: The scoping review is guided by the methodological framework developed by Arksey & O'Malley and further developed by Levac et al and Kahlil et al. The stages we will follow are as follows: (1) identifying the research question; (2) identifying relevant studies; (3) selecting studies; (4) charting the data; and (5) summarizing and reporting the results. We have developed two research questions to meet the aim of the study, which are as follows: (1) What usability methods are used to evaluate the usability of mobile apps for health care education? and (2) What usability attributes are reported in the usability studies of mobile apps for health care education? We will apply a comprehensive search of the literature, including 10 databases, a reference search, and a search for grey literature. Two review authors will independently screen articles for eligibility.

Results: The initial electronic database searches were completed in March 2019. The literature search identified 14,297 unique references. Following title and abstract screening, the full texts of 369 records were obtained. The scoping review is expected to be completed in spring 2021.

Conclusions: We expect the overview of usability methods and attributes reported in usability studies of mobile apps for health care education to contribute to the knowledge base for researchers and developers. It will give an overview of the research field and provide researchers and developers with relevant and important information on the usability research area, including highlighting possible research gaps.

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Introduction

Background

There has been increasing attention for e-learning technologies, including mobile apps, in health care education. Mobile apps can provide extendable learning environments and motivate students for adaptive and collaborative learning outside the classroom context [1,2]. However, mobile apps have small screen sizes and connectivity problems, and the context provides distractions for the user [3]. Developers of mobile apps need to ensure that apps are practical, effective, and easy to use [1]. Usability testing is important in app development in order to understand how mobile apps meet the needs of users [4]. According to the International Organization for Standardization (ISO), usability is defined as "The extent to which a system, product, or service can be used by specified users to achieve specified goals with effectiveness, efficiency, and satisfaction in a specified context of use" [5].

Usability Methods

Usability methods, which are currently referred to in usability studies, involve laboratory experiments and field studies [1,6]. There are advantages and disadvantages for both methods. Laboratory experiments take place in a usability laboratory, where the test procedure is conducted in a controlled environment. In a laboratory, researchers can record user activity while they fulfil predefined tasks for later analysis [6], and they can control other irrelevant variables [3]. It is however not possible to test real-world problems (eg, only brief episodes of available time during clinical placement) or problems with internet connection. The expense of instruments and dedicated space make laboratory experiments more costly than other methods [6]. Field studies involve the collection of real-time data from users performing tasks in the real-world environment. In field studies, data about task flows, inefficiencies, and the organizational and physical environments are collected [6]. Field studies allow for data collection within the dynamic nature of the context, which is almost impossible to simulate in a laboratory experiment [1]. However, as users move around in field studies, data collection and conditions are difficult to control [1]. It can also be challenging to collect data in a precise and timely manner [7].

Usability Attributes

Usability attributes are features used to measure the quality of mobile apps [1]. The three most common usability attributes are effectiveness, efficiency, and satisfaction [3], and all three are part of the ISO standard for usability [5]. Other attributes are learnability, memorability, errors, simplicity, comprehensibility, and learning performance [7]. Selecting appropriate usability attributes depends on the nature of the e-learning technology and the research question of the usability study [7]. It is unclear which usability attributes are most relevant to mobile apps for health care students, although Sandars [8] highlighted the following four main domains for usability testing of e-learning: the learner, technological aspects (navigation, learnability, accessibility, consistency, and visual design), instructional design aspects (interactivity, content and resources, media use, and learning strategy design), and the context.

Previous reviews on usability methods examined usability testing in general [9] or usability specifically related to mobile apps [3,6,7,10]. Only one systematic review specifically explored the usability of mobile learning apps [1], although it did not include studies from health care education. Thus, there is a need for an overview of studies reporting on usability evaluations of mobile apps related to health care education. The aim of this study is to perform a scoping review of usability methods and attributes reported in usability studies of mobile apps for health care education.

Methods

Overview

A scoping review summarizes and disseminates research findings to describe the breadth and range of research in a particular topic or field [11-13]. To address the objectives of this scoping review, we will follow the framework for scoping reviews developed by Arksey & O'Malley [11], which was further developed by Levac et al [12] and Kahlil et al [13]. We will adopt the following five stages of this framework: (1) identifying the research question; (2) identifying relevant studies; (3) selecting studies; (4) charting the data; and (5) summarizing and reporting the results [11-13]. A detailed presentation of each step is provided below. This scoping review will also follow the PRISMA-ScR checklist for reporting scoping reviews [14].

Stage 1: Identifying the Research Question

Research questions in a scoping review are broad and have a goal to summarize the breadth of the evidence, although the research questions should include a clear scope of inquiry [12]. We have developed two research questions to meet the aim of the study, which are as follows: (1) What usability methods are used to evaluate the usability of mobile apps for health care education? and (2) What usability attributes are reported in usability studies of mobile apps for health care education?

Stage 2: Literature Search (Identifying Relevant Studies)

The term usability is defined and used in multiple ways, making it hard to develop a comprehensive search strategy for the term. Using a broader search may be preferable [15]. Therefore, the sensitivity (finding as many relevant articles as possible) of the search is prioritized over the specificity (making sure retrieved articles are relevant), as recommended in order not to miss any relevant articles [16].

We will search the following 10 electronic databases covering technology, education, and health care: Engineering Village (Elsevier), Scopus (Elsevier), ACM Digital Library, IEEE Xplore, Education Resource Information Center (ERIC) (EBSCOhost), PsycINFO (Ovid), CINAHL (EBSCOhost),

Medline (Ovid), Embase (Ovid), and Web of Science (Clarivate Analytics). The database searches will be updated before final analysis. The search strategy has been developed in cooperation with a research librarian at Western Norway University of Applied Science. The search string has been peer reviewed by another research librarian, according to the Peer Review of Electronic Search Strategies (PRESS) [17]. A comprehensive search strategy combining text and mesh words relating to health care students and mobile apps was developed. The Boolean operator OR will combine words of similar meaning and the Boolean operator AND will combine searches with words of different meanings. The search strategy for PsycINFO is presented in Multimedia Appendix 1. We will tailor the search strategy to the other databases and present it in our scoping review.

We will browse OpenGrey for grey literature. We will perform a citation search in Google Scholar for included studies and screen reference lists for possible relevant studies. There will be no language restrictions. Studies from January 2008 to the date the searches are run will be sought. The year restriction has been chosen as mobile apps did not appear until 2008 [18].

Stage 3: Data Selection (Selecting Studies)

The Rayyan online management software [19] will be used for the selection of eligible studies. Based on the inclusion criteria outlined in Textbox 1, two authors will independently screen the titles and abstracts of studies retrieved from the searches to identify eligible studies We will include research articles of both quantitative and qualitative designs within the area of health care professional education. Commentaries, discussion papers, book editorials, and conference abstracts will be excluded. Moreover, studies relating to learner management systems, e-learning platforms, open online courses, or distance education will be excluded. Studies will be screened in full text, if one reviewer decides to include it. The full text of these potentially eligible studies will be retrieved, imported to the EndNote X9 reference management system [20], and independently assessed for eligibility by two review authors. Any eligibility disagreements will be resolved through discussion or with a third reviewer. A flow chart of the study selection process will be presented.

Textbox 1. Study eligibility.

Inclusion criteria

Population: Studies reporting on health care and allied health care students at the undergraduate and postgraduate levels.

Concepts: Studies of usability testing or usability evaluation methods of mobile apps, where the purpose is related to development of the apps. The usability attributes include effectiveness, efficiency, satisfaction, learnability, memorability, errors, simplicity, comprehensibility, and learning performance of the learning app.

Context: Typical educational settings (eg, classroom teaching, clinical placement, and simulation training).

Stage 4: Charting the Data

A standardized prepiloted data extraction form will be used to extract characteristics and data from the included studies. One review author will extract the data from the included studies, which will be checked by another review author. A combination of Microsoft Excel software [21] and NVivo 12 [22] will be used to facilitate this process. Discrepancies will be identified and resolved through discussion or with a third author when necessary.

The process of extracting information from the included studies in a scoping review is an iterative approach [12,13]. This means that we will extract predefined themes, although other relevant information may be included later in the process. Extracted information related to the purpose of the scoping review will include the following:

(1) Study: author(s) name(s), year of publication, title, country, publication journal, study setting, study design, research question, and research methods

(2) Population: number of participants, description of participants, and education level

(3) Concepts: usability methods, usability attributes, modes of delivery, usability phase, materials, procedures, type(s) of location(s), number of usability testing procedures, and modifications

(4) Context: educational setting

### Stage 5: Summarizing and Reporting the Results

The fifth stage of the scoping review involves summarizing and reporting the results of the included studies [11-13]. The characteristics of each study will be mapped, and a descriptive narrative account will be presented. We will perform a content analysis [23] to map the different usability methods and usability attributes used in the included studies. Tables and graphical illustrations will be used to bring together and present the usability methods and attributes.

Ethics

This protocol for a scoping review does not require ethical approval or consent to participate. The data consist of data from published articles and do not include individual data.

Results

The electronic searches for eight of the databases were completed on March 5, 2019. The literature search identified 14,297 unique references (Figure 1). Owing to the sensitivity of the search, many of these references were irrelevant and excluded. Following title and abstract screening, full texts of 369 records were obtained. Our next step is to assess these references for eligibility.

Figure 1. Flow chart of the search results and screening process.
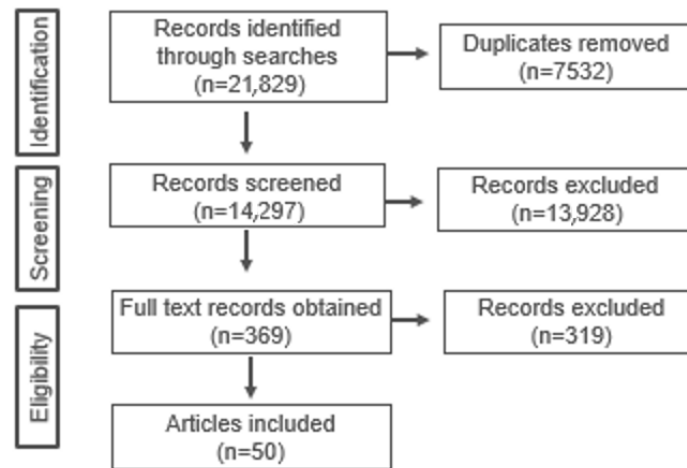
Discussion

Usability Studies of Mobile Apps for Health Care Education

The increasing acceptability and use of mobile apps in the health care education context can lead to improved learning outcomes. However, in order to make learning tools relevant to students, mobile apps must meet the expectations of users [4]. To our knowledge, no overview exists on usability studies of mobile apps for health care education. The results of this scoping review will provide valuable information to developers of mobile apps for health care education, as it will point to relevant usability methods and attributes. Furthermore, the review will identify areas where further research is needed.

A strength of this study is the broad search strategy. We searched ten different databases, and the search strategy was designed in collaboration with a research librarian and was peer reviewed by another research librarian. The search has a time restriction from 2008, but no language restriction. The time restriction was set from 2008, as mobile apps appeared in 2008. A broad search strategy may be associated with lower precision, making it challenging to retrieve relevant articles. We did however experience some challenges with the initial database searches. The authors and research librarians had little experience with databases in academic areas outside health care (eg, Engineering Village and Scopus). "Usability" was not used as a term in the search strategy, as studies on usability do not necessarily refer to or use the term usability. Designing an effective search strategy that balances sensitivity and precision was demanding. Consequently, the search was challenging to narrow, and the search yielded 14,297 unique hits. To ensure that members of the review team had a similar understanding of the inclusion and exclusion criteria, efforts were made to calibrate our screening. Reporting methodological rigor and transparency in a scoping review is of importance to the trustworthiness of the research [24]. Publishing a protocol of the scoping review will support the transparency of the methodology and will assist in the conduction of the scoping review. Following the reporting guidelines for scoping reviews (PRISMA-ScR) [14] will help ensure the methodological quality of the scoping review.

Conclusion

This scoping review will advance the field of mobile app development for health care education by presenting advice on the relevant usability methods and attributes to study. It will give an overview of the field and provide researchers and developers with relevant and important information on the usability research area, including highlighting possible research gaps.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search string for PsycINFO.
[DOCX File , 17 KB - resprot_v9i8e19072_app1.docx]

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Abbreviations

ISO: International Organization of Standardization

Digital Mental Health Resources for Asylum Seekers, Refugees, and Immigrants: Protocol for a Scoping Review

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Abstract

Background: Asylum seekers, refugees, and immigrants experience a number of risk factors for mental health problems. However, in comparison to the host population, these populations are less likely to use mental health services. Digital mental health approaches have been shown to be effective in improving well-being for the general population. Thus, they may provide an effective and culturally appropriate strategy to bridge the treatment gap for these populations vulnerable to mental health risks.

Objective: This paper aims to provide the background and rationale for conducting a scoping review on digital mental health resources for asylum seekers, refugees, and immigrants. It also provides an outline of the methods and analyses, which will be used to answer the following questions. What are the available digital mental health resources for asylum seekers, refugees, and immigrants? Are they effective, feasible, appropriate, and accepted by the population? What are the knowledge gaps in the field?

Methods: The scoping review methodology will follow 5 phases: identifying the research question; identifying relevant studies; study selection; charting the data; and collating, summarizing, and reporting the results. Searches will be conducted in the following databases: EBSCOhost databases (CINAHL Plus with Full Text, MEDLINE with Full Text, APA PsycArticles, Psychology and Behavioral Sciences Collection, and APA PsycInfo), PubMed, and Scopus. Additionally, OpenGrey, Mednar, and Eldis will be searched for gray literature. All primary studies and gray literature in English concerning the use of information and communication technology to deliver services addressing mental health issues for asylum seekers, refugees, and immigrants will be included.

Results: This scoping review will provide an overview of the available digital mental health resources for asylum seekers, refugees, and immigrants and describe the implementation outcomes of feasibility, acceptability, and appropriateness of such approaches for those populations. Potential gaps in the field will also be identified.

Conclusions: As of February 2020, there were no scoping reviews, which assessed the effectiveness, feasibility, acceptability, and appropriateness of the available digital mental health resources for asylum seekers, refugees, and immigrants. This review will provide an extensive coverage on a promising and innovative intervention for such populations. It will give insight into the range of approaches, their effectiveness, and progress in their implementation. It will also provide valuable information for health practitioners, policy makers, and researchers working with the population.

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Introduction

Background

It is well acknowledged that in comparison to host populations, asylum seekers, refugees, and immigrants are less likely to use mental health services [1-3]. Some of the reasons for their low use of mental health services are language and cultural barriers, low level of mental health literacy, concerns of stigma, experience of shame, and lack of culturally appropriate service models. Digital mental health approaches have gained much attention in the last couple of decades due to their potential cost-effectiveness, flexibility, and wide-reaching ability [4]. They may thus provide a promising strategy to bridge the treatment gap for such populations.

People have many reasons for migrating to a different country; some are volitional (immigrants), and some are forced (refugees and asylum seekers). People who voluntarily move to live away from their birth country are defined as first-generation immigrants. In the literature, second-generation immigrants can sometimes be defined as those born in the host (new) country with at least one parent born overseas or with both parents born overseas. The scoping review will adopt the latter, stricter, definition of second generations as that used in the Australian 2001 Census report [5]. An asylum seeker is a person looking for protection and resettlement in a foreign country due to fear of persecution, or because they have experienced violence or human rights violations. Those who have received protection are given refugee status [6]. The review will assess the scope of the literature on digital mental health resources for asylum seekers, refugees, and first- and second-generation immigrants living in both English and non-English–speaking countries. Henceforth, the term immigrants will be used to include both first- and second-generation immigrants. The term migrant refers to individuals who have moved away from their habitual place of residence, including movement within a country. However, for the purpose of this article, the term "migrant" will be used when referring to asylum seekers, refugees and immigrants, as a whole; it will apply only to those who have moved across international borders.

Mental health outcomes for migrants depend on multiple interacting factors, such as migration status (eg, refugee, asylum seeker, and immigrant), migration experience (pre-migration, during, and post-migration settlement factors), ethnicity or country of birth, and the host country of residency. Therefore, the prevalence of mental health outcomes for migrants is highly variable across studies [1,2]. However, there is more consistency in findings regarding the risk factors for poor mental health outcomes for migrant populations. Low socioeconomic status, poor language proficiency, experiences of intergenerational conflict, acculturation stress, racism, and perceived discrimination are some of the common factors associated with psychological distress. Particularly for refugees and asylum seekers, experiences of war, abuse, trauma, and detention centers increase the risks for developing mental health problems [3,7].

Digital Mental Health

Digital mental health is a relatively new concept coined around the early 2000s [8]. It describes the use of information and communication technology (ICT) to deliver mental health services for health promotion/psychoeducation, prevention/early intervention, crisis intervention/suicide prevention, treatment, recovery and mutual/peer support [9]. Some examples are smartphone app-based intervention, treatment delivered via video/teleconference, online support, and telephone crisis lines. It is important to note that although the present study uses the term "digital mental health," many other terms are used in the literature to describe the use of technology for such purposes, including e-health, e-mental health, telemedicine, and telepsychiatry. Several systematic reviews have shown the approach to be as effective as the traditional methods of care in promoting mental health and well-being in general population [10-12]. Therefore, digital mental health approaches may offer an innovative avenue to provide mental health services to a hard-to-reach population such as asylum seeker, refugee and immigrant populations.

Currently, there is no scoping review to provide an overview of the available digital mental health resources for migrant populations. One systematic review examined the efficacy of telepsychiatry for the refugee population and concluded that the intervention may be as effective as a traditional treatment [13]. Given that digital mental health resources cover a wide range of approaches (eg, smartphone apps, self-help, or clinician-guided online therapy), it would be useful to know what the available resources for migrant populations are and whether they are effective and can be successfully implemented. This information would benefit researchers to address research and treatment gaps, enhance or develop new interventions, and help health professionals and policymakers to provide culturally appropriate and effective services.

Goal of This Study

This protocol describes the methods and processes that will be used to conduct a scoping review, which aims to provide an overview of the available digital mental health resources that are used with migrant populations worldwide. The review will aim to answer the following research questions: (1) What are the types of digital mental health resources that are available for asylum seeker, refugee, and immigrant populations? (2) Are these resources effective, feasible, appropriate, and accepted by the population? (3) What are the knowledge gaps in the field? A preliminary search for the existing scoping reviews and systematic reviews on the topic was conducted on February 12, 2020, using the following databases: Cochrane Database of Systematic Reviews, PubMed, and JBI Database of Systematic Reviews and Implementation Reports. No scoping review was found, and only 1 systematic review was found [13]. This scoping review will thus be the first to provide an overview of the available digital mental health resources for refugee and immigrant populations and the implementation outcomes of those resources (eg, feasibility, appropriateness, and acceptability).

Methods

Protocol Development

The protocol is developed based on the scoping review framework proposed by Arksey and O'Malley [14] and the

enhancements proposed by Peters et al [15]. It involves the following 5-stage process: (1) identify and align the study's objective and research questions; (2) develop and align the inclusion criteria with the objectives and research questions to help identify relevant studies; (3) develop a systematic approach to evidence searching, selection, extraction, and charting; (4) chart the data from selected studies; and (5) summarize the evidence in relation to the research objective and questions. The recommendations of the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) are provided in Multimedia Appendix 1. We have not registered the document with PROSPERO, as scoping reviews are currently ineligible for registration in the database.

Inclusion Criteria

Type of Studies

The term "e-health" was first used at the 7th International Congress on Telemedicine and Telecare in London, at the end of November 1999 [8]. Telemedicine, one of the first aspects of ehealth was first entered into the Medical Subject Heading (MeSH) list of the National Library of Medicine in 1990. Therefore, we will include all primary studies published in English from January 1, 1990, to December 31, 2019. We will aim to include all studies conducted worldwide. However, we are limited to those published in English, as it is the only common language across the authors of this paper. All research designs will be included, although opinion pieces and reviews will only be used for reference searching and will not be included in outcome analyses. If full studies are not available, they will be requested from the corresponding author. When a full report is unobtainable, we will include published abstracts if there is sufficient information to assess study eligibility. Gray literature will also be included.

Participants

Studies that report on migrant populations (ie, asylum seekers who live outside their country of citizenship, refugees, and first- and second-generation immigrants) will be included. As previously mentioned, second-generation immigrants are those with both parents born overseas. Thus, the included studies will be those reporting on samples that meet one of the following criteria: (1) born in a country different from their residential country and (2) have both parents born in a country different from the person's residential country. Populations that are not considered as refugees or immigrants such as internal migrants, host populations, and indigenous populations will be excluded.

Intervention

All types of digital mental health approaches that use ICT to deliver services targeting mental health issues for migrant populations will be included. These include the following interventions: internet-based interventions, gamification-based interventions, email, videoconferencing, telephone interventions, mobile app-based interventions, virtual reality, and any other digital devices used to address mental health. The devices can be used for delivering services of mental health promotion/psychoeducation, prevention/early intervention, crisis intervention/suicide prevention, treatment, recovery, and mutual/peer support. Technologies used to assess an individual's

mental health outcomes as part of service delivery will be included. However, assessments carried out via digital technology for the purpose of assessing population-based mental health outcomes (eg, establishing prevalence of mental health illness in a population) will be excluded. Additionally, technology used for sending appointment reminders and communication of test results will also be excluded.

Comparators

Studies may or may not include comparison of processes or outcomes against other types of interventions, traditional methods of mental health services, or matched control groups. Given that comparators and control groups may vary significantly across the selected studies, we will note whether comparator groups are included and will describe them in detail.

Outcomes

We will include all outcome measures of mental health/social and emotional well-being to examine the effectiveness of digital mental health approaches in promoting migrant populations' mental health. The language and validity of the measures used with the population will also be noted. The implementation outcomes, specifically those of feasibility, appropriateness, and acceptability for the population will be included. Outcomes not related to mental health/social and emotional well-being (ie, medical/physical health outcomes) will be excluded.

Search Methods for Identification of Studies

Search Strategy

A 3-step search strategy, as recommended by the Joanna Briggs Institute [16], will be used. First, at least 2 independent reviewers will conduct an initial limited search of the 3 databases relevant to the topic (EBSCOhost databases, PubMed and Scopus). Text words contained in the title, abstract, and index term of the retrieved articles will be assessed for additional relevant keywords. The reviewers will then discuss and finalize the keywords to be used for the second search, which will be conducted by at least 2 reviewers independently, across the following databases: EBSCOhost databases (CINAHL Plus with Full Text, MEDLINE with Full Text, APA PsycArticles, Psychology and Behavioral Sciences Collection, APA PsycInfo); PubMed; and Scopus. The key words will also be searched in OpenGrey, Mednar, and Eldis for gray literature. Lastly, the reference list from relevant articles chosen for potential inclusion, opinion pieces, and review studies will be handsearched to identify further relevant studies. The corresponding authors will be contacted for the full article or further information, if required. The search strategies for the 3 databases: EBSCOhost databases, Scopus, and PubMed are presented in Multimedia Appendix 2.

Study Selection

At least 2 reviewers will independently apply the inclusion and exclusion criteria to the title and abstract of the studies retrieved through the search strategy. The inclusion criterion is the use of ICT to deliver services targeting mental health problems for migrant populations. The services provided can be for mental health promotion/psychoeducation, prevention/early intervention (including an individual's mental health assessment), crisis

intervention/suicide prevention, treatment, recovery, and mutual/peer support. Exclusion criteria are as follows: population not from refugee and immigrant backgrounds; interventions not related to mental health and well-being (ie, those for physical health); and ICT used for population-based mental health assessment and for sending notifications purposes.

The full text of the articles meeting the inclusion criteria at the title and abstract level will then be retrieved, read, and assessed by at least 2 independent reviewers. The following data will be extracted: demographic information of the population; the type of the digital mental health approach; the measures used to assess mental health and social and emotional well-being; the measures' outcomes; and the digital mental health approach's

outcomes with respect to its feasibility, appropriateness, and acceptability. The studies will also be assessed for exclusion criteria as described above. If there is any disagreement, a third reviewer will be asked to review the article. Corresponding authors of the studies will be contacted if further clarifications are needed. Decisions and reasons for exclusions will be documented. Endnote X9 (Clarivate Analytics) will be used to manage references throughout the process.

Data Extraction

At least 2 independent reviewers will use a standardized data collection form to collect relevant data (Textbox 1) from each study. Corresponding authors will be contacted for missing data.

Textbox 1. Data to be extracted from selected studies.

- Study citation details: authors, date, title, journal, volume, issue, and pages.

- Country of origin (where the study was conducted).

- Study's aims/objective/purpose.

- Study's design.

- Specific details of the study's sample if available (age; sex; ethnicity; country of birth; year of arriving in the host country; first- or second-generation immigration; languages spoken; immigration status, eg, refugee, asylum seeker; and sample size).

- The type of digital mental health intervention (eg, smartphone app, online support, online therapy, or website).

- The type of mental health services: mental health promotion/psychoeducation, prevention/early intervention, crisis intervention/suicide prevention, treatment, recovery, and mutual/peer support.

- Mode of delivery: self-guided, clinician supported, or both.

- Mental health and well-being outcomes (effectiveness of the intervention) and details of how they were measured (ie, quantitatively or qualitatively, which language was used, whether a translator was used, and whether the measurement method has been validated for that specific population).

- Outcomes of the intervention's feasibility, acceptability, and appropriateness for the population.

Charting the Data

Simple descriptive tables will be used to report basic information of the selected studies (ie, citation, objectives, the sample's demographic information, and relevant findings/outcomes). Thematic analysis as outlined by Braun and Clarke [17] will be used to identify categories and central themes from the literature review. No complex statistical analyses such as meta-analyses will be performed. This is because the review aims to be inclusive and will broadly describe the literature, and intervention outcomes may be too heterogeneous for such rigorous analyses. Reported outcomes will be extracted, analyzed separately, and compared across migrant groups (asylum seekers, refugees, first- and second-generation immigrants).

Results

The scoping review will provide an overview of the digital mental health resources available for migrant populations and will describe implementation outcomes with respect to their feasibility, acceptability, and appropriateness for different populations. Therefore, data on the breadth of digital mental health interventions addressing migrant populations and their

effectiveness, feasibility, appropriateness, and acceptability will be extracted, analyzed, and presented according to Arksey and O'Malley's [14] methods of reporting. A narrative thematic summary of the data will also be presented, and gaps in the literature will be highlighted.

Discussion

This scoping review will provide a comprehensive overview of the available digital mental health resources for migrant populations and summarize the outcomes in this field in terms of their effectiveness, feasibility, acceptability, and appropriateness for different migrant populations. This information will benefit policymakers, researchers, and service providers working with people from migrant backgrounds. It can be used to inform future policies and strategies for bridging the treatment gap for this population vulnerable to mental health risks. It will also provide evidence for potentially effective and culturally appropriate approaches for service providers to use or recommend. Moreover, since this scoping review is first of its kind in this research field, it will highlight important gaps in the literature, providing guidance and directions for future research.

Authors' Contributions

BR designed and wrote the manuscript. HM and TH helped design and edit the manuscript. KG and TN provided advice, reviewed, and revised the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P checklist for systematic reviews.
[PDF File (Adobe PDF File), 375 KB - resprot_v9i8e19031_app1.pdf]

Multimedia Appendix 2
Study search strategy.
[PDF File (Adobe PDF File), 589 KB - resprot_v9i8e19031_app2.pdf]

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Abbreviations

ICT: information and communication technology
MeSH: Medical Subject Heading
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols

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<u>Protocol</u>

Citizen-Patient Involvement in the Development of mHealth Technology: Protocol for a Systematic Scoping Review

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Abstract

Background: The development of mobile technology for information retrieval and communication, both at individual and health organizational levels, has been extensive over the last decade. Mobile health (mHealth) technology is rapidly adapting to the health care service contexts to improve treatment, care, and effectiveness in health care services.

Objective: The overall aim of this scoping review is to explore the role of citizen-patient involvement in the development of mHealth technology in order to inform future interventions. By identifying key characteristics of citizen-patient involvement in system development, we aim to improve digital communication and collaboration between health care providers and citizen-patients, including sharing of health care data.

Methods: The systematic scoping review will follow the Joanna Briggs Institute methodology for scoping reviews by searching literature in 3 steps. We will include literature reporting on the public, citizens, and patients participating in the development of mobile technology for health care purposes in MEDLINE, CINAHL, Scopus, EMBASE, and ProQuest Dissertations and Theses. A preliminary search was completed in MEDLINE and Scopus. The screening process will be conducted by 2 of the authors. Data will be extracted using a data extraction tool prepared for the study.

Results: The study is expected to identify research gaps that will inform and motivate the development of mHealth technology. The final report is planned for submission to an indexed journal in November 2020.

Conclusions: To our knowledge, this review will be the first review to provide knowledge about how citizen-patients participate in system developments for mHealth tools and the value that such involvement adds to the system development process.

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Introduction

Background

The development of mobile technology for information retrieval and communication, both at individual and organizational levels, has been extensive over the last decade. Electronic or digital technology is rapidly adapting to both mobile platforms and health care service contexts to improve treatment, care, and effectiveness in health care services. These technologies are sometimes referred to as telemedicine, health information systems, and, more recently, eHealth [1,2]. Mobile health (mHealth) technology has emerged from eHealth as mobile technological platforms expand for wireless web-based communication and are designed and developed in an appropriate mHealth interface context [3,4]. As mHealth is still quite new, there are few definitions of the concept [5]; all of the definitions describe the relationship or extension of mHealth from eHealth. The World Health Organization introduced this definition: "Mobile Health (mHealth) is an area of electronic health (eHealth) and it is the provision of health services and information via mobile technologies such as mobile phones and Personal Digital Assistants (PDAs)" [6]. mHealth platforms include tablet PCs and mobile smartphones. Programs or apps are being developed for these platforms and transformed through a new interface from existing eHealth applications or developed as new technologies. The use of such mobile apps makes access to health care information and communication unbound by time or place and potentially available for citizens and patients. The use of mHealth might be to improve or support health care or treatment for citizens, both within the public health domain and for marketing and sale in a commercial market [7,8]. Health care apps that are easily accessible to citizens and patients are generally welcomed and promoted by health authorities [9,10]. On the other hand, digital technology available for citizen-patients has not always been a success for end users. Both the lack of appropriate user interfaces and economic barriers have, until recently, also restricted the system adoption [11].

Political movements have, for several decades, influenced a demand for and the development of democratization and individualization in public policy in Western countries, which has also influenced health care service towards patient-empowered services [12,13]. mHealth development has further prompted new directions in health care policy. Health care models like person-centered health care emphasize a patient- and user-centered approach, regarding the patient or citizen as an equal or even dominant party to the care being offered [14,15]. Citizens are unlikely to assume a traditional passive patient role in which the health care provider (HCP) is the indisputable authority that is not open to argument [12,16]. The internet facilitates knowledge about health conditions and makes opportunities for communication potentially available to the public. There is now more opportunity for patients to influence health care [17]. Thus, the use of mHealth apps allows for the opportunity to support citizen-patient involvement and patient empowerment on health-related issues, even though many eHealth applications still lack a focus on patient involvement and empowerment [2,18]. The design and

development process for new apps might take political influence into account by understanding the importance of including the public and patients in their development processes and mapping and meeting their needs, including system functionality and interface requirements [19,20]. On the other hand, in spite of public trends and politics as we describe, new technologies may still be launched with little or no citizen-patient involvement in the system development phases, hitting the user's needs by chance or by parameters other than user participation strategies, as shown by Risling and colleagues [2]. Citizen-patient involvement may be emphasized for political as well as commercial reasons. However, if a tool developed is not used or if a system vendor does not hit the core target for requirements and needs of the public, commercial success will not be possible [21,22]. From a political viewpoint, a health care authority would benefit from citizen-patient involvement by reaching their target groups, if only for the purpose of improving health conditions in the population. Here, citizen-patient involvement may also be a matter of democracy and further empowerment, that is, being involved as a citizen [23,24].

There are many ways to involve system end users methodologically in the design and development process of digital technology. These methods can involve working with users directly in the requirements identification phase, through evaluation of prototypes, and through user evaluation and testing of the finished product [25]. The outcomes from both commercial and political strategies for citizen-patient involvement in system development and system use are expected to increase empowerment of the public as a whole. Any citizen involved in the use and development of the actual mHealth tools will likely experience empowerment. The successful use of mHealth relies on whether people want to, like to, and are able to use the apps offered [26-28].

A preliminary search in *JBI Database of Systematic Reviews and Implementation Reports*, Cochrane, MEDLINE, and Scopus returned a handful of reviews and review protocols covering the scope of mHealth [7,29-33]. The majority of the studies focused on technological issues or mHealth used for or by specific patient groups or medically diagnosed groups. An example of a technological approach is seen in the paper by Silva et al [7], which presents a methodological review that summarizes the state of the art of mHealth solutions. Silva et al [7] show the top mHealth apps available in the market in 2015 and discuss future strategies in mHealth development. Iribarren and colleagues [30] focus on text-messaging intervention platforms for mHealth applications. They also highlight the knowledge necessary for the development of technology that integrates text messaging in health intervention and research. Further, they discuss the advantages and disadvantages of the included platforms. Shah and Chiew [32] analyze design and usability of mobile apps for pain management but not if and how users were involved in the development of these mobile tools. Vo et al [33] focus on the strengths and weaknesses of the use of mHealth apps, showing increased health care engagement and empowerment for patients actively using such apps. Weaknesses found related to trustworthiness, appropriateness, personalization, and

accessibility of the tools. None of the studies identified have citizen-patient involvement in system development as a specific focus area. Our study will differ from existing reviews, as our scope is not limited to patients in illness categories, nor does it limit the use of mHealth to any specified reasons. Specifically, our review will address the role of citizen-patients and their involvement in the development of mHealth.

Aim and Review Questions

The overall aim of the scoping review is to explore the role of citizen-patients in the development of mHealth in order to inform future eHealth interventions. By identifying key characteristics of citizen-patient involvement in system development, we aim to improve digital communication and collaboration between HCPs and citizen-patients, including sharing of health care data.

Our review questions include the following: (1) How is the concept of citizen-patient involvement defined in the literature? (2) What research methods are used in the involvement of citizen-patients in the development of mHealth? (3) What are the advantages, disadvantages, and added value of citizen-patient involvement in the development of mHealth? (4) What are the challenges of involving citizen-patients in the different stages of the mHealth development process? and (5) What types of mHealth are identified in the literature?

Inclusion and Exclusion Criteria

Participants

The review will consider papers that include the public or citizens in general and patients or users in particular having access to mHealth technology, including (1) citizens and patients across their lifespan, (2) citizens as patients, (3) citizens and patients using mHealth, (4) citizens as next of kin in their participation in the development or use of mHealth, and (5) citizens and patients participating in the development of mHealth.

For some patient groups, next of kin, spouses, significant others, children, or parents will be users of such technology because of the context or age of the patient. Examples include young children and older or cognitively impaired adults in need of assistance who make use of mHealth. Only studies that include citizens acting as private persons will be included in our study. In other words, HCPs or stakeholders participating in the development of mHealth technology will be excluded.

Concept

The concept of the papers included in this review is the involvement of the public, citizens, and patients in system design or system development of mHealth technology.

Context

The context of the papers included in this review is any demographic or geographic setting, in accordance with the worldwide use of mobile phones and other mobile platforms.

The same mHealth apps may be available in different health care situations, providing information on a general basis everywhere. The study will consider the inclusion of any setting where citizen-patients contribute to system development of mobile apps for health information both as receivers and senders. We aim to describe how, when, or in which stages of the development processes participation takes place.

Types of Sources

We plan to include scientific peer-reviewed studies, dissertations, and conference proceedings. All scientific research approaches and types of scientific study design will potentially be included in this review. The study might also include opinion papers from scientific journals but will not include magazines or newspapers due to the anticipated large number of papers and low level of scientific validity. mHealth is quite new and is a rapidly evolving technology. Because of this, the review will not restrict its search for papers by year of publication. Studies in Scandinavian languages, English, and German will be examined for inclusion.

Methods

In an effort to assist in standardizing the conduct and reporting of scoping reviews, as proposed by Tricco et al [34] and supported by the Joanna Briggs Institute, the systematic scoping review will follow the template of the Joanna Briggs Institute methodology for scoping reviews [35,36].

Search Strategy

Following the Joanna Briggs Institute methodology for systematic scoping reviews [35], we will review literature according to the inclusion criteria in 3 steps.

First, we will conduct an initial search to explore terms and keywords for the searches.

Second, the identified terms and keywords will be applied to searches across the chosen databases, and the results will be systemized.

Third, the reference lists from all the identified papers will be examined in order to reveal additional material not found in the second step of the search. Literature will be included or excluded according to the aim and the inclusion criteria of our review.

Information Sources

The information sources in this systematic scoping review will include MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Scopus, EMBASE, and ProQuest Dissertations and Theses. Keywords for the initial search and the strategy for searching is shown in an example from two of the selected databases, MEDLINE and Scopus, in Table 1. The first four example searches in Table 1 show the initial search strategy, and the fifth search is the combination of searches.

Table 1. Preliminary search on Scopus and MEDLINE.[a]

Search number	Query	Results on MEDLINE	Results on Scopus
1	Patient(s)[b] OR user(s) OR citizen(s) OR citizen patient(s)	6,795,125	9,986,893
2	Patient(s) participation[b] OR Community participation[b] OR Crowdsourcing[b] OR participation OR involvement OR engagement OR patient and public involvement OR PPI OR patient(s) involvement/engagement OR citizen(s) involvement/engagement/participation OR citizen patient(s) involvement/engagement/participation OR public involvement/engagement/participation OR user involvement/engagement/participation OR community involvement/engagement	683,863	1,245,902
3	Community-based participatory research[b] OR Citizen science[b] OR system development OR system design(s) OR system analyse/analysis OR participatory design OR participatory research OR development OR co-design OR community system(s)	2,134,092	6,914,266
4	Telemedicine[b] OR Mobile application(s)[b] OR Cell phone(s)[b] OR Medical informatics[b] OR Medical informatics application(s)[b] OR Health information exchange[b] OR Medical informatics computing[b] OR mHealth OR eHealth OR electronic health OR mobile health OR health technology OR health informatics OR mobile phone(s) OR smartphone(s) OR mobile phone app(s) OR mobile health app(s) OR smartphone app(s) OR cell phone app(s)	95,279	266,291
5	#1 AND #2 AND #3 AND #4	1048	2433

[a]Ovid MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions 1946 to May 15, 2020.

[b]Medical subject heading term.

Study Selection and Extraction

The Rayyan online software platform (Qatar Computing Research Institute) will be used to facilitate the entire screening process [37,38]. We will use the bibliographic system Endnote X9 (Clarivate Analytics) to collect and upload all identified citations. Duplicates will be removed. Titles and abstracts of the papers of current interest will then be assessed independently by 2 reviewers against the inclusion and exclusion criteria listed above. The assessment will be documented, guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses template for flows of inclusion [39]. Potential papers for inclusion will undergo the same procedure, being assessed in detail against the inclusion criteria by 2 independent reviewers. Reasons for exclusion of studies will be recorded and reported in our scoping review publication. Data will be extracted from included papers by the use of a data extraction tool developed for the review study. Data to be extracted are shown in Textbox 1. The data extraction tool may be modified and revised during the data extraction process and eventual changes will be described in the final report. The extracted data will include relevant details about the population, concept, context, study methods, and key findings.

Textbox 1. Data to be extracted.

Study design

- Authors

- Year

- Country

- Aim of the study

- Population/participants involved

- Data collection methods

- System development methods

Study context and concept

- Context of system development

- Intervention/type of system development

- Scale/size and duration of development project

- Stage of participation in system development

- Identified outcomes: challenges, values, advantages, and disadvantages

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Any disagreements between the reviewers during the screening process will be resolved through discussion or by involving additional reviewers. The reviewers may also contact authors of papers to request missing or additional data.

Results

The extracted data will be presented to align with the objective of this systematic scoping review by using diagrammatic or tabular forms. The report will also include a narrative summary to accompany the tabulated or charted results in order to relate to the review's objective. These collated results will finally be presented in a systematic scoping review publication. This systematic scoping review protocol was first initiated by Nord University in October 2018. The study is undertaken without any external funding. We commenced preliminary data collection in January 2019, which was updated in April 2020. We expect the final results to be submitted in a systematic scoping review in November 2020.

Discussion

Contribution to mHealth Development

The results from this scoping review will aim to inform a variety of stakeholders, including authorities and vendors, about involving citizen-patients in the development of mHealth. Such knowledge may improve the development process and results for future mHealth. The review may also inform authorities about the possible success of their mHealth strategies and the effects of involving citizen-patients in the development processes on the achievement of their goal [6]. The results from the review might also address any challenges explored in involving citizen-patients in mHealth development processes. Identified knowledge from this review would be valuable for future projects to improve any citizen-patient involvement in the development of mHealth technology processes instead of such involvement being minimized or downgraded. When researchers consider applying strategies like participatory design or participatory action research in their projects by actively involving citizen-patients, knowledge from the review may inform their research protocols and add value to their results.

Conclusion

To our knowledge, this review will be the first systematic scoping review to provide knowledge about how citizen-patients participate in system developments for mHealth technology and the value that such involvement adds to the system development process. We aim to find answers to the review questions from the results of our analysis. This review will also seek to identify further research gaps and possible needs for further systematic reviews.

Conflicts of Interest

None declared.

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Abbreviations

CINAHL: Cumulative Index to Nursing and Allied Health Literature
HCP: health care provider
mHealth: mobile health

Protocol

An Employment Intervention Program (Work2Prevent) for Young Men Who Have Sex With Men and Transgender Youth of Color (Phase 1): Protocol for Determining Essential Intervention Components Using Qualitative Interviews and Focus Groups

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Abstract

Background: HIV continues to have a disparate impact on young cisgender men who have sex with men (YMSM), young trans women (YTW), and gender-nonconforming (GNC) youth who are assigned male at birth. Outcomes are generally worse among youth of color. Experiences of discrimination and marginalization often limit educational attainment and may even more directly limit access to gainful employment. Though seemingly distal, these experiences influence young people's proximity to HIV risk by limiting their access to health care and potentially moving them toward sex work as a means of income as well as increased substance use. Work2Prevent (W2P) aims to achieve economic stability through employment as a structural-level intervention for preventing adolescent and young adult HIV infection. The study will pilot-test an effective, theoretically driven employment program (increased individual income and independence [iFOUR]), for HIV-positive adults, and adapt it to the needs of black and Latinx YMSM, YTW, and GNC youth aged 16 to 24 years who are vulnerable to HIV exposure.

Objective: This paper aimed to describe the protocol for the exploratory phase of W2P. The purpose of this phase was to determine the essential components needed for a structural-level employment intervention aimed at increasing job-seeking self-efficacy and career readiness among black and Latinx YMSM, YTW, and GNC youth aged 16 to 24 years.

Methods: The exploratory phase of the W2P study consisted of in-depth interviews and focus groups with members of the target community as well as brief interviews with lesbian, gay, bisexual, transgender, and queer (LGBTQ)–inclusive employers. The study team will conduct in-depth interviews with up to 12 YMSM and 12 YTW and GNC youth, up to 10 focus groups with a maximum of 40 YMSM and 40 YTW and GNC youth, and up to 40 brief interviews with LGBTQ-inclusive employers.

Participants will be recruited through a community-based recruiter, passive recruitment in community spaces and on social media, and active recruitment by research staff in community spaces serving LGBTQ youth.

Results: In-depth interviews were conducted with 21 participants, and 7 focus groups were conducted with 46 participants in total. In addition, 19 brief interviews with LGBTQ-inclusive employers were conducted. The analysis of the data is underway.

Conclusions: Preliminary findings from the formative phase of the study will be used to inform the tailoring and refinement of the iFOUR adult-based intervention into the youth-focused W2P intervention curriculum. Perspectives from YMSM, YTW, GNC youth, and LGBTQ-inclusive employers offer a multidimensional view of the barriers and facilitators to adolescent and young adult LGBTQ employment. This information is critical to the development of a culturally appropriate and relevant youth-focused intervention.

Trial Registration: ClinicalTrials.gov NCT03313310; https://clinicaltrials.gov/ct2/show/NCT03313310

International Registered Report Identifier (IRRID): DERR1-10.2196/16384

KEYWORDS

HIV/AIDS; YMSM; YTW; GNC youth; LGBTQ; unemployment; homelessness; sex work

Introduction

Background

In the United States, young cisgender men who have sex with men (YMSM), young trans women (YTW), and gender-nonconforming (GNC) youth who are assigned male at birth experience high rates of HIV infection [1,2]. In 2017, roughly 39,000 people were diagnosed with HIV, with 13- to 24-year-olds representing 21% of all new diagnoses [1]. Among these adolescent and young adult HIV diagnoses, 81% were attributed to male-to-male sexual contact, according to the Centers for Disease Control, and 75% were among black and Latinx youth [1]. Although precise estimates of HIV infection among YTW and GNC youth are sparse, a meta-analysis of 88 studies found that an average of 14% of trans women tested positive for HIV across studies, whereas 16% self-reported a known HIV-positive status [2]. In a separate study of YTW of color, aged 16 to 24 years, Garofalo et al [3] found that 22% of YTW reported being HIV positive, and 59% reported engaging in condomless anal sex in the past year. HIV among YTW, YMSM, and GNC youth is further complicated by high rates of other sexually transmitted infections (STIs), low rates of HIV testing [4,5], high rates of HIV risk behaviors, and poor outcomes at each step of the HIV continuum of care [6-8]. However, for YMSM, YTW, and GNC youth of color, these outcomes are influenced by important social contextual factors, including social isolation, economic marginalization, and unmet HIV-prevention needs [3,9-15]. Addressing the social and structural drivers of HIV risk is critical to decreasing HIV incidence, particularly among YMSM, YTW, and GNC youth of color [16,17]. Phase 2 of this study has also been published [18].

Social and Structural Determinants of HIV Risk

Black YMSM, YTW, and GNC youth between 13 and 24 years accounted for 43% of all new adolescent and young adult HIV diagnoses, whereas Latinx YMSM, YTW, and GNC youth accounted for approximately 21% [1]. Given that census estimates indicate black and Latinx youth of all gender and sexual identities constitute approximately 14% and 23% of the adolescent and young adult population, respectively [19], these young people bear a disproportionate burden of infection. Although individual behaviors play a part in HIV acquisition, these disparities must also be understood in the context of structural factors that place these young people at an increased risk for HIV exposure [3,4,15,20-22]. Black and Latinx YMSM, for instance, have been shown to have lower levels of access than their white peers to pre-exposure prophylaxis (PrEP), an efficacious HIV-prevention medication [23]. Additionally, despite advancements in civil rights for people of color and LGBTQ individuals, LGBTQ people of color continue to face persistent stigma, discrimination, and victimization in school, the workplace, housing, and health care, related to their identities [6,7,24-28].

For YMSM, YTW, and GNC youth of color, experiences of bullying, harassment, and violence may mean that schools are unsafe environments [25,29]. Such social marginalization may force the youth to leave school altogether [25,30,31]. In the 2015 US Transgender Survey, 17% of transgender and GNC respondents indicated that they faced such severe mistreatment that they left a K-12 school, and nearly a quarter of respondents who reported being out or perceived as trans or GNC in college or vocational school had been verbally, physically, or sexually assaulted [26]. Among black respondents, outcomes were worse. Approximately 22% of black respondents had left a K-12 school due to mistreatment, and 10% had been expelled. Black YTW indicated a higher likelihood of having been verbally harassed (67%), physically attacked (55%), and sexually assaulted (38%) because of their trans identity compared with respondents of other genders. The school experiences indicated by YMSM, YTW, GNC youth of color lead to lower educational attainment and place marginalized youths at increased risk for subsequent employment challenges, associated economic instability, and negative health outcomes.

Sexual and gender minority youth of color also contend with additional challenges when seeking employment, including hiring bias, job discrimination, unequal pay, limited benefits, and having less access to tailored career services than their white peers [32,33]. Furthermore, men who have sex with men (MSM), trans women, and GNC individuals of color report having to navigate unwarranted background checks, limited

support in the workplace, and an absence of nondiscrimination laws to protect them from discrimination [32]. As a result, a substantial proportion of YMSM, YTW, and GNC youth of color live in poverty and experience negative structural outcomes, including homelessness, unemployment, and limited access to health care, LGBTQ services, and HIV prevention and care [6,10-14,34].

Faced with limited economic options and protections and often lacking traditional familial support [35,36], some black and Latinx YMSM, YTW, and GNC youth migrate to nontraditional economies as a means of survival. This work may include various forms of cash-for-service work, including unregulated labor, such as cleaning, childcare, or the exchange of sex for money, drugs, or food. A study of trans people living in Washington, DC, found that 76% (n=151) of YTW aged 15 to 24 years reported engaging in sex work, with 35% having done so in the past 3 months [9]. Among HIV-positive YTW, 23% were involved in sex work, compared with 6% who were not [9]. In a large study of YMSM of color (n=3316; median age 19 years), roughly 12% reported engaging in sex work at some point in the past 6 months [37]. Given the illegal nature of this work, migration to these nontraditional economies places black and Latinx YMSM, YTW, and GNC youth at risk for further marginalization and economic instability, should they be arrested. In addition, sex work can place these young people at increased risk for HIV and STIs through an increased number of sexual partners, exposure to higher prevalence sexual networks, and power dynamics that present barriers to negotiating condom use [38-43].

The Role of Structural Interventions in Reducing HIV Risk

Structural interventions facilitate the development of agency by intervening in systems and structures that constrain choice and have the potential to promote the uptake of behavioral and biomedical approaches to risk reduction [16,17]. For example, structural interventions, such as comprehensive sex education and increased health care coverage, have significantly reduced the incidence of HIV [44-50]. Although the impact of structural interventions on HIV incidence may not be seen immediately, these interventions can effect changes in a community's cultural, legal, political, and economic context that may facilitate subsequent reductions in HIV vulnerability [16,17]. Scalable but potentially high impact, structural interventions that trace and disrupt the pathways between social and economic marginalization and adolescent and young adult HIV infection are sorely needed [16,17,34]. However, few structural interventions targeting adolescent and young adult sexual and gender minorities exist, and we know of no studies that have explicitly examined the role of employment on HIV risk and prevention for black and Latinx YMSM, YTW, and GNC youth.

This paper aimed to describe the protocol for the exploratory phase of Work2Prevent (W2P). The purpose of this formative phase of the study is to determine the essential components of an employment intervention aimed at increasing job-seeking self-efficacy and career readiness among black and Latinx YMSM, YTW, and GNC youth aged 16 to 24 years vulnerable to HIV infection. This includes identifying target population

needs, barriers, strengths, preferences, and norms. The findings from this phase will be used to adapt and refine increased individual income and independence (iFOUR), an effective employment workshop series for HIV-positive adults [51], to the needs of YMSM, YTW, and GNC youth of color in Chicago, Illinois.

Methods

Study Design

This exploratory phase of the W2P study consists of in-depth interviews and focus groups with members of the target community as well as brief interviews with LGBTQ-inclusive employers, which will be used to adapt and refine iFOUR [51]. Given the increasing expansiveness of identity labels and expression, the study eligibility criteria pertaining to gender are intentionally broad, including individuals assigned male at birth with a range of gender identities. The study will take place in Chicago, which is the intended site for piloting the resulting intervention.

In-depth, semistructured interviews with YMSM, YTW, and GNC youth will be conducted to assess the individual-, social-, and structural-level factors that influence participants' employment and employment-seeking experiences, career trajectories, and career-related aspirations. Semistructured interviews ranging from 1 to 2 hours will be conducted by trained staff. Sample interview questions include (1) *Please walk me through all of the jobs you've had, starting with your very first paid employment*; (2) *How do you find out about jobs you might want to apply for?* (3) *What kinds of challenges have you faced when starting a new job as a young gay or bisexual man OR trans woman or gender-non conforming youth of color?* (4) *Imagine you could give a younger version of yourself advice around employment. What advice would you give yourself?* (5) *Can you describe any career-related goals you may have? How are you working toward those goals?* (6) *Has anyone helped you with your employment goals? Who were they, and what kinds of support did they provide?* (7) *How do you get by when money is tight?* (8) *Has anything gotten in the way of applying to jobs in the past?* (9) *How do you handle stress-related work or money?* Participants will also complete a short paper survey to capture sociodemographic and behavioral information.

Focus groups with black and Latinx YMSM, YTW, and GNC youth will assess community norms, attitudes, motivations, and perceptions regarding employment. Focus groups are facilitated by trained staff, include 4 to 8 participants, and will range from 1 to 2 hours. Participants will also complete a short paper survey to capture sociodemographic and behavioral information. Focus groups will be separated by self-identity (groups with YMSM and groups with YTW and GNC youth) so that gender-related differences can be explored. Sample focus group questions include (1) *What is the value of having paid employment? What does having a job mean to you?* (2) *What factors most help gay and bisexual men OR trans women and gender-nonconforming youth get and keep jobs?* (3) *What factors prevent gay and bisexual men OR trans women and gender-nonconforming youth from getting and keeping jobs?* (4) *What is a typical job for a young gay and bisexual man OR young trans woman and*

gender-nonconforming youth? Why do you think these jobs are so common? (5) *What makes a work environment LGBTQ-friendly? What could employers do to promote a supportive and safe environment?* (6) *What topics do you think would be important to cover in an employment workshop program for young gay and bisexual men OR trans women and gender-nonconforming youth of color?*

Brief interviews will be conducted with representatives from LGBTQ-inclusive employers to assess employer-level barriers and facilitators to securing and maintaining stable employment for YMSM, YTW, and GNC youth. Short, structured interviews will be implemented by trained staff and range from 10 to 15 min. Participants will also complete a short paper survey to capture information on employer policies and training regarding LGBTQ employees. Sample interview questions include (1) *How do you recruit LGBTQ employees to your organization?* (2) *How do you communicate LGBTQ inclusive policies and benefits to prospective and current employees?* (3) *What barriers to hiring and retaining young gay and bisexual men color, in particular, have you experienced, or have you witnessed?* (4) *What barriers to hiring and retaining young trans women and gender-nonconforming youth of color, in particular, have you experienced or witnessed?* (5) *Can you tell me about a time when an employee at your organization has experienced an incident of antiLGBTQ harassment or conflict? How did you or others at your organization respond?* These data will be analyzed to inform modules in the intervention focused on strategies for selecting and vetting of employers who report being LGBTQ-inclusive.

Study Setting

Interviews and focus groups with YMSM, YTW, and GNC youth will be conducted in a private room on the University of Chicago campus. Interviews with LGBTQ-inclusive employers will be conducted off-site at the employers' facilities or community-based LGBTQ job fairs.

Participants

The study team will conduct in-depth interviews with up to 12 YMSM and 12 YTW and GNC youth and up to 10 focus groups with a maximum of 40 YMSM and 40 YTW and GNC youth in total. Inclusion criteria include (1) being assigned male at birth; (2) identifying as YMSM, YTW, or GNC youth; (3) identifying as African American, black, Hispanic, or Latinx; (4) 16 to 24 years of age; (5) English-speaking; and (6) seeking employment or currently employed.

Additionally, up to 40 interviews with representatives of LGBTQ-inclusive employers will be conducted. Inclusion criteria include (1) being an employer or manager at an LGBTQ-inclusive company, defined as a company with a rating of 80% or higher on the Human Rights Campaign Foundation's Corporate Equality Index, a company currently listed as an Out & Equal, LGBT CareerLink employer, a nonprofit organization with an LGBTQ-focused mission, an LGBTQ-owned small business with <200 employees, or an organization participating in an LGBTQ job fair; (2) being aged 18 years or older; (3) speaking English as a primary language; and (4) located in the Chicago area.

Recruitment

YMSM, YTW, and GNC youth will be recruited to participate in interviews and focus groups by the research staff and study recruiters who are also members of the target population. Focus group and key informant interview participants will be recruited by the study staff through pre-existing network connections, including the Chicago Center for HIV Elimination, and snowball sampling.

LGBTQ-inclusive employers will be recruited actively by the research staff. Planned recruitment strategies include attending LGBTQ job fairs and emailing LGBTQ nonprofits, LGBTQ-owned small businesses, and employers in the Human Rights Campaign Foundation's Corporate Equality Index or Out & Equal, LGBT CareerLink lists.

Compensation

YMSM, YTW, and GNC youth will receive US $40 for participating in the in-depth interviews and focus groups. LGBTQ-friendly employers will be offered a US $10 gift card for completing the brief interview.

Data Collection

All interviews and focus groups will be recorded and transcribed. Transcripts will be subsequently verified and deidentified by the research team. All audio recordings will be destroyed on completion of the study. Surveys are completed on paper and entered into a computer-based data entry system by trained research staff. All data entry will be reviewed by the research team for quality assurance. All study records, including audio recordings, transcripts, and surveys, will be labeled with a unique participant identification number rather than identifying information. Paper records will be securely stored in locked filing cabinets at the University of Chicago. Electronic records will be securely stored in the University of Chicago network and the Sharepoint site for Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) at the University of North Carolina at Chapel Hill.

Analyses

The analytical plan includes a thematic content analysis of the interviews and focus groups and a descriptive statistical analysis of the survey data. The analysis of the interviews and focus groups will proceed in 2 steps. First, open-coding will be conducted by trained qualitative researchers to identify preliminary emergent themes. Next, this open-coding will be used to develop a codebook for the second stage of analysis. For a subsequent qualitative analysis, 2 independent coders will each use the developed codebook to analyze the data, and the coding schema will be compared for interrater reliability using the Cohen kappa coefficient. Given that the data focus on the experiences of individuals at the intersection of multiple marginalized identities, members of the analytic team will consider the roles of their own social locations and the social locations of the YMSM, YTW, and GNC youth of color engaged and discussed in the data [28,52,53]. In addition, the data will be interpreted with respect to the contexts in which these young people live and work, for example, racial, cultural, and socioeconomic contexts [54]. Descriptive statistics will be used to analyze the proportions and central tendencies for the survey

data. All qualitative coding will occur in Atlas.ti 7 (Scientific Software Development) [55], and statistical analysis will occur in SPSS 25 (IBM Corporation) [56].

Refinement and Adaptation of the Intervention

Preliminary analysis of the qualitative data will be used to inform the adaptation and refinement of iFOUR, an existing effective employment intervention curriculum for HIV-positive adults [56]. Curriculum modules will be revised or developed to (1) address the specific needs and barriers highlighted by the youth in the qualitative data; (2) leverage the strengths highlighted by the youth in the qualitative data; (3) include examples that are culturally and developmentally aligned with the experiences described by the youth in the qualitative data; (4) incorporate topics that the youth suggested in the qualitative data; (5) assist the youth in identifying LGBTQ-inclusive employers and navigating their hiring processes based on the insights from the employer interviews. A Youth Advisory Board will also review all existing, revised, and newly developed curriculum material for further tailoring and feedback.

Ethics, Consent, and Institutional Board Approval

The research and procedures presented in this study protocol have been approved by the University of Chicago and the University of North Carolina at Chapel Hill Institutional Review Boards (IRB), IRB 16-1152 and 17-0795, respectively. The National Institute of Child Health and Human Development provided a Certificate of Confidentiality for the study. A waiver of parental consent was obtained for participants aged 16 to 17 years. The study is registered on ClinicalTrials.gov (NCT03313310).

All participants will complete a signed written consent form before participation in interviews or focus groups. This form details information on study procedures, risks, and benefits of participation. As part of the informed consent process, research staff explain the study and consent form to each participant. To ensure comprehension, staff ask participants to summarize the study in their own words before asking them to sign the form. Consent forms are stored securely and will be kept for up to seven years, per our IRB protocol.

Results

In-depth interviews have been conducted with 21 participants between May and November 2017. Seven focus groups were conducted with 46 participants between May and September 2017. In addition, 19 brief interviews with LGBTQ-inclusive employers have been completed in September 2017. A qualitative analysis of the data is underway. Preliminary findings from these data were used to inform the development and refinement of the W2P intervention curriculum. The development of the intervention will be described in a separate manuscript.

Discussion

W2P is a structural-level employment intervention aimed at increasing job-seeking self-efficacy and career readiness among black and Latinx YMSM, YTW, and GNC youth, aged 16 to

24 years. This formative phase is a critical first step in assessing the structural needs of youth populations disproportionately impacted by HIV to optimally tailor structural-level interventions. Although individual-level interventions that target behaviors such as condom and PrEP use play a significant role in the reduction of HIV transmission, such interventions are enacted within a context influenced by social and structural factors. Given the range of barriers that many marginalized individuals experience, intervention at the structural-level can facilitate increased agency over a person's sexual health and associated decision making. W2P seeks to identify and remove barriers to black and Latinx YMSM, YTW, and GNC youth enacting change toward their own success and economic independence and stability.

Data collected in this phase of W2P are critical to adapting the adult-based iFOUR curriculum [49] to black and Latinx YMSM, YTW, and GNC youth. This initial phase of W2P provides clarity on the needs of the population to increase the cultural and developmental appropriateness of the intervention curriculum. Furthermore, interviews and focus groups will allow the team to identify experiences shared across the population to ensure that intervention material, including exercises and examples, are relevant. Participants will also be encouraged to communicate their preferences for an employment intervention if they were to take part in one. Although the formative phase of this project serves an important role, it may not capture nor be able to incorporate all relevant factors into one standalone intervention. Nevertheless, it may generate data that can be used to inform future interventions along with the W2P curriculum. W2P will target key facilitators of job readiness and job-seeking self-efficacy and ultimately assist the youth in securing and sustaining employment. Although identifying support networks to achieve goals is included in the curriculum, the intervention will not necessarily directly engage individuals' support systems. Thus, subsequent social and emotional support informed by data from this exploratory phase of the study may be necessary to augment the core components of the intervention.

The formative work described in this protocol may not be generalizable to the broader LGBTQ youth population. In particular, employment challenges faced by black and Latinx YMSM, YTW, and GNC youth in Chicago may not be representative of nonurban areas. Rural and periurban areas may face geographic challenges, including job scarcity, outsourcing, or erasure of industries, as well as agricultural and seasonal employment, which are beyond individual-level control and ultimately create a different employment landscape compared with the youth in urban settings. Nevertheless, the goal of the intervention design is to address the most pervasive challenges YMSM, YTW, and GNC youth of color face when seeking employment. Additionally, the formative phase of this study may underscore the necessity of additional resources beyond the scope of the intervention. Increased educational attainment such as completing high school or a General Educational Development program, housing stability, and criminal record expungement is strongly linked to employment outcomes but may not be directly addressed in the intervention curriculum. Therefore, providing a network of referral systems

to additional social services and support may be a necessary part of the intervention.

In summary, phase 1 of the development of the intervention will provide the necessary inputs to create W2P, a youth-centered and relevant job readiness and employment intervention. Economic stability and employment play a critical role in mitigating the migration of the youth to nontraditional and unregulated labor economies that are associated with HIV risk and exposure, such as survival sex work. Equipping the youth with the skills and resources to seek and attain employment offers an opportunity to address the social determinants of adolescent and young adult HIV, without explicitly focusing on individual-level sexual risk behaviors. Empowerment models that highlight the social capital and assets of the youth are essential in creating culturally and developmentally appropriate and relevant interventions for vulnerable youth, ultimately increasing uptake and efficacy.

Conflicts of Interest

None declared.

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Abbreviations

ATN: Adolescent Medicine Trials Network for HIV/AIDS Intervention
GNC: gender nonconforming
iFOUR: increased individual income and independence
IRB: Institutional Review Board
LGBTQ: lesbian, gay, bisexual, transgender, and queer
MSM: men who have sex with men
PrEP: pre-exposure prophylaxis
STI: sexually transmitted infection
W2P: Work2Prevent
YMSM: young men who have sex with men
YTW: young transgender women

Protocol

An Employment Intervention Program (Work2Prevent) for Young Men Who Have Sex With Men and Transgender Youth of Color (Phase 2): Protocol for a Single-Arm Mixed Methods Pilot Test to Assess Feasibility and Acceptability

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Abstract

Background: Young cisgender men who have sex with men (YMSM), young transgender women (YTW), and gender nonconforming (GNC) youth of color face substantial economic and health disparities. In particular, HIV risk and infection among these groups remains a significant public health issue. In 2017, 17% of all new HIV diagnoses were attributed to male-to-male sexual contact among adolescents and young adults aged 13 to 24 years. However, such disparities cannot be attributed to individual-level factors alone but rather are situated within larger social and structural contexts that marginalize and predispose YMSM, YTW, and GNC youth of color to increased HIV exposure. Addressing social and structural risk factors requires intervention on distal drivers of HIV risk, including employment and economic stability. The Work2Prevent (W2P) study aims to target economic stability through job readiness and employment as a structural-level intervention for preventing adolescent and young adult HIV among black and Latinx YMSM, YTW, and GNC youth. This study seeks to assess intervention feasibility and acceptability in the target populations and determine preliminary efficacy of the intervention to increase employment and reduce sexual risk behaviors.

Objective: The goal of the research is to pilot-test a tailored, theoretically informed employment intervention program among YMSM, YTW, and GNC youth of color. This intervention was adapted from Increased Individual Income and Independence, an existing evidence-based employment program for HIV-positive adults during phase 1 of the W2P study.

Methods: The employment intervention will be pilot-tested among vulnerable YMSM, YTW, and GNC youth of color in a single-arm pre-post trial to assess feasibility, acceptability, and preliminary estimates of efficacy.

Results: Research activities began in March 2018 and were completed in November 2019. Overall, 5 participants were enrolled in the pretest and 51 participants were enrolled in the pilot.

Conclusions: Interventions that address the social and structural drivers of HIV exposure and infection are sorely needed in order to successfully bend the curve in the adolescent and young adult HIV epidemic. Employment as prevention has the potential to be a scalable intervention that can be deployed among this group.

Trial Registration: ClinicalTrials.gov NCT03313310; https://clinicaltrials.gov/ct2/show/NCT03313310

International Registered Report Identifier (IRRID): DERR1-10.2196/16401

Introduction

Background

Youth assigned male at birth who have male sexual partners, including young cisgender men who have sex with men (YMSM), young transgender women (YTW), and gender nonconforming (GNC) youth, face substantial economic and health disparities. In particular, HIV risk and infection among YMSM, YTW, and GNC youth remains a significant public health problem. In the United States, YMSM, YTW, and GNC youth experience high rates of HIV infection [1,2]. In 2017, 17% of all new HIV diagnoses were attributed to male-to-male sexual contact among adolescents and young adults aged 13 to 24 years [1]. Additionally, 75% of adolescent and young adult HIV diagnoses were among black and Latinx individuals [1]. Epidemiological HIV estimates for transgender populations are limited due to a lack of existing data. However, a meta-analysis of US studies involving trans women found an average HIV prevalence rate of 14% across studies that included laboratory testing [2]. In this meta-analysis, prevalence rates were higher among black trans women at 44% [2].

However, these disparities cannot be understood solely in the context of individual-level risk behavior given that there are multiple social and structural factors that increase risk for HIV exposure and acquisition among YMSM, YTW, and GNC youth of color [3-10]. Despite advancements in lesbian, gay, bisexual, transgender, and queer (LGBTQ) rights, LGBTQ people face persistent stigma, discrimination, and victimization in school, the workplace, housing, and health care [11-14]. Such inequities are met with limited legal protections as few state laws specifically protect LBGTQ people. The consequences of this discrimination and lack of protections may be particularly pronounced for LGBTQ people of color, who face intersectional forms of discrimination and structural marginalization; a high proportion of YMSM, YTW, and GNC youth of color live in poverty; experience high rates of homelessness, unemployment, and violence; and have limited access to HIV and other health and human services [14-20].

Furthermore, these experiences of social and economic marginalization contribute to increased risk for HIV exposure and infection through their impacts on social determinants of health (eg, availability of pre-exposure prophylaxis [PrEP] providers in the community) as well as coping and survival behaviors (eg, substance use, sex work) [14-16,18,20]. In

particular, financial insecurity and socioeconomic disconnection may increase engagement with survival sex work or sex in exchange for money, drugs, food, and housing among YMSM, YTW, and GNC youth of color [21-23]. Engagement with survival sex work can place these individuals at heightened risk for HIV and sexually transmitted diseases (STIs) by increasing exposure to higher prevalence sexual networks, increasing their number of sexual partners, and presenting challenges to negotiating condom use [21-23].

Structural-level interventions have the potential to increase agency in members of marginalized groups and can facilitate health-positive actions that benefit the individual and the community [24]. Often focused on distal drivers of poor health, structural-level interventions can promote uptake of health-positive behaviors and improve access to health-promotive environments [24,25]. Given the ways that economic instability may place YMSM, YTW, and GNC youth of color at higher risk for HIV acquisition, structural intervention to promote economic stability may serve to allow these youth to enact health-promoting behaviors. Accordingly, employment as prevention has the potential to be a scalable intervention that can be deployed among this group. Phase 1 of this study has already been published [26].

Rationale for Employment as HIV Prevention

Faced with few economic options and protections, YMSM, YTW, and GNC youth of color may migrate to nontraditional economies or unregulated work as a means of survival. In a study conducted by Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) members in Los Angeles and Chicago, 76% of 151 YTW aged 15 to 24 years reported engaging in sex work, with 35% in the past 3 months [5]. Among HIV-positive YTW of color living in Washington, DC, 23% were involved in sex work—underscoring the link between adolescent and young adult sex work and HIV exposure [27]. In a large US study of YMSM (N=3316, median age 19 years), roughly 12% reported engaging in sex work in the past 6 months [28]. Sex work and HIV risk are further complicated by drug and alcohol abuse [16]. In order to effectively target economic stability as a route toward reducing HIV risk, there is an acute need for scalable, low-cost but potentially high impact structural-level interventions that address the distal drivers of economic marginalization and adolescent and young adult HIV infection [24,25,29,30]. The objective of the Work2Prevent (W2P) study is to adapt and pilot-test Increased Individual

Income and Independence (iFOUR), an effective, theoretically driven employment program for HIV-positive adults [31-34] to the needs of vulnerable YMSM, YTW, and GNC youth of color aged 16 to 24 years.

Theoretical Framework

The iFOUR intervention draws on the theoretical framework of the health belief model (HBM) [35], a widely used expectancy value model of health behavior change, and the conceptual framework of supported employment (SE), a model in which individuals with physical or intellectual disabilities or impairments, mental health issues, or chronic conditions are assisted with identifying their own capabilities and obtaining employment [36,37]. The objective of the iFOUR intervention is to help HIV-positive individuals identify barriers to obtaining employment, increase the perceived benefits of employment, and assess perceptions of the severity of their illness in order to increase behavioral intentions and self-efficacy for employment. Further, iFOUR participants gain the tools and skills needed to effectively seek, secure, and maintain employment and increase economic independence and stability [31-34].

In order to adapt and tailor the iFOUR intervention to the needs of adolescents and young adults of color, the intervention draws on positive youth development (PYD) in which young people understand, value, and develop external and internal assets such as community support, empowerment to act, clear boundaries, constructive use of time, commitment to learning, positive self-concept, and social and emotional competency [38-40]. PYD approaches orient young people toward future goals,

develop the skills necessary to engage youth in real-world roles and activities, and build or fortify young peoples' relationships with social networks [40]. PYD builds from resiliency research in assuming that all youth are capable of achieving positive health outcomes despite challenges they may face in their environment [38]. The adapted intervention will draw on PYD to provide the support, relationship-building skills, and increased social and emotional competency shown to help youth succeed in employment.

Methods

Conceptual Model

The W2P conceptual model shown in Figure 1 draws on the existing iFOUR theoretical framework to hypothesize the potential relationship between adolescent and young adult employment and HIV risk. The W2P model proposes that employment and subsequent economic connection and stability serve as a structural-level intervention for HIV prevention among adolescents and young adults. The hypothesis is that the adapted and tailored iFOUR intervention will facilitate increased job self-efficacy and job readiness (path A) and ultimately increase employment placement and maintenance (path B). Further, establishing economic stability will decrease engagement in HIV risk behaviors, increase HIV prevention and care (path C), and decrease involvement with known social determinants of HIV such as sex work and substance use (path D), which are directly linked to HIV transmission and acquisition among YMSM, YTW, and GNC youth of color (paths E and F).

Figure 1. Conceptual model.
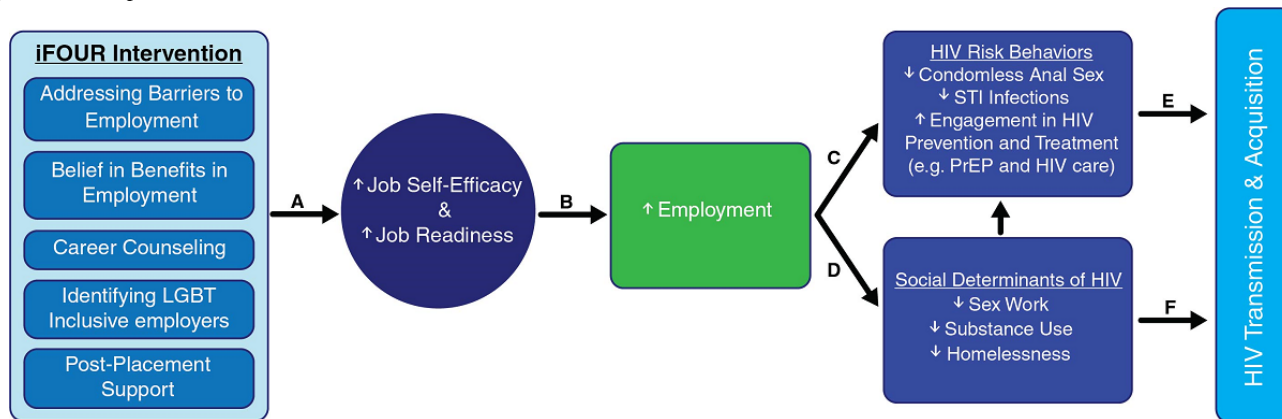
Study Design

W2P uses a mixed-methods design. Phase 1 involves the adaptation of relevant intervention components from the existing evidence-based iFOUR employment program for HIV-positive adults [31-34] to YMSM, YTW, and GNC youth of color. Phase 2, the topic of this paper, consists of pretesting the intervention and study assessments and then running a single-arm pilot test of the adapted intervention to assess feasibility and acceptability with YMSM, YTW, and GNC youth of color, as well as provide preliminary estimates of efficacy using pre-post comparisons.

Ethics, Consent, and Institutional Board Approval

W2P has been reviewed and approved by the University of Chicago institutional review board (IRB# 16-1152). Informed consent for this study is obtained in person by study staff before any study-related activities take place.

Participants and Study Setting

Study participants include up to 75 black or African American and Hispanic or Latinx YMSM, YTW, and GNC youth. Inclusion criteria include (1) being assigned male at birth, (2) reporting ever having sex with men, (3) identifying as African American or black or Hispanic or Latinx, (4) aged 16 to 24 years, (5) self-report HIV negative or unknown status, (6)

English-speaking, (7) currently unemployed but seeking employment or employed only part-time, defined as working 35 hours or less on average per week, and (8) able to attend a 4-session workshop. All study visits are conducted at the University of Chicago Center for Interdisciplinary Inquiry and Innovation in Sexual and Reproductive Health (Ci3).

Recruitment

Planned participant recruitment efforts include the distribution and posting of printed materials such as flyers, hand bills, and branded merchandise; online postings on websites and social media such as Facebook and Twitter; advertisements such as Chicago Transit Authority posters; and chats through the mobile app Jack'd. Study staff will also actively recruit from primary clinics serving YMSM, YTW, and GNC youth such as Howard Brown Health during their youth drop-in programs and at local gathering places and events frequented by the target population such as night clubs, LGBTQ centers, House & Ball events, Black Pride events, Pride Fest, and community outreach HIV testing events. Interested participants complete a prescreen survey to assess eligibility. All interested participants are contacted and informed whether they are eligible. Eligible and interested participants are scheduled for baseline study visits.

Visit Schedule and Data Collection

W2P consists of data collection across 3 time points, at baseline, postintervention, and 8-month postintervention, as referenced in Table 1. A 4-session intervention workshop series occurs between the first and second time points.

Table 1. Study procedures.

Study procedures	Baseline	Intervention	Postintervention	Month 8 follow-up
HIV/STI[a] testing	x			x
Substance use screening	x			x
ACASI survey[b]	x		x	x
Workshop sessions (4)		x		

[a]STI: sexually transmitted disease.

[b]ACASI: audio computer-assisted self-interview.

Incentives

Study participants are offered compensation for their time. Pretest participants may receive up to US $260 total, while pilot-test participants may receive up to US $330 total for complete participation. Participants will receive US $30 for each study visit, completed at baseline, postintervention, and 8-month follow-up, up to US $40 for biological specimens at baseline and 8-month follow-up, if provided, and US $40 for each workshop session attended. Payment is provided in the form of cash or Visa gift card equivalent.

Pretest

Up to 5 participants will be recruited for a pretest of the baseline study visit, the 4-session workshop series, and the postintervention study visit. Pretest participants will not complete the follow-up assessment. The purpose of the pretest is to give study staff an opportunity to familiarize themselves with the study visit procedures and workshop curriculum. The pretest will also allow staff to determine if any final adjustments to procedures, study instruments, or the curriculum are needed prior to full rollout of the pilot testing. Participants who enroll in the pretest are not eligible to participate in the phase 2 pilot.

Baseline

Participants will complete informed consent, confirm eligibility, and then complete an audio computer-assisted self-interview (ACASI) survey using an iPad. Survey items include questions pertaining to demographics, sexual behaviors, HIV-risk behaviors, relationships, employment, income, substance use, and other structural variables such as homelessness, food insecurity, and health care use. Optional biologic samples will be collected from participants who consent to them. These samples include a finger stick for rapid HIV testing using the Determine HIV-1/2 Ag/Ab Combo (Abbott); a urine sample for drug screening, chlamydia, and gonorrhea testing; and anal and oral swabs for chlamydia and gonorrhea testing.

Intervention

Participants complete a 4-session intervention workshop adapted from the existing iFOUR program [31-33]. Session 1 focuses on goal setting and identifying strengths; session 2 on communication, networking, and job searching; session 3 on balancing work with health and wellness; and session 4 on preparing job application materials and interview preparation. This adaptation of the curriculum was informed by interviews and focus groups with the target population as well as feedback from a youth advisory board. The protocol for conducting interviews and focus groups is published elsewhere [26].

Workshops sessions are delivered by two facilitators in groups of 6 to 12 participants across the course of 2 weeks with 2 sessions per week. The W2P Career Readiness Workbook is used as a guide for all workshop sessions and is given to all study participants at the first session. Facilitators use an annotated W2P Facilitator Guide that provides detailed instruction on delivery of the intervention curriculum. During each session, facilitators complete a fidelity assessment to help ensure fidelity to the W2P Career Readiness Workbook and after each session complete a workshop debriefing form to capture any workshop notes or comments.

Postintervention

Once participants complete the workshop sessions, participants complete a postintervention ACASI survey using an iPad.

Survey items include questions on workshop evaluation, job-seeking self-efficacy, and PrEP and HIV testing use.

Month 8 Follow-Up

The final study visit occurs 8 months after the intervention has been completed. During this visit, participants complete the baseline ACASI survey using an iPad and provide repeat biologic samples if they consented to them.

Outcomes

Primary Outcomes

Information Systems Success Model Score

The Information Systems Success Model (ISSM) will be used to assess for intervention acceptability and satisfaction. The 21-item scale yields a total score and measures 4 subdomains: information quality, handbook quality, perceived usefulness, and overall satisfaction. This scale has been adapted from Horvath et al [41].

Workshop Completion

Workshop completion will be used to assess intervention feasibility. Workshop or intervention completion is defined as having attended at least 2 of the 4 workshop sessions and is measured by tracking participant attendance.

Change in Job-Seeking Self-Efficacy Scale Score

Job-seeking self-efficacy is defined as one's perceived ability and confidence to perform job search and application activities. The 12-item Job-Seeking Self-Efficacy scale by Barlow et al [42] yields a total score where higher values indicate higher self-efficacy. Job-seeking self-efficacy has been found to be associated with employment in a previous study of transgender women of color [29].

Change in Protean Career Attitudes Scale Score

Protean career attitudes (PCAs) are defined as having self-direction in the pursuit of success in one's work. PCAs have previously been found to be associated with positive career satisfaction and self-perceived success [43]. The validated 7-item scale by Porter et al [44] yields a total score and measures 2 subdomains: self-directed attitudes and values-driven attitudes.

Secondary Outcomes

Change in Self-Reported Hours Worked per Week

Hours worked per week is self-reported at baseline and at the 8-month follow-up visit. Change in hours worked per week from the baseline to the 8-month follow-up will be used to assess change in employment status.

Change in Self-Reported Sexual Risk Behaviors

Sexual risk behaviors are defined as self-reported engagement in the following behaviors during the previous 6 months [45]:

- Condomless anal intercourse (receptive or insertive) with cisgender male partner of unknown HIV status
- Anal intercourse (receptive or insertive) with 3 or more cisgender males
- Sex with cisgender male partner with an STI

- Condomless anal intercourse (receptive or insertive) with HIV+ cisgender male partner
- Anal intercourse (receptive or insertive) with condom failure
- Transactional sex work involvement

The previous 6 months refers to the 6 months prior to the baseline visit for the first assessment and the 6 months prior to the 8-month follow-up visit for the second assessment. Change in sexual risk behaviors will be defined as the change in self-reported behaviors from baseline to the 8-month follow-up.

Change in Chlamydia Test Result

Prevalence of chlamydia infections will be assessed at baseline and 8-month follow-up using oral, anal, and urine samples. Each of the 3 tests yields a positive or negative result. Change in chlamydia test result will be defined as the change from baseline to the 8-month follow-up. Oral, anal, and urine tests are treated as separate outcomes.

Change in Gonorrhea Test Result

Prevalence of gonorrhea infections will be assessed at baseline and 8-month follow-up using oral, anal, and urine samples. Each of the 3 tests yields a positive or negative result. Change in gonorrhea test result will be defined as the change from baseline to the 8-month follow-up. Oral, anal, and urine tests are treated as separate outcomes.

Reactive HIV Test

Testing for reactive or nonreactive HIV will be assessed at baseline and 8-month follow-up. The reactive HIV test outcome uses the 8-month follow-up result.

Power

Given the exploratory nature of this study and limited access to this population, the analyses are not designed to have a specified level of statistical power. A repeated measures pre and post design is used to reduce the variability in the estimate of the treatment effect.

Statistical Analysis

Descriptive statistics will be used to analyze the proportions and central tendencies for participant sociodemographic characteristics collected in the surveys. We will first generate frequencies, means, and other measures of central tendency as appropriate to describe our sample and outcomes at each of the 3 time points: baseline, postintervention, and 8-month follow-up.

All participants who are enrolled at baseline and complete the baseline ACASI will be included in the primary and secondary analyses as applicable. Analysis population participants will be included in all primary and secondary analyses for which their data for the specified outcome are not missing. Participants who do not attend any workshop sessions will not be included in analyses involving workshop evaluation. Primary analyses will assess intervention acceptability, satisfaction, and feasibility as well as change in job-seeking self-efficacy and PCA score. Secondary analyses will evaluate the intervention by comparing employment and sexual risk behaviors pre- and postintervention.

Changes in primary and secondary outcomes between baseline and 8-month follow-up will be assessed using paired *t* tests for continuous variables (eg, ISSM, job-seeking self-efficacy, and

PCA scores) and the McNemar test for matched categorical variables (eg, STI results). We will use standard diagnostic tools to assess the appropriateness of the normality assumption and, if approximate normality of the residuals is not tenable, a nonparametric test for continuous paired data (ie, Wilcoxon sign-rank test) will be used. All hypothesis testing will be performed at an alpha level of 0.10, given the exploratory nature of the study. To the extent that data allows, multivariable analyses will adjust for sociodemographic characteristics, workshop attendance, baseline employment status, and study completeness. Analytical models will include linear regression or generalized linear models for continuous outcomes and logistic regression for binary outcomes.

Analysis of the primary and secondary outcomes are described in detail within the statistical analysis plan, which will be accessible on ClinicalTrials.gov once study results have been entered.

Results

Phase 2 W2P research activities began in March 2018 and were completed in November 2019. Overall, 5 participants were enrolled in the pretest, and 51 participants were enrolled in the pilot.

Discussion

The goal of this project is to pilot-test W2P, a structural-level employment intervention for YMSM, YTW, and GNC youth of color. Interventions that address the social and structural drivers of HIV exposure and infection are sorely needed in order to successfully bend the curve in the adolescent and young adult HIV epidemic. Although important for HIV prevention, few individual interventions consider the complex ecological factors that make YMSM, YTW, and GNC youth of color vulnerable to HIV. Thus, engagement with individual-level interventions, such as PrEP adherence and consistent condom use, may be impeded by broader issues such as homelessness, unemployment, and survival sex work. Addressing these factors is an important first step in mitigating risk for adolescent and young adult HIV.

Although employment is an important target for increasing economic stability and decreasing reliance on nontraditional economies such as survival sex work, one limitation of this protocol may be that an immediate individual reduction of HIV exposure may not be detectable. Often structural-level interventions rely on measurement of predictive outcomes that ultimately have downstream effects on health outcomes. To address this challenge, the study focuses on measures of job readiness, job-seeking self-efficacy, and career readiness as the strongest predictors of employment engagement and employability. Follow-up occurs at 8 months postintervention allowing participants time to enact skills and behaviors gained from the employment intervention. Additionally, there is a potential limitation that the results of the intervention may not be generalizable beyond urban YMSM, YTW, and GNC youth of color, as both the formative phase and intervention tailoring and refinement focused on the needs of this population. Subsequent adaptation and refinement may be necessary to engage youth outside of this target population.

If W2P demonstrates feasibility and acceptability among YMSM, YTW, and GNC youth of color in this pilot study, we plan to test the efficacy of the intervention in a multicity longitudinal trial across the ATN study sites. If W2P demonstrates efficacy, this intervention will provide vulnerable youth a tailored youth-focused way to gain employment and life-based skills necessary to achieve economic stability and ultimately reduce the propensity for HIV exposure and infection.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report with comments.
[DOCX File , 20 KB - resprot_v9i8e16401_app1.docx]

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Abbreviations

ACASI: audio computer-assisted self-interview
ATN: Adolescent Medicine Trials Network for HIV/AIDS Interventions
Ci3: Center for Interdisciplinary Inquiry and Innovation in Sexual and Reproductive Health
GNC: gender nonconforming
HBM: health belief model
iFOUR: Increased Individual Income and Independence
ISSM: Information Systems Success Model
LGBTQ: lesbian, gay, bisexual, transgender, queer
PCA: protean career attitudes
PrEP: pre-exposure prophylaxis
PYD: positive youth development
SE: supported employment
STI: sexually transmitted disease
W2P: Work2Prevent study
YMSM: young men who have sex with men
YTW: young transgender women

Protocol

Technology-Based Stepped Care to Stem Transgender Adolescent Risk Transmission: Protocol for a Randomized Controlled Trial (TechStep)

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Abstract

Background: Transgender youth demonstrate significantly higher rates of engagement in sexual risk behaviors relative to their cisgender or gender-conforming counterparts, including high rates of condomless anal intercourse and engagement in sex work. In addition, transgender youth experience increased physical or sexual abuse, victimization, substance use, mental health disorders, incarceration, and homelessness. Owing to these syndemic health disparities, transgender youth are at substantially increased risk of HIV infection.

Objective: This protocol aims to describe a randomized controlled trial (RCT), Adolescent Medicine Trials Network 160 TechStep (N=250), which assesses the differential immediate and sustained effects of each of 3 conditions (text messaging, WebApp, or information-only control) for reducing sexual risk behaviors and increasing pre-exposure prophylaxis (PrEP) uptake among high-risk, HIV-negative transgender youth and young adults (aged 15-24 years).

Methods: Participants will be recruited through web-based (targeted social media sites and apps) and offline (print ads and flyers) advertisements, peer and clinic referrals, and street- and venue-based outreach, and by contacting potential participants who have requested contact for future studies. Participants will be randomized into 1 of the 3 conditions: (1) text messaging, (2) WebApp, or (3) information-only control for 6 months. Assessments will occur at baseline and at 3, 6, and 9 months. Participants who do not show improvements in sexual risk or PrEP uptake at the 3-month assessment will be rerandomized to receive weekly electronic coaching (eCoaching) sessions in addition to their assigned text messaging or WebApp intervention, or remain in the original text messaging or WebApp intervention using a 2:1 ratio. Participants originally assigned to the information-only condition are not eligible for rerandomization.

Results: Funding for TechStep was awarded in June 2017. Phase 1 was approved by the Institutional Review Board (IRB) in April 2018. Recruitment began in November 2018 for phase 1, the formative phase. Initial phase 2 IRB approval came in June 2019. The data collection for phase 2, the RCT, is expected to be completed in April 2021. As of March 2020, 54 participants have been enrolled in TechStep. The final results are anticipated in May 2021.

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Conclusions: By providing culturally responsive, technology-based interventions, TechStep aims to improve sexual health outcomes among HIV-negative transgender youth and young adults at high risk of HIV. TechStep will evaluate the efficacy of technology-based interventions for reducing HIV sexual risk behaviors and increasing PrEP initiation, adherence, and persistence. The suite of technology-based interventions developed in TechStep, and assessed for efficacy in a 3-condition RCT, represents an important advancement in intervention science toward developing tailored and scalable interventions for transgender youth and young adults.

Trial Registration: ClinicalTrials.gov NCT04000724; http://clinicaltrials.gov/ct2/show/NCT04000724

International Registered Report Identifier (IRRID): DERR1-10.2196/18326

Introduction

Background and Study Objectives

National evidence suggests that as many as 8% of youth in the United States self-identify as *transgender*, *gender nonconforming*, or *other gender* (hereafter, trans) [1] and that trans youth face a *health syndemic*, in which a set of reinforcing structural, cultural, and behavioral factors place them at a dramatically increased risk for negative physical, social, and mental health outcomes [2-6]. For example, trans youth demonstrate significantly elevated rates of sexual risk-taking relative to their cisgender or gender-conforming peers [4,7-9], including rates of condomless anal intercourse ranging from 27% to 59% and rates of engagement in sex work ranging from 24% to 75% [9,10]. Increased rates of sexual risk behaviors among trans youth have been associated with the population's increased experiences of physical or sexual abuse and victimization, mental health disorders, incarceration, and homelessness [4,9,11] as well as substance use, sex work, and substance use during sex [4,9,12]. As a result of this health syndemic, trans youth, especially racially and ethnic minority trans youth, are at a substantially increased risk for HIV infection as well as other sexually transmitted infections (STIs) relative to their cisgender youth counterparts [10,12,13]. Despite these needs, there is persistent evidence of a lack of culturally competent care and inadequate training of traditional health care providers [14,15]; the difficulties trans youth report accessing traditional health care [8,16] and the frequent reports by trans youth of prejudice or discrimination when receiving traditional health care [3,5] demonstrate the critical need for avenues of sexual health information and interventions that extend beyond traditional *brick-and-mortar* services and cater to the special needs of trans youth.

All adolescents, including trans youth [17], demonstrate the frequent use of text messaging and mobile internet-enabled technology to seek protective sexual health information [18]. Trans youth explicitly cite mobile phones as critical tools in their ability to engage with sexual health information, as text messaging conversations, mobile apps, and other mobile health delivery modalities provide portals where trans youth report feeling comfortable seeking health-related knowledge specific to trans individuals (eg, hormone therapy, pubertal suppression [19]), adopt and express new and different identities, and connect to other trans youth to seek information and resources

[17,20,21]. Among mobile intervention modalities, text messaging and smartphone apps have been identified as particularly well suited to the needs of trans populations, whose gender expression may serve as an obstacle to standard in-person treatment [22].

A recent systematic review revealed that only 18% of mobile phone–based HIV prevention or care interventions provide any information tailored to the lesbian, gay, bisexual, transgender (LGBT) populations, and none were tailored specifically to trans individuals [23]. Thus, there is a clear need to develop effective prevention interventions that meet the needs of trans youth and young adults and are developed specifically for this population.

Objectives

The *TechStep* study will address a critical gap in the scientific advancement of technology-based interventions for trans youth by (1) creating the first technology-based trans youth–specific HIV prevention intervention optimized for mobile phone delivery and (2) employing the 2 intervention delivery modalities (ie, text messaging and mobile WebApp) identified as the most promising for use among trans youth and young adults. The suite of technology-based interventions developed in *TechStep* and assessed for efficacy in a three-condition randomized controlled trial (RCT) represents an important advancement in intervention science toward developing tailored and scalable interventions for trans youth.

Methods

Research Aims

As part of the University of North Carolina/Emory Center for Innovative Technology (iTech) [24], we proposed to test the efficacy of Adolescent Medicine Trials Network (ATN) 160 *TechStep* for trans youth and young adults. In this 4-year study, 250 high-risk trans youth and young adults aged between 15 and 24 years will be randomized to receive text messaging, a WebApp (ie, a website that is optimized for display on smartphones), or an information-only control intervention for 6 months, with assessments occurring at baseline and at 3, 6 and 9 months. Participants who do not show improvements in sexual risk or pre-exposure prophylaxis (PrEP) uptake at the 3-month assessment will be randomized to receive weekly electronic coaching (eCoaching) sessions in addition to their

assigned text messaging or WebApp intervention, or remain in the original text messaging or WebApp intervention using a 2:1 ratio. The primary endpoint is reduced sexual risk behaviors or PrEP uptake, adherence, and persistence at month 6 and sustained through month 9.

The aims of the research include the following:

1. Primary aim 1: conduct formative research to develop stepped care (text messaging, WebApp, and eCoaching) interventions and refine iterations through input from focus groups with trans youth and young adults at the 4 study sites (Houston, Texas; Los Angeles, California; New York, New York; and Philadelphia, Pennsylvania) and with a trans-specific youth advisory board (YAB).

2. Primary aim 2: in a 3-condition RCT (N=250), assess the differential immediate and sustained effects of a low-intensity information (*Info*) condition compared with a text messaging stepped care intervention (text messaging plus step to eCoaching for youth and young adults with continued high risk) condition compared with a WebApp stepped care intervention (WebApp plus step to eCoaching for youth and young adults with continued high risk) condition for reducing sexual risk behaviors and increasing PrEP uptake among high-risk, HIV-negative trans youth (15-24 years old):
   - Hypothesis 1a: there will be significantly greater reductions in sexual risk behaviors among those in the text and WebApp conditions compared with the low-intensity info condition.
   - Hypothesis 1b: there will be significantly greater uptake of PrEP among those in the text and WebApp conditions compared with the low-intensity info condition.

3. Secondary aim 1: determine the added benefit of text messaging plus eCoaching (text+eCoaching) versus text messaging alone and of WebApp plus eCoaching (WebApp+eCoaching) versus WebApp alone to reduce sexual risk behaviors and increase PrEP uptake.

4. Secondary aim 2: assess the differential immediate and sustained effects of low-intensity information compared with text messaging only compared with WebApp only for reducing sexual risk behaviors and increasing PrEP uptake.

5. Secondary aim 3: determine the impact of structural-level (eg, transphobia, housing insecurity, educational attainment, access to health care) and individual-level (eg, identity formation, gender transition, gender expression, stigma, discrimination) trans-specific factors as moderators of intervention outcomes.
   - Hypothesis 2: structural- and individual-level trans-specific factors will moderate intervention outcomes, such that participants who report higher amounts and degrees of these factors will require more intensive intervention steps (ie, eCoaching).

Ethics Statement

The Institutional Review Board (IRB) at the University of North Carolina, Chapel Hill, NC, is the IRB on record for all participating institutions and subject recruitment venues (SRVs)

participating in the study. The study procedures were approved by the University of North Carolina IRB 18-0519. A waiver of parental consent was obtained for participants aged 15 to 17 years. The study was registered as a clinical trial (Clinical Trials #NCT04000724).

Interventions

Text Messages

The theoretical construct for the text message intervention was based on 3 proven theories of behavioral change, and the text messages will be equally distributed across the 3 behavioral change theories: Social Cognitive Theory, Health Belief Model, and Social Support Theory.

Social Cognitive Theory

The Social Cognitive Theory posits interactive causal relationships among personal determinants, behavior, and environmental influences [25,26]. Effective HIV prevention interventions must increase individuals' self-efficacy and guide them in developing self-regulation skills, offering practice and feedback opportunities, and engaging social support resources to maintain prevention behavior.

Health Belief Model

The Health Belief Model asserts that individuals' beliefs regarding threats to their health, and that specific health behaviors can reduce these threats, predict their likelihood of engaging in protective health behaviors [27]. The Health Belief Model is most effective when messages regarding threats and beliefs are culturally appropriate to the specific target population.

Social Support Theory

According to the Social Support Theory, social support encompasses instrumental, emotional, and informational assistance provided by members of one's social network. These forms of social support have been shown to mediate the relationship between stressful events and health outcomes [28,29].

Text Message Delivery

Participants assigned to the *TechStep* text message intervention will receive 2 cycles of the 90-day text messaging intervention, that is, participants will receive the same intervention twice, once from 1 to 90 days and then again from 91 to 180 days. During the intervention period, participants will receive 3 scripted, theory-based, trans-specific text messages per day (a total of 270 text messages that will be repeated once). Text messages will be transmitted through gradual automation administration every day, including weekends, in real time, within a 10-hour period. Thus, participants will receive a text message approximately every 5 hours starting at either 9:00 AM or noon local time (eg, at noon, at 5:00 PM, and at 10:00 PM). Timing was determined based on findings from the 3 previous text messaging studies conducted by the Protocol Co-Chair [30-32] and supported by feedback from focus group participants. Participants will select whether to start receiving messages in the morning, starting at 9:00 AM, or in the afternoon, starting at noon. The text messages were specifically scripted, with input from the focus group participants and YAB

members, for HIV-negative trans youth and young adults who are at risk of HIV infection. The automated text message delivery system was developed specifically for this study by Dimagi [33], a digital software company that specializes in global health technology.

Table 1 illustrates how the text message library was developed to have both a theoretical foundation and be transculturally responsive.

Table 1. Sample of scripted text messages by behavioral change theory.

| Social Support Theory			Health Belief Model		Social Cognitive Theory		
Informational support	Emotional support	Instrumental support	Health threat	Health behaviors to reduce threat	Awareness of health risks	Self-regulation skills	Self-efficacy
Think you might have been exposed to HIV? Start PEP[a] within 72 hours, and taking it every day for 28 days will keep you protected	Your body and soul are beautiful. See a health care provider	PrEP[b] exists, take advantage of it!	Untreated STIs[c] can steal your beauty	Take care of yourself and your trans community. Check out resources at (hyperlink)	Lead your community by example, take your PrEP daily!	Taking care of yourself is loving your trans body	Know your health info, be empowered, see your doctor
Get the "T" on STI info and testing call (phone number)	Trans Pride is taking care of yourself	Seen your partner lately? See your doctor, too	We love you, don't be a statistic, take your PrEP!	Be smart, safe, and sexy	Protect your cute trans body, see your doctor	Had unprotected sex? No shame, get on PrEP	Nothing compares to you, you can be safe

[a]PEP: post-exposure prophylaxis.

[b]PrEP: pre-exposure prophylaxis.

[c]STI: sexually transmitted infection.

WebApp

The theoretical construct for the WebApp intervention was based on the Information Motivation Behavior (IMB) model of behavioral change (Figure 1).

Figure 1. TechStep WebApp components and the Information, Motivation, Behavior model. PrEP: pre-exposure prophylaxis.
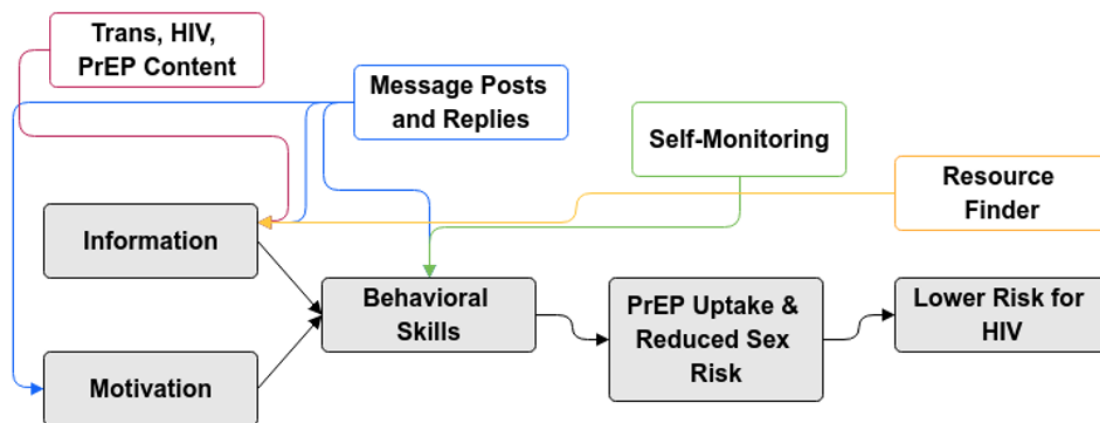
IMB

The IMB model proposes that health behavior and behavior change results from being well and accurately informed, having the personal and social motivation to engage in the behavior, and having the appropriate behavioral skills and self-efficacy to use them [34-36]. The associations between core WebApp intervention components (described in detail below) and the IMB model components are shown in Figure 1. The IMB model has been used to predict risky sexual behavior among adolescents in Los Angeles, California [37], and has been used as the theoretical basis of adolescent risk reduction interventions [38].

WebApp Development

The WebApp intervention will be developed as a safe digital space for sharing information and helping trans youth and young adults feel empowered and supported to make healthy sexual health choices. To be available to answer questions and enforce community standards (eg, no hostile exchanges), the WebApp will be moderated by research staff (primarily graduate-level students) trained by the study Protocol Co-Chair on how to identify and respond to problematic posts. Moderating includes reading through posted comments on the wall each day and identifying posts that are concerning (eg, suicidal ideation, pleas for assistance, and potentially hostile comments to other users). Posts made by participants are not delayed or held until *cleared* for posting. Rather, the moderator reviews posted material and

acts accordingly. This is to retain the immediacy of posting, which users of social media largely expect. The following are the core components of the WebApp intervention.

Message Posting and Receiving

The WebApp homepage will consist of an interface for participants to asynchronously interact with one another through message posting (Multimedia Appendix 1). Unlike widely used social networking platforms such as Facebook, participants will view all posts on one shared feed (vs individual feeds or direct messaging). Other users may comment on a post as well as use reaction buttons (eg, thumbs up, combined LGBT and trans flag). Message posting is the primary social support component of the intervention as it allows participants to directly and voluntarily interact with one another in a similar manner as a face-to-face peer support group.

HIV Prevention and Trans-Specific Information

Staff members who are a part of the community wrote brief informational pieces of content, called *Tips*, on the WebApp, covering a broad range of topics including HIV prevention, sexual health, PrEP, and transphobia. Youth in the WebApp intervention condition will receive approximately 3 tips each day. Each tip contains a combination of written content and a video, meme, or graphic. The study staff created approximately 250 tips in total, with approximately three-fourth dedicated to specific content areas (eg, PrEP and sexual health) and the remaining considered *grab bag* tips related to other important topics to the community. Tips may be favorited and reviewed later or explored through tags that will display all the tips related to that tag.

Self-Monitoring

Participants will have the ability to self-monitor one or more behaviors under the *Tracker* tab. Participants can create a new tracking behavior by inputting the behavior they would like to track, with *hormones* and *PrEP* suggested, but also offering the ability to key in the behavior of their choice. Next, participants are asked how they would like to be reminded (through SMS or on the app) and the frequency of the reminder (daily or weekly). Once they set up the behavior to be tracked, they will be able to indicate whether they performed that behavior that day. Underneath, a monthly calendar will be displayed that reflects the frequency with which they reported the behavior and the ability to toggle between the different behaviors they are currently tracking.

Resource Locator

Participants will be able to search for local trans-specific resources in their area through the *Resources* tab. Resources (eg, HIV testing, PrEP provision, housing assistance) were identified through web-based searches and by asking local SRV contacts to provide a list of trans-specific resources. Next, the study staff called each agency to confirm that they were still in operation and that they serve transgender persons as part of their services. Once confirmed, the study staff entered information about the resources in the WebApp database, including hours of operation, testing services, and address, which can use the location of the phone to show the distance from the participant. Participants can rate (using a five-point star system) and

comment on the resource for others to view as well as suggest new resources for the database (Multimedia Appendix 2).

Weekly SMS Engagement Message

All participants will receive a weekly SMS (text) message that prompts and encourages them to visit the *TechStep* WebApp. SMS messages are designed to engage youth with different aspects of the site by providing a link within the message that will take youth directly to the WebApp.

Game Mechanics

The WebApp uses points that accumulate as youth use intervention components to reinforce engagement with the site. As points accumulate, youth move through higher levels (ie, *levelling up*) during the intervention period, which unlocks new features of the site (eg, new avatar choices and color theme choices) when a new level is achieved. Points are earned through posting on the WebApp feed (wall), responding to other users' comments, setting new goals, clicking on a tip, and other actions that may be taken in the WebApp. Youth will be able to view the number of points and their current level as part of their profile.

eCoaching

Participants in the text or the WebApp conditions who do not reduce sexual risk behaviors or who self-report a recent STI diagnosis and do not initiate PrEP or adhere to PrEP during the first 3 months of those interventions will be rerandomized to additionally receive eCoaching. The eCoaching intervention integrates theoretical constructs of Motivational Interviewing (MI) and Cognitive Behavioral Therapy (CBT) to assist trans youth and young adults in establishing health behavior goals, discussing facilitators and barriers to behavior change, and providing behavioral skills to enhance goal attainment [39].

MI

MI is a style of communication fostering collaboration and goal setting to build personal motivation for behavior change [40]. MI techniques build upon the essential elements of partnership, acceptance, compassion, and evocation through 4 different MI processes. A session commences with *engagement* to build a rapport and therapeutic alliance. *Focusing* allows the participants to discuss their own goals and priorities as it relates to the target behavior. *Evoking* elicits change talk by exploring a participant's thoughts on behavior. Finally, *planning* allows for specific goal setting, summarizing, identifying potential barriers, and discussing options for overcoming barriers. eCoaches move participants through these processes with MI techniques of asking open-ended questions, using simple and complex reflections, sustaining change talk, and summarizing.

CBT

CBT is an action-orientated treatment that addresses maladaptive cognitive beliefs and behaviors [41]. It is based on the premise that all behavior is learned and can be *unlearned* with the introduction of new behavioral skills, including problem solving, assertiveness and communication training, self-monitoring, environmental control, distress tolerance, and how thoughts and feelings affect behavior.

eCoaching sessions are conducted through a Zoom portal (Zoom Video Communications Inc) to have a common meeting place for video conferencing and electronically sharing intervention activity materials. Participants will be asked to join eCoaching sessions through their mobile device or desktop. Sessions are 30 to 40 min long and held weekly on an agreed-upon day and time.

Participants rerandomized to eCoaching are virtually introduced to their eCoach during the 3-month assessment appointment, called the First Contact session. The First Contact session is a 20-min mini session during which the participant meets their eCoach, learns about the eCoaching intervention, establishes rapport, introduces the functional assessment, and establishes an agreed-upon day and time for subsequent weekly virtual sessions. There are up to 8 sessions of content available to occur over a 12-week period. Sessions 1 to 4 are core sessions: session 1: Planning for My Plan; session 2: You Getting to Know You; session 3: Intimacy and Communication; and session 4: Getting PrEPared. Sessions 5 to 8 are optional and are based on answers to the functional assessment and subsequent collaborative treatment planning. Session 5: Keeping It Cool; session 6: Alcohol and Drugs; session 7: Checking In; and session 8: You Don't Have to Do It Alone. The functional assessment is a 20-item survey completed between first contact and session 1 with yes, no, and maybe response options. Endorsing certain items (yes or maybe) map onto recommended modules for sessions 5 to 8 and allows the eCoach to work with the participant during the session 1 collaborative treatment plan to decide which sessions would be most beneficial.

eCoaching is facilitated by highly trained transgender and cisgender paraprofessionals centrally located at Hunter College. All eCoaches attend 5 days of MI, CBT, and protocol training conducted by a Motivational Interviewing Network of Trainers–certified trainer followed by mocking and supervision for session clearance. Fidelity is monitored through the completion of the MI coach ratings scale by the clinical supervisor and weekly supervision sessions [42].

Information Control Condition

The information control condition is a static website that comprises 6 pages: *Welcome*, *HIV Information*, *PrEP Information*, *Trans Information*, *Trans Resources*, and *Study Sites Contact Information*. The *Welcome* page introduces participants to the site and highlights values around trans empowerment and trans rights. The *HIV Information* page provides information on a number of HIV topics, including HIV transmission, HIV and oral sex, HIV risk in pregnancy, condom use, undetectable=untransmittable, HIV and other STIs, HIV and substance use, and HIV stigma. The *PrEP Information* page includes information about PrEP usage, methods of acquisition, and web-based and local PrEP resources in the 5 study site cities: Boston, Massachusetts; Houston, Texas; Los Angeles, California; New York, New York; and Philadelphia, Pennsylvania. The *Trans Information* page provides subsections on language, definitions, and trans history. The *Trans Resources* page provides local resources for trans youth and young adults in the 5 study site cities. Those randomized into the information control condition remain in the control condition throughout the 6-month intervention period and are not eligible for the 3-month rerandomization or the eCoaching intervention.

TechStep Study Design

The *TechStep* study will be evaluated in a randomized controlled efficacy trial. There are 2 phases of the *TechStep* study.

Phase 1: Formative Research and Community Input

A total of 2 trans-specific YABs will be convened throughout the life of the study. There is a physical YAB in Los Angeles, and a virtual cross-site YAB conducted via telecommunication comprised members from the Houston, New York, and Philadelphia SRVs. The YABs will meet at least biannually and will provide feedback on all aspects of the *TechStep* study.

We conducted 7 focus groups at 4 SRVs (n=34); 2 were held in Los Angeles (n=11), 2 in Houston (n=7), 2 in New York (n=11), and 1 in Philadelphia (n=5). The New York and Philadelphia focus groups gave feedback on the text messaging intervention, whereas the Los Angeles and Houston focus groups gave feedback on the WebApp. In each city, the focus groups were stratified by age, 1 focus group consisting of participants between the ages of 15 and 20 years and the other focus group consisting of participants between the ages of 21 and 24 years (only 1 focus group, with participants aged 21-24 years, occurred in Philadelphia). This stratification ensured that the perspectives of both youth and young adults were explored. Focus groups were transcribed verbatim, and content analysis was conducted using the iTech Analytic Core. Feedback from the focus groups was used to inform phase 2.

The focus group inclusion criteria were as follows: (1) self-identification as trans feminine, trans masculine, or gender nonconforming or birth sex and current gender differ; (2) self-reported 15 to 24 (inclusive) years of age at screening; (3) report any sex with another person in the previous 12 months; (4) self-reported HIV-negative serostatus; (5) live in the area and have the availability to attend the group; (6) have a mobile device with SMS and internet access capabilities; and (7) proficient in English as determined by study staff (as the focus groups were conducted in English).

All persons who screened eligible for a focus group were guided through the informed consent process on the day of the focus group. Following informed consent, participants completed a brief paper-and-pencil focus group participant survey (eg, additional demographics and technology use survey).

Focus groups were conducted by research staff and lasted approximately 120 min. Food was served in each group. Participants were compensated for their time once the focus group ended.

Phase 2: RCT to Test the Efficacy of TechStep

We propose to enroll 250 trans youth and young adults in the RCT (approximately n=83 for text, n=83 for WebApp, and n=83 for information control; Figure 2). Trans youth and young adults will be recruited from 5 SRVs (Baylor College of Medicine Adolescent Medicine Trials Unit in Houston, Children's Hospital of Philadelphia, Children's Hospital Los Angeles, the PRIDE [Promoting Resilience, Intersectionality, Diversity, and

Equity] Health Research Consortium in New York City, or the Fenway Institute in Boston) to participate in a three-condition RCT to determine immediate and sustained effects of the text

intervention versus the WebApp intervention compared with an information control condition (*Info* condition).

Figure 2. TechStep study design. eCoaching: electronic coaching.
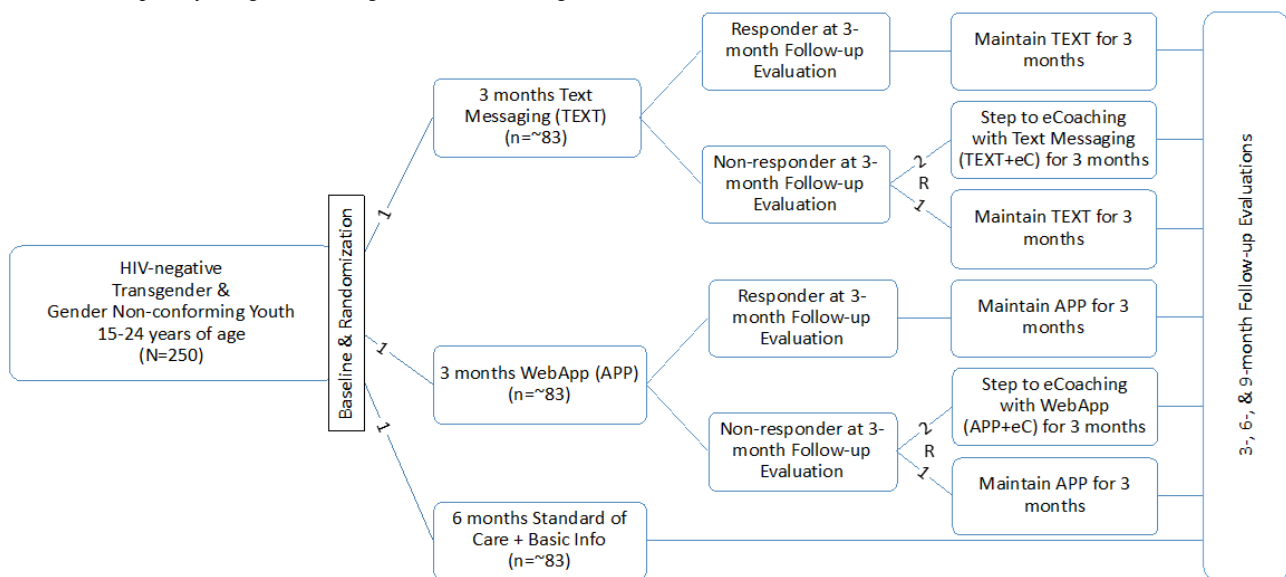
All participants will receive one of the interventions for 6 months, with assessments occurring at baseline and every 3 months thereafter through Month 9. Trans youth and young adults randomized to either of the technology-based intervention conditions (text or WebApp) will be evaluated at the three-month follow-up assessment time points to determine whether they remain at the current level of intervention or whether they are eligible for rerandomization to also receive eCoaching sessions in addition to their originally assigned intervention (ie, text+eCoaching or WebApp+eCoaching). At the first follow-up assessment time point, information about their sexual behavior in the past 3 months and whether they began or stopped using PrEP will be used to determine whether they require a more intensive intervention approach. Participants who do not demonstrate intervention responsiveness at the 3-month follow-up assessment will be rerandomized, in a 2:1 ratio, to either add eCoaching to their original intervention (ie, text+eCoaching or WebApp+eCoaching) or remain in their original intervention (ie, text or WebApp). This rerandomization will allow for a comparison of intervention effects between the technology-based interventions (ie, text or WebApp) plus eCoaching with the technology-based intervention alone. The control condition will receive the same information-only intervention for the entire 6-month intervention period.

The RCT inclusion criteria were as follows: (1) self-identify as trans feminine, trans masculine, or gender nonconforming or birth sex and current gender differ; (2) aged 15 to 24 years (inclusive) at the enrollment visit; (3) self-report vaginal or anal sex (either insertive or receptive, excluding sex toys) with another person in the previous 12 months; (4) negative HIV rapid test; (5) live in the area and be available to meet with research staff at 1 of the 5 SRVs; (6) have a mobile device with SMS and internet access capabilities; and (7) be able to read and speak English (as the interventions will be built in English).

Study Recruitment

The following recruitment strategies will be used to ensure diversity of the participants enrolled:

1. Web-based: web-based banner advertisements will be placed through geomapping on websites and social media in the SRV cities. Digital flyers will be distributed to community leaders to disseminate to their email distribution lists.
2. SRV and community-based reach: flyers and posters will be distributed in SRVs and other community-based organizations and clinic settings that cater to trans youth and young adults.
3. Peer long-chain referral: participants who screen eligible will be asked to refer friends who are also trans youth and young adults.
4. Clinic: clinic-based recruitment may include reviewing the medical charts of existing patients for potential eligibility or referrals from other providers in the clinic.
5. Previous participants: participants from other studies who have previously given consent to be contacted for future research may also be contacted directly.
6. Print media: advertisements may be placed in print media identified through the YABs.
7. Street- and venue-based outreach: research assistants will use a semistructured time-space sampling methodology to conduct street- and venue-based outreach identified through the YABs [43].

Screening

All potential participants will complete a web-based screening survey to obtain consent or assent to be screened and verify all inclusion criteria. Screening may occur on the same day as enrollment (or beforehand, if screening on the web). The web-based screening survey will begin with a script to explain the purpose of screening and clarify that if they are eligible,

they will be invited to participate in the study. The script will also provide general information about *TechStep*, the nature of the screening questions and related potential risks, the approximate length of the screening (approximately 5 min), the confidentiality and use of the screening information, the ability to skip any question or withdraw at any time, and contact information of key study personnel. Participants who agree to voluntarily complete the screening procedure will electronically indicate their agreement and then participate in the screening survey. SRV staff may also screen participants in person or over the phone using a web-based assessment.

RCT Enrollment

All persons who screened eligible for the study will be guided through the informed consent process on the day of their enrollment appointment in person at one of the SRVs. Enrollment procedures will last approximately 120 min and consist of informed consent or assent; the baseline audio

computer-assisted self-interview (ACASI) survey; HIV, STI, and drug screen testing; and Mitra blood analysis for detection of PrEP concentrations among those who self-reported PrEP use (Table 2). Research staff will stop enrolment if any potential participants appear confused or otherwise unable to complete the informed consent process. Following the baseline measures, the participant will be randomized into the text condition, the WebApp condition, or the information-only (ie, *Info*) condition, after which they will be considered enrolled. After randomization, participants will receive more information about the condition they are randomized to (ie, the frequency of text messages, how to use the WebApp, or how to access the information website). Participants will be compensated with the following US dollar cash or cash equivalent: US $50 at the enrollment visit, US $55 at the 3-month follow-up visit, US $60 at the 6-month follow-up visit, and US $65 at the 9-month follow-up visit.

Table 2. Study outcome variables and data collection schedule.

Variables	Baseline	3-month assessment	6-month assessment	9-month assessment
Rapid HIV test	✓[a]	✓	✓	✓
STI[b] tests[c]	✓	✓	✓	✓
Blood microsampling for PrEP[d,e]	✓	✓	✓	✓
Sexual behavior	✓	✓	✓	✓
Demographics: date of birth, race and ethnicity, sex assigned at birth	✓	—[f]	—	—
Demographics: gender identity, sexual identity, education, employment status, health insurance, family income, housing stability, history in the criminal justice system	✓	✓	✓	✓
Health care utilization	✓	✓	✓	✓
Gender congruence, stress, and resilience	✓	✓	✓	✓
Substance use	✓	✓	✓	✓
Mental health	✓	✓	✓	✓
Technology adaptation and use	✓	✓	✓	✓
Intervention ease of use, acceptability, and satisfaction	—	✓	✓	—
User engagement	—	✓	✓	—

[a]Outcome assessed in this data collection period.

[b]STI: sexually transmitted infection.

[c]STI tests include gonorrhea and chlamydia testing via throat and rectal swabs and urine and syphilis testing via a blood draw.

[d]PrEP: pre-exposure prophylaxis.

[e]Mitra blood microsampling will be performed only when participants report PrEP use before a study visit.

[f]—: outcome not assessed in this data collection period.

RCT Randomization

Participants will be randomized 1:1:1 to the text intervention or WebApp intervention or control condition. Study staff will not be blinded to the condition that participants are randomized to. The randomization sequence will be stratified by city and use random permuted blocks of size 3.

Follow-Up Evaluations

Follow-up evaluations will occur at 3, 6, and 9 months postenrollment. The data collection schedule is presented in Table 2. Participants in the text or the WebApp conditions who do not reduce sexual risk behaviors or who self-report a recent STI diagnosis and do not initiate PrEP or adhere to PrEP will be rerandomized 2:1 into either additional eCoaching with their originally assigned intervention (ie, text+eCoaching or WebApp+eCoaching) or to remain in their originally assigned

intervention without the addition of eCoaching. Those that are rerandomized to step up to additional eCoaching will meet the eCoach at the 3-month visit, immediately following the assessment, for an introductory visit and to schedule their first eCoaching session. The active intervention period ends after 180 days. To measure the sustained effects of the intervention, the final data collection period comes during the 9-month visit, 3 months after the end of the intervention period.

Measures

Study outcome measures and the timing of their administration are provided in Table 2. The outcomes are described below.

Outcomes of Interest

1. Change in condomless intercourse events: participants will be asked to report the frequency of condom use during sex in the last 3 months (*never* to *always*) as well as during the last 3 sexual encounters.
2. Change in condomless intercourse events when high on drugs or alcohol: participants will be asked to report whether they or their partners used substances during the last 3 sexual encounters.
3. Change in condomless intercourse events during sex work: participants will be asked to report condom use and partner type for sexual encounters over the previous 3 months as well as during the last 3 sexual encounters.
4. PrEP adherence: participants will self-report PrEP medication uptake and adherence on the ACASI. PrEP adherence is measured by blood sample levels of tenofovir diphosphate and emtricitabine triphosphate (TFV-DP/FTC-TP) with blood concentrations consistent with >4 doses per week.
5. HIV seroconversion: HIV tests will be administered at each study visit. Reactive results after baseline will be recorded as a seroconversion.
6. Incident STIs: participants will be asked to self-report new STI diagnoses from the past 3 months on the ACASI and they will be tested for gonorrhea and chlamydia via throat and rectal swabs and urine and syphilis via a blood draw.

Secondary Outcome

Transgender syndemic health index: participants will self-report education, employment status, housing stability, history in the criminal justice system, health care utilization, gender congruence, stress and resilience, substance use, and mental health.

Demographic Factors

Common demographic factors will be collected, including date of birth, race and ethnicity, gender identity, sex assigned at birth, sexual identity, education, employment status, health insurance, family income, housing stability, and history in the criminal justice system.

Health Care Use

Participants will be asked to rate their own health and medical services they may have used, including primary health care location, recent hospitalization, access to a primary care provider, comfort in discussing sexual relationships and gender identity, and HIV and STI testing. PrEP knowledge and use will

be assessed using the PrEP Motivational Cascade [44]. Barriers to PrEP uptake or use are assessed using a measure developed and adapted by the ATN [45]. Gender confirmation surgery, medical procedures, hormone therapy, needle hygiene, and other gender presentation enhancements will be assessed using the Los Angeles Transgender Health Survey [46].

Gender Congruence, Stress, and Resilience

Gender congruence (ie, the alignment of gender expression and identity) is measured using items from the National Health Behavior Survey [47]. The adolescent version of the Gender Minority Stress and Resiliency Scale is used to assess gender-related discrimination and victimization, internalized transphobia, and pride [48]. The experiences of racism are captured using the Adolescent Discrimination Distress Index [49].

Substance Use

Substance use will be assessed via a urine screen to assess amphetamines, methamphetamines, cocaine, marijuana, and opiates using a generic 5-panel screening test (model HDOA-254; Confirm BioSciences) and an adapted version of the National Institute on Drug Abuse-modified alcohol, smoking, and substance involvement screening test [50].

Mental Health

Depression symptoms will be assessed using the 8-item Patient Health Questionnaire (PHQ-8) [51]. Participants will first be asked the first 2 items for the PHQ-8; those who report having some depressive symptoms (≥3 across the 2 PHQ items) will be asked to complete the remaining items of the scale.

Intimate Partner Violence

Experiences of relationship violence, including sexual assault, physical violence, isolation, privacy, and financial violations, are assessed [52,53]. Participants will be asked if they or their partners shared intimate photos of the other without permission [54].

Sexual Behavior

Sexual behavior will be assessed by asking whether they have engaged in vaginal, anal, or oral sex in the past 3 months. If they reported having sex in the past 3 months, participants will be asked how many main, casual, and exchange partners they had in the past 3 months, and how frequently (from none of the time to all of the time) they used a condom during insertive and receptive anal sex and vaginal sex. Participants are then asked about their 3 most recent sexual encounters and are asked to report on the number, genders, and types (ie, main, casual, exchange) of partners, sexual positioning, condom use, HIV status of partners, partner PrEP use, viral suppression of HIV-positive partners, and substance use by either the participant or their partners before or during sex [55].

Technology Adoption and Use

Technology use questions and items assessing participants' attitudes toward technology were taken from items developed by the Pew Research Center's Internet, Science, and Tech initiative. Participants are asked to report device ownership and operating system; how they access the internet; how they pay

for service; how many hours a day they spend on the internet; how often they use mobile apps; frequency of internet use for social, sex-seeking, work, and health-seeking activities; and whether and how they may have faced discrimination when looking for partners on the web. In addition, the 8-item eHealth Literacy Scale will be used to assess participants' perceptions of their skills for using the internet for health [56].

Ease of Use, Acceptability, and Satisfaction of the Intervention

Participants in the WebApp condition will be asked to rate the ease of use of their activities at the 3- and 6-month follow-up visits using the System Usability Scale (SUS) [57]. The SUS is a 10-item measure that asks participants to rate on a 1 (strongly disagree) to 5 (strongly agree) scale how much they agree with statements about the ease with which they were able to navigate the WebApp intervention. Participants in the text messaging condition will be asked at the 3- and 6-month follow-up visit the proportion of *TechStep* text messages they read. Participants in all conditions (including the information-only website condition) will be asked to answer questions on information quality, perceived usefulness of the information, and overall satisfaction with the intervention. We will also ask participants to rate their respective intervention on information quality and usefulness using items adapted from Horvath et al [58]. Finally, we will collect qualitative data on youth experiences by asking participants to state the 2 things they like most and least about *TechStep*.

User Engagement for the WebApp Intervention Arm

The WebApp intervention uses data collected during the active trial period to assess user engagement with the intervention. Standard use data include (1) log-in date and time, (2) type of device used, and (3) total duration of the session. Intervention use data for each participant will include the following variables reflecting peer-to-peer interaction: (1) date and content of original posts and (2) the number and content of replies to the original post. Additional user engagement variables collected are (1) frequency of posts; (2) number of comments; (3) number of tips viewed or favorited; (4) number of tracking behaviors established, frequency of tracking, and for each tracked behavior, the frequency of endorsing that behavior; (5) frequency of resource locator use and subtypes of resources sought; (6) total number of active intervention days; (7) number of times the participant updated their outward-facing profile features; and (8) total points earned.

Data Analysis

Individuals' baseline characteristics will be summarized by randomization arm using appropriate measures of central tendency and variability. We define intervention effects based on the difference in the average cumulative number (for count-valued outcomes such as instances of condomless anal intercourse) or proportion (for binary-valued outcomes such as PrEP uptake) of outcomes observed over 9 months of follow-up comparing a given active condition (eg, text messaging or WebApp) versus the info condition. We will estimate these effects using longitudinal targeted minimum loss-based estimation (LTMLE) [59-61]. LTMLE is a robust and efficient method for estimating treatment effects in the present context. First, it appropriately accounts for the study design and the fact that only some participants are eligible for rerandomization into the eCoaching intervention. Second, the method accounts for predictive and prognostic time-varying participant-level covariates, thereby increasing the power to detect intervention effects [62]. Finally, the method accounts for possibly informative participant dropout, which can reduce bias in effect estimates [63].

Implementation of LTMLE involves fitting several prespecified models that adjust for participant-level information. First, a sequence of outcome regressions is fit to model the average outcome (eg, average number of condomless anal intercourse events) at each time point, adjusting for baseline and time-varying covariates. Second, a regression is fit to model the cumulative probability of participant dropout, adjusting for baseline and time-varying covariates. These models will be fit using the super learner, a cross-validation–based technique for estimator selection [64]. This method aggregates results from a library of candidate regression estimators to build the most powerful predictor given the data at hand. In large samples, the method is guaranteed to perform as well as the unknown best-performing regression in the library. The method has also been validated in smaller samples via extensive simulation studies [65].

We will use level 0.05 Wald tests for each hypothesis using influence function-based standard error estimates. More information on this approach can be found in the paper by Benkeser et al [66].

Power and Sample Size

The sample size was determined using Monte Carlo simulations. We designed a program to simulate trial data and calibrate the simulation to an existing data source to determine the appropriate distributions of risk behaviors in the study population. We evaluated the power to detect treatment effects across a range of sample sizes, intervention effect sizes, levels of missingness, strength of prognostic measurements in predicting outcomes, and proportion of participants who become eligible for rerandomization. Overall, we found that there would be >80% power to detect a difference of about 1.5 events of risky sexual behavior between the 2 intervention arms with 250 participants enrolled in the trial.

Results

Funding for TechStep was awarded in June 2017, and phase 1 was approved by the IRB in April 2018. Phase 1 of the study was completed in December 2018. Initial phase 2 IRB approval came in June 2019. Data collection for phase 2 began in August 2019 and is expected to be completed in April 2021. As of March 2020, 54 participants have been enrolled in phase 2 of TechStep. Final results are anticipated in May 2021.

Discussion

TechStep was designed to evaluate the efficacy of technology-based interventions for reducing HIV sexual risk behaviors and increasing PrEP initiation, adherence, and

persistence among HIV-negative trans feminine, trans masculine, and gender nonconforming youth and young adults at risk of HIV and aims to improve their HIV and sexual health outcomes by providing culturally responsive, technology-based interventions.

There are a number of challenges to the *TechStep* clinical trial. First, it will require a multipronged effort to meet our recruitment goals as trans youth and young adults may not be accessible through traditional health care clinics. To address this, we will leverage social media advertising in both general (eg, Facebook) and trans-specific (eg, trans-specific subreddits) sites as well as recruitment at trans community events. Second, we do not provide smartphones or other web-enabled devices to study participants, but rather require that participants own or have access to a web-enabled device. This may restrict participation by lower socioeconomic status trans youth and young adults. However, if successful, it will increase the potential for scale-up. However, given that nearly 95% of teens have access to a smartphone [67], we believe that we will be able to capture the majority of the target population for this study. Third, given the high rates of mental health concerns among trans youth and young adults [68], medical and psychological services must be available during the study period. We will implement SRV-specific protocols to assess and provide referrals to medical and psychological services in the event that a participant should report a need for these services or experience any adverse reactions resulting from study procedures. In addition, the coaches for the eCoaching component have a protocol for managing crises that may arise during the eCoaching sessions and referrals to location-specific mental health resources.

The multilevel intersecting factors that impact the health and well-being of trans youth and young adults will require an equally complex response to reach these communities. The interventions designed and tested within TechStep provide highly scalable methods for reaching trans youth both in highly resourced urban areas and potentially also in geographically isolated rural areas. TechStep is designed so that comparisons may be made between those who receive the technology interventions in the control condition as well as to assess the additional benefit of receiving eCoaching compared with the text messaging or WebApp intervention alone. Thus, the lessons learned in *TechStep* will provide a strong foundation for subsequent technology-facilitated interventions with trans youth and young adults, and elucidate for whom more intensive interventions are required to reduce their risk for HIV. Thus, we believe that these lessons will move the field forward in important ways to address the complex needs of trans youth.

Conflicts of Interest

None declared.

Multimedia Appendix 1
TechStep WebApp Homepage.
[PNG File , 3622 KB - resprot_v9i8e18326_app1.png]

Multimedia Appendix 2
TechStep WebApp Resource Locator.
[PNG File , 1286 KB - resprot_v9i8e18326_app2.png]

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Abbreviations

ACASI: audio computer-assisted self-interview
ATN: Adolescent Medicine Trials Network
CBT: Cognitive Behavioral Therapy
eCoaching: electronic coaching
IMB: Information, Motivation, Behavior
IRB: Institutional Review Board
LGBT: lesbian, gay, bisexual, transgender
LTMLE: longitudinal targeted minimum loss-based estimation
MI: Motivational Interviewing
PHQ: Patient Health Questionnaire
PrEP: pre-exposure prophylaxis
RCT: randomized controlled trial
SRV: subject recruitment venue

STI: sexually transmitted infection
SUS: System Usability Scale
YAB: youth advisory board

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