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Protocol

Effects of a Text Messaging Smoking Cessation Intervention Among Online Help Seekers and Primary Health Care Visitors in Sweden: Protocol for a Randomized Controlled Trial Using a Bayesian Group Sequential Design

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Abstract

Background: A steady decline of the smoking prevalence in Sweden has been recorded over the past decade; however, people still start and continue to smoke. There is a need for effective smoking cessation interventions that can scale to a national level and that are designed to reach individuals requiring smoking cessation support in the general population.

Objective: Previous randomized controlled trials of smoking cessation interventions among high school and university students in Sweden have found consistent evidence that text messaging interventions are effective in helping students quit smoking. However, there are no studies that investigate the effects of text messaging interventions in a more general population. The objective of this study is to estimate the effects of a text messaging intervention on individuals seeking help to quit online and individuals visiting primary health care units.

Methods: A 2-arm, parallel-group (1:1), randomized controlled trial will be employed to address the study objectives. The trial will follow a Bayesian group sequential design. Recruitment will be conducted using online advertisement (Google, Bing, and Facebook) and through health care professionals at primary health care units. All participants will receive treatment as usual; however, participants who are allocated to the intervention arm will also be given access to a 12-week text message smoking cessation intervention. Primary outcomes are 8-week prolonged abstinence and 4-week point prevalence, measured 3 months and 6 months postrandomization. Mediator variables (self-efficacy, importance, and know-how) will be measured to estimate causal mediation models.

Results: Recruitment commenced in September 2020 and will not exceed 24 months. This means that a complete dataset will be available at the latest towards the end of 2022. We expect to publish the findings from this trial by June 2023.

Conclusions: This trial will further our understanding of the effects of text messaging interventions among a more general population than has previously been studied. We also aim to learn about differential effects between those who seek support online and those who are given facilitated support at primary health care units. Trial recruitment is limited to the Swedish population; however, a strength of this study is the pragmatic way in which participants are recruited. Through online advertisements, individuals are recruited in reaction to their own interest in seeking help to quit. At primary health care units, individuals who were not necessarily looking for smoking cessation support are given information about the trial. This closely mimics the way the intervention would be disseminated in a real-world setting and may therefore strengthen the argument of generalizability of findings.

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KEYWORDS

smoking cessation; text messaging; online help seekers; primary healthcare units; randomized controlled trial; Bayesian group sequential design; Bayesian; smoking; protocol; intervention

Introduction

Background and Rationale

In 2017, the Global Burden of Diseases, Injuries, and Risk Factors Study found that globally, the second leading risk factor for disability adjusted life years was smoking [1], closely following high systolic blood pressure among the factors considered. Smokers are at higher risk of contracting several noncommunicable diseases, including cancer, diabetes, and cardiovascular and respiratory diseases. Despite strong evidence for the negative consequences of smoking, it continues to be a legal substance that harms and kills many individuals when used as intended by manufacturers [2].

A steady decline of the smoking prevalence in Sweden has been recorded over the past decade [3]. The most recent data from 2018 indicate that the prevalence rate was as low as 7% in the general population, lower than the 12% prevalence rate of daily use of snus (a type of tobacco placed under the lip), but higher than vaping, which is only used by 0.6% of Swedes on a daily basis [4]. This means that we are closer than ever to eradicating one of the most important causes of disease in Sweden. However, as there still are smokers and young individuals still start smoking, there is a need for effective smoking cessation interventions that can scale to a national level and that are designed to reach individuals requiring smoking cessation support in the general population.

Mobile phone–based interventions such as text messaging interventions could potentially have far reach among those who may benefit, in particular due to their reliance on standard technology and the high mobile phone ownership in Sweden. Typically, these interventions consist of a series of messages sent to participants' mobile phones over the course of 8-12 weeks. The messages motivate participants to make a quit attempt and then reinforce and support this decision throughout the intervention period. In addition, text messaging interventions may also increase access to education and support services that promote smoking cessation [5].

Several randomized controlled trials (RCTs) have been conducted to estimate the effects of text messaging interventions for smoking cessation [5-11], notably the txt2stop trial [9] (n=5800), which found strong evidence in favor of the intervention with respect to both biochemically verified abstinence (odds ratio [OR] 2.20, 95% CI 1.80-2.68, P<.001) and self-reported abstinence (OR 1.47, 95% CI 1.40-1.66, P<.001). Three meta-analyses concluded that text messaging interventions have a positive effect on smoking cessation: One reported a summary effect size (Hedges' g) of 0.25 (95% CI 0.13-0.38) [6], the second meta-analysis reported an overall summary OR of 1.37 (95% CI 1.25-1.51) of smoking cessation in favor of text messaging interventions [5], and the third analysis similarly found that quit rates were higher among those who had access to text messaging interventions (OR 1.36, 95% CI 1.23-1.51) [7]. Thus, there exists a relatively strong body of evidence for the average treatment effect of text messaging interventions.

In Sweden, our research group has previously conducted RCTs of smoking cessation interventions among high school [12,13] and university students [11,14-16]. Here, we found consistent evidence that a text message intervention was effective in increasing the prevalence of smoking abstinence. We are also currently conducting an RCT of a text message smoking cessation intervention tailored to patients undergoing elective surgery [17,18]. However, these interventions have recruited participants from well-defined contexts (ie, high schools, university campuses, and surgical departments) but have not taken a broader approach to recruitment in the general population. Also, there have not been any studies in Sweden of text message smoking cessation interventions targeting the general population.

Objectives

The objective of this study is to estimate the effects of a text message smoking cessation intervention as a complement to treatment as usual in the general population of Sweden. In addition, the study aims to gain knowledge on the differences between individuals recruited from 2 distinct settings: online advertisement and primary health care units. In particular, the objectives of the trial are to (1) estimate the effects of a text messaging smoking cessation intervention on prevalence rates of smoking abstinence compared to individuals without access to the intervention; (2) estimate the degree to which the total effect is mediated through motivation, importance, and know-how; (3) estimate the degree to which the total effect is moderated by the mode of recruitment: online advertisements versus primary health care units; and (4) investigate differences in baseline characteristics between participants recruited through online advertisements and participants recruited through primary health care units.

Trial Design

A 2-arm, parallel-group (1:1) RCT will be employed to address the study objectives. The trial will follow a Bayesian group sequential design [19-21] (see Sample Size). All participants will receive treatment as usual; however, participants who are allocated to the intervention arm will also be given access to a text message smoking cessation intervention.

Methods

This trial was preregistered on July 27, 2020 (ISRCTN13455271) and received ethical approval from the Swedish Ethical Review Authority (Dnr 2020–01427, 2020-06-16).

Participants, Interventions, Outcomes

Study Setting and Recruitment

Recruitment will take place in 2 distinct settings. First, online advertisements on Google, Bing, and Facebook (restricted to Sweden) will be used to recruit individuals who are seeking help to quit smoking. Individuals clicking on the advert will be taken to the study website where information will be presented about the study and how to sign up. Second, health care professionals at participating primary health care units across Sweden will advertise the trial to patients through printed media (eg, flyers, leaflets, business cards, posters). The printed media will contain information about the study and how to sign up.

Regardless of setting, individuals will sign up for the trial by sending a text message to a dedicated telephone number. Within 5 minutes, they will receive a text message in response, with a hyperlink to an informed consent form (see Multimedia Appendix 1). Participants consenting to take part in the trial will immediately be redirected to the baseline questionnaire, after which eligible participants will be randomized (see Assignment of Interventions).

Eligibility Criteria

Individuals self-reporting smoking at least 1 cigarette per week and who are aged ≥18 years will be eligible for the trial. Individuals who self-report not smoking or doing so less than weekly or are aged <18 years will be explicitly excluded from the trial. The majority of study information and all questionnaires will be delivered to participants through a mobile phone and will be in Swedish; thus, participants without access to a mobile phone and who do not comprehend Swedish well enough to sign up for the trial will be implicitly excluded.

Interventions

Both the intervention and control groups will be given treatment as usual, and neither will be restricted from using other available smoking cessation aids. The intervention group will in addition be given access to a text message intervention.

Treatment as usual will in this trial be defined as follows. For participants recruited through online advertisements, it is defined as referral to national quit lines (sluta-röka-linjen [22]) and general information about smoking and health (1177 Vårdguiden [23]). For participants recruited through primary health care units, it is defined as referral to national quit lines (sluta-röka-linjen [22]) and referral to general information about smoking and health (1177 Vårdguiden [23]). In addition, primary health care units will offer all smokers a meeting with a nurse or smoking cessation specialist to have a conversation about smoking cessation and health.

Participants allocated to the intervention group will be given access to a text message intervention. Two versions of the intervention exist: one general version and one that has been tailored specifically for individuals undergoing elective surgery. Both versions are based on findings from our previous research [11-18]. The elective surgery intervention will be allocated to participants in the intervention group who report having elective surgery planned in the next 3 months.

Both versions of the intervention consist of a 12-week text message program with messages sent to participants' mobile phones on a daily basis. Over the first few weeks, all participants will receive 2-4 messages per day, which will be reduced to 2 messages per day during the middle part of the intervention and further reduced to 1 message per day during the latter part of the intervention. The content of the messages is primarily informational and encouraging, and some messages ask participants to do certain tasks, such as throw away ashtrays. None of the messages ask participants to respond, but participants can request extra supportive messages by sending a text message with 1 of 3 keywords: weight, relapse, or craving. A message is then sent back to participants with specific information about potential weight gain, what to do if one relapses and has a cigarette, or help if they are experiencing nicotine cravings.

Unique for the elective surgery version is that some of the messages include hyperlinks that take the participants to interactive web-based modules. There is a total of 9 such modules and, throughout the intervention period, participants will be reminded to revisit previously completed modules.

Briefly, the 9 interactive modules included in the elective surgery version of the intervention are (1) set of tips and tasks, of which participants choose 5 that suit them; (2) set of reasons to quit smoking, of which the participants choose 5 (or enter their own reason); (3) series of questions that result in a plan for how to deal with certain situations in which the temptation to smoke is increased, such as "When I have had my dinner, I will have a piece of fruit" or "While I am waiting for the bus, I will listen to music."; (4) set of information boxes that relate to withdrawal symptoms; (5) set of tips that participants choose, or enter on their own, on what to do when craving cigarettes; (6) set of information boxes with information about what happens to the human body after smoking cessation; (7) set of information boxes with information about good habits that can replace the smoking habit; (8) series of questions that lead to suggestions of physical activities that the participant might want to try in order to improve his or her health further and relieve abstinence; and (9) pros and cons list created by the participant.

Outcomes

All outcomes will be self-reported through questionnaires. Please see Multimedia Appendix 2 for all questionnaires used in the trial.

The primary outcomes include prolonged abstinence, following the Russell standard definition of not having smoked more than 5 cigarettes in the past 8 weeks (thus allowing for a 4-week grace period) [24]. The abstinence period will be adjusted to 5 months at the 6-month follow-up. Another primary outcome is the point prevalence of smoking abstinence, defined as not smoking any cigarette during the past 4 weeks, as recommended by the Society for Research on Nicotine and Tobacco [25].

Secondary outcomes include the 7-day point prevalence of complete smoking abstinence, number of cigarettes smoked weekly (if still smoking), number of quit attempts since baseline, and number of uses of other smoking-cessation aids since baseline.

Mediator Outcomes

Mediator outcomes include the confidence in being able to quit smoking (self-efficacy; measured on a scale from 1 to 10), importance of quitting (scale from 1 to 10), and knowledge of how to quit smoking (scale from 1 to 10).

Participant Timeline

A timeline for participants' progress throughout the trial is presented in Figure 1. The baseline questionnaire will assess for eligibility, and after completion, participants will be immediately randomized. The intervention period will last for 3 months, and mediator and outcome measures will be assessed at 3 months and 6 months after randomization. Mediator outcomes will also be assessed 1 month after randomization. Participation is complete after the 6-month assessment.

Figure 1. SPIRIT figure representing participant progress throughout the trial.

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Close-out
TIMEPOINT	$-t_1$	0	*1 month*	*3 months*	*6 months*	*6 months*
ENROLMENT:	X					
Eligibility screen		X				
Informed consent		X				
Allocation		X				
INTERVENTIONS:						
Intervention group		←	—	→		
Control group		←	—	→		
ASSESSMENTS:						
Baseline		X				
Mediators			X	X	X	X
Outcomes				X	X	X

Assignment of Interventions

Allocation will be done according to a computer-generated random sequence. Prior to randomization, participants will be stratified according to which of the 2 versions of the intervention is appropriate (general or surgery). Block randomization will be used to ensure equal number of participants in each group within stratum. Random block sizes of 2 and 4 will be used in order to prevent subversion of allocation concealment.

Randomization will be done immediately after responding to the baseline questionnaire, which is done by participants on their mobile phones. Once responses are received by the backend server, automatic randomization will take place, and participants will be told about group allocation via a text message. Research personnel will not be able to affect the allocation.

Participants will be aware of their group allocation; however, research personnel will be blinded. All questionnaires are completed by participants on their own mobile phones, without supervision by research personnel. These automated procedures ensure no unblinding. Nonresponders to questionnaires will be called by phone (see Data Collection), and during this time, it is possible that participants will reveal their allocation to assessors (see Generalization and Limitations).

Data Collection

Baseline questionnaires will be completed by participants on their mobile phones at the time of enrollment. There are 3 follow-up intervals: 1 month, 3 months, and 6 months after randomization. All follow-ups will be initiated by sending text messages to participants with hyperlinks to questionnaires. Only mediators will be assessed at the 1-month follow-up; there will be no smoking cessation outcomes. In all cases, the following attempts will be made to collect data:

1. A total of 2 reminders will be sent 2 days apart to those who have not responded.
2. If no response is given to (1), then we will send questions directly in a text message, asking participants to respond directly with a text (no hyperlink). At 1 month, we will ask

all 3 mediator questions. At 3 months and 6 months, we will only ask for primary outcome measures.

3. If there is no response given to (2) at 3 months and 6 months, we will attempt to call participants to collect responses to the same questions as in (2). No phone calls will be made to collect 1-month follow-up data. A maximum of 5 call attempts will be made.

The 2 smoking cessation outcome follow-up intervals of 3 months and 6 months measure the immediate effect of the intervention and the prolonged effect of the intervention, respectively. As such, we are not proposing either to be primary above the other. Note that since our analyses are not primarily based on null hypothesis testing (see Statistical Analyses), we are not majorly concerned about the increased error rate by having multiple primary follow-up intervals.

Statistical Analysis

Overview

All randomized individuals will be included in analyses, following intention-to-treat principles. Missing data will initially be handled by available case analysis under the missing completely at random (MCAR) assumption. Systematically missing data will invalidate the MCAR assumption; thus, evidence of such will be sought. If data are missing systematically, then it may be the case that early responders differ from nonresponders and, in extension, that late responders are more like nonresponders. Therefore, one analysis will regress primary outcomes against the number of attempts to collect follow-up data before a response was recorded. Attrition analyses will further explore the MCAR assumption by investigating if responders and nonresponders are different with respect to baseline characteristics.

We anticipate approximately a 10%-20% attrition rate, as this is what we have experienced in previous trials of text messaging interventions in Sweden when we used a similar scheme for data collection [11,14,26-28]. We have no reason to believe that attrition rates will be different between recruitment settings, as all follow-up procedures will be the same, but we will investigate such differences and report our findings in light of them. Sensitivity analyses that include imputed values for missing outcome data will be performed, and limitations of the imputed analyses will be considered in face of the actual attrition rate. In addition, data will be graphically examined for outliers or data input errors, and sensitivity analyses will be performed excluding any erroneous data points.

We will estimate all models using Bayesian inference [29-31] and report the marginal posterior probability of an effect of group allocation on each of the outcomes. We will use the median as a point estimate of the effect and report 95% compatibility intervals. We will complement the Bayesian inference with null hypothesis tests at the .05 significance level. Both posterior distributions and significance tests will create a basis for scientific inference.

Models

Baseline characteristics will be compared between the intervention and control groups using Fisher exact tests and Mann-Whitney U tests. Using logistic regression, we will compare characteristics of participants recruited through the online setting versus those through facilitated recruitment and between those eligible for the general version versus the surgery version of the intervention.

For the primary and secondary outcome measures, differences between the 2 groups (control and intervention) at the different follow-up stages with respect to prolonged abstinence, point prevalence of smoking abstinence, and 7-day point prevalence will be analyzed using logistic regression. Negative binomial regression will be used to analyze the number of quit attempts, use of other smoking cessation services, and cigarettes smoked weekly (among those who still smoke). Models will be adjusted for baseline characteristics (gender, age, nicotine dependence, importance, self-efficacy, and know-how) as well as the stratifying variable in the randomization procedure (general or surgery eligibility).

Effect-modification analyses will be performed for the 2 primary outcomes. The following potential effect modifiers measured at baseline will be explored: gender, age, years of smoking, mean number of cigarettes smoked weekly, use of snus, nicotine dependence, importance, self-efficacy, and know-how. In addition, effect modification based on which setting (online or primary health care) participants were recruited will be explored and which version of the intervention they were eligible for (general vs surgery). Effect-modification analyses will be performed by including interaction terms in the adjusted regression models for each potential moderator (one model per moderator).

For the mediator outcomes, mediators will be explored using a causal inference framework [32-34] using Bayesian inference to estimate the natural direct effect and natural indirect effect (as per the definitions of Pearl [34]). We will report on the posterior distributions of these 2 estimates, as well as the proportion of the total effect that is accounted for by the natural indirect effect. Four models will be created for each primary outcome measure, 3 investigating the mediating factors on their own and a fourth incorporating all mediators at once. If any baseline characteristics are found to moderate the effect in the primary analysis, then additional mediator models will be created to include these as moderators.

Exploratory Analyses

RCTs traditionally contrast 2 or more groups, however do not address individual variability (also known as heterogenous treatment effects). Some individuals may respond well to an intervention, while others might not, and some may be harmed; however, contrasting 2 heterogenous groups does not identify such differences. Predicting how individuals will respond to an intervention using baseline characteristics is one way of early identification of individuals who may benefit, but also allows us to identify groups of individuals who are less likely to respond well to the intervention [35]. We will therefore learn prediction models from the trial data to predict outcome given baseline values and use a combination of clustering and multinomial regression to identify and label groups of individuals who may be more or less helped by the novel intervention.

We will investigate differences in outcomes between control subjects with respect to the 2 modes of recruitment (online and primary health care). All control subjects will receive links to online resources; however, those who have been recruited at primary health care units will in addition be told about resources available at the unit. Also, participants may react differently to being allocated to the control arm (see Generalizability and Limitations). Thus, these analyses will help to inform potential biases in effect estimates and to inform if offering additional support at the unit is effective above online resources.

Sample Size

We will use a Bayesian group sequential design to monitor recruitment with interim analyses planned every other week after the first 20 participants have completed the 6-month follow-up. Each of the primary outcomes (prolonged abstinence and point prevalence) will be modelled according to the analysis plan (see Statistical Analysis), and the coefficient for group allocation will be assessed for effect, harm, and futility. Let $ß_{k,i}$ represent the regression coefficient for group allocation at time k for outcome i and D all the data currently accumulated, then the target criteria will be: $p(ß_{k,i} > 0 \mid D) > 97.5\%$ and $p(ß_{k,i} > \log(1.3) \mid D) > 50\%$ for effect; $p(ß_{k,i} < 0 \mid D) > 97.5\%$ and $p(ß_{k,i} < \log(1/1.3) \mid D) > 50\%$ for harm; and $p(\log(1/1.3) < ß_{k,i} < \log(1.3) \mid D) > 95\%$ for futility.

For the effect and harm criteria, we will use a standard normal prior for dummy covariates (mean 0, SD 1.0) and a slightly wider prior will be used for the futility criterion (mean 0, SD 2.0). The criteria should be viewed as targets; thus, at each interim analysis, we will evaluate each criterion for each covariate and make a decision if we believe that recruitment should stop or continue. However, recruitment will not exceed 24 months.

Note that this Bayesian approach allows us to look at the data an unlimited number of times without worrying about multiplicities and error rates, as would be necessary using a frequentist approach [36]. Also, since no fixed effect size is prespecified, we reduce the risk of stopping both too early and too late [21].

Results

Recruitment commenced in September 2020 and will not exceed 24 months. This means that a complete dataset will be available at the latest towards the end of 2022. We expect to publish the findings from this trial by June 2023.

Discussion

Effects of text messaging interventions

This trial will further our understanding of the effects of text messaging interventions among a more general population than has previously been studied. We also aim to learn about differential effects between those who seek support online and those who are given facilitated support at primary health care units.

We expect to expand upon current knowledge on how text messaging interventions may work by the investigation of mediators. The text2quit trial found that self-efficacy, know-how, and the sense that somebody cared partially mediated the intervention's effect on smoking cessation [37]; however, there are no other similar mediator studies. Thus, the body of evidence needs to be expanded. Finally, we will also investigate for whom the interventions work by analyzing heterogenous treatment effects.

Generalizability and Limitations

Trial recruitment is limited to the Swedish population; however, a strength of this study is the pragmatic way in which participants are recruited. Through online advertisements, individuals who decided to look for support without interference by study procedures will be recruited. At primary health care units, individuals who were not necessarily looking for smoking cessation support are given information about the trial. This closely mimics the way the intervention would be disseminated in a real-world setting and may therefore strengthen the argument of generalizability of findings.

The pragmatic design of the study aims to estimate the effects of the public health initiative as a whole (ie, recruiting participants in both online and primary health care settings). These effect estimates are also the target of our Bayesian group sequential design, which dictates the sample size. This design does however limit our ability to estimate differential effects of the 2 versions of the intervention, as well as moderating effects of the study setting. We have however decided upon this pragmatic design as it is uncertain how many participants are in need of the surgery version of the intervention, as well as the recruitment rates in the different settings, thus forming a hypothesis of the differential effect among versions and setting targets for future research.

There are well-known artifacts that arise from knowledge of participation in research that may both dilute and inflate effect estimates [38-41]; thus, these should be considered when generalizing the findings from this and other trials. Participants recruited through online advertisements are actively seeking help, and baseline assessment may therefore be an effective way for them to decide to change their behavior, diluting the effects of the intervention, as there is a ceiling limit for the intervention's effect. Those recruited through primary health care centers are less likely to be looking for cessation support at the moment, although they may have thought about it in the past, and baseline assessment may make participants allocated to the intervention arm more receptive to the intervention than they would have been otherwise, possibly inflating effect estimates. We will have an opportunity to explore the differences between control and intervention subjects with respect to mode of recruitment to estimate these biases.

The lack of blinding of participants may introduce forms of performance bias, including both movement away and towards behavior change due to disappointment about being in the control group, and while we may hypothesize about the magnitude of this bias, we will consider it a limitation of the trial that we have no means of accounting for quantitatively.

A risk of detection bias stems from the scheme used to decrease attrition bias, by calling participants not responding to initial attempts to collect data (see Data Collection). In such a scenario, it is possible that participants disclose their group allocation to research personnel, who are otherwise blinded, during the follow-up interview. We believe that the advantage of higher follow-up rates gained by calling nonresponders outweighs this risk of bias, and personnel making the calls will be instructed to not prompt and to avoid engaging in conversation about group allocation.

Outcome measures will be self-reported, which may be susceptible to recall and social desirability bias. The Society for Research on Nicotine and Tobacco does however recommend that, in studies with limited face-to-face contact, it is neither required nor desirable to use biochemical verification [25]. Despite this recommendation, results from this trial should be understood under this limitation, as the risk of bias is exacerbated due to participants not being blinded.

Summary

While the prevalence of smoking in Sweden has decreased over the past decade, people still start smoking, and current smoking cessation aids may not be sufficient to push the prevalence further towards zero. This trial will be the first to estimate the effects of a smoking cessation text messaging intervention among both online help seekers and primary health care patients in Sweden. If effects are found to be important, then dissemination can be quick due to the trial's pragmatic design, which may help to further reduce the smoking prevalence in Sweden.

This trial also contributes to the overall body of evidence for text messaging interventions, as it looks to increase our understanding of how effects are mediated through psychosocial variables and how effects are differential with respect to passive online recruitment and active facilitated access. Understanding how the effects of text messaging interventions are differential will help us develop more tailored and effective interventions and make support decisions about how to disseminate the interventions into real-world practice.

Acknowledgments

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Conflicts of Interest

MB and PB own a private company (Alexit AB) that develops and distributes lifestyle interventions to be used in health care settings. Alexit AB had no part in funding or planning of the trial but does provide the necessary text messaging service for the intervention.

Multimedia Appendix 1
Informed consent.
[DOCX File , 15 KB - resprot_v9i12e23677_app1.docx]

Multimedia Appendix 2
Questionnaires.
[DOCX File , 16 KB - resprot_v9i12e23677_app2.docx]

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Abbreviations

MCAR: missing completely at random
OR: odds ratio
RCT: randomized controlled trial

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Protocol

An Artificial Intelligence–Based, Personalized Smartphone App to Improve Childhood Immunization Coverage and Timelines Among Children in Pakistan: Protocol for a Randomized Controlled Trial

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Abstract

Background: The immunization uptake rates in Pakistan are much lower than desired. Major reasons include lack of awareness, parental forgetfulness regarding schedules, and misinformation regarding vaccines. In light of the COVID-19 pandemic and distancing measures, routine childhood immunization (RCI) coverage has been adversely affected, as caregivers avoid tertiary care hospitals or primary health centers. Innovative and cost-effective measures must be taken to understand and deal with the issue of low immunization rates. However, only a few smartphone-based interventions have been carried out in low- and middle-income countries (LMICs) to improve RCI.

Objective: The primary objectives of this study are to evaluate whether a personalized mobile app can improve children's on-time visits at 10 and 14 weeks of age for RCI as compared with standard care and to determine whether an artificial intelligence model can be incorporated into the app. Secondary objectives are to determine the perceptions and attitudes of caregivers regarding childhood vaccinations and to understand the factors that might influence the effect of a mobile phone–based app on vaccination improvement.

Methods: A mixed methods randomized controlled trial was designed with intervention and control arms. The study will be conducted at the Aga Khan University Hospital vaccination center. Caregivers of newborns or infants visiting the center for their children's 6-week vaccination will be recruited. The intervention arm will have access to a smartphone app with text, voice, video, and pictorial messages regarding RCI. This app will be developed based on the findings of the pretrial qualitative component of the study, in addition to *no-show* study findings, which will explore caregivers' perceptions about RCI and a mobile phone–based app in improving RCI coverage.

Results: Pretrial qualitative in-depth interviews were conducted in February 2020. Enrollment of study participants for the randomized controlled trial is in process. Study exit interviews will be conducted at the 14-week immunization visits, provided the caregivers visit the immunization facility at that time, or over the phone when the children are 18 weeks of age.

Conclusions: This study will generate useful insights into the feasibility, acceptability, and usability of an Android-based smartphone app for improving RCI in Pakistan and in LMICs.

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KEYWORDS

artificial intelligence; AI; routine childhood immunization; EPI; LMICs; mHealth; Pakistan; personalized messages; routine immunization; smartphone apps; vaccine-preventable illnesses

Introduction

Background

Pakistan has an under-5 mortality rate of 69.3 per 1000 live births [1], and is one of the five countries that contributed to half of the under-5 deaths in 2018, with 70% of the deaths being attributed to infectious diseases [2,3]. Pakistan ranks third among countries with the lowest immunization rates for diphtheria-tetanus-pertussis (DTP)–containing vaccine; 40% of children not vaccinated with a 3-dose series of DTP vaccine in 2015 belonged to Pakistan [4]. The low vaccine coverage has led to a number of challenges, including uninterrupted polio transmission and measles outbreaks [5]. In 2013 alone, a measles outbreak resulted in 14,000 cases with 306 deaths [6].

According to the nationwide 2017-2018 Pakistan Demographic and Health Survey (PDHS), 66% of children between the ages of 12 and 23 months had all received the basic vaccines, but only half of the children had age-appropriate vaccines [7]. The yearly PDHS surveys since 1990 have consistently shown that the coverage for age-specific vaccines falls as children grow older, with the highest coverage being seen with the birth vaccine, bacillus Calmette Guérin (BCG) (85%), and the lowest coverage being seen for the 9-month measles-1 vaccine (61%) [8]. In another study, the rate of timely BCG vaccination was 89.3%, with the measles-2 vaccine, given at 15 months of age, having a drop of 2.3% [9]. Low rates of age-appropriate vaccination, even with relatively higher rates of late immunizations, can be extremely detrimental for children as they prolong the duration for which they are vulnerable to illnesses [10].

The barriers preventing widespread immunization are multifaceted, including lack of financing, lack of good governance, supply chain interruption, and lack of awareness in the local population [8]. A case study on the Expanded Programme on Immunization (EPI) in Pakistan considered community misperceptions and misinformation to be one of the most important issues; the program recommended addressing misinformation while taking the local context into account, as the perceptions can vary from region to region and blanket communication may not resonate with all of the communities [11]. Losing vaccination cards is another major reason for low uptake, as many families rely on vaccination cards to know when it is time for the next vaccine. In one study performed on 10,000 caregivers, 76.9% did not have vaccination cards or were missing some data regarding their vaccination status [10]. With a further decrease in immunization rates due to the COVID-19 pandemic, vaccination coverage has plummeted to an all-time low due to disruption in vaccination services and demand, causing new outbreaks of previously controlled diseases, such as new polio strains, measles, and rubella [12]. Therefore, innovative and cost-effective measures need to be taken to understand and address the causes of low immunization rates.

Mobile phones provide an innovative and cost-effective public health intervention and the number of cellular phone subscribers in Pakistan has been steadily growing, with 166 million subscribers as of May 2020 and a tele-density of 78% [13]. Mobile apps and social media have been shown to be effective in various public health programs in developed countries [14-16]. However, the data from low- and middle-income countries (LMICs) are limited on the use of mobile phone–based interventions for improving routine childhood immunization (RCI) coverage; however, a few studies have shown significant promise, even when no additional financial incentives were provided to participants [17]. Most of these studies have used one-way reminder SMS text messages as the study intervention and a few used different forms of messages, such as two-way messages, educational messages, or personalized messages addressing the barrier specific to the recipient [18-23]. There is a need to invest our focus into research that explores the use of mobile phone technology and the design of robust interventions to better understand the utility of these gadgets to bring about a change in the traditional health system.

Study Objectives

Primary Objectives

Our first objective is to evaluate whether a personalized mobile app can improve on-time visits at 10 and 14 weeks of age for RCIs as compared with standard care. Our second objective is to evaluate whether an artificial intelligence (AI)–based model can be incorporated into the app to improve RCI coverage and behavior change.

Secondary Objectives

Our secondary objectives are to learn about the perceptions and attitudes of caregivers regarding childhood vaccinations and to find out about factors that might influence the use of mobile phone–based apps for improvement in vaccination coverage.

Methods

Target Population

Our target population is caregivers of newborns or infants visiting the Aga Khan University Hospital (AKUH) vaccination center for their children's 6-week vaccination and whose children are due for their RCIs at ages 10 and 14 weeks, according to Pakistan's EPI schedule.

Study Goal

The study goal is to conduct a mixed methods study to assess the acceptability and usability of a personalized, smartphone-based, behavioral intervention to improve vaccine uptake at 10 and 14 weeks of age, according to Pakistan's EPI and the recommended schedule.

Study Hypothesis

An Android smartphone–based personalized app will improve vaccination uptake among children at 10 and 14 weeks of age compared to standard care.

Outcomes

Primary Outcomes

We aim to see the following primary outcomes: (1) a 10% increase in RCI through a personalized smartphone–based app at 10 and 14 weeks of age, according to the EPI schedule, versus standard care and (2) a 10% increase in RCI within 1 week of the original timeline at 10 and 14 weeks versus standard care.

Secondary Outcomes

We aim to achieve the following secondary outcomes: (1) to understand the perceptions and barriers of caregivers regarding immunization, (2) to understand caregivers' perceptions, acceptability, and usability of a personalized mobile phone–based app for vaccination improvement, and (3) to achieve 85% accuracy in correctly predicting the likelihood of children defaulting from subsequent RCI visits.

Study Site

This study will be conducted at the AKUH in Karachi, Pakistan. The caregivers visiting the vaccination center at the AKUH Community Health Center (CHC) will be enrolled in the study.

Study Design

A mixed methods study will be conducted in which a smartphone app will be developed based on the findings of the qualitative component of the study, in addition to *no-show* study findings [24]. The smartphone app will include text, voice, video, and pictorial messages to help the caregiver participants adhere to their children's RCI schedules at 10 and 14 weeks of age.

Qualitative Component: Pretrial Interviews

The qualitative component of this study involves determining caregivers' perceptions about RCI and the role of the mobile phone–based app in improving RCI coverage. In-depth interviews will be conducted with the caregivers visiting the CHC vaccination center. We explored the caregivers' perceptions and attitudes regarding childhood vaccination, the reasons for missed visits at the CHC vaccination center, the perceived role of staff and services provided through the CHC vaccination center, the usability and acceptability related to the use of the personalized mobile phone–based app for improvement in vaccine uptake, the potential barriers related to the app's usage, and their expectations of the app regarding reminders for RCI coverage and timeliness. We used the purposive sampling strategy to interview 15-20 consenting parents over 15 days. This method of sampling allows for the identification of well-informed participants who can provide insights and personal experiences regarding the subject being examined. A semistructured interview guide was developed in English and Urdu and was further modified after each pilot interview to explore the concerns recognized through constant analysis of consecutive interviews. Data collection continued until data saturation was reached. Each interview took around 30-45 minutes. Information gathered through the interviews helped us in (1) understanding the types of RCI and mobile phone app barriers perceived by caregivers, (2) designing the randomized controlled trial (RCT), and (3) developing a mobile app.

Intervention

An Android-based mobile app is being developed. The app will have features and capacity for text, voice, pictorial, and video messages. The content of the messages will be based on the previous study that utilized automated SMS text messages and calls in various local languages to improve RCI coverage [25].

The four message domains will be educational, reminder, religious, and adverse effects. In addition, pictorial and video messages freely available through open sources focusing on immunization among children in Pakistan will be utilized.

Development of the Smartphone App

This smartphone app, as part of the Capacity Building in Technology-Driven Innovation in Healthcare (CoNTINuE) project, will be developed on an Android platform, as 95% of smartphone users in Pakistan use Android phones [26]. Functionality validation exercises will be carried out using cognitive validation and cultural probes before using the app in this research. The app will be installed on the phones of the participants in the intervention arm by the study administrators. Once the app has launched and privacy policies have been accepted, the participants will be asked to enter information into the app, including their child's medical record number, their child's date of birth, their preferred mode of messages such as audio or text, their language and time preferences to receive the messages, and the barriers they face to vaccinate their child; these features will help personalize the type and content of messages they will receive. The data will be stored in local secured systems and immediately anonymized using digitally available tools to ensure privacy and avoid any potential identity breach.

After entering the enrollment data, the phone will need to be connected to the internet for a few minutes to allow for necessary content to be downloaded, which will enable timely notifications in the future. At the enrollment site, free Wi-Fi will be available for the participants. However, in the event of

a disruption in downloading the app or prolonged time consumption due to the size of the app, an alternate Wi-Fi connection, whose cost is covered by the project, will be provided to download the app. This feature of one-time downloading of the data allows for the app to be functional even in the case of internet unavailability. Once the content is downloaded, the first screen to be displayed will be the app logo layout followed by the main home layout. The user can then navigate to the (1) *vaccination schedule* layout, (2) *resources* layout, (3) *notification detail* layout, or (4) *about us* layout pages, as shown in Figures 1 and 2. This app will be developed to catalyze a behavioral change in its users through its many functionalities. In the *vaccination schedule* layout, a calendar indicating the child's specific, scheduled vaccination days will be displayed. In the *resources* layout, the users will be able to access the official websites of the EPI, the AKUH CHC, and World Health Organization vaccines, among others. The *notification detail* layout will display notifications every week regarding upcoming vaccinations or educational messages. The notifications will be displayed as summaries, and additional information and content from the text or audio message will be able to be accessed upon clicking the individual notification. The notifications will be delivered in the participant's preferred language (ie, Urdu, English, Sindhi, Roman Urdu, and Roman Sindhi), preferred mode of messaging (ie, text or audio), and preferred time for receiving the notifications (ie, morning, afternoon, or evening). Lastly, the *about us* layout will provide insight into the vision of the CoNTINuE project. These navigation panels and their labels will also be displayed in the preferred local language. Also, at the time of enrollment, a detailed walk-through process of the app will be conducted with the caregivers.

Figure 1. Flow diagram of the user interface.

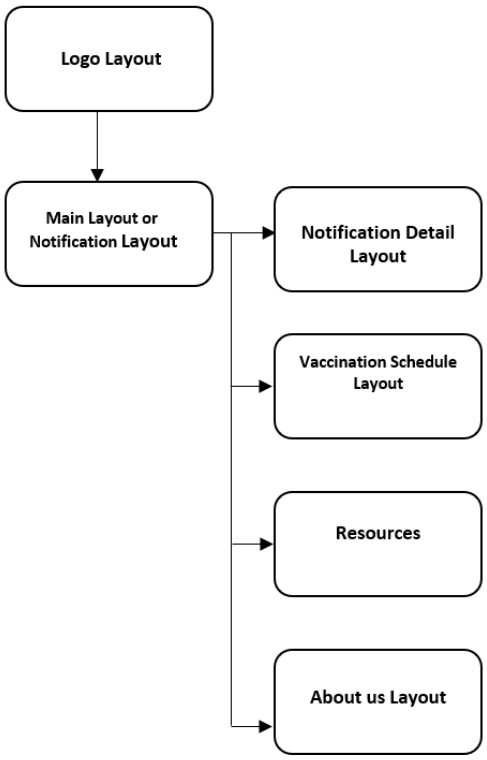
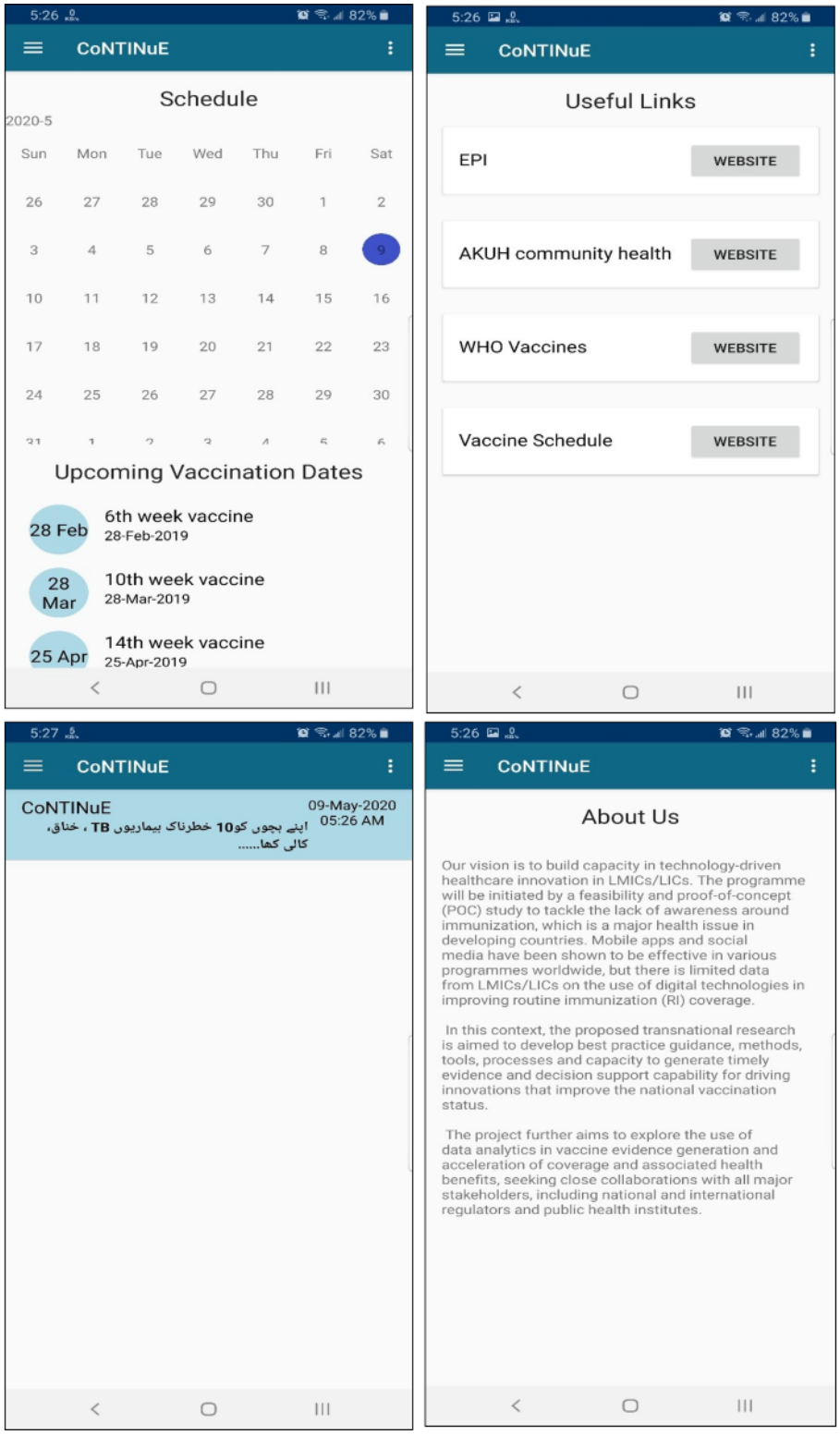


Figure 2. Screenshots of the various layouts of the app: vaccination schedule layout (top left), resources layout (top right), notification detail layout (bottom left), and about us layout (bottom right).



Development of the AI-Enabled App

AI is being applied in this study in two different manners. First, AI is being applied to the baseline data and RCT results from a previous study, which is based on an automated SMS text message and voice call intervention [25]. Paigham-e-Sehat is a recently completed study that includes data from 3300 children, in which RCI-related messages were sent to caregivers via SMS text messages or automated calls to improve their children's vaccine coverage at 6, 10, and 14 weeks of age. An AI model, using decision tree classification, random forest, naïve Bayes, and k-nearest neighbor algorithms, generated through that study is being used to train the system for predicting the likelihood of a family defaulting from subsequent RCI visits. This system will be tested during this study by validating the system's prediction ability against the actual outcome of this

study. Further, the important predictors and barriers identified in the previous study will be used for extending the work on data obtained from this study [25]**.** After the availability of the study results, factors related to the effect of users' app behavior on the vaccination outcomes, including their preferred modes, timing, and interactivity with the app, will be analyzed through pattern recognition using a mixture of hidden Markov models. These findings will then be used to train the next version of the app to automatically adjust to individual user behaviors that have been found to be effective in improving RCI coverage (eg, the pattern recognition may identify a cluster of participants that have a better chance of getting their children immunized if they interact with app notifications during the weekend, when they are more likely to plan the next week).

Trial RCT

Study Design, Settings, and Timeline

The study design is an RCT, consisting of two parallel arms with the allocation of 1:1 to the intervention group or the standard care group (ie, control group). After obtaining informed consent, eligible infants and their caregivers will be randomly allocated into one of two groups using randomly generated computer assignments, where allocations will be placed in sealed opaque envelopes to be opened at the time of enrollment. IDs will be generated in blocks, with 6 cases in each block. Details of each group are as follows:

1. Intervention group: the intervention group, in addition to the standard counseling group, will receive text, voice, pictorial, and video messages regarding vaccinations; messages will be received once a week until the child turns 14 weeks of age.
2. Control group: the control group will receive one-time, standard, verbal counseling at the time of the initial visit for on-time EPI vaccines at 10 and 14 weeks of age, as recommended by the EPI and the government of Pakistan.

The trial was registered at ClinicalTrials.gov (NCT04449107).

Inclusion and Exclusion Criteria

The study inclusion criteria will be as follows: (1) a parent or guardian, or at least one person in the household, has a working Android-based smartphone, (2) the parent or guardian has a basic ability to use an Android-based smartphone, and (3) the parent or guardian provides consent. The study exclusion criterion is that the family does not plan to visit the AKUH for scheduled CRI visits when their child is 10 and 14 weeks of age.

Sample Population and Size

Target enrollment is 328 infants, 164 in each arm; assumptions used for calculating sample size are an increase in RCI coverage rate from 40% to 60%, power of 0.80, α error rate of .05, and allowing for 10% dropout [27].

Sampling Methodology

The study staff will approach families visiting the AKUH CHC vaccination center, who have brought an infant for their 6-week RCI. Staff will explain the study objectives to the parents or caregivers. If the parent or caregiver is interested in the study, the infant will be evaluated for enrollment. One child per household will be selected. In a household where there is more than one child due for a 10- or 14-week vaccination, a random selection will be made by a program designed in the mobile phone device. After meeting the eligibility criteria, informed consent will be obtained, and the infant will be enrolled in the study.

Randomization

The intervention and control group ratio will be 1:1; the randomization list will be generated through computer assignments with blocks of 6 children; participant allocation will be placed in sealed opaque envelopes that will be opened at the time of enrollment after informed consent.

Data Analysis

Qualitative Data

The data will be transcribed into a written form from audio recordings and will be analyzed via the qualitative data analysis software NVivo 11 (QSR International). Written transcripts will then be uploaded into NVivo 11 software to offer easy and organized retrieval of data for analysis. The data analysis will be conducted according to discourse analysis to identify the themes and subthemes conveying the underlying conscious or unconscious intent of the caregivers through language. The interview guides will also be pretested in a similar community.

Quantitative Data

Analyses will be conducted according to the intention-to-treat principle. The primary outcome is to assess the difference in vaccination status between the intervention and control arms. The chi-square test will first be used to compare sample characteristic proportions between the groups.

Exit Survey

A second survey will be conducted when the child visits the CHC vaccination center for their 14-week CRI or at 18 weeks of age, whichever comes first. If the caregiver did not visit the facility at 14 weeks, they will be phoned when their child reaches 18 weeks of age to complete the exit survey in order to identify their vaccination coverage according to the schedule, to be confirmed by physical examination of their EPI card.

Ethical Considerations

The study protocol and associated study instruments, including consent forms in English and local languages, have been approved by Aga Khan University's Ethics Review Committee. The study will be conducted in accordance with the Declaration of Helsinki and established guidelines. All participants will provide informed consent before participation. Participants will have the right to refuse to participate in the study or leave the study at any time; this will not affect any services provided to them at the health center. Data confidentiality will be maintained at all times. No personal identifiers will be used in any reports or publications of the study.

Data Management, Confidentiality, Privacy Protection, and Quality Assurance

The audio recording and transcripts will have unique identifiers; original and backup files will be archived in a password-protected computer system at Aga Khan University. Only transcripts and themes will be shared at NED University and the University of Surrey without nominative information. All study-related data including the recordings will be stored in an encrypted server with password protection and will only be accessible by the study-specific personnel.

Baseline and follow-up data will be collected on a smartphone device via a survey. The entry program will be designed to capture data as well as the location of the interviewer along with some monitoring parameters. Each child participant will be given a structured unique identifier. Business rules; skips, using skip logic; and consistency checks will be incorporated, and important fields will be marked as *must enter* in the questionnaire to maintain data collection quality. The database will reside on a central computer at Aga Khan University, which will be managed by the study staff. A web-based dashboard will be designed to report daily study progress. Mobile phone numbers will not be shared except to track and analyze patterns of use. Only relevant study staff will have access to study the data that has been allowed by the local ethics committee. All study staff will undergo basic research ethics training. Participants' information will be given a study code, and no personal identifiers will be shared. Data confidentiality will be maintained at all times. No personal identifiers will be used in any reports or publications of the study. No individual identifiers, such as names of participants or their locations, will be shared. In addition, a confidentiality agreement has been signed with the universities stating that the ID numbers provided will only be used for the trial. All audio recordings will be destroyed within 5-7 years of the study, according to the recommendation of the AKUH ethics committee.

Results

Pretrial, qualitative, in-depth interviews were conducted in February 2020. The main theme extracted was that mothers are the decision makers of the family regarding child health. The majority of the caregivers said that they preferred text messages rather than audio messages because (1) they can be stored in mobile phones and can be accessed anytime, (2) sometimes audio is not clear, and (3) audio cannot be played everywhere, but text can be read easily. There were no time preferences regarding the receipt of app notifications by the caregivers. Most of the parents and caregivers used Android-based smartphones. English and Urdu were the preferred languages for immunization-related messages. According to the caregivers, the mobile app should have information regarding the doses and purpose of all the childhood immunizations to be given until 5 years of age. In addition to immunization-related messages, the parents were also interested in monitoring their children's health progress through the app. Parents found the idea of a mobile app helpful, as it will remind them of their children's vaccine due dates, will provide additional information regarding immunization, and will have no installation charges.

Discussion

Overview

The COVID-19 pandemic and distancing measures have further drastically decreased CRI coverage in LMICs settings, mainly because caregivers avoid tertiary care hospitals or primary health centers for obtaining their children's vaccines. This study is the first one of its kind to evaluate the efficacy of an AI-incorporated, Android-based, immunization app offering different kinds of messages—text, pictorial, and audio—in LMICs. The messages will be sent to the participants once a week. We will also assess the sharing of information and communication between the family members regarding immunization in the exit survey.

The pretrial qualitative interviews will generate insights into the perceptions and beliefs of the families regarding immunizations and their expectations of the smartphone app. This information will be extremely valuable in designing interventions that take local context and challenges into account.

The findings of this study will be useful for any future studies in Pakistan and in LMICs, in general. This information will be disseminated on a continuous basis among governmental and nongovernmental organizations, policy makers, community leaders, the telecom sector, and other stakeholders in the digital health sector in Pakistan. Study findings will be submitted for publication in a peer-reviewed journal with an international public health audience.

Strengths

This is the first study of its kind to examine the efficacy of an Android-based mobile phone health app in improving CRI coverage in an LMICs setting. This is a mixed methods study augmented by qualitative interviews and an RCT.

Limitations

This study will be conducted in a private, tertiary, health care hospital which may not be truly representative of the low socioeconomic status of the region's population. The app will only be available for Android users and, therefore, iOS users will be excluded from the study; however, both control and intervention arms will only include participants with Android-based mobile phones.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-eHEALTH checklist (V1.6.1).
[PDF File (Adobe PDF File), 1093 KB - resprot_v9i12e22996_app1.pdf]

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Abbreviations

AI: artificial intelligence
AKUH: Aga Khan University Hospital
BCG: bacillus Calmette Guérin
CHC: Community Health Center
CoNTINuE: Capacity Building in Technology-Driven Innovation in Healthcare
DTP: diphtheria-tetanus-pertussis
EPI: Expanded Programme on Immunization
LMICs: low- and middle-income countries
PDHS: Pakistan Demographic and Health Survey
RCI: routine childhood immunization
RCT: randomized controlled trial

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Protocol

Twitter-Based Social Support Added to Fitbit Self-Monitoring for Decreasing Sedentary Behavior: Protocol for a Randomized Controlled Pilot Trial With Female Patients From a Women's Heart Clinic

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Abstract

Background: Prolonged sitting is an independent risk behavior for the development of chronic disease. With most interventions focusing on physical activity and exercise, there is a separate need for investigation into innovative and accessible interventions to decrease sedentary behavior throughout the day. Twitter is a social media platform with application for health communications and fostering of social support for health behavior change.

Objective: This pilot study aims to test the feasibility, acceptability, and preliminary efficacy of delivering daily behavior change strategies within private Twitter groups to foster peer-to-peer support and decrease sedentary behavior throughout the day in women. The Twitter group was combined with a Fitbit for self-monitoring activity and compared to a Fitbit-only control group.

Methods: In a 2-group design, participants were randomized to a Twitter + Fitbit treatment group or a Fitbit-only control group. Participants were recruited via the Stanford Research Repository System, screened for eligibility, and then invited to an orientation session. After providing informed consent, they were randomized. All participants received 13 weeks of tailored weekly step goals and a Fitbit. The treatment group participants, placed in a private Twitter support group, received daily automated behavior change "tweets" informed by theory and regular automated encouragement via text to communicate with the group. Fitbit data were collected daily throughout the treatment and follow-up period. Web-based surveys and accelerometer data were collected at baseline, treatment end (13 weeks), and at 8.5 weeks after the treatment.

Results: The initial study design funding was obtained from the Women's Heart Clinic and the Stanford Clayman Institute. Funding to run this pilot study was received from the National Institutes of Health's National Heart, Lung, and Blood Institute under Award Number K01HL136702. All procedures were approved by Stanford University's Institutional Review Board, #32127 in 2018, prior to beginning data collection. Recruitment for this study was conducted in May 2019. Of the 858 people screened, 113 met the eligibility criteria, 68 came to an information session, and 45 consented to participate in this pilot study. One participant dropped out of the intervention, and complete follow-up data were obtained from 39 of the 45 participants (87% of the sample).

Data were collected over 6 months from June to December 2019. Feasibility, acceptability, and preliminary efficacy results are being analyzed and will be reported in the winter of 2021.

Conclusions: This pilot study is assessing the feasibility, acceptability, and preliminary efficacy of delivering behavior change strategies in a Twitter social support group to decrease sedentary behavior in women. These findings will inform a larger evaluation. With an accessible, tailorable, and flexible platform, Twitter-delivered interventions offer potential for many treatment variations and titrations, thereby testing the effects of different behavior change strategies, peer-group makeups, and health behaviors of interest.

Trial Registration: ClinicalTrials.gov NCT02958189, https://clinicaltrials.gov/ct2/show/NCT02958189

International Registered Report Identifier (IRRID): DERR1-10.2196/20926

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KEYWORDS

support group; sedentary behavior; eHealth; Twitter; Fitbit; intervention; behavior change theory; mobile phone

Introduction

Background

Sedentary behavior is a major risk factor for heart disease and early mortality, particularly among women [1-6]. Due to technological conveniences and more office-bound occupations, prolonged sitting now accounts for over half of our waking hours [7-9]. Fortunately, a growing evidence base indicates that even small increases in light-intensity physical activity can result in cardiometabolic, physical function, and mental health benefits in women and men of any age [10-12]. Compared to physical activity interventions, relatively few interventions have addressed prolonged sitting [13,14], and there is a need for more controlled trials to specifically target reductions in objectively measured prolonged sedentary behavior [14,15], especially in women at risk or with extant heart disease [1-6].

Social Media Interventions

Social media, in particular, or web apps that allow users to receive, generate, react to, and share content via a social network are a specific type of web-based platforms harnessed in health interventions, with modest effectiveness [16]. Different from a single bout of planned exercise, prolonged sitting occurs in multiple contexts throughout the day. Interventions with an accessible, dynamic web-based component like social media, available at any and many timepoints, may show a particular benefit for reducing sedentary behavior [17]. Not only can social media deliver in-context health information with broad reach, customizability, and easy access [18,19], it can also allow users to react and add to the content and provide social support to other users (an evidence-based behavior change technique [16,20-22]).

Twitter is a choice intervention platform, with high prevalence of use (73% of the adults in the United States use social media sites, and the majority use these sites daily [23]) and often accessed via mobile devices (80% of the Twitter users access via their mobile devices [24]). Twitter has the capability of allowing for private groups to be created that are protected from the public and even friends, making it ideal for delivering and privatizing a research intervention. Additionally, Twitter messages (called tweets) have a 280-character limit, which enables messages to be short and accessible. Often used as a supplementary aid, the potential for utilizing Twitter as a stand-alone to deliver health behavior interventions is not yet fully realized [16]. When used, engagement strongly predicts the benefits [25,26]. Tweet2Quit, a Twitter-based intervention for smoking cessation, is among the first successful interventions designed to promote smoking cessation with sustained long-term engagement and maintenance of changed behavior [27,28].

Wearable Activity Trackers

Consumer-based wearable activity trackers provide real-time self-monitoring feedback for the consumers on their activities throughout the day. Brickwood et al [29] found a nonsignificant decrease in sedentary behavior in their meta-analysis, but in their meta-analysis, Compernolle et al [30] found interventions specifically targeting sedentary behavior and using objective self-monitoring significantly reduced sedentary time. Fitbits are used in this study, and these devices have a feature, “active hours,” which tracks the consumer’s hours of 250 steps or more (equivalent to 2 minutes of walking). A secondary benefit of using a consumer-grade device is the opportunity to track the objective physical activity of participants for the entire duration of the intervention, thereby complimenting the short-duration periods measured by accelerometers [31,32].

Behavior Change Techniques

The CONSORT (Consolidated Standards of Reporting Trials) guidelines call for precise reporting of behavior change interventions [33]. Michie et al [34] provided a taxonomy of behavior change techniques, which provide consistency and comparability across interventions, as well as facilitate identification of successful components within an intervention. The participants in our study were divided into 2 groups: the control group that only used Fitbit and the treatment group that used Fitbit and Twitter engagement, in which selected behavior change techniques were delivered. Therefore, self-monitoring with Fitbit [30] was used for both groups of participants (see Multimedia Appendix 1 for the sample of messages, the accompanying behavior change techniques, and theoretical domains [35], the behavior change theories that informed all the messages [21,36,37], and our study categorization). To simplify characterization and comparison within our intervention, we organized the behavior change techniques we delivered via the Twitter intervention into 2 types of strategies: those that occur inside the mind, or internal strategies, and those

that utilize the world outside the mind, or external strategies [38,39]. Internal strategies target one's cognitions about the behavior to be motivated, for example, promoting a growth mindset or focusing on the anticipated benefits of the behavior. External strategies utilize the outside world to help motivate the behavior, for example, using a timer to remind oneself to move or enlisting a friend to go for a walk. We used both types of strategies in this pilot study to target moving more often or breaking up prolonged sitting.

Tweet4Wellness Intervention

This pilot study builds upon the successful, private Twitter-based social support group intervention structure of Tweet2Quit and applies it to the less studied space of decreasing sedentary behavior, with the intervention titled as Tweet4Wellness [20]. Tweet4Wellness intervention messages are delivered daily to a private peer support group; these messages utilize behavior change techniques categorized by internal and external strategies that are shown to be effective in changing behavior and they target increased movement throughout the day [21,34,35,37,40,41]. Tweet4Wellness is paired with a wearable device (Fitbit) to facilitate objective self-monitoring. The aim of this intervention is to see if adding a social component (Tweet4Wellness) would be feasible, acceptable, and lead to greater reductions in sedentary behavior relative to self-monitoring (Fitbit) alone. A secondary benefit of using a consumer-grade device is the opportunity to track the objective physical activity of the participants for the entire duration of the intervention, thereby complimenting the short-duration periods measured by accelerometers [31,32].

Aims of This Study

Our *primary aims* are to test the feasibility, acceptability, and preliminary efficacy of Tweet4Wellness for reducing sedentary behavior when paired with self-monitoring compared to self-monitoring alone. We hypothesized that the intervention would be feasible and acceptable for women recruited from the heart clinic. The outcomes of feasibility and acceptability were operationalized by a number of emails and phone call assistance from study staff to participants; feedback from the participants informally and via a survey on usability, likability, and suggestions for improvement; and description of the study procedure challenges. Research has yet to define the clinically relevant length of a break or length of prolonged sitting that impacts health risks, and a single measure does not adequately capture all the sedentary behavior features relevant to health [42]. Therefore, to test the preliminary efficacy on sedentary behavior outcomes, we used several measures of sedentary behavior, each capturing a different component. One is an outcome provided by Fitbit: the number of active hours or daily hours achieving over 250 steps (Fitbit's estimate equivalent of 2 minutes of walking). We chose this measure because it is the trackable behavior each participant could self-monitor throughout the intervention. We also used the following interpretable measures proposed by Byrom et al [43] in their comprehensive coverage of sedentary behavior measurement: the maximum daily sedentary bout (longest, continuous, unbroken periods of sitting/no steps); daily weighted median sedentary bout (a measure of centrality capturing the distribution of the sedentary bouts); the total number of sedentary minutes; and the total number of steps (a measure of physical activity overall) [43]. We hypothesized that Tweet4Wellness + Fitbit group will increase their active hours (hours over 250 steps), increase their information entropy, have shorter maximum sedentary bouts and daily weighted median sedentary bouts, and fewer total number of sedentary minutes relative to baseline, compared to the Fitbit-only group.

The *secondary aims* will test the same hypotheses based on the 8.5-week follow-up period with no active intervention. The exploratory aims are within the Tweet4Wellness group. We will investigate the differences in the sedentary behavior summary measures by Twitter engagement or the number of tweets sent over the study period and by the type of behavior change strategy delivered each week (internal vs external).

Methods

Study Design: Design, Recruitment, and Inclusion/Exclusion Criteria

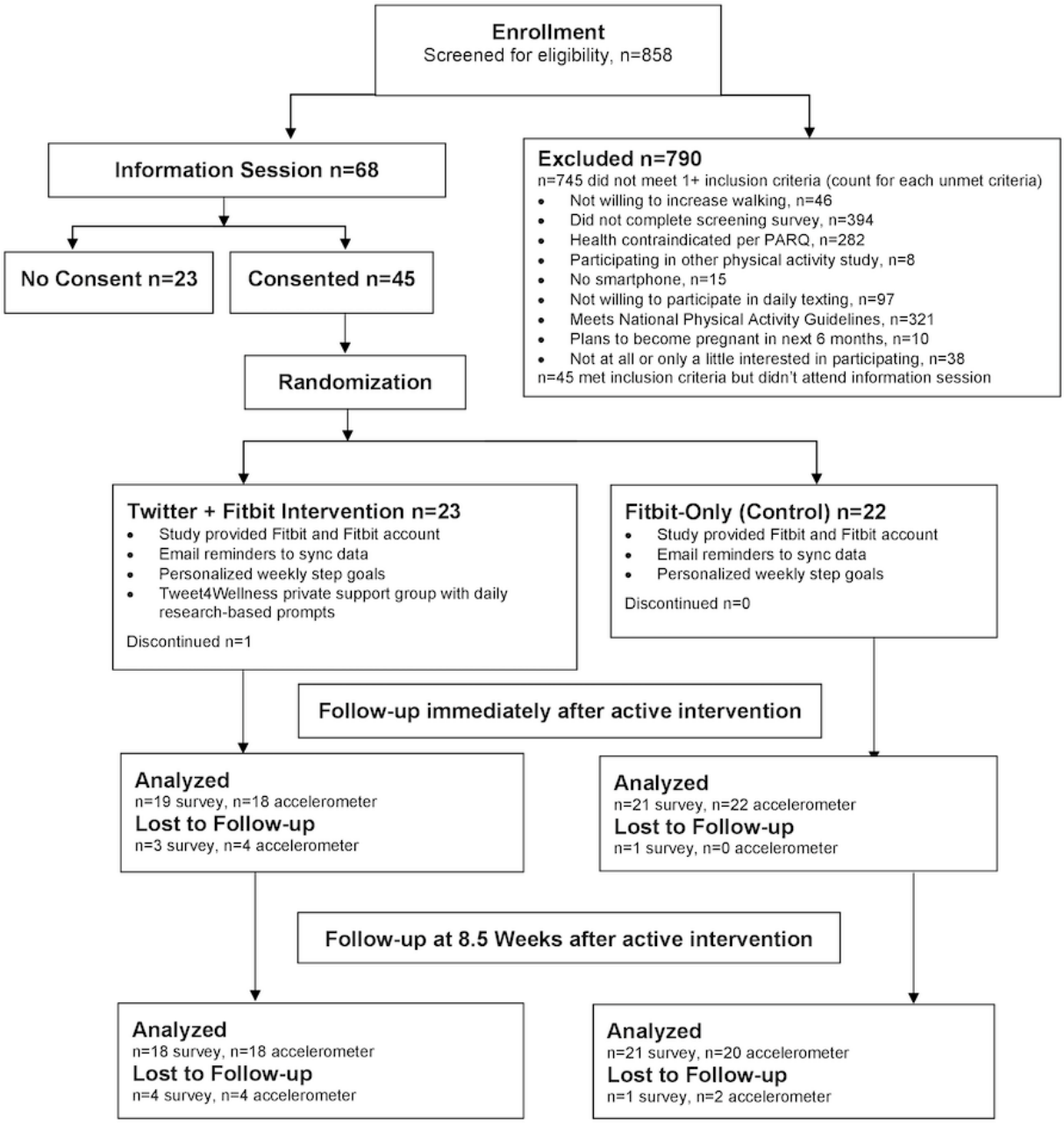
Trial Design

This pilot study was a 2-group randomized design. Treatment and control groups were run concurrently in time, and the study setting was largely virtual with an option for in-person orientation session attendance.

Recruitment

Figure 1 shows the CONSORT diagram for this study. Participants were recruited via an email from the Stanford Research Repository System to women who had been referred to or seen at the Women's Heart Health clinic (we did not require a diagnosis of heart disease). Recruitment emails were securely sent to women by the director of the Women's Heart Health clinic and they were provided information about the study with a link to the screener to confirm eligibility.

Figure 1. CONSORT diagram. CONSORT: Consolidated Standards of Reporting Trials.



Inclusion Criteria

The major inclusion criteria on the screener were being female, older than 18 years, willing to participate in daily tweets or texts for up to 13 weeks, having an active email account to receive study communications, having a mobile phone with unlimited texting and internet to receive text and Twitter messages, being familiar with communicating on Twitter, Facebook, or other social media (proxy for computer literacy), English-speaking (for group communication), and answer No to all 7 of the Physical Activity Readiness Questionnaire questions (physical readiness to safely perform physical activity [44]).

Exclusion Criteria

The major exclusion criteria were having health or physical limitations for walking (as the study encouraged walking to break up prolonged bouts of sitting) and meeting current physical activity guidelines of 150 minutes of moderate or 75 minutes of vigorous activity per week.

Procedure

Table 1 shows the study flow from enrollment and allocation to condition (Twitter + Fitbit or Fitbit-only) through the 13-week intervention, with assessments at baseline, 13 weeks, and 21.5 weeks.

Table 1. Study flow.

Study activity	Study period and timeline						
	Enrollment	Allocation	Postallocation				
	0 month	0 month	1 month	2 months	3 months	4 months	5 months
Enrollment							
Eligibility screen	✓						
Information session	✓						
Informed consent	✓						
Randomization		✓					
Treatments							
Twitter + Fitbit			✓	✓	✓		
Fitbit only			✓	✓	✓		
Measures							
Web-based surveys			✓		✓		✓
7-day accelerometers			✓		✓		✓
Continuous Fitbit monitoring			✓	✓	✓	✓	✓

The participants had 6 scheduled touchpoints: an orientation session (in-person or remote attendance), web-based consent and baseline survey (electronic via REDCap [Research Electronic Data Capture] [45]), a phone call with the research staff for setting up study accounts, baseline accelerometer wear (remote), posttreatment web-based survey (at 13 weeks after the baseline, electronic), accelerometer wear (mailed with a prepaid return package), and follow-up web-based survey (at 21.5 weeks after the baseline, electronic). All surveys included both closed and open-ended questions and they were emailed automatically by REDCap, with automatic reminders sent up to 2 times if participants did not respond. Participants received US $10 gift cards for completion of the 13-week posttreatment and 21.5-week follow-up surveys, and US $10 gift cards for returning the accelerometers at post and follow-up assessments. Figure 1 shows the CONSORT flow of the participants through the trial. All procedures were approved by Stanford University's Institutional Review Board, #32127, and registered at clinicaltrials.gov, NCT02958189, prior to beginning data collection. This study was based on the most recent protocol version, June 2019. During the course of the study, there were no major study revisions.

Orientation Session

Eligible women per the screener were contacted from the study email and invited to attend a mandatory orientation session either in-person or in a video conference. The session described the study design, timeline, and consent; explained research methods principles; and incorporated motivational interviewing techniques. The session was based on Goldberg and Kiernan's [46] work showing increased participant retention [46,47]. One group activity had participants think through the pros and cons of being in each condition (Twitter + Fitbit or Fitbit-only) or choosing to not participate. Women who were still interested sent an email after the orientation, after which they received the electronic consent form and the baseline questionnaire. A waiver of documentation was obtained for study consent. Each page had the following sentence before moving onto the next page: "Please check here to indicate you have read and understand this information."

For this pilot study, of the 34 women who attended the web-based orientation session, 18 (53%) consented; of the 30 women who attended the in-person session, 23 (77%) consented; and of the 4 women who had private phone call orientation sessions, all consented. The orientation session was the only in-person meeting, while the remaining parts of the study, including data collection, were remote.

Randomization

Randomization was done in blocks with a 1:1 randomization ratio to achieve balance across the 2 conditions (Twitter + Fitbit or Fitbit-only). After 10 participants consented and completed the baseline questionnaires, they were sorted from most to least on total weekly minutes of physical activity reported on the baseline survey. The first participant was randomized to either treatment or control using a random number generator website [48], and the next participant in the pair was allotted to the other condition. The process was repeated until all of the consented participants were randomized (the last randomization in the pilot included 15 participants).

Account Set-Up

All participants scheduled a phone call with the study staff to set up their Fitbit devices and study-provided Fitbit accounts, and they downloaded the Fitbit app on their smartphones. Participants were instructed to begin wearing the Fitbit continuously for the entire study period after the baseline accelerometer week and to open their app daily to sync their data. They could reach out to study staff via email to troubleshoot problems.

Twitter + Fitbit group participants also set up their study-provided Twitter accounts and downloaded the Twitter app on their smartphones during the call. For each Twitter

account, all privacy features were turned on to prevent participants from being searched on Twitter or from having their tweets seen by people outside the treatment group. Other group norms were provided: participants were not to follow any accounts outside the private Twitter group, they were to keep their personal Twitter accounts separate from the study account, and they were instructed to use proper etiquette when messaging (no personal attacks or bullying). Tweets were monitored daily by the study staff.

Intervention

Both the treatment (Twitter + Fitbit) and control (Fitbit-only) group received the Fitbit self-monitoring component. The treatment group also received the Twitter intervention.

Fitbit Self-Monitoring Component

All participants, both control (n=22) and treatment (n=23), received a study-provided Fitbit Inspire and study-provided Fitbit account connected to Fitabase, a web-based analytics and data aggregation system (Small Steps Labs). The Fitbit allowed for self-monitoring of daily steps and number of active hours. Participants were encouraged to open the Fitbit app daily to monitor their activities and to sync their data with Fitabase. When a participant did not sync their Fitbit data for over 24 hours, a study team member who monitored the Fitabase data site daily would send an email reminding the participant to open the app and sync their device. Additionally, all study participants received weekly text messages to achieve an average of 10% more steps per day, given their average step count the previous week (automatically generated and sent by the study platform). This was done to provide personalization as well as encourage data syncing (required for accurate personalized step goals). Weekly texts stopped after 13 weeks of active treatment, while Fitbit data were still collected during the follow-up period.

Twitter Component

Treatment participants were signed up with study-provided accounts for a private Twitter group. The study-provided account preserved participant anonymity, allowed for study control of the privacy settings within the group, allowed researchers to discontinue an account if any personal threats or harming messages were posted by a participant; and facilitated tweet captures if any direct messages between group members occurred. Twitter group participants received daily prompts suggesting a behavior change strategy and encouraging group sharing and discussion (see Multimedia Appendix 1 for examples). The behavior change strategies in the daily prompts were informed by theories of behavior change, namely, Bandura's Social Cognitive Theory [21], Prochaska's Transtheoretical Model of Behavior Change [49], Dweck's Implicit Theories model [50,51], and Gollwitzer's implementation intentions [37]. We also tied each strategy to a behavior change technique in the taxonomy for consistent language and constructs proposed by Michie et al [34]. All of the strategies were more broadly organized into 2 categories: (1) internal strategies, directed at thoughts or self-talk (eg, "by paying attention to how you feel before and after a walk, you can start to 'show' your brain the real-time benefits of physical activity. Each time you do this, you strengthen the connection. Try this today for your 'move more' walk. Share how it worked!") and (2) external strategies, directed at changing the outside world to help achieve the behavior change (eg, "What's your 'slump time' of the day when you feel most rundown? Even light movement can combat it and will replace less healthful fixes (like candy!). Schedule a 5-minute walk during your slump time today and how you will remind yourself to take it. Have you tried this before?"). Having 2 categories simplified message scheduling and allowed for exploratory analyses to compare the relative effectiveness of each category (eg, did weeks with external strategies result in more sedentary behavior reduction than weeks with internal strategies?). Each week alternated between 3 sedentary behavior goals: move more (total steps per day), move more often (frequency of steps per day), and sit less (breaking up prolonged sitting). The message organization scheme is shown in Multimedia Appendix 1. Participants were encouraged to tweet in the group daily either for support or to address the prompt or both. The research staff monitored the daily activity for bullying or threatening messages.

Treatment group participants also received daily automated texts directly in their phone, providing feedback on their tweeting behavior on the prior day, praising tweeters, and encouraging nontweeters to engage. The automated text, delivered via the study web platform, considered the prior day(s)' activity. If a participant tweeted within the previous 24 hours, they received a praise or reinforcement text at the following frequencies: every other day for weeks 1-2, every 3 days for weeks 3-6, every 4 days for weeks 7-10, and every 5 days for weeks 11-13. If a participant did not tweet within the previous 24 hours, they received an encouragement or a reminder to tweet text at the following frequencies: every day for weeks 1-4, every other day for weeks 5-10, and every 3 days for weeks 11-13. The automated text message frequency was originally scheduled for every day; however, several participants complained about the frequency and 1 participant requested that the messages stop (which was honored for that participant); therefore, a gradated schedule beginning week 5 was created for all. The frequency of encouragement texts remained higher than that of the praise texts, as encouragement has been shown to improve or increase engagement [27,28].

Measures

Surveys

The survey questions assessed the participants' goals and motivations regarding walking and sedentary behavior, access to green environments, self-efficacy to make physical activity changes, and current physical activity status (see Multimedia Appendix 2 for sample questions [21,50-55]).

Feasibility

Feasibility was measured in several ways. Use of the self-monitoring component, Fitbit, was measured via Fitabase, with number of days with no steps considered as nonwear/nonsynced days. Use of the Twitter intervention was determined by the number of sent tweets and number of days that the participant tweeted. The ability to recruit was measured by the proportion of the screened eligible women/women sent

emails and the proportion of interested eligible women/women who attended the orientation. The acceptability of the Fitbit component was assessed for both conditions via several close-ended survey questions: some questions on support (eg, I felt I received a significant amount of support for being more active throughout the day when using Fitbit, 6-point Likert scale from strongly disagree to strongly agree) and some questions on perceived utility of the added adherence features (eg, how helpful did you find the weekly step goal texted to you, 5-point Likert scale from not at all helpful to extremely helpful). Acceptability of the Twitter component was assessed via close-ended survey questions parallel to the Fitbit questions and 2 open-ended questions: "What did you find helpful/would you change about the Twitter support group?" Emails sent and received by the study staff, troubleshooting issues, and various procedural challenges were all tracked and documented.

Behavioral Outcomes

Sedentary behavior was measured in 2 ways. First, participants wore triaxial accelerometers (wrist-worn Axivity AX3, [Newcastle upon Tyne, UK] or GENEActiv [Activinsights Limited, Cambridge, UK] [56]) continuously for 7 days at baseline, posttreatment, and at 8.5 weeks follow-up. Second, after the initial baseline accelerometer data collection, participants wore Fitbits continuously throughout the 21.5 weeks of the study and follow-up. The summary measures of the sedentary behavior we derive from these devices and time periods as behavioral outcomes are averaged at the day level: the number of active hours, the maximum sedentary bout length, the weighted median sedentary bout length, total sedentary minutes, and total step count.

Exploratory Outcomes

Engagement via tweeting was measured as the number of tweets sent and the number of days the participant tweeted. Internal versus external strategies will be separated into 2 groups, with time as a factor for analyses (week 1 internal vs week 5 internal).

Analysis Plan for Pilot Data

We will describe the feasibility outcomes both quantitatively (descriptive statistics of survey responses and engagement data) and qualitatively (describing unexpected events). The mixed-effects models that will be used to analyze the change from baseline to postintervention and at follow-up on the sedentary behavior outcomes by condition are outlined in more detail in Multimedia Appendix 3. Exploratory aims looking within the Twitter condition only for differences by the type of strategy (internal vs external) will add strategy type as a predictor to the mixed-effects model and use the number of tweets and number of days tweeted as engagement covariates.

Trial Sample Size/Data Safety and Privacy

Sample Size

Given this was a pilot, we intended to run all eligible and interested participants. The Tweet2Quit results, the Twitter-based intervention that the current Tweet4Wellness was based on, and research on active web-based participation group size [20,27,28] suggested a Twitter group size of 17-25.

Data Safety and Privacy

As the intervention was a low risk, a data safety monitoring board was not required. The study recorded any adverse events in the Food and Drug Administration study binder. Data were collected and kept in secure web-based databases such as REDCap [45] that are password-protected with access limited to the study team. Daily Twitter activity was monitored by the study staff.

Results

The initial study design funding was obtained from the Women's Heart Clinic and the Stanford Clayman Institute. Funding to run this pilot study was received from the National Institutes of Health's National Heart, Lung, and Blood Institute under Award Number K01HL136702. All procedures were approved by Stanford University's Institutional Review Board, #32127 in 2018, prior to beginning data collection. Recruitment for this study was conducted in May 2019. Of the 858 people screened, 113 met the eligibility criteria, 68 came to an information session, and 45 consented to participate in this pilot study. One participant dropped out of the intervention; complete follow-up data were obtained from 39 of the 45 participants (87% of the sample). Data were collected over 6 months from June to December 2019. Feasibility, acceptability, and preliminary efficacy results are being analyzed and will be reported in the winter of 2021.

Discussion

Principal Findings

This study intervention and design were built upon the positive findings of the Tweet2Quit smoking cessation platform [20,27,28]. In this study, we extend the intervention framework to sedentary behavior reduction in female patients at a women's heart clinic. We investigated the additive effects of Tweet4Wellness on top of providing a Fitbit with weekly personalized step goals for reducing sedentary behavior. We tested the feasibility, acceptability, and preliminary efficacy of the Twitter + Fitbit and Fitbit-only conditions to inform a larger trial.

Strengths and Limitations

There are several strengths to the Tweet4Wellness intervention. First, it contributes to the literature on sedentary behavior reduction, where there is a need for more randomized controlled trials that primarily focus on prolonged sitting [14]. Sedentary behavior is an independent risk factor for heart disease, particularly in women, [2,4,6] and is less studied than physical activity interventions [1,2,4,14]. Second, with a private social media group, it allows for mutual social support with the ability to automatically deliver intervention content. Third, this intervention utilizes a consumer-grade product to track daily activity throughout the entire intervention period, which provides 2 simultaneous benefits: (1) participants can self-monitor their behavior, thereby increasing their motivation to wear the Fitbit compared to accelerometers, which provide no user feedback [30,31] and (2) it provides data on the entire time course of the trial, thereby complementing the endpoints

where accelerometers were used. Finally, the intervention uses behavior change theories to inform daily messages, ties messages to a commonly used taxonomy of behavior change techniques to aid in cross-study comparisons, and organizes the messages into 2 categories (internal and external) to facilitate comparison of the effectiveness within our study. Given the behavioral design, condition blinding was not feasible. Another limitation is that the conditions are not balanced for attention, as the Tweet4Wellness condition had daily intervention touchpoints. A strength of the additive design of this study is that an active treatment was offered to all who were eligible, potentially increasing enrollment and retention.

With both groups wearing Fitbits, this study has the advantage of providing rich data to fill in the gaps between standard accelerometer measurement timepoints. Challenges include the numerous issues that come with free-living data collection, and operationalizing distinctions between nonwear and sedentary behavior in the Fitbit in the absence of current research consensus. Therefore, the design purposefully has participants wearing both the triaxial accelerometer and the Fitbit during posttreatment and follow-up periods to allow for cross-comparison of device outputs.

Owing to the small sample size of this pilot study, we are not powered to test full efficacy. We instead look for trends in the sedentary behavior to serve as preliminary findings to inform a full-size powered randomized controlled trial to evaluate efficacy.

Conclusions

If Tweet4Wellness is found to be feasible and acceptable and has some preliminary evidence of efficacy with regard to reduced sedentary behavior, these pilot findings would guide any adjustments in scaling to a full-size randomized controlled trial to evaluate efficacy. Tweet4Wellness could provide a far-reaching program for anyone to receive social support from others to reduce sedentary behavior, while also learning behavior techniques for change. Given the current shelter-in-place orders during the COVID-19 pandemic, evaluating the evidence of remote participation, health promotion platforms, and protocols is of timely value. Future studies will titrate the active ingredients in this protocol, vary the group dynamics to have mixed sex groups, and identify the optimal frequency of intervention messaging to maximize long-term engagement.

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The initial study design funding was obtained from the Women's Heart Clinic and the Stanford Clayman Institute. Funding to run this pilot study was received from the National Institutes of Health's National Heart, Lung, and Blood Institute under Award Number K01HL136702. The sponsors were not involved in any of the research or analyses. The trial above would not have been completed without the dedicated help of several persons. We recognize Dr. Cornelia Pechmann at the University of California at Irvine for her seminal efforts in developing the original Tweet2Quit study, a social media–based smoking cessation intervention. Douglas Calder, with technical and intervention experience from the Tweet2Quit trials, provided technical support and account oversight for this trial. Mark Sanders and Lauren Wegner were the key research assistants aiding in participant communications, account set-ups, and data collections. A special thank you to Dr. Gotzone Garay, Brynn Kronn, and Stephanie Middleton for their detailed organization and management. We also thank Dr. Ashley Sanders-Jackson for her help with the initial analysis and refinement of the intervention messages.

Authors' Contributions

MO and JJP designed the intervention, assessments, and protocol. JJP and Dr. Cornelia Pechmann's original project Tweet2Quit was the template for this study. MO and JJP designed the intervention messages. JT aided in the recruitment, mentorship, and provided medical oversight of the participants, as well as aided the research coordinators who organized the study mailings and data collection. MD is an advisor on the grant and provided guidance with the design and data analyses. MB aided in the study design, randomization schemes, statistical instruction, and mentorship of MO. MC provided guidance and mentorship to MO to help navigate the challenges of running clinical trials. DR provided guidance on the social media aspects with regard to group size and engagement.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Behavior change techniques and theoretical domains of Twitter intervention messages.
[DOCX File , 56 KB - resprot_v9i12e20926_app1.docx]

Multimedia Appendix 2
Sample survey questions.
[DOCX File , 208 KB - resprot_v9i12e20926_app2.docx]

Multimedia Appendix 3
Description of the sedentary measures data.
[DOCX File , 17 KB - resprot_v9i12e20926_app3.docx]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
REDCap: Research Electronic Data Capture

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Protocol

The Web-Based Uprise Program for Mental Health in Australian University Students: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: University students are vulnerable to poor mental health, psychological distress, and loneliness relative to nonuniversity student peers. However, the rate of seeking mental health treatment among university students is low. Web-based psychological interventions may provide an opportunity for supporting vulnerable university students who are unlikely to otherwise seek support.

Objective: The aim of this study is to examine the feasibility, acceptability, safety, and efficacy of an existing web-based transdiagnostic cognitive behavioral therapy (CBT) mental health program for use among Australian university students.

Methods: This is a pilot randomized controlled trial comparing a self-directed web-based CBT mental health program with a waitlist control. The self-directed modules will be augmented with optional webchat or telephone coaching with a therapist. The recruitment target is 70 university students who do not present with a clinical mental health disorder. Allocation will be made in a 1:1 ratio and will occur after the initial baseline assessment. Assessments will be completed at baseline, upon completion of a 4-week waitlist (waitlist group only), upon completion of the program, and at 3 months after completion of the program.

Results: The trial was funded in June 2018, and the protocol was approved by the Swinburne University Human Research Ethics Committee in September 2018. Recruitment commenced in October 2018, with the first participant allocated in November 2018. A total of 70 participants were recruited to the trial. The trial recruitment ceased in June 2019, and data collection was finalized in December 2019. We expect the final data analysis to be completed by November 2020 and results to be published early in 2021. The primary outcomes are feasibility, acceptability, safety, and symptoms of depression, anxiety, and stress. The secondary outcomes are psychological wellbeing, quality of life, loneliness, self-reported physical health status, emotion regulation, and cognitive and mindfulness processes.

Conclusions: The acceptability, feasibility, safety, and efficacy of a web-based mental health program in university students will be evaluated. Web-based mental health programs offer the opportunity to engage university students who may be reluctant to seek support through traditional face-to-face mental health services, and the transdiagnostic approach of the program has the potential to address the breadth of mental health concerns of university students.

Trial Registration: Australian New Zealand Clinical Trial Registry ACTRN12618001604291; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12618001604291

International Registered Report Identifier (IRRID): DERR1-10.2196/21307

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KEYWORDS

digital technology; e-mental health; university students; mental health; randomized controlled trial

Introduction

Young adults aged 16 to 24 years report the highest prevalence of mental health disorders of any age group in the Australian population [1]. University students within this age group are particularly vulnerable to experience poor mental health and psychological distress relative to nonuniversity student peers [2,3]. The most commonly identified mental health issues for university students are depression, anxiety, and stress [4,5]. University students further report unhelpful psychological processes, including negative/critical thinking, self-blame, worry, pessimism, confusion, thoughts of death, loss of confidence, and poor self-esteem [5]. Changes in social relationships specifically may exacerbate the development of mental health symptoms, especially for those who are socially isolated (eg, those living alone or off-campus and those who have migrated for study [3,6,7]). This is consistent with research findings that earlier loneliness predicts more severe depression, social anxiety, and paranoia at a later time [8], and that living away from home for young people may increase their risk of loneliness and poor mental health [9,10].

Despite the high rates of mental health disorders (including anxiety and depression [4,11]) and high psychological distress among university students, the rate of seeking mental health treatment is low [12]. Only about one-third of students who report psychological distress also report accessing on-campus counselling services [13]. According to qualitative reports from university students, stigma related to mental ill health remains a major factor in preventing them from seeking support or treatment for mental health symptoms [5]. Given the reluctance of university students to seek mental health treatment despite high levels of psychological distress, alternate intervention methods to enhance mental health in this population are required. One approach that shows promise to address mental health symptoms and psychological distress for university students is the use of e-mental health or online psychological interventions [14-18]. University students report a willingness to use online mental health resources [19] and perceive multiple benefits of doing so, such as avoidance of stigma, immediacy and ease of access, anonymity and privacy, and greater sense of control over the help-seeking journey [20,21]. Furthermore, students who report being least likely to seek support through an on-campus counselling service or mental health service are most likely to indicate that they would access a web-based student wellbeing program [22]. Thus, online mental health programs and interventions provide a useful approach for supporting vulnerable university students who are unlikely to otherwise seek support.

Uprise (Uprise Services [23]) is an existing web-based mental health program that applies a transdiagnostic cognitive behavioral therapy (CBT) approach for reducing mental health symptoms and improving psychological wellbeing. CBT is considered to be the current gold standard for psychological intervention and has strong evidence for efficacy in reducing symptoms across a range of mental health disorders [24,25]. There is some evidence that CBT-based interventions also influence psychological processes underlying the manifestation of symptoms in many mental health disorders, including correcting habitual thinking errors, reducing biases in attention or memory, and improving emotion regulation [26,27]. The Uprise program comprises a series of self-directed modules that address mindset, values, mindfulness, and stress management. The self-directed modules are augmented with optional telephone or webchat coaching with a trained mental health professional. The option for the self-directed modules to be augmented with coaching support is consistent with results from previous surveys of user preferences indicating that format flexibility is important for the delivery of effective e-mental health interventions [16,28]. Previous trials of similar web-based programs have demonstrated this self-directed CBT-based approach to be effective in reducing symptoms of generalized anxiety, panic disorder, social phobia, obsessive compulsive disorder, and posttraumatic stress disorder in clinically diagnosed adult and student populations [18,29-31]. However, the potential for these interventions to change psychological processes was not examined in these prior studies, and many studies did not present acceptability outcomes.

The primary aim of this trial is to evaluate the acceptability, feasibility, safety, and efficacy of the Uprise program in reducing mental health symptoms among Australian university students. The secondary aims include evaluating the holistic impact of the Uprise program and investigating whether the Uprise program influences psychological processes, such as emotion regulation, cognitive appraisals, and mindfulness. This trial extends on the outcomes of previous trials of similar web-based CBT interventions by examining the broader holistic impact of the intervention rather than focusing only on symptom reduction.

Methods

Trial Design

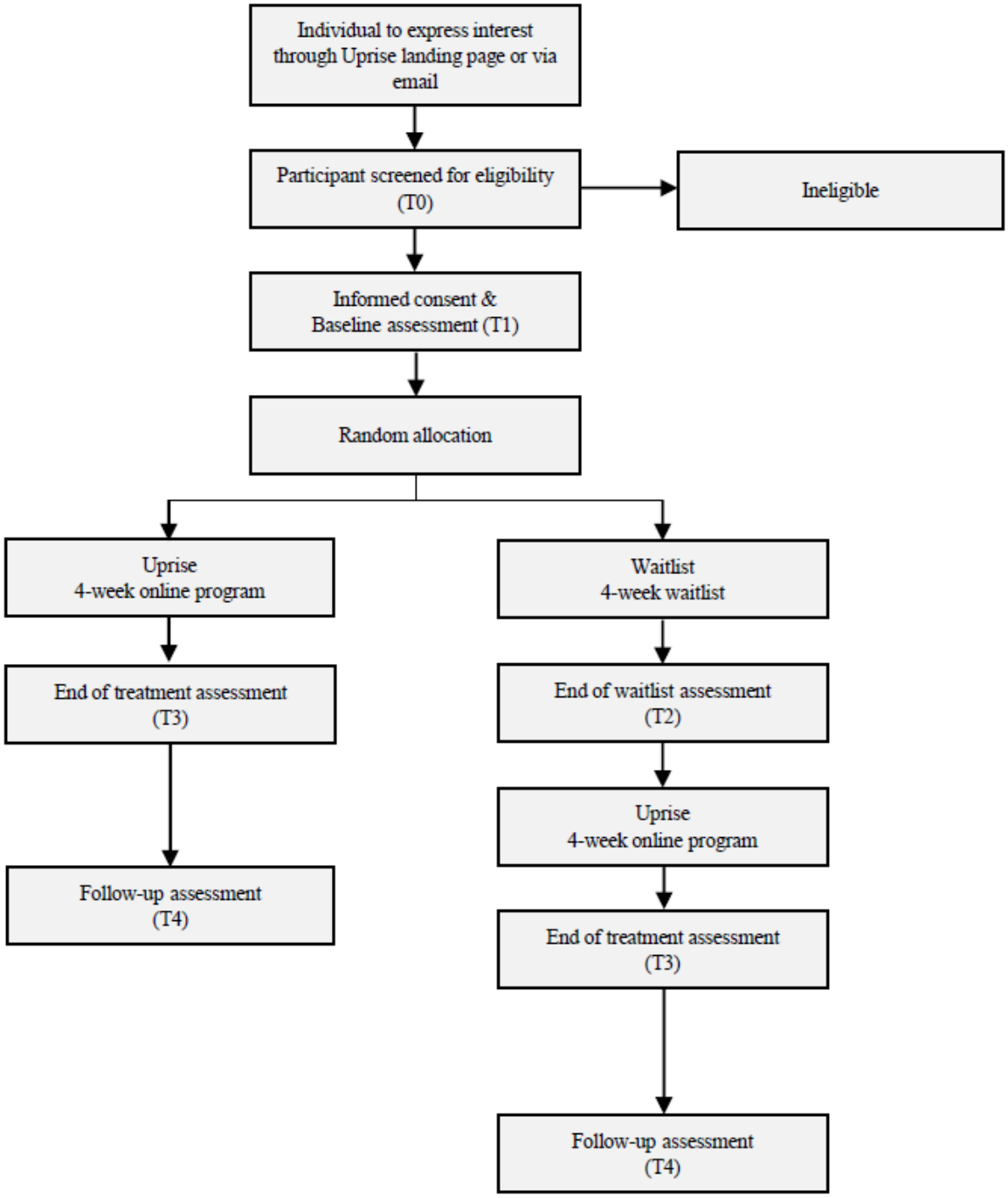
The study will be a pilot randomized waitlist-controlled trial, with two parallel groups, using a 1:1 allocation ratio. Waitlist was selected as the control condition to enable comparison of the Uprise program to students' usual daily life, while ensuring that all participants had the opportunity to access the Uprise program. Figure 1 presents the study design.

Participants will initially undergo screening for eligibility via telephone interview (T0). Eligible participants will be invited to complete the baseline assessment (T1). Informed consent will be obtained at the baseline assessment. Following the baseline assessment, each consenting participant will be randomized to either the Uprise program or waitlist for the following 4 weeks. Those allocated to the Uprise program will be given access to the program and asked to complete one module per week across the following 4-week period. At the end of the program, these participants will be invited to complete an end-of-treatment assessment (T3). Participants allocated to waitlist will be asked to continue with their usual activities

across the following 4-week period, at the end of which they will be invited to complete an end-of-waitlist assessment (T2). Waitlist participants will then be given access to the Uprise program and asked to complete one module per week for the following 4 weeks, at the end of which they will be invited to complete an end-of-treatment assessment (T3). Participants will also be invited to complete a semistructured interview at the end-of-treatment (T3) assessment regarding their experience with the intervention. The interview will be recorded and later transcribed for qualitative analysis. All participants will be invited to complete a follow-up assessment (T4) 3 months after their end-of-treatment (T3) assessment.

The Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the study procedure is shown in Figure 1. The protocol was designed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) and good clinical practice (GCP) guidelines (see Multimedia Appendix 1 and Multimedia Appendix 2 for relevant checklists).

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram showing the trial design.



Study Setting

This trial will be coordinated from Swinburne University of Technology in Melbourne, Australia, and will aim to include students from multiple universities across Australia. Trial assessments will be conducted remotely via telephone and online questionnaires. The trial intervention will also be administered remotely via the Uprise web platform and phone app, with

optional coaching calls conducted via either telephone or webchat according to participant preference.

Sample Size

Seventy participants will be recruited to the trial. Power analysis was conducted using G Power 2.0 for the mental health primary outcome variables (social anxiety and depression), with estimates based on published means and standard deviations and reported effects of similar interventions [32]. The analysis indicated that a minimum of 27 to 45 participants per group would be required to detect moderate changes with 80% power in social anxiety and depression (standardized Cohen *d* of 0.43 to 0.57). Owing to funding constraints, only 35 participants will be recruited to each arm.

Recruitment and Enrolment

Participants will be recruited from Australian universities via social media advertisements, flyers, and student newsletter articles. At Swinburne University, students who are identified as being "at risk" of dropping out of the university owing to mental health concerns will also be emailed and invited to participate in the study. Identification of "at risk" students will be completed by Swinburne University student wellbeing officers according to whether a student did not receive a passing grade for one or more subjects in the previous semester. Student names and email addresses will be shared with the researchers for the purpose of targeted trial recruitment. No other details will be shared with the research team. This targeted recruitment approach has been included to reach vulnerable students who may not have otherwise been motivated to engage in a research study, as well as to emulate potential pathways to accessing the Uprise program if it were to be rolled out as a wellbeing program at universities.

Participants will be invited to register their interest in the study via direct email to the research team or by registering their interest on the study landing page. Some participants may directly comment on social media posts, in which case we will direct them to email the research team or visit the trial landing page. The research team will then email potential participants an information sheet and informed consent form. Once participants have provided their contact details and a preferred contact time, researchers will telephone participants to conduct eligibility screening. The study sponsors will not have access to any identifiable recruitment information.

Eligibility Criteria

Participants meeting the following criteria will be eligible for the study: (1) aged 17 to 26 years; (2) currently enrolled as a student at an Australian university; (3) competent in English reading and comprehension; and (4) able to receive phone or video conference calls or visit the research center for assessments. The exclusion criteria are as follows: (1) self-reported acute or distressing clinical psychiatric symptoms in the past month (ie, symptoms that the individual reported experiencing as distressing or interfering with their usual daily activities); (2) psychiatric hospitalization in the past month; (3) self-report of any level of suicidality risk; (4) self-report of moderate or severe levels of distress (score equal to or more than 25 on the Kessler Psychological Distress Scale) during screening assessment; (5) self-report of any level of risk of harm to others; and (6) self-report of any level of risk of damage to objects or property.

Participants who report mental health symptoms of a severity that deems them ineligible for the trial will be referred to appropriate mental health services. This is to ensure that these participants receive the appropriate level of care to address the severity of mental health symptoms, as the Uprise program is not designed to address severe symptoms or suicidality. To ensure equitable access to the trial and to minimize sampling bias, these participants will be given the option to undergo eligibility screening again at a later time and to participate in the trial should they meet criteria at this second screening.

Allocation and Blinding

Participants confirmed to be eligible following the screening assessment (T0) will be invited to complete the baseline assessment (T1). Following the baseline assessment, participants will be subject to random allocation to either waitlist or treatment with the Uprise program. Block randomization will be applied in this study with a 1:1 allocation ratio using random block sizes of 4 and 6. The randomization sequence will be generated using the Sealed Envelope online randomization sequence generator [33]. Randomization and allocation of participants will be performed by a member of the trial research team (KDH). Allocation will occur within 7 days of the baseline assessment. Participants will be contacted to notify them of their allocation, with those allocated to the treatment group given instructions to access the Uprise program and those allocated to the waitlist group notified of the date for their next assessment (T2).

All outcome assessments will be completed online by participants. It is not possible to blind participants to their allocation owing to the nature of the trial design. The psychologists who provide "coaching" as part of the Uprise program will be blind to participant allocation.

Materials

Table 1 presents the SPIRIT schedule of measures in this study. The primary outcomes will focus on the acceptability, feasibility, and safety of the Uprise program, as well as efficacy as indicated by the change in mental health symptoms (depression, anxiety, and stress). The secondary outcomes will include psychological wellbeing, quality of life, loneliness, physical health, emotion regulation, and cognitive and mindfulness processes.

Demographic variables will include age, gender, sexuality, ethnicity, work status, level of education, previously attempted university degrees, current university course load, postcode, and religion. The Lubben Social Network Scale-12 items (LSNS-12 [34]) will be used as a demographic assessment of the participants' risk of social isolation. The Positive and Negative Affect Schedule-Trait (PANAS [35]) will be used as a measure of trait-level positive and negative affect.

Table 1. SPIRIT schedule of enrolment, interventions, and assessments.

Variable	Study period						
	Enrolment	Baseline	Postallocation				Close out
			Waitlist	End of waitlist	Uprise	End of treatment	3-month follow-up
Timepoint	T0	T1	N/A[a]	T2	N/A	T3	T4
Enrolment							
Eligibility screen	Yes	No	No	No	No	No	No
Informed consent	No	Yes	No	No	No	No	No
Allocation	No	Yes	No	No	No	No	No
Interventions							
Uprise program	No	No	No	No	Yes	No	No
Waitlist	No	No	Yes	No	No	No	No
Assessments							
Demographic form	No	Yes	No	No	Yes	No	No
UCLA-LS3[b]	No	Yes	No	Yes	No	Yes	Yes
CES-D[c]	No	Yes	No	Yes	No	Yes	Yes
SIAS[d]	No	Yes	No	Yes	No	Yes	Yes
DASS-21[e]	No	Yes	No	Yes	No	Yes	Yes
PANAS[f]	No	Yes	No	Yes	No	Yes	Yes
K10[g]	Yes	No	No	Yes	No	Yes	Yes
LSNS-12[h]	No	Yes	No	Yes	No	Yes	Yes
ERQ[i]	No	Yes	No	Yes	No	Yes	Yes
FFMQ[j]	No	Yes	No	Yes	No	Yes	Yes
CBPQ[k]	No	Yes	No	Yes	No	Yes	Yes
BCIS[l]	No	Yes	No	Yes	No	Yes	Yes
PWB-42[m]	No	Yes	No	Yes	No	Yes	Yes
AQoL-8D[n]	No	Yes	No	Yes	No	Yes	Yes
PHQ[o]	No	Yes	No	Yes	No	Yes	Yes
SF-12[p]	No	Yes	No	Yes	No	Yes	Yes
WHO-5[q]	No	No	No	No	Yes	No	No
PSS-4[r]	No	No	No	No	Yes	No	No
Modified SDS[s]	No	No	No	No	Yes	No	No
Acceptability measure	No	No	No	No	Yes	No	No
Qualitative interview	No	No	No	No	No	Yes	No

[a]N/A: not applicable.

[b]UCLA-LS3: UCLA Loneliness Scale Version 3.

[c]CES-D: Centre for Epidemiological Studies-Depression.

[d]SIAS: Social Interaction Anxiety Scale.

[e]DASS-21: Depression, Anxiety, and Stress Scale-21 items.

[f]PANAS: Positive and Negative Affect Schedule-Trait and State versions.

[g]K10: Kessler Scale of Distress-10 items.

[h]LSNS-12: Lubben Social Network Scale-12 items.

[i]ERQ: Emotion Regulation Questionnaire.
[j]FFMQ: Five Facet Mindfulness Questionnaire.
[k]CBPQ: Cognitive Behavioral Processes Questionnaire.
[l]BCIS: Beck Cognitive Insight Scale.
[m]PWB-42: Psychological Well-Being Scale-42 items.
[n]AQoL-8D: Assessment of Quality of Life-8 Dimensions.
[o]PHQ: Physical Health Questionnaire.
[p]SF-12: Short-Form Health Survey-12 items.
[q]WHO-5: World Health Organization-Five Well-Being Index.
[r]PSS-4: Perceived Stress Scale-4 items.
[s]SDS: Sheehan Disability Scale.

Primary Outcomes

Acceptability, Feasibility, and Safety of the Uprise Program

A self-report scale created by the developers of the Uprise program and designed to measure participant satisfaction with the program will be used to determine the acceptability of the program to participants. Participants will be asked to rate out of 10 how satisfied they were with each of the program modules and coaching calls, as well as how likely they are to recommend Uprise to friends or family. Attrition rates from the trial will also be used as indicators of acceptability. Themes identified from the qualitative interviews conducted at the end-of-treatment (T3) assessment will also be used to determine acceptability of the intervention. The interview will include questions regarding the participants' experiences and preferences regarding the different modules of the Uprise program. Feasibility will be assessed by the proportion of interested people who complete the baseline assessment, the attrition rate across both groups, and the proportion of participants who complete the four core Uprise program modules within the 6-week intervention period. Safety will be determined according to the number of adverse events occurring across the trial period.

Mental Health

Psychological distress will be measured with the Kessler Scale of Distress-10 items (K10 [36]). Depression will be measured with the Centre for Epidemiological Studies-Depression (CES-D [37]) and depression subscale of the Depression Anxiety Stress Scale-21 items (DASS-21 [38]). Anxiety will be measured with the anxiety subscale of the DASS-21, and social anxiety will be measured with the 20-item Social Interaction Anxiety Scale (SIAS [39,40]).

Stress

The Perceived Stress Scale (PSS-4 [41]) and stress subscale of the DASS-21 will be used to measure stress. The Modified Sheehan Disability Scale (modified SDS [42]) will be used to measure the effects of mental illness, physical illness, and stress on work and study.

Secondary Outcomes

Wellbeing and Quality of Life

The Psychological Well-Being Scale-42 items (PWB-42 [43,44]), the World Health Organization-Five Well-Being Index (WHO-5 [45]), and the Assessment of Quality of Life-8 Dimensions (AQoL-8D [46]) will be used to measure global wellbeing and life satisfaction. The PWB measures psychological wellbeing across the following dimensions: autonomy, positive relations with others, environmental mastery, personal growth, purpose in life, and self-acceptance. The AQoL-8D measures wellbeing across the following dimensions: independent living, happiness, mental health, coping, relationships, self-worth, pain, and senses.

Loneliness

The UCLA Loneliness Scale-Version 3 (UCLA-LS [47]) is a 20-item self-report measure and consists of both positively and negatively worded items that assess loneliness (eg, How often do you feel that you are no longer close to anyone?).

Physical Health

Question 1 from the Short-Form Health Survey-12 items (SF-12 [48,49]) will be used as a single measure of health, and it asks participants to rate their perception of their overall health quality. The Physical Health Questionnaire (PHQ [50]) is a 14-item brief self-report scale of physical health symptoms.

Emotion Regulation, Cognitive, and Mindfulness Processes

The Emotion Regulation Questionnaire (ERQ [51]) will be used to measure participants' tendency to use cognitive reappraisal and expressive suppression strategies to regulate their emotions. Activated affect in the past week, measured with the Positive and Negative Affect Schedule-State (PANAS-State [35]), will be used as a secondary indicator of emotion regulation. The Cognitive Behavioral Processes Questionnaire (CBPQ [52]) will be used to measure internal and external cognitive and behavioral maintenance processes. The Beck Cognitive Insight Scale (BCIS [53]) will be used to measure participants' self-reflectiveness and self-certainty in their interpretations of their experiences. The Five Facet Mindfulness Questionnaire (FFMQ [54]) is a measure of mindfulness and comprises the following five subscales: observing, describing, acting with awareness, nonjudging of experience, and nonreactivity to experience.

Planned Intervention

The Uprise program will be made accessible to participants as both an app and a website. Participants will complete all intervention activities online at a time and location that is convenient for them. Activities will include a series of

self-directed modules and optional coaching sessions with a psychologist or counsellor.

Participants will complete four core modules over 4 to 6 weeks, with an additional six optional modules. Each module consists of a short introductory video and a series of 1 to 6 additional videos or exercises. The module length ranges from 6 to 28 minutes. The modules are mindset, personal values, mindfulness, and stress management (outlined in Table 2). To support adherence to the intervention protocol, a member of the research team will contact participants weekly to check on their progress and address any technical issues.

Table 2. Outline of the Uprise module content.

Module	Content
Core modules	
Mindset	Identifying unhelpful thinking styles and changing unhelpful thoughts.
Personal values	Identifying values system, making behavioral choices based on values system, and scheduling activities.
Mindfulness	Developing mindfulness skills to pay attention to and observe thoughts instead of trying to control and change them.
Stress management	Developing stress reduction and relaxation breathing skills.
Optional modules	
Helping others	Skills for managing relationships with mental health in mind.
Perspective taking	Learning to understand the perspectives of others.
Advanced mindset	Advanced skills in retraining thinking related to stress, guilt, metacognition, and beliefs.
Improving sleep	Strategies to improve sleep habits.
Advanced mindfulness	Advanced skills in awareness and mindfulness.

Optional Coaching Sessions

The Uprise program also provides participants with in-website links to telephone or online coaching sessions with a trained mental health professional at any point during the program. Participants will be able to choose from a list of psychologists and counsellors to select their "coach" and schedule weekly 30-minute telephone or webchat sessions with their coach. It will be up to the participant to decide whether to engage with this aspect of the program.

Waitlist Condition

It will be clearly outlined to participants that the trial involves a waitlist control prior to enrolment, and informed consent will include agreement to undergo a 4-week waitlist period and an additional assessment prior to commencing the Uprise program. Waitlist participants will be instructed to continue with their usual activities throughout the waitlist period.

Planned Data Analysis

Summary data will be provided to describe the number of participants who registered interest in the trial, the number deemed ineligible for the trial and why, and the number who completed each stage of the trial.

Data will be analyzed on an intention-to-treat basis (ie, including all enrolled participants regardless of whether they completed the trial). Acceptability, feasibility, and safety will be evaluated using descriptive statistics. Qualitative interviews will be analyzed using the six-step approach by Braun and Clarke [55] for qualitative data analysis to identify and develop themes from the data to further inform about the acceptability of the intervention to participants.

Results will be summarized as means and standard deviations (or median and range/percentage and number as appropriate) for both groups at baseline (T0) and for the relevant group at the end of waitlist (T2)/end of treatment (T3) for all outcome measures. For both groups, this will demonstrate their results at baseline and again 4 weeks after baseline.

Additionally, the *t* test and chi-square test will be used to evaluate baseline group differences in all demographic and outcome measures. This will be performed to compare the waitlist and intervention groups, and to compare those who drop out from the trial to those who complete the trial. This will enable identification of potential baseline moderator variables or factors that contribute to attrition that can be included as covariates in subsequent analyses.

Multilevel linear mixed effects modeling (MLM) will be used to assess acute and long-term treatment effects in each of the outcome measures. MLM is a regression-based approach that is robust to missing data and provides a more powerful means of analyzing longitudinal data than the ANOVA family of analyses [56]. MLM is robust to missing data because it does not delete cases list-wise due to missing data, but instead includes all available data points for each participant. Missing data analysis will be conducted to determine whether data are missing completely at random. If it is identified that data are missing not at random, covariates will be added to all models to account for systematic variation related to missingness.

To assess short-term treatment effects, the trajectory of change in each of the outcomes will be examined from baseline (T1) to the end of waitlist (T2) for the waitlist group and from baseline (T1) to the end of treatment (T3) for the intervention group. The trajectory of change in each of the outcomes will be compared between groups. Each analysis will include time

(fixed), group (fixed), and the fixed interaction between time and group (time × group) as predictors. A significant time × group interaction effect will indicate a differential rate of change in outcomes between the groups from baseline (T1) to the end of waitlist (T2)/end of treatment (T3).

To assess long-term treatment effects, the trajectory of change in outcomes from baseline (T1) to 3-month follow-up (T4) will be examined in the intervention group only. Sensitivity analysis will also be conducted to determine the trajectory of change from baseline (T1) to 3-month follow-up (T4) in the waitlist group only.

Secondary analyses will include per protocol analysis (only those who complete the four core modules within 6 weeks) and analyses controlling for moderator variables (eg, age, sex, baseline symptom severity, number of Uprise program modules completed, number of coaching calls completed, and number of days accessing the platform). We will report 95% confidence intervals for each test statistic.

Data Monitoring and Management

Assessment Data

Data collected in this pilot randomized control trial will be managed in accordance with GCP guidelines. Restrictions to the data will be made such that only those listed as authors in this protocol, as well as the host institutes, will have access to the data. The host institutes' access will be specific to audit and regulatory processes and will not be used for any purpose outside the scope of the trial registry.

All researchers will be provided training on assessment administration and scoring, as well as relevant ethics procedures and protocols for managing and storing data. Assessment data will be collected online via the Qualtrics survey platform [57] using a digital case report form. Data will be extracted to a secure data file and stored on a secure network. For each stage of data cleaning and analysis that is performed, a separate time-stamped computer file will be created and saved within an organized file system. To aid data quality, checks will include examination of recorded data for out-of-range values and data entry errors. Local ethics guidelines do not require a data monitoring committee for this type of trial. No interim analysis is anticipated.

Uprise Program Data

The Uprise program and online platform used in this study are existing clinical tools used in workplaces to support worker mental health. Uprise Services data security policies are fully compliant with Australian data protection and health record legislation [23]. Data collected via the Uprise online platform will be securely transferred to the research team via a 128-bit AES-encrypted data file. The password for the secure data file will be provided to researchers via telephone calls from a member of the Uprise Services team.

Research Governance and Ethics

The trial will be administered by Swinburne University of Technology. The study has been approved by Swinburne University Human Research Ethics Committee (SUHREC; project 2018/205). The trial will be conducted in accordance with the Declaration of Helsinki, GCP guidelines, and the Australian National Statement on Ethical Conduct in Human Research [58]. Major protocol amendments will be submitted to SUHREC for review and approval and detailed in the trial registry. Full written informed consent will be obtained from participants at the time of the baseline assessment by a member of the research team. A copy of the consent form can be obtained by request from the corresponding author. There are no restrictions of the reporting findings of this trial. Trial results will be published in full in peer-reviewed literature.

Serious Adverse Events

Any serious adverse events discovered by a research team member on the trial will be reported to the chief investigator Dr Michelle Lim and SUHREC. In the context of the trial, serious adverse events are defined as events that lead to participant death, are life-threatening, require inpatient hospitalization, or result in persistence of high disability/incapacity in accordance with the National Statement on Ethical Conduct in Human Research [58]. Any such events will be recorded and reviewed by the Chief Investigator to determine the likelihood of any relationship to the intervention, with action taken as appropriate. This may include referral to the Swinburne University Psychology Clinic or other health service for clinical treatment as required. All participants are provided with details for support services on the Participant Information Statement, including contact information for the Swinburne University Psychology Clinic and two crisis telephone lines.

Trial Management Committee

A trial management committee will involve the named authors on this protocol as well as an independent academic not associated with the project. The project will be coordinated by the chief investigator (MHL) who will also collaborate with senior coinvestigators (KDH and RE) with regard to overseeing the trial. The chief investigator will ensure that each member of the trial management committee holds current GCP training and will be responsible for ensuring the safety of the participants and that the quality of the trial is not compromised.

Results

The trial was funded in June 2018, and this protocol was approved by the Swinburne University Human Research Ethics Committee in September 2018. Recruitment commenced in October 2018, with the first participant allocated in November 2018. A total of 70 participants were recruited to the trial. The trial recruitment ceased in June 2019, and data collection was finalized in December 2019. We expect the final data analysis to be completed by November 2020 and results to be published early in 2021.

Discussion

The Uprise program is derived from evidence-based psychological interventions; however, the efficacy of the program has not previously been formally evaluated. Therefore, the aim of the study is to determine the acceptability, feasibility,

and safety of Uprise, and evaluate its efficacy in addressing mental health symptoms in university students. The trial extends on previous similar trials by also considering the holistic impact of the Uprise program and specifically evaluating changes in psychological processes that are relevant to the intervention. Digital platforms, such as the Uprise program, have the potential to engage university students who may be reluctant to engage traditional face-to-face services.

Digital or web-based psychological interventions offer an opportunity to support vulnerable university students who are unlikely to otherwise seek support. Young people often use digital tools to interact with peers [59] and, as such, are likely to find online mental health solutions acceptable [32]. In fact, those students who are least likely to access traditional mental health services report the greatest interest in accessing online student wellbeing programs [22]. Uprise is a transdiagnostic program that can be delivered via an app or a website and is based on the principles of CBT. The Uprise program is specifically designed to address mindset, personal values, mindfulness, and stress management skills. Given the breadth of mental health concerns and factors that contribute to psychological distress among university students, such a transdiagnostic approach to improving mental health has the potential to be beneficial for this population.

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Authors' Contributions

MHL developed the project proposal and is responsible for the study implementation, study management, and supervision. KDH and RE contributed to refinement of the protocol, participant recruitment, and data collection. KDH drafted the initial version of the manuscript. RE and MHL were major contributors in writing the manuscript. All authors critically reviewed the manuscript for content and approved the final manuscript.

Conflicts of Interest

KDH is a director and shareholder of Wellbeing Strategies Pty Ltd. The other authors have no conflicts of interest.

Multimedia Appendix 1
CONSORT eHEALTH Checklist V 1.6.1.
[PDF File (Adobe PDF File), 2077 KB - resprot_v9i12e21307_app1.pdf]

Multimedia Appendix 2
SPIRIT Checklist.
[PDF File (Adobe PDF File), 118 KB - resprot_v9i12e21307_app2.pdf]

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Abbreviations

AQoL-8D: Assessment of Quality of Life-8 Dimensions
BCIS: Beck Cognitive Insight Scale
CBPQ: Cognitive Behavioral Processes Questionnaire
CBT: cognitive behavioral therapy
CES-D: Centre for Epidemiological Studies-Depression
DASS-21: Depression, Anxiety, and Stress Scale-21 items
ERQ: Emotion Regulation Questionnaire
FFMQ: Five Facet Mindfulness Questionnaire
GCP: good clinical practice
K10: Kessler Scale of Distress-10 items
LSNS-12: Lubben Social Network Scale-12 items
MLM: multilevel linear mixed effects modeling
PANAS: Positive and Negative Affect Schedule
PHQ: Physical Health Questionnaire
PSS-4: Perceived Stress Scale-4 items
PWB-42: Psychological Well-Being Scale-42 items
SDS: Sheehan Disability Scale
SF-12: Short-Form Health Survey-12 items
SIAS: Social Interaction Anxiety Scale
SUHREC: Swinburne University Human Research Ethics Committee
UCLA-LS: UCLA Loneliness Scale Version 3
WHO-5: World Health Organization-Five Well-Being Index

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Protocol

A Digital Program (Hope) for People Living With Cancer During the COVID-19 Pandemic: Protocol for a Feasibility Randomized Controlled Trial

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Abstract

Background: During the COVID-19 lockdown period in the United Kingdom that began on March 23, 2020, more than a quarter of a million people with cancer reported worsening mental health. Help to Overcome Problems Effectively (Hope) is a self-management program for people with cancer, designed to provide support for distress, unmet needs, and poor psychological health. In light of social distancing during the COVID-19 pandemic, digital delivery of the Hope Programme has become ever more vital for people with cancer. Previous pre-post studies of the digital Hope Programme have found reduced anxiety and depression and improved well-being for people with cancer. However, evaluation of this evidence has been limited by the lack of a control group in these previous studies.

Objective: We now present a protocol for a feasibility randomized controlled trial of the digital Hope Programme for people with cancer during the COVID-19 pandemic. Primary outcomes will be recruitment, dropout, and adherence rates, and estimations of sample and effect size. To detect signals of efficacy, secondary outcomes will be participant mental health and well-being.

Methods: Participants will be recruited by Macmillan Cancer Support (MCS) through their social media networks. The study will employ a feasibility wait-list randomized controlled trial (RCT) design, with people with cancer being randomized to join the digital Hope Programme immediately (intervention group [IG]) or join a 6-week waiting list (wait-list control group [WLCG]) with a 1:1 allocation ratio. Participants will complete digital measures of depression, anxiety, mental well-being, and confidence in managing their own health. Online questionnaires will be administered preprogram and 6 weeks postprogram.

Results: All people who had requested access to the Hope Programme from MCS (N=61) will be invited to participate in the trial. Baseline data collection commenced in April 2020, and the Hope Programme began for the IG in May 2020 and for the WLCG in June 2020. Postprogram data collection was completed by the end of August 2020.

Conclusions: This feasibility study will provide data to inform the design of a future definitive trial. Wider-scale provision of the digital Hope Programme has potential to improve the lives of thousands of people with cancer and reduce the burden on health care providers during these unprecedented times.

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KEYWORDS

self-management; survivorship; cancer; feasibility; randomized controlled trial; COVID-19; protocol; digital health; intervention

Introduction

Background and Rationale

The COVID-19 pandemic has created additional challenges for people with cancer, both in terms of physical and mental health. Many people with cancer are considered at increased risk of serious complications if they were to contract the COVID-19 virus [1]. People with cancer have reported concerns about the further risks to their health from COVID-19, increased anxiety relating to potential cancellation or reduction in treatments and advice from oncology and other medical teams, and significant anxiety and fears of contracting COVID-19 as restrictions in lockdown arrangements are eased [2]. The pandemic has negatively impacted both the cancer health systems and the people using them. Overall, 1 in 5 (20%) people with cancer in the United Kingdom report that they will not feel safe enough to leave their home until an effective treatment or vaccine for COVID-19 becomes widely available [3].

People with cancer are already known to face challenges following primary treatment, including fatigue, pain, sexual problems, issues with cognitive functioning, depression, anxiety, social isolation, and financial issues [4-8]. A significant number of patients with cancer experience long-term negative impacts on their psychological well-being and mental health, including hypervigilance, anxiety, posttraumatic stress, and depression [9-14]; indeed, 2 years postdiagnosis, up to 20% met criteria for major depression and up to 40% met criteria for an anxiety disorder [13,14]. Many of these difficulties are experienced long-term, after regular contact with health care professionals has ceased, which leads to many patients feeling vulnerable and unsupported [5,7,8]. A recent review published before the COVID-19 pandemic came to light highlights the need for urgent research into the longer-term effects of cancer treatment on mental health, as increasing numbers of people live with and beyond cancer [15]. During lockdown, one in four (28%) people with cancer have experienced depression, anxiety, and stress, and one in seven (14%) people with cancer experienced further decline in their physical health (eg, sleep problems, extreme tiredness, and pain) [3]. Macmillan Cancer Support (MCS) have called for the UK government to ensure that holistic physical and mental health support for people with cancer is not forgotten as a result of the COVID-19 pandemic [3].

In the United Kingdom, the National Health Service (NHS) "Long Term Plan" of 2019 [16] places great emphasis on the need for holistic, person-centered care, with greater digital delivery for both NHS services overall and specifically those relating to living well with and beyond cancer. A holistic approach is timely, as recent research shows complex interrelationships between fatigue, fear of cancer recurrence, anxiety, and depression in people with cancer [17,18]. In response to the COVID-19 pandemic, there has also been a rapid and essential growth in the provision of health care digitally, to allow remote care [19,20]. A recent review and meta-analysis showed that digital psychoeducational interventions are effective in significantly reducing depression and fatigue in people with cancer [21]. Many people, including older adults, have become more motivated to use, accepting of, and familiar with digital technologies for health care and social connection [22]. This is essential to meet the needs of people with cancer, as traditional face-to-face support is cancelled and social isolation increases, particularly as in the United Kingdom and many other countries, people with cancer are being advised by the government to isolate or "shield" from others for prolonged periods [23,24].

Around 10 years ago, in response to the shortage of available, tailored self-management support for people with cancer, we codesigned a program together with people with cancer, clinicians, and other experts. The result was a group-based self-management program called the Help to Overcome Problems Effectively Program, known as the "Hope Programme," for survivors of all types of cancer [25,26], which was originally delivered in-person. The Hope Programme recognizes the common challenges and unmet needs across all types of cancer including fatigue and psychological distress [4-14]. The Hope Programme differs from many other cancer self-management programs due to its roots in positive psychology [27-29] and its focus on hope and gratitude [30] to improve well-being and coping. It has been delivered in person to groups of survivors of all cancers and specifically for survivors of breast cancer, and participants have reported feeling more confident and hopeful and less alone [25,26]. The face-to-face version has been adapted for digital delivery, and initial pretest-posttest evaluation suggested potential effects on anxiety, depression, and positive well-being, with positive user evaluations [31]. A feasibility randomized controlled trial (RCT) study is the next step in the testing of this digital intervention and is required to assess whether participants consent to being randomized, and to test the feasibility of operating a wait-list control group. Owing to COVID-19, in-person service provision has largely been cancelled and this presents the opportunity to conduct the feasibility RCT of the digital intervention. This protocol has been prepared in accordance with SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines for clinical trials [32].

Objectives

The aim of this study is to test the feasibility of a digitally delivered self-management program for people with cancer. This will inform the design of a definitive RCT. Additionally, preliminary assessment of the impact of the Hope Programme, via secondary outcomes, will be used to assess signals of efficacy in a trial context.

The planned primary outcomes (trail feasibility objectives) of the study are to investigate the following:

- Recruitment rates for participation and for randomization
- Retention and follow-up rates as the participants move through the trial
- Adherence rates to study procedures, intervention attendance, and engagement
- Sample size and effect size estimation for a definitive trial
- Progression criteria for a definitive trial

The secondary outcomes are the following:

- Measures of depression, anxiety, confidence to self-manage cancer (patient activation), and mental well-being, as indicated by scores on validated measures

Trial Design

This study will employ a feasibility, randomized wait-list control group design, to explore the feasibility of a trial of the digital Hope Programme for people with cancer. The intervention is a 6-week digital self-management program. Quantitative monitoring of participant progress through the online program will be undertaken. Participants will be asked to complete standardized measures of depression, anxiety, mental well-being, and confidence in managing their cancer.

Methods

Study Settings

This is a digital study and the recruitment, intervention, and data collection will be carried out entirely online. Participants are referred by MCS.

Eligibility Criteria

Inclusion criteria for the feasibility RCT are the following:

- Diagnosis of any type of cancer, at any stage
- Adult (≥18 years)
- Located in the United Kingdom
- Access to the internet and a device that will allow them to engage with the intervention
- Fluent in English to be able to engage with all the material in the intervention
- Not recruited via the NHS

Intervention

The Hope Programme will be delivered by Hope for the Community (H4C) Community Interest Company, which is a research social enterprise spinout company from Coventry University [33]. Full details of the digital Hope Programme content are described in Multimedia Appendix 1. All Hope Programme modules have the same structure and format, consisting of quizzes, videos, educational content, activities with homework suggestions, and a module review page. The digital Hope Programme is adapted from the in-person Hope Programme, which was developed in conjunction with cancer survivors and MCS staff. The Hope Programme content comprises text, images, downloadable documents, and links to external websites. The content delivered is configured into interactive activities (eg, quizzes, self-monitoring tools, diaries) that can be used by participants to learn and consolidate the program content. The Hope Programme uses forums and messaging facilities that act as a conduit for communication between participants and facilitators. The Hope Programme is asynchronous, and content is released at set times over the 6 weeks. The Hope Programme is moderated by trained peer facilitators.

Primary Outcome Measures (Trial Feasibility Objectives)

Recruitment Rates

Recruitment rates for participation and randomization will be collected through Qualtrics. All eligible participants identified by MCS will be sent a link to the Qualtrics study survey, so we will calculate recruitment rates from those providing consent and/or completing baseline questionnaires.

Retention and Follow-up Rates

Follow-up will be online. Participants who become lost to follow-up will be identified through Qualtrics as those not completing postprogram questionnaires. It is possible that these participants may still complete some or all of the Hope Programme, and so participant retention can be identified separately through engagement with the Hope platform (see below). Participants who explicitly request to be withdrawn from the study will be categorized accordingly, but we will not contact participants to obtain reasons for not completing questionnaires.

Adherence Rates

The Hope platform collects user engagement data such as login frequency and duration, which assists the moderators with participant engagement and experience. Participants also have the option of receiving system-generated automatic nudge reminders sent to their email address. We will analyze this user engagement data to generate usage patterns and provide an overview of session attendance and participant engagement.

Sample Size and Effect Size Estimation

To inform sample size estimation for a future definitive trial, we will calculate the standard deviations of the continuous secondary outcomes pertaining to depression, anxiety, mental well-being, and participant confidence in managing their cancer. To estimate potential effect sizes for a primary outcome in a future definitive trial (namely, change in scores on key secondary outcome measures from preprogram to postprogram), we will calculate the difference between the mean difference preprogram and postprogram for the intervention and control groups and divide by the pooled standard deviation at baseline [34].

Progression Criteria

We will collate the data from all participants in this feasibility RCT to inform progression to a definitive trial, based on the following criteria:

- Recruitment rate >70% of eligible participants consented
- Questionnaire completion rate >70% of participants completing T1 questionnaires

- Program completion rate >50% of participants attending all 6 Hope Programme sessions

Secondary Outcome Measures

We will administer a sociodemographic and health questionnaire at baseline only, requesting the following personal information from participants: gender, age, ethnicity, marital status, highest level of education, employment and occupation, and some details about their cancer diagnosis and any other medical conditions.

Participants will complete a set of validated questionnaires preprogram and postprogram, to give an indication of changes in depression, anxiety, mental well-being, and confidence to self-manage their cancer across the intervention and control groups. These questionnaires are detailed below.

The Patient Health Questionnaire (PHQ-9) [35] is a 9-item measure that assesses the frequency of depression symptoms (eg, "over the past two weeks, how often have you been bothered by any of the following problems … i) little interest or pleasure in doing things; ii) feeling down, depressed or hopeless; iii) poor appetite or overeating"). Responses to each of the 9 items range from 0 to 3 (0=not at all, 1=several days, 2=more than half the days, 3=nearly every day), leading to a summed score between 0-27, with higher scores indicating greater severity of depression. Scores of ≥10 are presumed to be above the clinical range, and so scores of ≥10 are classed as "cases" of depression. Recovery rates are calculated as those patients who score ≥10 (cases) prior to treatment and <10 posttreatment.

The Generalized Anxiety Disorder scale (GAD-7) [36] is a 7-item scale measuring symptoms of generalized anxiety disorder (eg, "Over the past two weeks, how often have you been bothered by the following problems … i) feeling nervous, anxious or on edge; ii) trouble relaxing; iii) becoming easily annoyed or irritable"). Responses to all 7 items range from 0 to 3 (0=not at all, 1=several days, 2=more than half the days, 3=nearly every day), providing a total score of 0-21, with higher scores indicating greater anxiety. Scores of ≥8 are classed as "cases" of generalized anxiety disorder. Recovery rates are calculated as those patients who score ≥8 (cases) prior to treatment and <8 posttreatment.

The Warwick Edinburgh Mental Wellbeing Scale (WEMWBS) [37] is a scale of 14 positively worded feelings and thoughts, used to assess mental well-being within the adult population. The scale includes measures of positive affect, satisfying interpersonal relationships, and positive functioning (eg, "Below are some statements about feelings and thoughts. Please tick the box that best describes your experience of each over the last two weeks … i) I've been feeling optimistic about the future; ii) I've been thinking clearly; iii) I've been feeling loved"). Participants rate each of the 14 items on a scale of 1 to 5 (1=none of the time, 2=rarely, 3=some of the time, 4=often, 5=all of the time), providing a total positive mental well-being score ranging from 14-70, with higher scores representing greater positive mental well-being. A change of ≥3 is seen as a clinically "meaningful" change [38].

The Patient Activation Measure (PAM) [39] is a validated, licensed tool that has been extensively tested with reviewed findings from a large number of studies. It helps to measure the spectrum of knowledge, skills, and confidence in patients and captures the extent to which people feel engaged and confident in taking care of their condition.

Individuals are asked to complete a short survey and based on their responses, they receive a PAM score (0-100). The resulting score places the individual at one of four levels of activation, each of which reveals insight into a range of health-related characteristics, including behaviors and outcomes. The 4 levels of activation are the following:

Level 1: Individuals tend to be passive and feel overwhelmed by managing their own health. They may not understand their role in the care process.

Level 2: Individuals may lack the knowledge and confidence to manage their health.

Level 3: Individuals appear to be taking action but may still lack the confidence and skill to support their behaviors.

Level 4: Individuals have adopted many of the behaviors needed to support their health but may not be able to maintain them in the face of life stressors.

Participant Timeline

Participants referred by MCS will be sent an email from H4C, with brief information about the Hope Programme and the feasibility study. The email will contain a link to a Qualtrics survey that contains digital versions of (1) the participant information sheet (PIS), (2) the consent form, and (3) study questionnaires. The PIS and consent form are included in Multimedia Appendix 2. Participants are explicitly informed that they will be randomly assigned to one of two Hope Programmes, starting either in May or in June. Informed consent will be obtained online in accordance with relevant UK legislation (ie, Data Protection Act 2018). The PIS and consent form must be read and agreed to (eg, by checking relevant boxes) before the participant can proceed to the study questionnaires.

After providing informed consent to take part in the study, all participants will be guided through the process of completing the baseline questionnaires (Time 0; hereafter, T0). Upon completion of T0 questionnaires, participants will be randomized via the Qualtrics randomization function, to either attend the Hope Programme starting in May 2020 (intervention group [IG]) or in June 2020 (wait-list control group [WLCG]). Participants are notified which group they have been randomized to at the end of the survey. There will be approximately 30 participants in each group. The IG will then be sent an email link that provides access to the Hope Programme. Those randomized to the WLCG will be informed that they will receive an email link shortly before the start of the Hope Programme in June (ie, approximately 6 weeks later). After 6 weeks (T1), all participants will be emailed a link to the Qualtrics survey containing the secondary outcome questionnaires, and IG participants will also receive a participant debrief at T1. The debrief contains information reminding the participant why the study is being conducted and what will happen to the results, thanking them for their time, and includes sources of additional

support if they experienced any distress through completing the questionnaires, such as their own general practitioner or the Samaritans. The WLCG also receive the survey link via email again, with secondary outcome measures and debrief, after they have received the intervention (T2). Table 1 provides a list of all digital study documents presented to participants at each time point (T0, T1, T2). All information and questionnaires at T0, T1, and T2 will be delivered via the Qualtrics survey platform. The Hope Programme will be delivered via the H4C platform.

Table 1. Information and questionnaires presented to IG and WLCG participants at each time point (T0, T1, and T2), across the duration of the study.[a]

Study documents	T0	T1		T2
	IG and WLCG	IG	WLCG	WLCG
Participant information sheet	✓			
Informed consent	✓			
Sociodemographic and health questionnaire	✓			
Warwick Edinburgh Mental Wellbeing Scale	✓	✓	✓	✓
Patient Health Questionnaire	✓	✓	✓	✓
Generalized Anxiety Disorder scale	✓	✓	✓	✓
Patient Activation Measure	✓	✓	✓	✓
Poststudy debrief information		✓		✓

[a]T0 refers to the beginning of the study; T1 is 6 weeks later, after the intervention group (IG) has completed the Hope Programme; T2 is an additional 6 weeks later, after the wait-list control group (WLCG) has completed the Hope Programme.

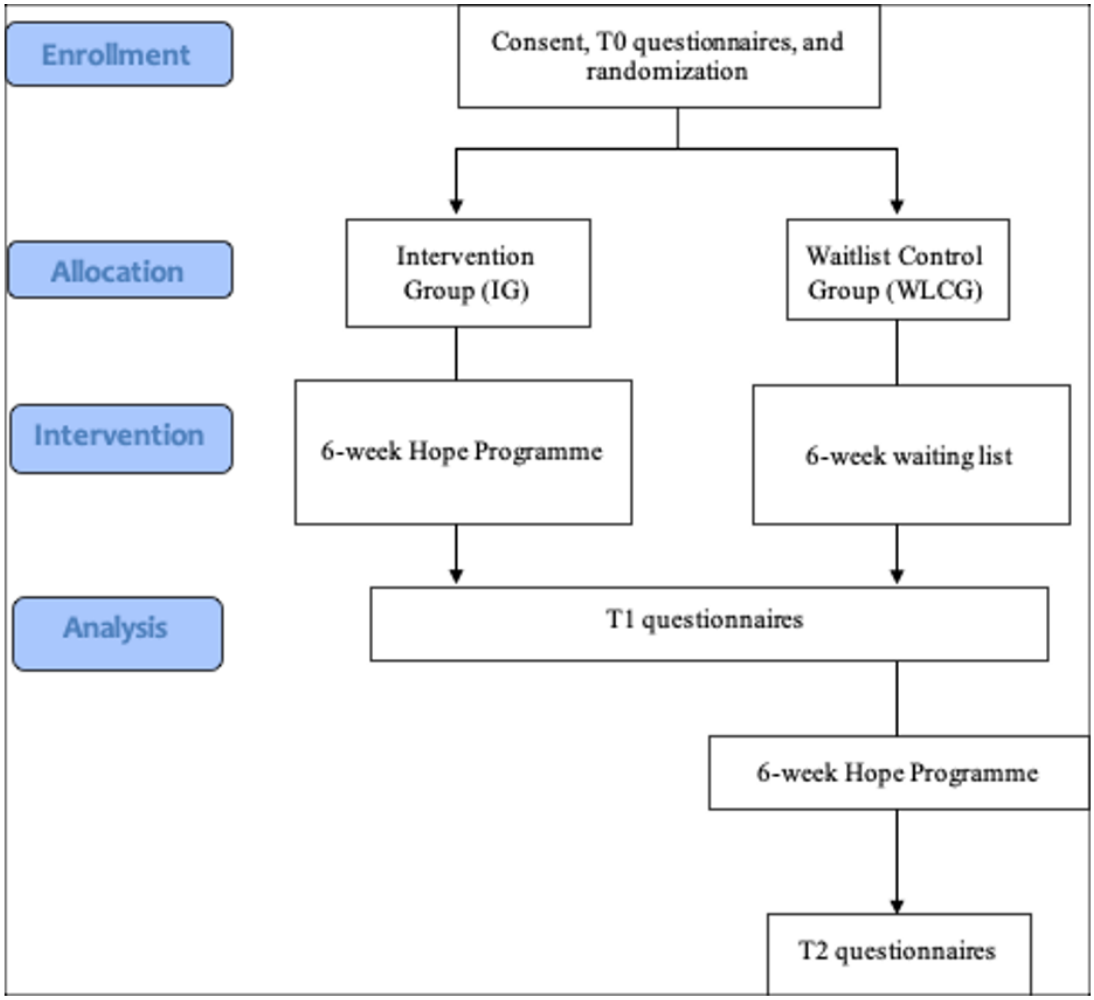
Sample Size

Participants for this feasibility RCT were drawn from an opportunity sample, referred by MCS, of people with cancer who had expressed an interest in joining the Hope Programme (N=61). As a feasibility study, it was not necessary to conduct sample size calculations to power the study [40]. An arbitrary sample size of n=40 was deemed appropriate for this feasibility study, informed by similar studies in this area [41].

Recruitment

We contacted all 61 people with cancer from an opportunity sample of people who expressed interest in attending the in-person MCS Hope Programme and invited them to participate in a trial of the digital program. MCS originally recruited these participants through their social media networks (eg, Macmillan Facebook page and website) and Macmillan Information Centres. Given the urgent need to provide immediate support during the COVID-19 crisis, we did not want to delay the study by seeking National Health Service (NHS) ethics approval to recruit NHS patients. Instead, with University ethics approval in place, we only recruited participants who were recruited via non-NHS sources such as the MCS website and their social media networks. Participant recruitment flow is depicted in Figure 1.

Figure 1. Flow diagram showing participants' route through the study.



Assignment of Intervention

Allocation Sequence Generation

The participants will be randomly assigned to the IG or WLCG using a 1:1 allocation ratio. Randomization and the allocation sequence will be generated automatically on completion of the online consent form and baseline questionnaires, using the randomization function in Qualtrics Survey Software (Qualtrics). The research team will be unable to influence any aspect of the randomization procedure.

Allocation Concealment Mechanism

Participants were informed upon completion of the T0 questionnaires, via a notification in Qualtrics, whether they had been randomized to the IG (in this case, starting in May 2020), or the WLCG (in this case, starting in June 2020). The research team remained unaware of participant allocation until group contact lists were created at the next data collection point (ie, T1).

Blinding

It will not be possible to "blind" participants to allocation. Analysis of outcome measures will be conducted blind to participant allocation where possible (eg, IG and WLCG data will be arbitrarily renamed "Group A" and "Group B" for the purpose of analysis).

Data Collection, Management, and Analysis

Data Collection Methods

All data will be collected via online questionnaires administered through Qualtrics. The validated questionnaires (PHQ-9, GAD-7, WEMWBS, and PAM) have been described in the section on Objectives above. Participants will be entered into a prize draw to win a £50 Amazon voucher as an incentive to complete all study questionnaires.

Data Management

Each participant in this study will have a unique identifier (ID) generated by Qualtrics at enrollment, and this will be used to link participants' survey data together at the end of the trial. The user engagement and analytics data collected by the Hope platform will be linked to the survey data by the unique ID. The linked survey and analytics data will be prepared initially in Microsoft Excel (Microsoft Corp) format, and will then be exported to IBM SPSS Statistics 26 (Version 26; IBM Corp), cleaned, and checked for missing values (all data will remain within the shared, password-protected project folder). Once the research team agree that all required data is present and complete, all survey data will be permanently deleted from Qualtrics. The complete anonymized research data files will be stored on the research team's shared, password-protected project folder located on the university server. To comply with UK regulations (ie, General Data Protection Regulation and the

Data Protection Act 2018), the research data will be retained for 3 years after the study has ended and will then be deleted. Only members of the research team will have access to the data files.

Statistical Methods

Quantitative data will be analyzed descriptively. Measures of mean and variance, including confidence intervals and standard deviations, and number and percent for categorical variables, will be used to describe the full range of data at baseline and postprogram. An intention-to-treat analysis will be incorporated, where missing data will be rectified using the last observation carried forward [42]. Between-group inferential comparisons will not be performed as the study was not designed to be powered for this analysis, in concordance with the CONSORT (Consolidated Standards of Reporting Trials) extension for pilot and feasibility trials [43]. All analyses will be performed using IBM SPSS Statistics 26.

Monitoring

Data Monitoring

In this small feasibility trial, it was not deemed necessary to employ an independent data monitoring committee. However, participant data was screened at T0, T1, and T2 by the research team to check for indications of suicidal thoughts on the PHQ-9 questionnaire.

Harms

Participants who indicate they are feeling suicidal at any point during the study on the PHQ-9 measure will be provided with the contact details of local mental health agencies and Samaritans, and will be encouraged to visit their general practitioner. We will also contact the MCS administrator. At postprogram, all participants' data will be analyzed to examine if any people have reached a probable clinical level of depression or anxiety where they previously were not at this level. This will be recorded and listed as possible adverse effects of the intervention. These participants will be contacted and encouraged to visit their general practitioner and will be signposted to further sources of support as listed above.

Auditing

Auditing of trial conduct will not be necessary. The Hope Programme has been developed and tested in various studies, so the current feasibility trial will focus on recruitment and randomization procedures.

Ethics and Dissemination

Research Ethics Approval

This study was reviewed and approved by the Coventry University Ethics Committee (P106024).

Protocol Amendments

Any amendments to the protocol will be submitted to the Coventry University Ethics Committee for review, and any research study activity will be suspended until approval is granted.

Consent

Informed consent will be taken online via Qualtrics. Participants will be required to answer "yes" to all consent statements before proceeding to the study questionnaires. If participants answer "no" to any consent statements, they will be directed to the end of the survey and no data will be collected. Consent statements for this study are included in Multimedia Appendix 2.

Confidentiality

MCS will send names and email addresses of interested participants to H4C (with the assent of participants), who will email interested participants introductory information and a link to the study website (Qualtrics). At the point of consent, participants will be assigned a unique identifier (ID) through Qualtrics, which will be used to link study data from multiple timepoints (T0, T1, T2). Participant data will be identifiable via this unique ID for the duration of the study. For the prize draw, this unique ID will be linked back to the participant name and email address only for email delivery of the prize (£50 Amazon voucher).

Access to Data

HW, FM, CC, and AT will have access to the final data set.

Ancillary and Posttrial Care

There is no postprogram follow-up scheduled after the T1 questionnaires for IG, and the T2 questionnaires for WLCG. However, a participant debrief is provided at the end of the study, giving details of where participants can find additional support if they feel they need it.

Dissemination Policy

The results of the feasibility RCT will be submitted for publication via the open access route in a relevant journal (eg, Journal of Medical Internet Research), and a lay summary of the findings will be presented in a blog on the H4C website for participants to access. A link to this blog will be emailed to all participants by H4C.

Results

Recruitment into this feasibility RCT began in April 2020, with all participants completing informed consent and baseline questionnaires before being randomized. Data collection from postprogram questionnaires was completed at the end of August 2020.

Discussion

Study Rationale

This feasibility trial is designed to provide evidence about whether it is possible to conduct a definitive trial of a digital self-management program for people with cancer. Digital health care has become more important than ever in the wake of COVID-19, and provision of an acceptable and effective digital self-management program for people with cancer is both timely and necessary [2,19,20].

Strengths and Limitations

Digital delivery of the Hope Programme has rapidly become essential in light of the COVID-19 pandemic, and the resulting social distancing measures required for those who are clinically vulnerable or required to quarantine. Owing to recent research revealing the number of people with cancer who have experienced declining mental health and increasing fear during the pandemic [3], the Hope Programme is well placed to deliver timely and much-needed support for people with cancer, particularly while treatments and contact with health care teams are reduced [2].

It is noteworthy that there is not always a linear relationship between time spent in a digital intervention, the number of sessions completed, and participant outcomes [44]. For example, it is possible that the participants who access only a couple of sessions may be "e-attainers" (as described in [45]). These participants may achieve what they need from the program, such as practicing gratitude, or gaining reassurance that their challenges are shared by others [46]. In our comprehensive statistical analyses, we plan to use a combination of data from our usability measures and the user engagement data extracted from the platform to develop a more thorough understanding of engagement and attrition, which can then be used to inform the content and design of future versions of the Hope Programme.

A challenge for many digital interventions is completion of postprogram questionnaires. Achieving an acceptable postprogram questionnaire completion rate is a key criterion for progression to a definitive trial. In this feasibility trial, we have included entry to a prize draw for those that complete the postprogram questionnaires. This will enable us to determine whether this is sufficient to secure an acceptable postprogram completion rate in this population. Exploring the feasibility of achieving acceptable completion rates for questionnaires is particularly pertinent with a wait-list control group design. There is some evidence that wait-list controls for studies of psychological interventions may overestimate intervention effects relative to other forms of control group [47]. Wait-list control participants are hypothesized to delay taking action while they are waiting relative to no active treatment control participants [48]. Testing the feasibility of this approach will enable us to establish whether this is an acceptable trial design and an ethical approach to RCTs for people with cancer in these unprecedented times.

Conflicts of Interest

GM is the CEO of Hope For The Community (H4C) CIC, and AT is a non-executive director of Hope For The Community (H4C) CIC. The other authors declare no conflicts of interest.

Multimedia Appendix 1
Hope Programme development and content.
[DOCX File , 24 KB - resprot_v9i12e24264_app1.docx]

Multimedia Appendix 2
Informed consent materials.
[DOCX File , 27 KB - resprot_v9i12e24264_app2.docx]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
GAD-7: Generalized Anxiety Disorder scale
H4C: Hope for The Community
MCS: Macmillan Cancer Support
NHS: National Health Service
PAM: Patient Activation Measure
PHQ-9: Patient Health Questionnaire
PIS: participant information sheet
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
WEMWBS: Warwick Edinburgh Mental Wellbeing Scale

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Protocol

Recruitment of Youth Living With HIV to Optimize Adherence and Virologic Suppression: Testing the Design of Technology-Based Community Health Nursing to Improve Antiretroviral Therapy (ART) Clinical Trials

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Abstract

Background: Despite advances in HIV diagnosis and treatment, adolescents and young adults 12-25 years old have high HIV incidence, poor engagement and retention in treatment, and low rates of adherence and virologic suppression when compared to their older counterparts. HIV has emerged as a chronic disease for which antiretroviral therapy (ART) adherence is critical for virologic suppression and long-term survival. Virologic suppression has been elusive for many youth with HIV (YHIV). Novel strategies designed to facilitate health care systems' support for YHIV between medical visits are essential for improving ART adherence, virologic suppression, and long-term survival.

Objective: The aim of this study is to compare the effectiveness of a technology-enhanced community health nursing intervention (TECH2CHECK) to a standard of care (SOC) control group for improving ART adherence and subsequent viral suppression using a randomized trial design. The objectives are to assess the feasibility, acceptability, and cost-effectiveness of TECH2CHECK as compared to SOC for management of HIV in the outpatient setting and to examine the sustainability of self-care behavior, adherence, and virologic suppression among youth following the intervention period.

Methods: We will recruit 120 adherence-challenged YHIV being followed at clinics specializing in HIV care in the Baltimore-Washington metropolitan area and in Jacksonville. Eligible participants complete an audio, computer-assisted self-interview and are randomized to either TECH2CHECK intervention or the SOC (60 participants in each arm). The primary outcome of interest is virologic suppression (viral load <20 copies/mL) and improved treatment adherence. Participants in the intervention arm receive community health nursing visits at 2 weeks, 6 weeks, 10 weeks, 14 weeks, and 26 weeks. The intervention arm also receives SMS messaging comprising daily adherence and appointment reminders and positive reinforcement for medication adherence daily for 2 weeks, on alternate days for 2 weeks, thrice weekly for 1 month, weekly for 3 months, and every 2 weeks for the rest of the study duration. The control group receives appointment reminders and SOC per clinic protocol. Exploratory

analysis will be conducted to determine differences in medication adherence and virologic suppression in the 2 arms and to assess cost-effectiveness and study feasibility and acceptability.

Results: In the first 23 months of the study (July 2018-April 2020), 56 (55%) of 102 eligible patients were enrolled and randomized. At present, participating youths are primarily African American (53/56, 95%), male (37/56, 66%), and ≥18 years old (53/56, 95%). Follow-up study visits, as required per the protocol, have been completed by 77% (43/56), 94% (45/48), 95% (37/39), 96% (24/25), and 100% (10/10) of participants at the 1-month, 3-month, 6-month, 12-month, and 18-month follow-ups, respectively.

Conclusions: Preliminary accrual and retention data suggest that TECH2CHECK is feasible and acceptable.

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KEYWORDS

adolescent; youth; community health nursing; HIV; adherence; viral suppression; mobile health

Introduction

Background

Youth aged 12-24 years comprise 21% of all new HIV infections in the United States, with 8000 diagnoses yearly [1]. In this age group, the high infection rate is coupled with poor engagement and retention in care, low rates of treatment initiation, and low rates of antiretroviral therapy (ART) adherence and virologic suppression [2,3]. The HIV care continuum is a framework for understanding the status of persons living with HIV (PLWH), including being aware of HIV diagnosis, linkage to care, retention in care, receipt of ART, and attainment and maintenance of virologic suppression [4]. It is estimated that only 6% of youth with HIV (YHIV) are virologically suppressed [5]. Failure to initiate treatment and attain suppression increases the risk of disease progression and transmission in sexual networks [6]. Adherence to outpatient provider visits, filling prescriptions, and consistent use of ART are the keys to virologic suppression. However, durable virologic suppression eludes many YHIV due to a combination of cognitive, developmental, and psychosocial challenges specific to this population. Barriers to care include stigma and lack of accessible and affordable youth-friendly services along with poor health literacy [7,8]. Even in adolescent-focused clinics like the 13 clinics that comprise the National Institutes of Health–funded Adolescent Medicine Trials Network, youth continue to have challenges. Recently published data on 1411 youth aged 12-24 years who were referred to one of the Adolescent Medicine Trials' Network for HIV/AIDS sites through SMILE (Strategic Multisite Initiative for the Identification, Linkage, and Engagement in Care of Youth) demonstrated that, even with dedicated outreach workers and tailored initiatives, only 12% of youth achieved viral suppression after a median of 5 months [9]. Youth with poor virologic control are predisposed to antiretroviral drug resistance, immunologic decline, and greater health care costs (hospitalizations, emergency department utilization) [10-12]. When given the tools, YHIV are able to engage and adhere to ART, though there are limited evidence-based approaches specifically targeted to this population [13]. Short-term interventions (eg, directly observed therapy, financial incentives) have had limited success and sustainability [13]. Given the consequences and costs of nonadherence to care and ART in this population, novel strategies that remove barriers to care and allow for provision of care for YHIV between medical visits and outside of the clinic setting are essential to improving outcomes for YHIV. Rigorously designed and tested strategies using randomized controlled designs are therefore critical to reducing the treatment disparities observed among YHIV.

Efforts to improve the care continuum among YHIV have generally focused on the first 2 components of diagnosis and linkage to care. However, modeling by Shah et al [14] indicates that smaller population-level impact (reduced incidence, survival) is seen with improvements in the upstream components of the care cascade (diagnosis, linkage), while more dramatic effects occur with improvement in the latter components (retention, sustained virologic suppression) of the care continuum [15,16].

With the advent of ART, HIV has evolved into a chronic disease with life expectancy equivalent to that of uninfected individuals [17,18]. The current model of care includes patients attending appointments with their HIV provider quarterly or less frequently. The reliance on patient responsibility for follow-up in care may pose challenges for YHIV. The Department of Health and Human Services HIV guidelines state that PLWH can be seen by their provider as infrequently as once yearly if stable [19]. Our data have demonstrated that reduced frequency of HIV provider visits (<3 in a calendar year) is indeed associated with decreased rates of ART initiation and continuation among YHIV [20,21]. Importantly, this profile is associated with higher hospitalization rates due to HIV-related and unrelated diagnoses for YHIV [11]. Effective HIV management of YHIV may require a model of care different than what is currently being employed. Alternate models of care are being explored for management of individuals with chronic illnesses, particularly for youth, where flexibility, convenience, and technology may be invaluable components of their care [22]. We will therefore need to consider interventions that change the paradigm (eg, enhance delivery systems, strengthen the health system, improve self-management support, inform and activate the patient) and thereby sustainably improve outcomes.

Evidence-based interventions that specifically target YHIV are understudied. A systematic review of adherence interventions targeting YHIV 13-24 years old reported on outcomes of adherence, viral load (VL) suppression, or CD4 from 10 studies (8/10 US-based) [23]. The review included 346 YHIV with an average of 35 participants per study. The varied interventions included directly observed therapy, cell phone and text message reminders, guided problem solving about adherence, motivational interviewing, other reminder strategies, individual and family counseling, and financial incentives, lasting from 12 weeks to 24 weeks, with outcomes assessed at 24-96 weeks. The studies were limited, as most were pilot studies without a control group, and underpowered to detect statistical differences. Two randomized controlled trials (RCTs) that utilized individualized cell phone adherence reminders with problem-solving strategies and weekly in-person or internet-facilitated patient and family counseling for training and skills building resulted in improved adherence, as confirmed with reduced VL measures after 12-14 months [24,25].

When considering potential interventions, the feasibility of delivery mechanisms is critically important, with much attention paid to technology integration. A 2018 nationally representative survey of adolescents found that 95% owned or had access to a smartphone [26]. African American youth were most likely (85%) to have smart phones. US cell phone penetration currently stands at 120.7%, up from 69% in 2005 [27], and there is high penetration of cell phones or smart phones among YHIV cared for in the participating clinics [28]. Text messaging is a viable method of successfully communicating health messages with patients, including a successful sexual health text messaging service (SEXINFO), which improved basic sexually transmitted infection and HIV information and referral sources for in-person consultation for San Francisco youth [29]. It has also been shown to improve virologic suppression and retention in care in HIV-positive youth on ART and in promoting sexual health education among sexually active HIV-negative youth in the United States [30,31]. Text messaging has become an essential component of daily life for YHIV that needs to be optimized from a systems perspective to extend care and adherence support [32].

Community health nurse (CHN) home visiting interventions have been shown to reduce repeat pregnancy rates [33], improve utilization of resources for pregnant and parenting adolescents [34], and optimize care for chronic diseases like asthma [35]. The maximum benefit is seen with participants at highest risk when nurses are assigned solely to implement a protocol [36]. The TECH-N study, a community-based nursing intervention study, also demonstrated that delivery of CHN services in the community was more successful than referral for clinic-based services and proved to be highly feasible and acceptable among low-income youth living in neighborhoods with high sexually transmitted infection or HIV prevalence who were diagnosed with acute pelvic inflammatory disease [37]. The CHN model has not been specifically studied among YHIV 12-25 years old [38]. One Ugandan study examined the benefits of long-term (average 4.2 years) community health–based care vs a clinic-based approach in children 0-18 years of age living with HIV, demonstrating better retention, but no difference in survival [39]. The TECH2CHECK intervention was designed to address unmet care needs designed to further assist YHIV to reach undetectable status. The aim of this trial is to specifically evaluate the effectiveness of the intervention on retention in care, ART initiation and maintenance, and rates of virologic suppression among urban minority YHIV who have been unable to reach virologic suppression. The cost-effectiveness of the intervention will also be assessed.

Objectives

The primary aim of the TECH2CHECK study is to compare the effectiveness of TECH2CHECK to standard of care (SOC) in improving viral suppression using an RCT among urban YHIV demonstrating suboptimal adherence to treatment as evidenced by HIV viremia (VL >20 copies/mL). We will compare the feasibility, acceptability, and cost-effectiveness of TECH2CHECK to SOC for management of HIV in the outpatient setting and examine the sustainability of self-care behavior, adherence, and virologic suppression among youth following the intervention period. Drawing from the success of the TECH-N study, we will extend the same skills to study the challenges among YHIV [37]. Given the convincing TECH-N data and the similarities between YHIV targeted in this project, we repurposed the CHN approach used in TECH-N for nonadherent YHIV. The aim of this paper is to describe the methods and preliminary recruitment, intervention delivery, and retention outcomes of TECH2CHECK as an initial assessment of the feasibility of this work.

Methods

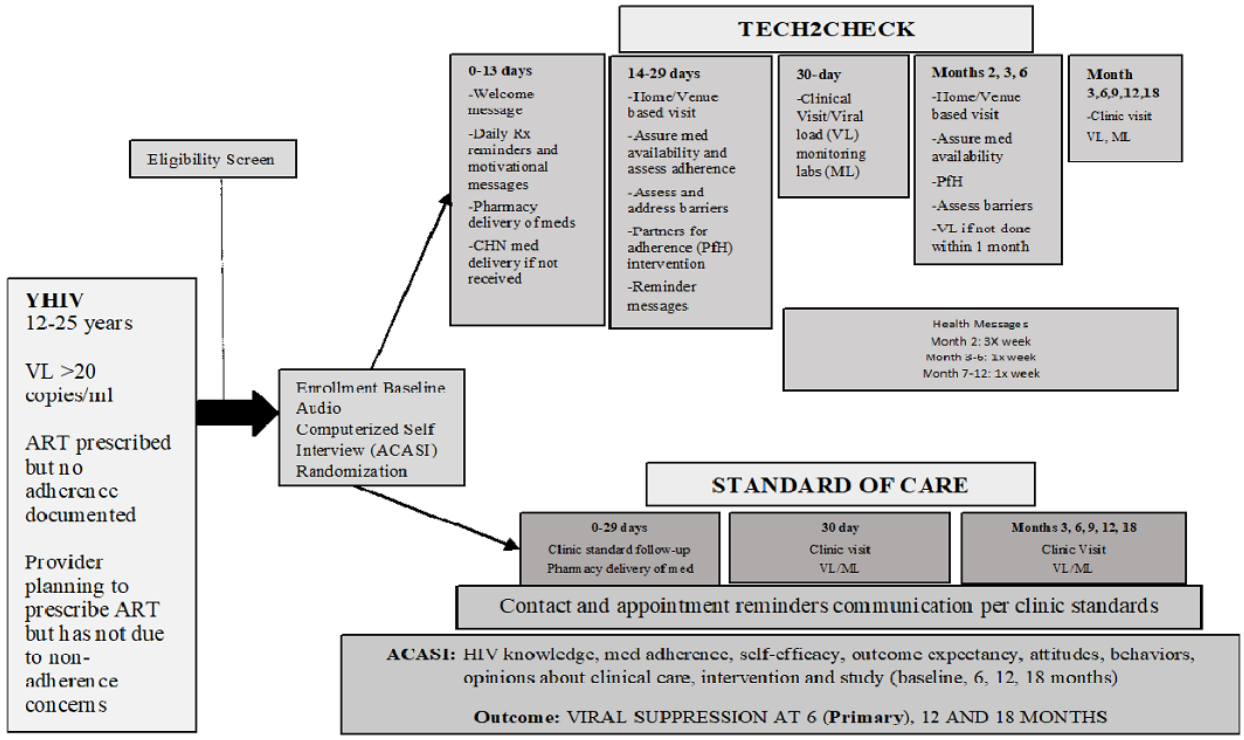
Study Design, Population, Sampling, and Randomization

The study is a single-blinded RCT enrolling YHIV in Baltimore, Maryland (site 1), Washington, D.C. (site 2), and Jacksonville, Florida (site 3). The Baltimore recruitment site is made up of 2 interconnected clinics, both geographically located in one of the highest HIV prevalence areas in the city. All 3 clinical sites are referral sites for newly diagnosed youth, actively involved in HIV clinical service delivery using national standards and proactively involved in youth-centric HIV-related research activities. The most recent data from the study-affiliated clinics reveal high viremia rates (VL >20 copies/mL) among 12-25-year-olds of 30-36% (Site 1), 34% (Site 2), and 60% (Site 3). All the clinics are located in areas targeted in the government's Ending the HIV Epidemic: A Plan for America [40].

We are enrolling and randomizing 120 YHIV aged 12-25 years with HIV nonadherence to either TECH2CHECK (Arm 1) or SOC control group (Arm 2) using a permutated block design to ensure group balance at each of the sites at the end of the trial period. This strategy helps to minimize any systematic differences between patients enrolling at different times during the study. Participants in Arm 1 (intervention group) receive community-based health visits, SMS text messages with positive health messages, ART and clinic appointment adherence reminders, and a 3-5-minute behavioral intervention described in a later section. In Arm 2 (control group), YHIV receive SOC

as dictated by their primary HIV provider and clinic standards and communication and appointment reminders as per the standard clinic practice. Participants in both arms have their regularly scheduled clinic visits as dictated by their provider (usually every 3 months; see Figure 1). The protocol is described according to the CONSORT-EHEALTH checklist [41].

Figure 1. Schematic of TECH2CHECK design. ART: antiretroviral therapy; CHN: community health nurse; YHIV: youth with HIV.



Recruitment, Eligibility, and Informed Consent

YHIV are being recruited from the clinical sites by trained research staff after being referred by providers and clinical teams during routine clinical care visits for this study approved for human subjects. Eligible participants are aged 12-25 years, have been diagnosed with HIV, are prescribed ART or eligible for ART but nonadherent to initiation, have VL >20 copies/mL, permanently reside in the recruitment area, and are willing to sign informed consent. Informed consent includes willingness to complete study procedures, agreement to study randomization and community-based follow-up by our team, and the ability to speak and read English. Patients are excluded if there is existing mental health, cognitive, or behavioral dysfunction that would impair effective participation if present or in the event of severe illness requiring hospitalization at the time of enrollment. Consent will be obtained directly from subjects aged ≥18 years and from parents or guardians of younger subject across all but one site where parental consent is not required for the enrollment of younger patients.

Training, Follow-Up, and Tracking

Research staff have been trained on the recruitment and consent protocol, interview surveys, and confidentiality of data collection. Ongoing communication between the sites enables the team to identify and address barriers to referral or recruitment. Involvement of key study personnel in clinic leadership further enhances the focus on the study. Research staff track eligible patients, those approached, and outcome of the approach. Detailed contact information obtained from the patient at the time of the initial recruitment includes home and work numbers, cell phone numbers, email addresses, Facebook, other social networking sites (user names and IDs), school attended, and the names of 2 individuals who usually know their whereabouts and can be contacted to locate them. Participants are advised to notify study staff of changes in their living environment or contact info and receive a small US $5 gift card incentive for this notification, a successful initiative from the TECH-N trial [37].

Intervention and Control Conditions

TECH2CHECK involves field visits by a CHN trained in disease intervention protocols, including clinical assessment, case management, counseling, and behavioral intervention. The CHN conducts community-based visits at mutually agreed-upon home and venue-based locations monthly or every 3 months. After enrollment, the first CHN visit occurs within 1-3 weeks of the enrollment or randomization, then at 2 weeks, 6 weeks, 10 weeks, 14 weeks, and 26 weeks. Nursing visits stop at 6 months, but participants and nursing staff will maintain communication

via phone and the Emocha messaging app [42].Visits include clinical assessments, laboratory draw and assessment, adherence counseling and management, symptom assessment, and case management. CHNs assess ART adherence and actively assist with ART delivery as needed. At the end of the visit, the CHN determines a plan of action using 2 conditional algorithms based on the clinical assessment: one for participants requiring immediate attention (eg, symptoms needing acute management) and the other for participants for whom nonimmediate follow-up is indicated (eg, patient has nonurgent medical or psychosocial needs). The CHN nurse gives referral resources to assist patients who may have other issues identified during the visit (eg, utilities, housing). SMS messages comprising adherence reminders, positive reinforcement for HIV management, and appointment reminders are provided to participants in the intervention arm. Specifically, they receive a welcome message, daily SMS messages, and directly observed treatment in the first month; SMS messages thrice weekly in the 2nd month; SMS messages once weekly for months 3-6; and weekly reinforcement and retention messages for months 7-18. Communication via study cell phone allows for 2-way communication so that participants can both respond and initiate. Integral to the TECH2CHECK intervention is the use of an effective behavioral intervention to improve HIV adherence and self-care behaviors. TECH2CHECK utilizes the Centers for Disease Control and Prevention's Partnership for Health to provide skill-based adherence and risk-reduction counseling [43]. Standard operating procedures were developed for triage and referral if the CHN goes out and the participant has an acute issue or complaint. The CHNs have 24/7 back up by the site principal investigators to assure clinical coverage by a physician.

In the control arm, patients receive SOC and appointment reminders. After completion of study enrollment procedures; an audio, computer-assisted self-interview (ACASI) baseline survey; and collection of baseline blood draw, the usual SOC as dictated by the provider is employed. The participant is given instructions for medication administration and information about side effects, and their next appointment is scheduled prior to leaving the clinic. All communications and interactions are performed per the clinic standard and recorded by the study team.

Data Collection and Measures

The primary outcome measures of virologic suppression and secondary outcome measures of clinical outcomes (pharmacy refill, medication adherence, completed encounters, visits) and cost-effectiveness will be assessed at the end of the study. We will build upon and adapt the previously developed ACASI survey to collect perceived barriers to treatment and self-efficacy data from YHIV. The measures on the baseline survey include demographics, HIV treatment and adherence history, disclosure, mental health, substance use, sexual history, HIV adherence self-efficacy and perceived barrier scales, social provisions scale, and the short-form survey instrument (SF-12) as a measure of health-related quality of life [44]. Medical history (clinic attendance, hospitalization, acute care visits), medication adherence (self-reported adherence, pill counts, pharmacy records), side effects, non-ART medication usage, vital signs, symptoms, and visit diagnoses are obtained at all visits. At the TECH2CHECK nurse visits, the CHN records contact tracing data and performs a detailed clinical assessment including interval medical history, symptom reporting, medication usage, supportive care, side effects, activity level, and patient education. Permission to obtain medical records and health providers, if health care utilization is reported, is requested at the time of enrollment so that project staff can verify self-reported clinical data in the case of unreturned forms.

Standard HIV measurements include CD4, VL, and toxicity monitoring (chemistries) collected at clinic visits. VL and chemistries are collected by CHN at home or venue-based visits in the intervention arm only if not collected within the prior 4 weeks. Samples for CD4 measurements are collected by the CHN at 26 weeks if missed in the past 4 months.

Feasibility and Acceptability

At the end of the study, data on study feasibility, acceptability, and refusal rates will be reported. Follow-up completion and study dropout rates will be used as indicators of study acceptability. Collection of basic demographic data and the outcome of recruitment effort will be conducted to determine the number of referral patients who are ineligible or decline to participate in the intervention and the similarities and differences from those who ultimately participate.

Study Incentives and Benefits

All participants receive a US $25 gift card at enrollment and US $35 for each completed ACASI (baseline, 3 months, 6 months, 12 months, and 18 months). YHIV in the TECH2CHECK intervention arm do not receive compensation for home visits or for clinic visits attended given the current standards of care and because adherence to the CHN clinical visit is a behavior under study that must be made without any form of additional incentive. Transportation fare is provided to participants in both arms for SOC care visits and for labs as needed. We provide a disposable cell phone to allow for SMS messaging to those who are assigned to the intervention arm but do not have a cell phone. Overall, we anticipate this to be a minority of the youth given the 93% cell phone penetration among US youth, which we have confirmed in our prior local studies [26].

Sample Size and Power

From the 4 participating clinics, we expect to enroll 144 nonadherent YHIV subjects over the period of this study, with about 120 subjects agreeing to participate and be evaluable for the primary outcome at 6 months and 12 months. Attrition rates of 10%-30% over the course of the study indicate that the study will have 80% (α=.05) power to detect differences in the proportions with virologic suppression between the control and intervention groups of at least 30%, assuming that the control group's rate is 30%-40%.

Data Analysis

The overall approach will be an intention-to-treat analysis. To test the hypotheses, in addition to data cleaning and exploratory data analysis, we will first review the demographic characteristics of the 2 study groups and between the clinical sites. Additionally, we will explore the characteristics of survey

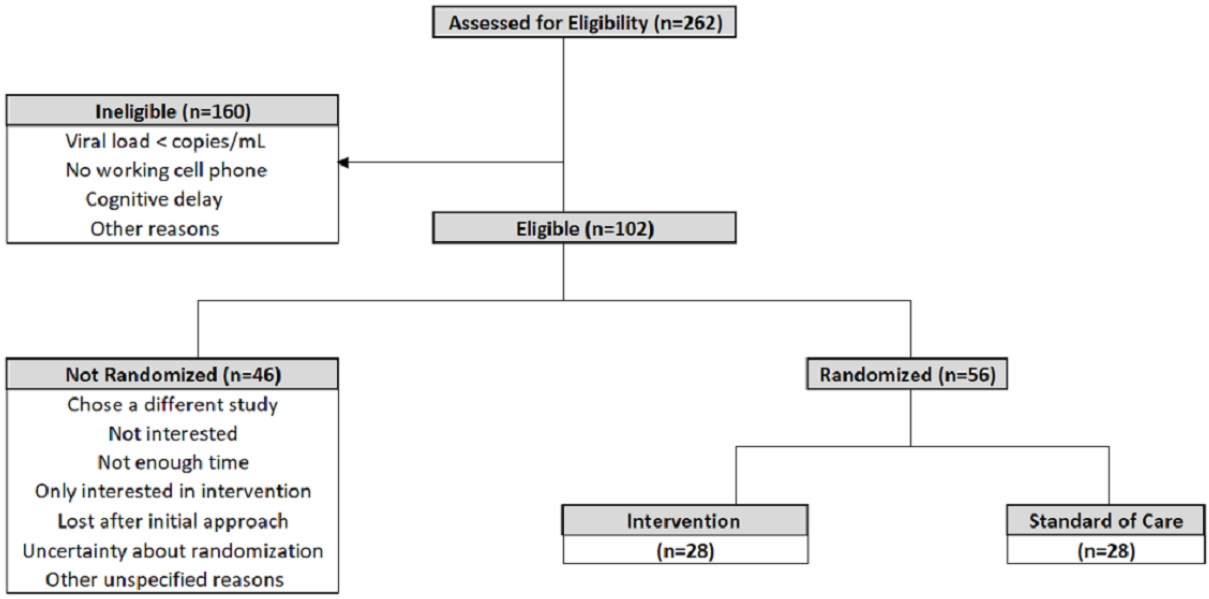
nonresponse and attrition. The plan for addressing each of the challenges and for hypothesis testing is described below. Data analysis will be performed using STATA Version 15.0 or comparable statistical software and the Tree Age software. The extent of data missing due to survey nonresponse will be assessed; two approaches, multiple imputation and pattern-mixture-modeling, will be considered for adjusting [45]. We present a descriptive analysis of the preliminary recruitment, baseline demographics, intervention delivery, and retention to assess feasibility and acceptability.

Results

The study opened for accrual in July 2018 at the Baltimore site, followed by the D.C. site in Jan 2019, and is currently ongoing. Due to unforeseen changes in the research staff infrastructure, the D.C. site ceased enrollment in June 2019 but continues to follow participants that were previously enrolled in the study. The team subsequently recruited and implemented the study at an additional site in Jacksonville, Florida; they began enrollment in February 2020. As of April 2, 2020, 262 patients were assessed for eligibility, and 38.9% (102/262) were deemed eligible and approached; 56 (56/102, 54.9%) were successfully recruited into the study (Figure 2). Of these, 95% (53/56) are African American, 66% (37/56) are male, and 95% (53/56) are ≥18 years old. Median VL at enrollment was 90 copies/mL (IQR 1553 copies/mL). Study accrual is on track and expected to be completed as planned. Participants are spread across different follow-up time points, reflecting the variations in the time of recruitment into the study. Presently, 77% (43/56), 94% (45/48), 95% (37/39), 96% (24/25), and 100% (10/10) of participants at the 1-month, 3-month, 6-month, 12-month, and 18-month follow-ups, respectively, have completed follow-up study visits as required per protocol. Additionally, 77% (20/26), 78% (21/27), 81% (21/26), 96% (23/24), and 90% (18/20) of subjects expected to receive CHN visits at 2 weeks, 6 weeks, 10 weeks, 14 weeks, and 26 weeks, respectively, have completed those visits. Of the 56 enrolled participants, 98% (55/56) have completed some or all study follow-ups; only 1 patient was lost to follow-up. There have been no safety concerns nor significant adverse events.

Final data collection and conclusion of the study are anticipated for July 2022, although research disruption due to the COVID-19 pandemic may extend the study completion timeline [46]. Formal analysis of data to evaluate the primary aims will proceed following study completion of data collection.

Figure 2. Recruitment of Study Participants.



Discussion

Findings from this study show that the recruitment of YHIV with poor medication adherence and virologic suppression is both feasible and acceptable. Virologic suppression among YHIV on ART remains suboptimal when compared with older age groups, as less than 30% of YHIV on ART achieve virologic suppression compared to 50% of adults [44,47]. The need for ART treatment delivery beyond the traditional clinic-based model and strategies to optimize treatment adherence in YHIV is highlighted by a growing body of evidence on the comparatively low adherence rates observed in youth in care for HIV [9]. TECH2CHECK builds upon past advancements in YHIV and addresses existing gaps in youth virologic control. First, we focus on identifying the impact of a community health intervention on adherence to ART by YHIV. While there have been a few RCTs that have sought to improve ART adherence through community-based interventions, the outcomes assessed are limited by the nonobjective assessment of adherence (ie, no viral load measurements) [48,49]. The statistical power of our study allows for the determination of statistically significant differences in the efficacy and cost-effectiveness of the intervention between both arms, if present, a frequently missing piece from studies [50,51]. An extended follow-up period of

18 months as opposed to shorter durations of follow-up will also allow for the assessment of long-term adherence, virologic suppression, and associated positive behavioral changes related to the intervention [48,50,51]. As there is a need for real-world interventions that address diverse YHIV infection with poor ART adherence whose behaviors and attitudes may differ by acquisition category, TECH2CHECK will include both youth who have acquired HIV perinatally (~30% of YHIV) and through high-risk behaviors [50,52,53]. Finally, we have chosen a viral load of >20 copies/mL as an indicator of nonadherence because, with the potency of newer regimens, we are of the opinion that elevations in VL even at these low levels often indicate adherence challenges and thereby allow deployment of adherence interventions before behavior patterns become solidified and before complete loss of virologic control [52]. Given the paucity of data on the effectiveness of alternative methods for improving ART adherence among YHIV, we anticipate that TECH2CHECK will be cost-effective and efficient in addressing barriers to ART adherence, improving retention in care and thereby leading to an improvement in the elusive control of HIV among YHIV, with potential for a substantial health impact. Although studies integrating community health interventions have been used in the TECH-N study of youth diagnosed with pelvic inflammatory disease, TECH2CHECK represents the first of its kind among YHIV in the United States and can potentially improve the status quo of YHIV [37].

Limitations

An important limitation to consider is that the intervention may not be generalizable to clinics and locales serving nonminority populations. However, given that the demographics of YHIV in the United States resemble that of those that we anticipate will be enrolled in TECH2CHECK, this is less of a limitation. If effective, the intervention could subsequently be modified for other populations. Additionally, the current COVID-19 pandemic and shelter in place orders have impacted some aspects of the study as recruitment has been temporarily halted. However, all study sites continue to work remotely, collection of study data has continued, and nursing visits have been replaced by virtual visits. While it is difficult to estimate the impact of the COVID-19 pandemic on enrolled participant behavior within the study at this time, we recognize how vitally important it is to assess this in the final analysis at the end of the study. We have had extensive experience recruiting youth at risk for and living with HIV through our activities in the TECH-N study, Adolescent Medicine Trials' Network for HIV/AIDS, and collaborations with our Centers for AIDS Research, International Maternal Pediatric Adolescent AIDS Clinical Trials, and HIV Prevention Trials' Network activities. We have established working relationships with other clinics in the local jurisdictions, the local health department, and other academic centers in Baltimore, to which we have expanded recruitment through the primary site. We anticipate being able to reach our long-term accrual targets.

Conclusion

Engaging YHIV in ART care and treatment and ensuring treatment adherence and virologic suppression are necessary prerequisites in the attainment of better health-related quality of life and in alleviating the morbidity and mortality associated with HIV for YHIV. Well-designed and rigorously assessed youth-targeted adherence interventions that directly address the current disparities in treatment outcomes and continuum of care between youth and adults are essential. TECH2CHECK, if successful, will provide evidence for a strategy to improve adherence to care and viral suppression for YHIV, an often-marginalized population in need of tailored and well-resourced interventions that increase the likelihood of leading lives as near normal as possible. Preliminary recruitment and retention data support the feasibility and acceptability of the approach being used in the trial.

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Conflicts of Interest

MT receives funding from the National Institutes of Health (NINR, NICHD, NIMHD) and research supplies from Hologic Inc and SpeeDx LLC through Johns Hopkins University. She also serves on the Trojan Sexual Health Advisory Council (Church and Dwight Inc). AA receives funding from the National Institutes of Health (NICHD, NIAID, NIMHD) and serves as a member of scientific advisory boards of Gilead Pharmaceuticals and expert advisor panel for Merck Pharmaceuticals.

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Abbreviations

ACASI: audio, computer-assisted self-interview
ART: antiretroviral therapy
CHN: community health nurse
ML: monitoring labs
PfH: Partnership for Health
PLWH: persons living with HIV
RCT: randomized controlled trial
SMILE: Strategic Multisite Initiative for the Identification, Linkage, and Engagement in Care of Youth
SOC: standard of care
VL: viral load
YHIV: youth with HIV

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Protocol

Feasibility and Effect of the Exergame BOOSTH Introduced to Improve Physical Activity and Health in Children: Protocol for a Randomized Controlled Trial

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Abstract

Background: Despite the well-known beneficial health effects of physical activity (PA), the majority of Dutch primary school children do not meet the recommended PA guidelines. Although there is growing evidence on the effectiveness of exergames for PA in children, there is limited evidence on their effect on health outcomes, such as cardiovascular health and health-related quality of life (HRQOL), and on factors influencing their effectiveness and feasibility. The exergame BOOSTH uses a wrist-worn activity tracker to measure steps per day. As a reward for the performed PA, children can unlock levels in the online BOOSTH game. In addition, “BOOSTH battle” enables competition between groups.

Objective: This protocol describes a cluster randomized controlled trial in 16 primary schools in the Netherlands investigating the effect of BOOSTH on moderate-to-vigorous PA (MVPA) using accelerometry. Secondary aims are to investigate the feasibility of BOOSTH (mixed methods: questionnaires and focus group interviews) and its effect on cardiovascular risk factors (anthropometrics, blood pressure, and retinal microvasculature) and HRQOL.

Methods: Stratification variables and relevant variables related to outcomes (such as BMI [z-score], sex, age, and parenting style) and/or missingness will be taken into account. Measurements will be performed at baseline and after 3, 6, and 12 months.

Results: The study has received funding from Province Limburg (SAS-2015-04956) and received ethical approval from the Medical Ethics Committee of Maastricht University Medical Centre (METC172043/NL64324.068.17). The results of the analyses are expected to be published in 2021.

Conclusions: With this study, the ability of the exergame BOOSTH to increase PA and improve health in children of primary school age will be investigated. The insights into effectiveness and feasibility will result in scientific and societal recommendations, which could potentially contribute to widespread implementation of exergames for children.

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International Registered Report Identifier (IRRID): DERR1-10.2196/24035

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KEYWORDS

exercise; sedentary lifestyle; mHealth; mobile health; serious game; exergame; prevention; pupil; randomized controlled trial

Introduction

Physical activity (PA) is associated with numerous health benefits in children [1], including the prevention of cardiovascular disease and obesity, and a better health-related quality of life (HRQOL) [2-4]. Moreover, higher levels of cardiorespiratory fitness in childhood are associated with a better cardiovascular health profile later in life [5]. Unfortunately, according to Jago et al, the levels of moderate-to-vigorous PA (MVPA) decrease with increasing age starting from the age of 6 years [6]. In 2019, 44.1% of Dutch children (age 4-11 years) and 59.5% of adolescents (age 12-18 years) did not meet the public health guidelines of performing a minimum of 60 minutes of MVPA each day [7]. Therefore, it is of major importance to promote PA from a young age.

Several studies have evaluated the effects of interventions aiming to increase PA on health outcomes in children (age 3-18 years) [4]. Most interventions showed improvements in HRQOL [4], physical fitness, and vascular structure in response to increasing PA [8,9]. Although the results of the majority of previous studies showed that higher PA in children (between the ages of 6 and 15 years) was associated with improved retinal microvascular health, the study by Lundberg et al is the only one that investigated objectively measured PA [8-10]. This study included 307 Danish children (mean age 15.4 years [SD 0.7]) and found that higher PA was associated with narrower retinal venules. Although questionnaires are easy to use, self-report methods may lead to recall bias. Especially in young children (age <10 years), questions on PA might be difficult to interpret or answer, and they may not fully understand the concept of PA. Longitudinal data on the effects of objectively measured PA on vascular function, sedentary behavior, and HRQOL and in the school-based population are scarce.

Nowadays, the majority of children spend a considerable amount of their time playing digital games, and as a result, the amount of screen time is high [11]. Among primary school children in the Netherlands, in 2015, 87% played digital games, of which 33% played on a daily basis [12]. Moreover, 53% of all children spend 1 to 4 hours on each gaming session, which highly contributes to sedentary time. However, the interest for video games also provides new opportunities to increase PA via exergames. An exergame is a game designed for a primary purpose beyond that of pure entertainment and aims to increase the player's PA [13,14]. Exergames (ie, Wii Fit, Wii Sports, and Dance Dance Revolution) are videogames that combine PA with video gaming technology, thereby increasing energy expenditure and controlled body movements [15,16]. Previous studies have shown that exergames are more attractive and enjoyable for children in comparison with regular PA [17], suggesting that exergames are a promising tool to promote exercise in this population. Moreover, by improving the intrinsic motivation to perform PA, exergames might support healthier lifestyle habits in the long term [18].

To increase impact, exergames have recently been introduced in the school setting. This approach is promising, as children spend a considerable amount of time at school and children of all social economic classes are reached. The majority of school-based exergames showed enhanced PA [19-23]. For example, Gao et al showed that exergaming and regular physical education had similar effects on children's (mean age 8.27 years [SD 0.70]) MVPA, light PA, sedentary behavior, and energy expenditure [22]. Exergame interventions have even more potential if they are applicable both within the school setting and during leisure time, since parental involvement increases success rates [24].

BOOSTH is a newly developed exergame that incorporates these principles. In order to unlock new levels in the online game, a child needs to be physically active (ie, take steps), thereby promoting the intrinsic motivation to move. BOOSTH makes use of a wearable device (activity tracker around the wrist) and can therefore be used within and outside the school setting, as well as during indoor and outdoor play.

This paper describes the protocol of a longitudinal approach to determine the effect of BOOSTH on PA (MVPA and sedentary behavior), BMI, cardiovascular risk factors (ie, blood pressure, retinal microvasculature, and maximal aerobic performance), and psychological parameters (ie, HRQOL and motivation towards PA) in a school-based setting that includes 16 schools in the Netherlands (BOOSTH study; ClinicalTrials.gov NCT03440580). Previous studies evaluating the effect of exergames focused mainly on PA, whereas measures of energy expenditure or BMI were included in a limited number of studies [17,21]. Stratification variables and relevant variables related to outcomes (such as BMI [z-score], sex, age, and parenting style) and/or missingness will be taken into account. Furthermore, in order to explain and interpret the findings and for future development of the BOOSTH intervention, the feasibility of implementation in a school setting will be investigated.

Methods

Recruitment and Participants

The BOOSTH study is a cluster randomized controlled trial at 16 primary schools located in the province of Limburg (the Netherlands). Schools will be randomized to standard physical education curriculum plus BOOSTH (intervention schools) or standard physical education curriculum only (control schools). Stratified randomization will be applied by an independent researcher. Stratification variables are community (ie, schools need to be located within the same community) and school size (ie, number of children in a school). Control schools will only be visited for physical measurements. The inclusion criteria for the children are as follows: boys and girls in classes five to seven (age range 7-12 years) at the moment of inclusion and written informed consent from both parents and children older than 12 years. Children will be excluded if they are wheelchair dependent.

Sample Size Requirements

The sample size calculation is based on the primary outcome as follows: to detect a difference in MVPA between the intervention and control groups after 12 months. Children are nested within schools, with eight intervention and eight control schools.

Children from grades five till seven (age range 7-12 years) will be included in this study. Based on the participation rates of other Dutch school-based PA interventions, it is expected that about 60 children per school will participate. Therefore, 480 children per condition (intervention/control) (8×60=480) will be included. It is assumed that the intraclass correlation coefficient is between 0.05 and 0.10 [25]. When an intraclass correlation coefficient of 0.10 is used, the design effect (accounting for clustering of 60 children within a school) is equal to 6.9 (1+[60−1]×0.10). Accounting for a dropout rate of 20%, the effective sample size (sample size after dropout divided by design effect) is equal to 55 per school.

With the given sample size and assuming a significance level (α) of .05 and a power of 80%, we can demonstrate a Cohen *d* of 0.54, which means we can detect a moderate effect size on MVPA [26]. Based on a within-group SD of 20.38 [27], a difference in mean absolute MVPA of 11 min/day between the intervention and control groups can be detected.

BOOSTH Intervention

The BOOSTH intervention consists of an online arcade game that can be synchronized with a BOOSTH activity tracker using the BOOSTH mobile app. In addition, the app includes "BOOSTH battle" to enable competition between groups.

After baseline measurements, children at the intervention schools will receive the BOOSTH activity tracker for free. The activity tracker, accompanied with a user manual and an oral instruction on how to use BOOSTH, will be provided to all children and parents during a regular school day. To install the BOOSTH app, a mobile device with Bluetooth and internet access is needed. Parents are asked to download the app together with their child. The children will receive an instruction to wear the BOOSTH activity tracker around their wrist during waking hours, except during water activities (eg, showering and swimming). One week after BOOSTH delivery, the research team will visit participating schools. Children, their parents, and their teachers will have the opportunity to ask questions about possible issues they encounter during the first week. No further instructions, activities, or support are part of the intervention.

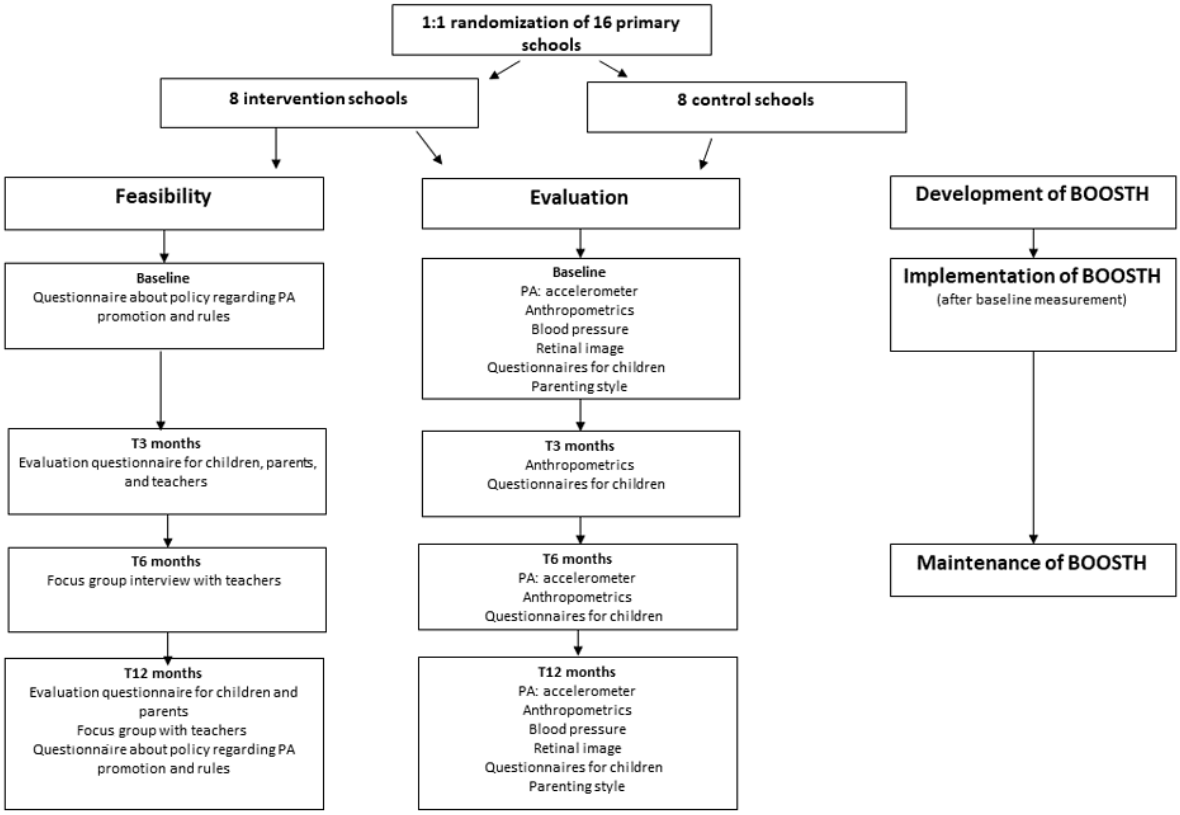
The BOOSTH intervention includes several behavioral change techniques with the intention to stimulate PA and positively change the attitude toward PA. Using the BOOSTH activity tracker, the child can track step count. The use of activity trackers could help children set achievable goals and monitor their progress toward the goals [28,29]. The step count registered by the activity tracker can be synchronized with the BOOSTH app, which, depending on the magnitude of PA levels, is rewarded by online playtime and gaming incentives such as unlocked levels and special features. In order to unlock the next level, 30 minutes of PA are required (ie, about 6000 steps). A level in the BOOSTH game takes around 5 minutes to play. According to international guidelines, a maximum of 2 hours of screen time is recommended for children between the ages of 4 and 11 years [30]. Therefore, the amount of performed PA, which is needed to unlock the next level in the game, is six times higher compared with the amount of playtime. Rewards can motivate children to engage in PA, especially when combined with PA monitoring [31-33]. The first four levels are freely accessible in order to increase the interest and enthusiasm of the child. In addition, there is an optional function of a "BOOSTH battle" that enables competition between groups. Teachers and children can create their own battles in the BOOSTH app as they like.

Measurements

Data Collection

As shown in Figure 1, study measurements will be performed at baseline (T0) and after 3 months (T3), 6 months (T6), and 12 months (T12). A trained research team will perform the measurements during school hours at the primary schools. The research team will be instructed to complete the questionnaires together with the children. Stratified intervention and control schools will be measured within the same week to prevent confounding effects of, for example, different seasons and weather-dependent factors influencing PA. Measurements will be performed using a standardized protocol.

Figure 1. Overview of the BOOSTH study and measurements. The questionnaires for children included subjective PA behavior, screen time, health-related quality of life, and motivation toward PA. PA: physical activity.



Physical Activity

The primary outcome is MVPA (min/day), which will be measured with Actigraph GT3X (ProCare). This is a triaxial accelerometer, and it has been validated for the measurement of PA behavior in children. The children will be asked to wear the accelerometer attached via a waistband on the right hip for 7 consecutive days during waking hours, except during water activities (eg, showering and swimming) and contact sports (eg, judo). Accelerometry data will be downloaded with 10-s epochs using the Actilife software (Actigraph). Valid wear time will be defined as a minimum of 4 days, with at least 480 minutes per day of recording, including 1 weekend day. Derived data are expressed as mean counts per minute (cpm). To establish time spent in different intensity categories (sedentary behavior, light PA, and MVPA), the cutoff points developed by Everson et al will be used [34].

In addition, the self-administered validated Baecke questionnaire (for children) will be used to assess the amount of habitual PA ranging from 1 (lowest activity) to 5 (highest activity) [35]. Data on PA at school, during leisure time, and during organized sports will be collected.

Anthropometrics

Height, weight, and waist circumference will be measured in duplicate, and the average of both measurements will be reported. Body weight will be measured using an electric scale (Seca 877, Seca) to the nearest 0.1 kg. Heavy clothing and shoes will be removed before the measurement. Standing height will be measured using a portable stadiometer (Seca 213 stadiometer, Seca), and children will be asked to stand straight and look forward. Subsequently, BMI (weight [kg]/height [m]^2) will be calculated and age- and sex-specific BMI z-scores will be calculated (TNO Growth Calculator, TNO) [36]. In addition, weight classifications will be performed using the International Obesity Task Force classification system [37]. Moreover, waist circumference will be measured using a nonelastic tapeline after normal exhalation. Height and waist circumference will be measured to the nearest 0.01 m.

Cardiovascular Risk Factors

Systolic and diastolic blood pressure will be measured using an automated sphygmomanometer (Mobil-O-Graph, Revision 4.6 08/2011, IEM GmbH). Blood pressure will be measured on the nondominant arm in the sitting position. Measurements will be performed thrice, with 1 minute of rest in between measurements. The reading will be recorded to the nearest 1 mmHg. A mean value will be calculated out of these three readings. The mean systolic and diastolic blood pressure values will be computed into z-scores using the LMS method (L, curve Box-Cox; M, curve median; S, curve coefficient of variation) and reference values as described by Wühl et al [38,39].

Retinal microvasculature will be measured with fundus photography, which is a noninvasive tool to measure cardiovascular risk factors. The retinal characteristics that have received the most attention so far in predicting cardiovascular disease are the central retinal arteriolar equivalent (CRAE) and the central retinal venular equivalent (CRVE). Photographs of the retinal microvasculature will be taken using a fundus camera

(Topcon TRCNW-300, Topcon Corporation). Subjects will be seated with their head resting on a chinrest, thereby looking straight in the camera. The fundus camera automatically focuses on the subject's pupils and will take a photo of the retina of the right eye. A fundus photo with a centralized optic disc will be obtained for each subject. Fundus photos will be analyzed using RetinaCheck, and manual modification will be done using the retinal health information and notification system (RHINO). These programs are developed in collaboration with the Department of Biomedical Engineering at Eindhoven University of Technology in the Netherlands, using a series of innovative brain-inspired algorithms as described by ter Haar Romeny et al [40]. The region between two times and three times the radius of the optic disc will be used to calculate the CRAE and CRVE, and to calculate the ratio between the CRAE and CRVE (arteriolar-to-venular diameter ratio).

The maximum aerobic performance of the children will be assessed with a maximum multistage 20-m shuttle run test. Children run back and forth on a 20-m course and have to touch the 20-m line before or at an audio signal that is emitted from a prerecorded tape. The frequency of the audio signal is increased by 0.5 km/h each minute from a starting speed of 8.5 km/h. The test ends when the child has to stop owing to fatigue or when the child fails to reach the 20-m line concurrent with the audio signal on two consecutive occasions. The children will be constantly encouraged to run for as long as possible throughout the course of the test. The last completed oxygen uptake (VO_{2max}) (Y, mL/kg/min) will be calculated from the speed (X, km/h) corresponding to that stage (speed=8+0.5 stage number) and age (A, year) as follows: Y=31.025+3.238X−3.248A+0.1536AX [41].

Screen Time

Self-reported screen time will be reported separately for weekdays and weekend days using the following questions: "How many hours a day during the last 4 weeks did you watch TV on a normal weekday/weekend day?" and "How many hours a day during the last 4 weeks did you play console games or use a computer for your free time activities on a normal weekday/weekend day?" Possible responses are "not at all," "0.5 hours per day," "one hour per day," "2 hours per day," "2.5 hours per day," "3 hours per day," "3.5 hours per day," and "4 hours or more per day." Total screen time will be reported as minutes spent on watching television plus computer use. At 3, 6, and 12 months, a question about changes in screen time since the introduction of BOOSTH will be included in the questionnaire.

Psychological Parameters

HRQOL will be assessed using the validated Kidscreen and validated Pediatric Quality of Life Inventory (PedsQL) questionnaires. The 23-item PedsQL addresses the multidimensional scales of physical, emotional, social, and school functioning. The questionnaire consists of five options ranging from "never" to "almost always" [42]. Additionally, the 27-items Kidscreen will be used to measure HRQOL for five dimensions (physical well-being, psychological well-being, autonomy & parent relation, peers & social support, and school environment) [43].

Motivation toward PA will be measured using the self-administered validated Behavioral Regulation in Exercise Questionnaire-2 (BREQ2). The BREQ2 consists of 19 questions with a 5-point scale, which measures different aspects of motivation (external regulation, identification, introjection, integration, motivation, and intrinsic regulation) and has been shown to have good factorial validity [44].

Parenting Questionnaires

Parents will be asked to fill in an online questionnaire regarding family composition, country of birth, educational level, and self-reported height/weight. In addition, parents will be asked to fill in the validated 85-item comprehensive general parenting questionnaire (CGPQ). The CGPQ assesses the following five key parenting constructs that have been identified across multiple theoretical approaches of parenting: "nurturance," "structure," "behavioral control," "coercive control," and "overprotection" on a five-factor scale [45].

The parent version of the validated Kidsscreen-27 questionnaire will be used to determine a HRQOL score of the child, and it consists of 27 questions. These questions are similar to the Kidsscreen-27 child version [43].

Feasibility

To understand which components of the intervention are successful, feasibility of the BOOSTH intervention will be assessed using a mixed-methods design including semistructured focus groups with teachers and evaluation questionnaires. In addition, the strengths, limitations, opportunities, and recommendations for future development will be asked.

Semistructured focus group interviews will be performed with teachers from the intervention schools. Prefixed interview guides will be used, with the possibility of additional follow-up questions, which allows the researcher to cover both contextual factors and intervention implementation. Questions will be asked about the introduction lesson of BOOSTH, the implementation and stimulation of BOOSTH by the teachers, and suggestions for future development of BOOSTH.

Children and their parents will be asked to fill in an evaluation questionnaire about their experiences with BOOSTH. Teachers will be asked to fill in an evaluation questionnaire about the implementation of the BOOSTH intervention.

BOOSTH Step Count

Children who are allocated to the intervention schools will receive the BOOSTH activity tracker. The BOOSTH activity monitor is a lightweight triaxial accelerometer–based activity monitor, which is worn around the wrist and measures the step count. Moreover, the BOOSTH activity monitor resets automatically at midnight and stores data of the previous day automatically on the device. Data are stored on the device for 30 days. A child or parent has to synchronize the BOOSTH activity monitor with a smartphone or tablet to retrieve the measured step count. The BOOSTH activity tracker will be used as a motivation tool to promote PA. The step count on the BOOSTH activity tracker will not be used for research purposes.

Statistical Analysis Plan

Numerical variables will be presented as mean and SD or median and IQR where appropriate. Categorical data will be presented as number and percentage of participants in each of the possible categories. Baseline characteristics will be analyzed for differences between the groups, using independent sample *t* tests or Mann-Whitney *U* tests for numerical variables and chi-square or Fisher exact tests for categorical variables. The effects of BOOSTH on numerical outcome parameters (such as MVPA, cardiovascular parameter, and HRQOL) will be analyzed using linear mixed models in order to correct for dependent observations owing to repeated measurements within a child and clustering of children within a school. Stratification variables and relevant variables related to the outcomes (such as BMI [z-score], sex, age, and parenting style [measured with the CGPQ]) and/or missingness will be taken into account. A random intercept on school level and an unstructured covariance structure for repeated measures will be included. A *P* value <.05 will be considered statistically significant. All analyses will be performed using IBM SPSS Statistics for Windows version 25.0 (IBM Corp).

The feasibility of the study will be investigated using a mixed-methods design. Qualitative data of the focus group interviews will be audio recorded and transcribed verbatim. Interview transcripts will be coded by themes and concepts using NVivo version 12 software (QSR International). Coding will be performed by two researchers.

Results

The study has received funding from Province Limburg (SAS-2015-04956) and received ethical approval from the Medical Ethics Committee of Maastricht University Medical Centre (METC172043/NL64324.068.17). In September 2018, the inclusion procedure was started, and 16 primary schools were included and randomized into intervention school (n=8) and control school (n=8) groups. The results of the analyses are expected to be published in 2021.

Discussion

The observation of children spending a considerable amount of their time on gaming creates a window of opportunity to use gaming to increase their PA. To promote PA throughout the day, the combination of an activity tracker and an exergame is a promising and innovative intervention. It seems that exergames are more attractive and enjoyable for children in comparison to regular PA, which could be the result of improving the intrinsic motivation of children to perform PA [17,18]. Studies evaluating the effects of exergames on PA and influencing factors are important to obtain more insights into the possibility of using these tools for health promotion. More importantly, information on the effects of exergaming on cardiovascular risk factors and other health parameters is scarce. The majority of previous studies that investigated the effect of PA on cardiovascular risk factors or other health parameters like HRQOL used self-reported measures for PA behavior. There is a need to confirm these results with objectively measured PA behavior, especially for cardiovascular risk factors such as retinal microvasculature [8,9]. BOOSTH is an exergame that combines an activity tracker, which measures step count, and an online jump-and-run game as a reward for the performed PA. BOOSTH takes a novel approach since it could be incorporated both inside and outside the school setting to have even more potential. Moreover, in contrast to other exergames that combine the PA element with the game (eg, Nintendo Wii), BOOSTH is an exergame in which users need to perform PA in the real world before they can play the BOOSTH game. The aim of this study is to evaluate whether an intervention with BOOSTH promotes PA, health, and HRQOL in primary school children. In addition, the feasibility of the BOOSTH intervention in a school setting will be investigated. The insights gained from the results of this study will enable us to formulate recommendations for future strategies for increasing PA in children at this crucial age. In addition, if the results of this study show that the exergame BOOSTH has a positive effect on PA levels and health of children, the implementation could be widespread as a unique and innovative addition to current PA activity interventions.

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Conflicts of Interest

None declared.

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Abbreviations

BREQ2: Behavioral Regulation in Exercise Questionnaire-2
CGPQ: comprehensive general parenting questionnaire
CRAE: central retinal arteriolar equivalent
CRVE: central retinal venular equivalent
HRQOL: health-related quality of life
MVPA: moderate-to-vigorous physical activity
PA: physical activity
PedsQL: Pediatric Quality of Life Inventory

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Protocol

Impact of a Serious Game on the Intention to Change Infection Prevention and Control Practices in Nursing Homes During the COVID-19 Pandemic: Protocol for a Web-Based Randomized Controlled Trial

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Abstract

Background: Nursing home residents are at high risk of complications and death due to COVID-19. Lack of resources, both human and material, amplifies the likelihood of contamination in these facilities where a single employee can contaminate dozens of residents and colleagues. Improving the dissemination of and adhesion to infection prevention and control (IPC) guidelines is therefore essential. Serious games have been shown to be effective in developing knowledge and in increasing engagement, and could motivate nursing home employees to change their IPC practices.

Objective: Our aim is to assess the impact of "Escape COVID-19," a serious game designed to enhance knowledge and application of IPC procedures, on the intention of nursing home employees to change their IPC practices.

Methods: We will carry out a web-based randomized controlled trial following the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) guidelines and incorporating relevant elements of CHERRIES (Checklist for Reporting Results of Internet E-Surveys). Participants will be randomized to either the control or the serious game (intervention) group. First, both groups will be asked to answer a questionnaire designed to gather demographic data and assess baseline knowledge. The control group will then receive a quick reminder of the current national guidelines and links to IPC guidelines for health care professionals, while the other group will play the game. Both groups will then have to answer a second questionnaire designed to assess their willingness to change their IPC practices after having followed their respective material. After completing this questionnaire, they will be granted access to the material presented to the group they were not assigned to and receive a course completion certificate. The primary outcome will be the proportion of participants willing to change their IPC practices according to group. Secondary outcomes will include the analysis of specific

questions detailing the exact changes considered by the participants. Factors associated with participant willingness or reluctance to change behavior will also be assessed. Attrition will also be assessed at each stage of the study.

Results: The study protocol has been presented to our regional ethics committee (Req-2020-01262), which issued a declaration of no objection as such projects do not fall within the scope of the Swiss federal law on human research. Data collection began on November 5, 2020, and should be completed by December 4, 2020.

Conclusions: This study should determine whether "Escape COVID-19," a serious game designed to improve compliance with COVID-19 safe practices, modifies the intention to follow IPC guidelines among nursing home employees.

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KEYWORDS

COVID-19; transmission; serious game; infection prevention; health care worker; SARS-COV-2; nursing home; randomized controlled trial; elderly; older adult; infection control; infectious disease

Introduction

Background and Importance

Nursing home residents are at high risk of complications and death if they develop symptoms of COVID-19 after being infected with SARS-CoV-2 [1-4]. If infected, a single nursing home employee can potentially contaminate dozens of residents and colleagues [5], since allowing the virus to enter nursing homes leads to rapid interresident transmission [6]. Many long-term care facilities (LTCFs) were ill-prepared to face the first wave of the pandemic and should be helped as much as possible to prevent health care–associated transmission during potential future waves [7]. Such waves seem all the more likely as new COVID-19 cases have been identified since September 2020 in LTCFs located in Geneva, Switzerland, 14 weeks after the last infection was diagnosed here [8]. In addition to aiding efforts to combat the pandemic and to avoid infection, showing a high level of support for nursing home employees may also enhance their motivation [9]. Indeed, since the start of the pandemic, many researchers have pointed out the dramatic lack of resources, both human and material, faced by many LCTFs [10-13].

In nursing homes as in other facilities, viral transmission is often facilitated by the suboptimal application of infection prevention and control (IPC) guidelines [14]. Accordingly, a recent systematic review has identified the promotion of hand and respiratory hygiene and the use of appropriate personal protective equipment to be some of the most critical IPC practices that could help prevent viral transmission among nursing home residents and staff [15]. Dissemination of these guidelines and practices might however be hampered by the current need for physical and social distance [16]. Moreover, application of IPC guidelines may be jeopardized by the presence of divergent and sometimes contradicting messages [17,18], and even by mistrust in guidelines issued by health care authorities [19].

The probability of actually executing an action is strongly linked to the intention of performing it [20]. By increasing engagement and developing knowledge [21,22], serious games could prove instrumental regarding the effective dissemination of IPC guidelines and the promotion of COVID-19 safe practices [23,24]. Using Nicholson's [25] concept of meaningful gamification, we recently developed "Escape COVID-19," a serious game specifically designed to motivate health care workers in adopting good IPC practices [26]. Indeed, building and strengthening their intrinsic motivation might be at least as important as reminding them of the most current guidelines to help avoid infection [27]. The usefulness and cost-effectiveness of computer-based serious games is however still debated, and previous studies have pointed out a considerable lack of evidence regarding this education modality [28].

Objective

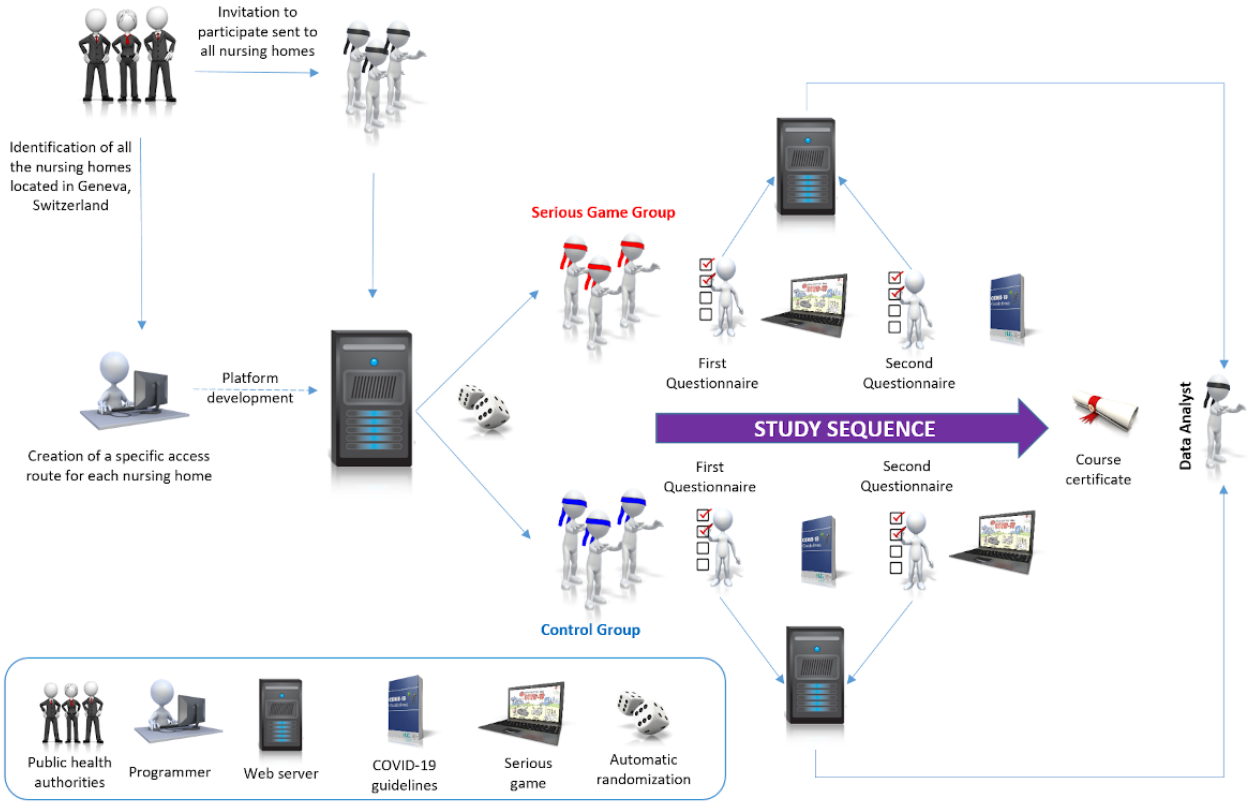
Our principal objective is to assess the impact of this serious game on the intention of nursing home personnel to change their IPC practices. We will also aim to determine the factors explaining the reasons that motivate change and those explaining the lack of willingness to change one's behavior.

Methods

Study Design and Setting

We will carry out a web-based, triple-blind (investigator, participants, and data analyst) randomized controlled trial, following the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) guidelines [29]. Elements from CHERRIES (Checklist for Reporting Results of Internet E-Surveys) will be included when relevant [30]. The design and sequence are summarized in Figure 1.

Figure 1. Study design and sequence.



A list of all the nursing homes located in Geneva was obtained through the city's public health authorities. All staff from these nursing homes will be invited to take part in this study, on a voluntary basis, regardless of their professional status. Information regarding the study and its objectives, including data security, will be provided. Consent will be gathered electronically.

Online Platform

A specific and fully automated platform created using the latest version of the Joomla content management system [31] and hosted on a Swiss server will be used in this study. All data will be stored on an encrypted, MySQL-compatible database. Only one author (LSu) will be able to access the database. The platform will be secured by the RSFirewall (RSJoomla) [32] and Admin Tools (Akeeba) [33] components. The questionnaires will be administered using Community Surveys Pro (Corejoomla) [34], which allows for the use of branching logic and for the export of responses in CSV format. The Membership Pro (Joomdonation) component will be used to handle registrations [35]. Randomization will be achieved by the GegaByte Random Article module (GegaByte Technologies) [36]. Therefore, randomization will be fully automated, and participants or investigators will not be able to influence group allocation.

Access to the different steps of the study sequence will be managed through Joomla's native access control list (PHP functions *JUserHelper::addUserToGroup* and *JUserHelper::removeUserFromGroup*). PHP functions will be embedded using Sourcerer (Regular Labs) [37]. Redirect-on-Login (Pages-and-Items) will be used to allow users to immediately access the appropriate section when resuming their study path [38]. Certificates will be generated using RSForm!Pro (RSJoomla) [39]. Daily backups will be scheduled using a cron job script and uploaded on a physically separate server through an encrypted connection.

First Questionnaire

Participants will be asked to fill in 2 questionnaires. Immediately after activating their account, the first questionnaire will be displayed. This questionnaire is designed to gather demographic data and to assess the initial level of knowledge regarding SARS-CoV-2 transmission and IPC guidelines. To limit attrition, the number of initial questions will be kept at a minimum and branching logic will be used to avoid displaying irrelevant items. The structure of this questionnaire, the original questions in French and their translation in English, are displayed in Multimedia Appendix 1.

Serious Game

The experiment will be conducted using version 2.1.1 of the "Escape COVID-19" serious game [26], which is freely available on the internet [40]. This serious game has been created under Storyline 3 (Articulate Global) and can be played on many different platforms, including smartphones and tablets, due to its HTML5 compatibility. The game was designed using the SERES framework [41] and Nicholson's RECIPE (reflection, engagement, choice, information, play, exposition) for meaningful gamification [25]. It is made of 4 different levels representing the typical phases that most health care employees experience daily. To make the game more engaging, the graphics included in the game were designed by Eric Buche, a well-known Swiss cartoonist [42].

Throughout the game, players are asked to make choices (Figure 2) or to answer questions directly related to the exposition element (Figure 3), which aims at creating a meaningful narrative in the serious game [25].

Feedback is used extensively [43] to allow the player to correct an answer (Figure 4) and to reinforce the expected behavior (Figures 5-7).

Figure 2. Simple-choice interaction.

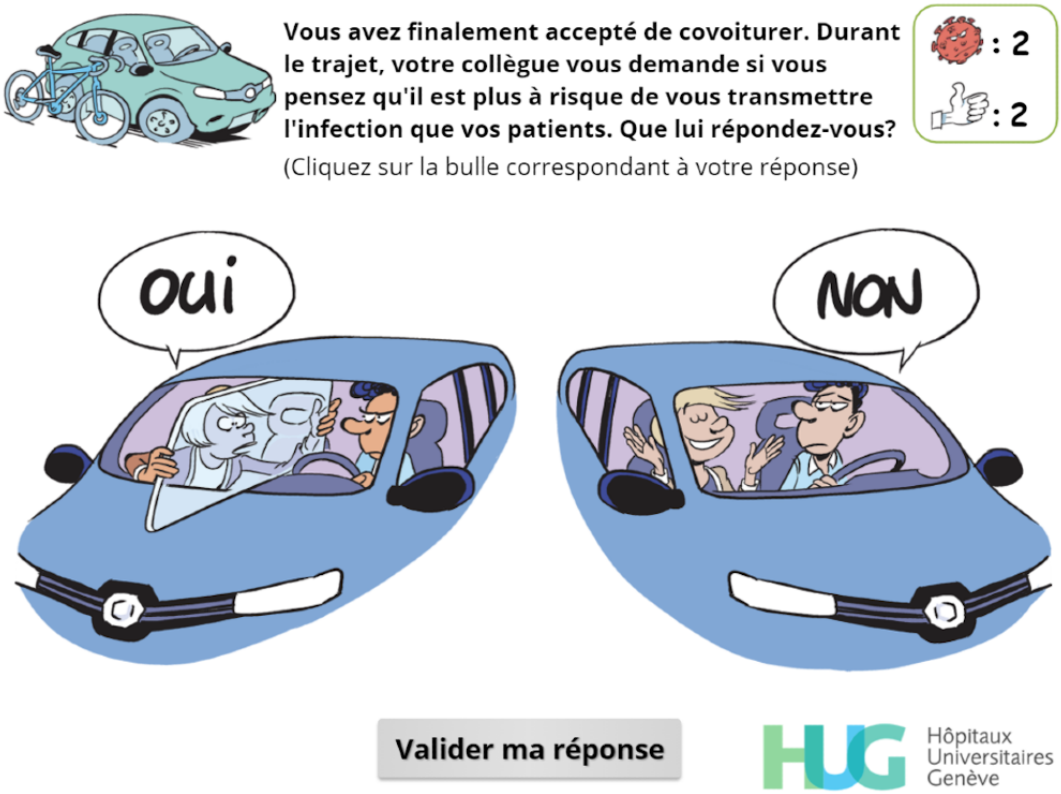


Figure 3. The player has to identify the precautions they should take when joining their colleagues for breakfast.

Figure 4. Feedback. The player has submitted an initial answer and is informed that they have selected 3 wrong answers (“3 mauvaises réponses”) and that 2 correct answers are missing (“il vous manque 2 réponses correctes”). They can retry (“Réessayer”) once.

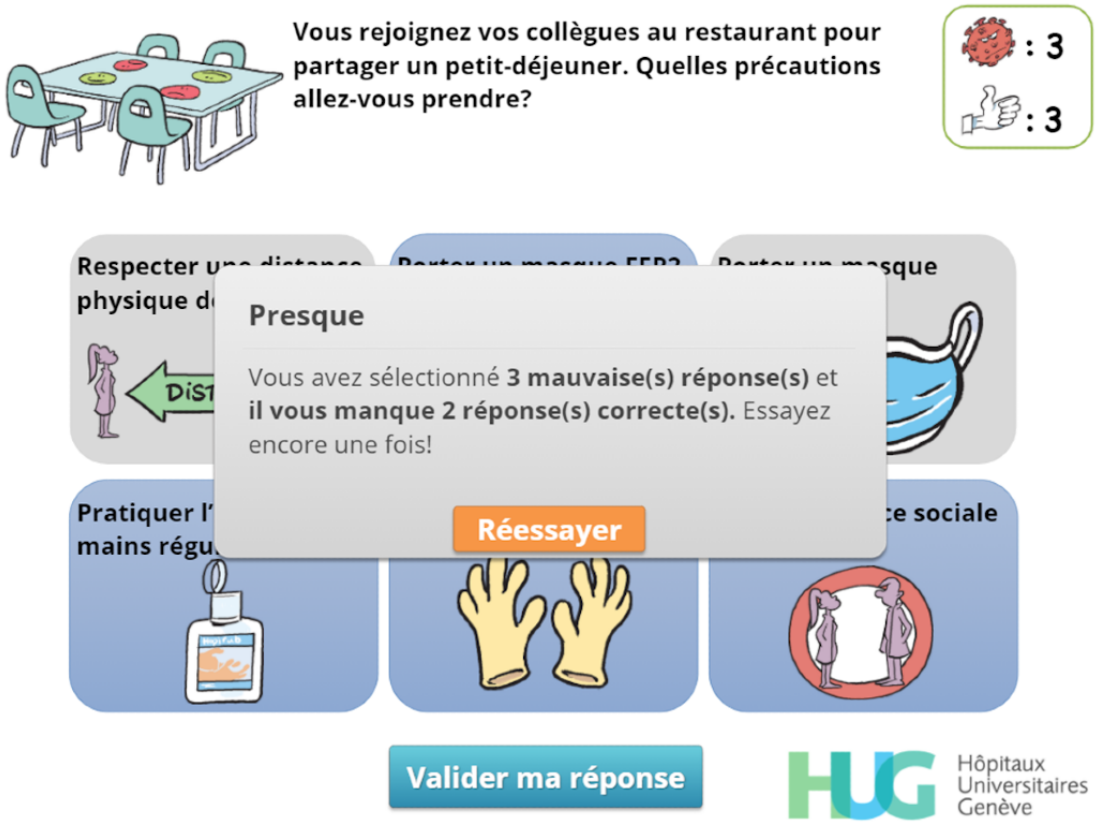


Figure 5. Feedback. The user has correctly answered the question. Visual hints related to the correct answers are displayed (mask, distance arrow, alcohol-based handrub) and a short text emphasizes the expected answers. A thumbs-up image and a plus sign appear, rise, and progressively fade out before the thumbs-up count is updated.

Figure 6. Feedback. The player has retried but has failed to identify the correct answers. Visual hints related to the correct answers are displayed (mask, distance arrow, alcohol-based handrub) and a short text emphasizes the expected answers, which will be displayed when the player clicks on continue ("Continuer"). A virus and a plus sign appear, rise, and progressively fade out before the virus count is updated.

Figure 7. Feedback. When the user has failed to correctly answer the question, the correct answers are displayed with a green background.

Each time the player performs a desirable action or selects the correct answer, a "thumbs up" is awarded. Conversely, the player gets a red virus for each incorrect answer or behavior. If the player accumulates a total of 5 viruses, a game-over screen is displayed (Figure 8). The player can then choose to spend their thumbs up to decrease the virus count (1:1) or to restart the level.

Figure 8. Game-over screen. The player has accumulated 5 viruses and can either spend their thumbs up to decrease the virus count or restart the level.

Control Materials

The control materials include a quick reminder of the current national guidelines published by the Federal Office of Public Health of the Swiss Confederation [44] and links to IPC guidelines for health care professionals (Vigigerme) provided by the Geneva University Hospitals and freely available on the internet [45].

Second Questionnaire

The second questionnaire is designed to assess whether the participants intend to change their IPC practices after completing the first set of learning materials (Multimedia Appendix 2). Therefore, the control group will complete it after seeing the standard guidelines, and the serious game group after finishing the game. Once again, branching logic will be used to try to limit attrition.

All multiple-choice and multiple-answer questions are mandatory. A completeness check will be performed at the end of each survey page. Mandatory questions will be highlighted and will have to be answered before allowing participants to move on to the next step. There will be no way to change the answers after completing a page.

Outcomes

The primary outcome will be the proportion of nursing home employees reporting they are willing to change their IPC practices according to group.

Secondary outcomes will be a composite of the questions based on a 5-point or 6-point Likert scale according to group. Each individual question will also be assessed. We will also aim at identifying the factors associated with participant willingness to change their behavior and analyze the reasons given by participants who are opposed to making changes [46].

We will also assess attrition at each stage of the study according to group [47-50].

Participants and Sample Size

Health authorities were asked for a comprehensive list of the email addresses of all nursing home employees working in Geneva, to construct a convenience sample. We decided to include all employees, regardless of their professional status or of the potential specificities of the facilities they work in, without any exclusion criteria. To detect a difference of 10% at the .05 significance level with a power of 80%, 388 participants will be needed for each group. The number of eligible employees is estimated to be approximately 4000 people. Therefore, a participation rate of around 20% will be required.

All employees will be invited to participate regardless of their professional status. Participation will be encouraged by delivering a course completion certificate upon completing the study path. No financial incentives will be provided.

To avoid potential duplicates, participants will be required to register on the site using a valid email address. No other personal information, including names, will be asked for during the registration process. The system will automatically send an activation email to check whether the email address provided is valid. Participants will be told that clicking the activation link will be considered as consent to participate in the study.

Statistical Analysis

Stata 15.1 (StataCorp LLC) will be used for data curation and statistical analysis. Data will be curated by the first author (LSu) and neutral names will be randomly assigned to the control and serious game groups before transferring the DTA file to the blinded data analyst (LSt). To avoid any potential conflicts of interest, the analyst was not part of the serious game

development team and did not participate in the original publication describing its development. There will be no interim analysis.

Incomplete answer sets will be excluded. Imputation techniques will not be used. Answer sets marked as completed should not contain any missing value by virtue of the completeness checks automatically performed by the survey component.

Univariate and multivariable logistic regression will be used to assess the primary outcome. Adjustment will be done according to prior knowledge (expressed as percentage of correct answers), professional status, and nursing home. The expected sample size should prevent overfitting. We will check the log-linearity assumption graphically and test the goodness of fit using the Hosmer-Lemeshow test.

The analysis of secondary outcomes will be carried out by assigning numerical values to the answers gathered through the use of Likert scales. As the 6-point Likert scale ranges from 1 (not at all) to 6 (very much), the same numbers (ie, a score ranging from 1 to 6) will be used for each item. The composite outcome will be the sum of the 9 questions and will be analyzed using univariate and multivariable linear regression analyses, with the same adjustment variables as the primary outcome. Each question will be analyzed separately.

For the 5-point Likert scale, values ranging from –2 to +2 will be assigned to each answer, with positive values attributed to changes enhancing IPC behavior. A composite outcome will be generated, which will be the sum of these values. We made the choice to treat this discrete variable as continuous and use a linear regression analysis, first univariate, then multivariable (with the same adjustment variables as the primary outcome). The same weight will be applied to all questions when computing composite outcomes. As a reduction in the use of N95 respirator masks can also be considered as enhancement depending on the setting, a sensitivity analysis will be done by analyzing the composite outcome with and without the N95 respirator mask item.

Descriptive statistics will be used to detail the factors associated with participant willingness to change or refuse to change behavior. The Student *t* test and the chi-square test will be used to assess differences between groups.

The curated data file will be made available on the Mendeley Data repository.

Results

The study protocol has been presented to our regional ethics committee (Req-2020-01262), which issued a declaration of no objection as such projects do not fall within the scope of the Swiss federal law on human research [51]. The public health authorities of Geneva did not have access to a list of email addresses of all nursing home employees. However, they provided us with a comprehensive list of all nursing homes to allow us to create specific access routes for each nursing home. They were reluctant to provide us with the email addresses of nursing home managers but were nevertheless willing to send information and invitation emails on our behalf.

The online platform was finalized on November 3, 2020 [52]. It was created by authors LSu and MS and thoroughly tested by all coauthors. We provided the health care authorities with a generic email template (Multimedia Appendix 3) and a list of nursing home–specific accreditations, which acted as passwords to prevent participants from enlisting under the wrong nursing home. This email template informed the recipients that, should they agree to participate, all data would be processed anonymously but could and would be used for research purposes. The email stated that the study path would let participants access IPC guidelines as well as a serious game but did not tell them in which order these materials would be accessed. The approximate time required to complete the whole path (30 minutes) was given, along with an email address that could be used to contact the investigators. Participants were also told that they would receive a course completion certificate after completing the study path.

Data collection began on November 5, 2020, and is scheduled to end on December 4, 2020.

Discussion

Main Considerations

This study should help determine whether a serious game can improve the adoption of IPC guidelines among nursing home personnel. This game should appeal to at least 3 of the 4 types of players described by Bartle [53] in 1996: achievers, who might want to gather all the thumbs up while avoiding getting a single virus to get the highest score possible; explorers, who might find the narrative created through the use of the exposition element of Nicholson's RECIPE appealing; and socializers, who might associate the use of the thumbs up sign with social networks. Nevertheless, some participants might be recalcitrant to this kind of intervention. Identifying the profile of these participants and the reasons underlying their resistance to change could help either improve the game or devise better targeted interventions [46]. Conversely, the identification of factors enhancing the adoption of safe IPC practices will help explore ways of strengthening COVID-19 safe messages.

To avoid a potential conflict of interest as 5 of the authors of this protocol were also members of the team that developed the serious game, the data analyst, who will be blinded, was not part of the development team.

Limitations

Some limitations can already be anticipated. First, as we were unable to obtain a comprehensive list of all potential participants, and because we cannot be sure that nursing home managers will actually transmit the information to their personnel, we will be prevented from determining the actual number of potential participants. While this could lead us to underestimate the participation rate, another mechanism could result in overestimating this rate. Indeed, we will have no way of preventing nursing home–specific accreditations to be transferred to third parties, and some participants might not be part of the target population. To alleviate this concern, we will, upon request, create specific accreditations to allow other categories of personnel to create accounts on the platform and

follow the study path. Any data gathered through the use of such accreditations will not be included in the analysis.

Despite its design, which is intended to attract different types of players, this serious game might be more successful for certain profiles. Because we decided on a limited number of questions to try to reduce attrition, we elected not to include questions pertaining to the identification of the player type. Other studies would therefore be needed to explore a potential correlation.

The convenience sample used in this study might not be representative of other systems. Moreover, even though only 20% of the target population will be required to participate to reach our estimated sample size, we cannot be certain of the participation rate. A low participation rate will intrinsically carry the risk of a selection bias.

Another important limitation is that, even though the theory of planned behavior has proven its worth in the field many times, we will have no way of proving that the intention of adopting COVID-19 safe IPC practices correlates with actual changes in the field. Direct observations should be performed to ascertain this fact, but limitations in human resources and funds will prevent us from carrying such observations as part of the present study.

Finally, the importance of rapidly deploying this study and the serious game did not allow us to wait for the peer-review process to be completed before proceeding with the study. Therefore, we will be unable to change either the study design or the questionnaires despite the valuable input the reviewers will provide us with.

Conclusion

This study should determine whether “Escape COVID-19,” a serious game designed to improve compliance with COVID-19 safe practices, modifies the intention of applying IPC guidelines in nursing homes.

Acknowledgments

The authors would like to warmly thank Mr Eric Buche, who designed the graphical elements used in the “Escape COVID-19” serious game. We would also like to thank Monica Perez, Valérie Sauvan, and Tomas Robalo Nunes from the Geneva University Hospitals Infection Prevention and Control Department, who were actively involved in the development of the serious game. Finally, we would like to extend our thanks to Audrey Morard and Jérôme Divorne from the Communication Department of the Geneva University Hospitals for their unfailing and most precious support.

Conflicts of Interest

None declared.

Multimedia Appendix 1
First questionnaire.
[DOCX File , 21 KB - resprot_v9i12e25595_app1.docx]

Multimedia Appendix 2
Second questionnaire.
[DOCX File , 19 KB - resprot_v9i12e25595_app2.docx]

Multimedia Appendix 3
Generic email template.
[PDF File (Adobe PDF File), 57 KB - resprot_v9i12e25595_app3.pdf]

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Abbreviations

CHERRIES: Checklist for Reporting Results of Internet E-Surveys
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
IPC: infection prevention and control

LTCF: long-term care facility
RECIPE: reflection, engagement, choice, information, play, exposition

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Protocol

Web-based Self-help Program for Adjustment Problems After an Accident (SelFIT): Protocol for a Randomized Controlled Trial

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Abstract

Background: Accidents and the resulting injuries are among the world's biggest health care issues, often causing long-term effects on psychological and physical health. With regard to psychological consequences, accidents can cause a wide range of burdens including adjustment problems. Although adjustment problems are among the most frequent mental health problems, there are few specific interventions available. The newly developed program SelFIT (German acronym: Selber wieder fit nach einem Unfall; "fit again after an accident") aims to remedy this situation by offering a low-threshold, web-based self-help intervention for psychological distress after an accident.

Objective: The overall aim is to evaluate the efficacy and cost-effectiveness of the SelFIT program plus care as usual (CAU) compared to only CAU. Furthermore, the program's user-friendliness, acceptance, and adherence are assessed. We expect that the use of SelFIT will be associated with a greater reduction in psychological distress, greater improvement in mental and physical well-being, and greater cost-effectiveness compared to CAU.

Methods: Adults (n=240) experiencing adjustment problems due to an accident they had between 2 weeks and 2 years before entering the study will be randomized into either the intervention or control group. Participants in the intervention group receive direct access to SelFIT. The control group receives access to the program after 12 weeks. There are 6 measurement points for both groups (baseline as well as after 4, 8, 12, 24, and 36 weeks). The main outcome is a reduction in anxiety, depression, and stress symptoms that indicate adjustment problems. Secondary outcomes include well-being, optimism, embitterment, self-esteem, self-efficacy, emotion regulation, pain, costs of health care consumption, and productivity loss, as well as the program's adherence, acceptance, and user-friendliness.

Results: Recruitment began in December 2019 and will continue at least until January 2021, with the option to extend this for another 6 months until July 2021. As of July 2020, 324 people have shown interest in participating, and 48 people have given their informed consent.

Conclusions: To the best of our knowledge, this is the first study examining a web-based self-help program designed to treat adjustment problems resulting from an accident. If effective, the program could complement the still limited offerings for secondary and tertiary prevention of psychological distress after an accident.

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International Registered Report Identifier (IRRID): DERR1-10.2196/21200

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KEYWORDS

accidents; adjustment problems; e-mental health; guidance on demand; online; psychological prevention; psychological self-help; study protocol; web-based

Introduction

Background

The World Health Organization reports tens of millions of accidents annually, with about 5 million people dying from the consequences of their injuries [1,2]. Accidents and resulting injuries are therefore among the world's biggest health care issues, often causing long-term effects on psychological and physical health. Due to their unpredictability, uncontrollability, suddenness, and threat to one's health and integrity, accidents have a high potential for traumatization [3,4]. Medical treatment immediately after the accident and rehabilitation treatments for injured persons have reached a comparatively high standard of care. However, secondary and tertiary prevention of psychological distress are not yet part of routine care [3]. Furthermore, the need for both physical and psychological rehabilitation is growing, and existing services cannot meet the demand [2,5]. Thus, easily available, flexible, and affordable accident rehabilitation and trauma prevention programs are essential to meet the growing demand and improve existing treatment options in accident rehabilitation. Therefore, we have developed SelFIT (German acronym: Selber wieder fit nach einem Unfall; "fit again after an accident"), a low-threshold, web-based psychological self-help program for people who experience psychological distress after an accident. This program will be evaluated in a randomized controlled trial (RCT).

Psychological Distress and Adjustment Problems After an Accident

Not everybody who suffers an accident develops psychological problems. Nonetheless, when taking into account possible short-term implications such as fear, pain, or helplessness, as well as potential long-term consequences like permanent physical damage or financial challenges, the development of psychological problems after an accident is easily understandable [6]. Therefore, experiencing an accident can lead to the development of various psychological problems and disorders including anxiety, depression, and post-traumatic stress disorder [6,7]. Stress-related problems such as *adjustment problems* are especially common and frequent among accident victims [8,9]. By adjustment problems, we mean a "maladaptive reaction to a stressful event or ongoing psychosocial difficulties characterized by symptoms of preoccupation with the stressor, recurrent and or distressing thoughts about the stressor, or rumination about its implications" [10]. Adjustment problems can interfere with everyday functioning, cause a loss of interest in different areas of life, and result in an impairment in social or occupational functioning [10]. If persistent, adjustment problems can turn into an adjustment *disorder.* A longitudinal study on adjustment disorder after trauma exposure and major injury conducted in Australia found that participants with adjustment disorder 3 months after the trauma were more likely to meet the criteria for a further psychiatric disorder 12 months post-injury [11]. Thus, the existence of an adjustment disorder heightened the risk for developing other, more serious psychological disorders. Moreover, it was found that the presence of an adjustment disorder increases the risk for suicidality [12]. This highlights the importance of developing and implementing interventions to treat psychological distress after trauma exposure, like experiencing an accident, as early as possible [7,13].

Web-based Psychological Interventions

One possibility to implement early interventions for the treatment of psychological distress due to an accident is the development of web-based interventions. Numerous studies have shown that web-based interventions are an effective treatment option for various psychological problems and demographic groups [14,15]. There are many different forms of and applications for such interventions. An important distinguishing factor is guidance, that is, the degree of contact with a health care professional given within the program. Unguided or self-guided programs do not involve any contact with a health care professional, whereas guided programs involve some form of contact or support [16]. Both guided and unguided programs have proven to be effective treatment options. However, the results of several meta-analyses indicate that guided programs tend to yield greater effects than unguided programs [16,17]. This may be explained by a heightened sense of responsibility in the user when in contact with another person compared to nonhuman contact with a machine program [18]. The heightened sense of responsibility can increase adherence, which in turn can be associated with better patient results [19,20]. However, the question arises as to how much and what type of contact is needed to increase adherence and achieve better treatment effects [20].

In this respect, studies on another form of guidance, namely guidance on demand, are of particular interest. With the guidance on demand approach, contact with a professional is only established at a participant's request but is not scheduled or planned per se.

The findings on the effectiveness of guidance on demand are mixed. In a study on the treatment of tinnitus via the internet, Rheker et al [21] reported that there was no difference between a program version with guidance on demand and an unguided version. Krieger et al [22] used the guidance on demand approach in a web-based intervention for increased self-criticism. Compared to a control group, their results indicate that the treatment with guidance on demand is effective. The guidance on demand approach was also tested by Kleiboer et al [20]. They conducted an RCT on the role of support in a web-based problem-solving treatment for depression and anxiety, comparing 5 different forms and degrees of guidance. Participants either received (1) the program without guidance, (2) the program with guidance on demand, (3) the program with weekly support, (4) no program but nonspecific chat or email support, or (5) allocation to a wait-list control group. Concerning program adherence, the guidance on demand group showed rates comparable to the group with weekly support and significantly higher rates compared to the unguided group. Regarding the treatment effects, however, the guidance on demand group did not show superior effects to the control group [20].

These findings suggest that the guidance on demand approach lies between guided and unguided programs in terms of

effectiveness. The approach thus offers a middle way and has the potential to combine some of the most prominent advantages of both guided and unguided treatments: Participants are given the security of knowing that they can turn to a specialist for help and are therefore not completely on their own. However, since no regular contact is scheduled, fewer staff are needed. Thus, programs with on-demand guidance generate lower costs and are less limited to the time and resources of a project's employees than guided programs. This allows for flexible use at a self-determined pace. Due to the voluntary nature of the contact with a specialist, the participants' social exposure in a program with guidance on demand can be as low as in an unguided program. Programs with guidance on demand also have other advantages of web-based interventions such as easy availability and scalability (ie, the capacity to increase the number of people who can use the program).

In recent years, various web-based treatment options for adjustment problems and disorders have been developed. One of them is Trastornos Adaptivos Online [23,24]. The guided program comprises psychoeducational elements, strategies from positive psychology, and techniques to manage negative emotions and improve problem solving. In addition to the program, participants receive short weekly therapist support via telephone. Trastornos Adaptivos Online was well received by both clinicians and patients in a pilot study [24]. The program is currently being tested for its effectiveness in an RCT [23].

A further web-based intervention for the treatment of adjustment disorders is the Brief Adjustment Disorder Intervention [25,26]. This program is unguided and consists of four modules, which the participants can process in a self-determined order. The program's theoretical approach is mainly CBT-based but also contains elements of mindfulness as well as findings from research on stress and coping [27]. Preliminary results of an RCT indicate that participants who used the program at least once within a month showed a decrease in symptoms of adjustment disorders and an increase in psychological well-being. However, there was a very high dropout rate, which is mentioned as the study's most prominent limitation [26]. The authors tested the effects of additional therapist support on the program's effectiveness. The additional support did not contribute significantly to the study's outcomes [26]. This supports previous findings by Maercker et al [28] that web-based self-help interventions may be a promising treatment option for adjustment problems and further indicates that such interventions do not necessarily need scheduled guidance from a specialist.

Another unguided web-based program for adjustment problems is ZIEL (German acronym: Zurück Ins Eigene Leben; "back to your own life") [29]. The ZIEL program comprises different evidence-based techniques from treatments for depression, anxiety disorders, and post-traumatic stress disorders. ZIEL consists of 5 sections which participants can work through freely and as needed over a course of 4 weeks. In an RCT, the participants of both the experimental and the control group showed an improvement in the severity of symptoms of adjustment problems. The intervention group, however, showed a significantly greater improvement in terms of depressive symptoms and quality of life. However, the authors of ZIEL also report challenges with a high dropout rate and suggest different measures to address this. One of these suggestions is to focus on certain subgroups of people with adjustment problems or on certain triggers of adjustment problems. This, in turn, would allow for a more tailored response to the needs of the users, thereby creating a better user-program fit and greater relevance for the users [29].

Rationale

Against the background that accidents can have various long-term psychological consequences such as adjustment problems, which are often not or insufficiently treated, we have developed SelFIT. The program was realized as a web-based program in order to provide an easily accessible psychological treatment option to accident victims. Considering the results and conclusions from previous research on web-based self-help interventions for adjustment problems described above, SelFIT was not created as a treatment for adjustment problems in general, but specifically for the treatment of psychological distress and adjustment problems after an accident. This focus allows for more specific thematic tailoring to the needs of the target population. Additionally, the guidance on demand approach was chosen in order to take advantage of as many benefits of guided and unguided programs as possible without generating excessive additional costs.

Aims and Objectives

The aim of this study is to conduct a randomized controlled trial to evaluate the new SelFIT program developed for people who experience adjustment problems after an accident. Specifically, the objectives are to evaluate the efficacy and cost-effectiveness of SelFIT used in addition to care as usual (CAU) compared to only CAU; to analyze the acceptance and user-friendliness of the SelFIT program and draw conclusions for further development of the program and the type of guidance applied in the program (ie, guidance on demand); and to explore and analyze moderators (eg, age, sex, or satisfaction with the program), mediators (eg, adherence), and predictors (eg, adherence, embitterment, or optimism) for the efficacy of the program.

Methods

Study Design

Overview

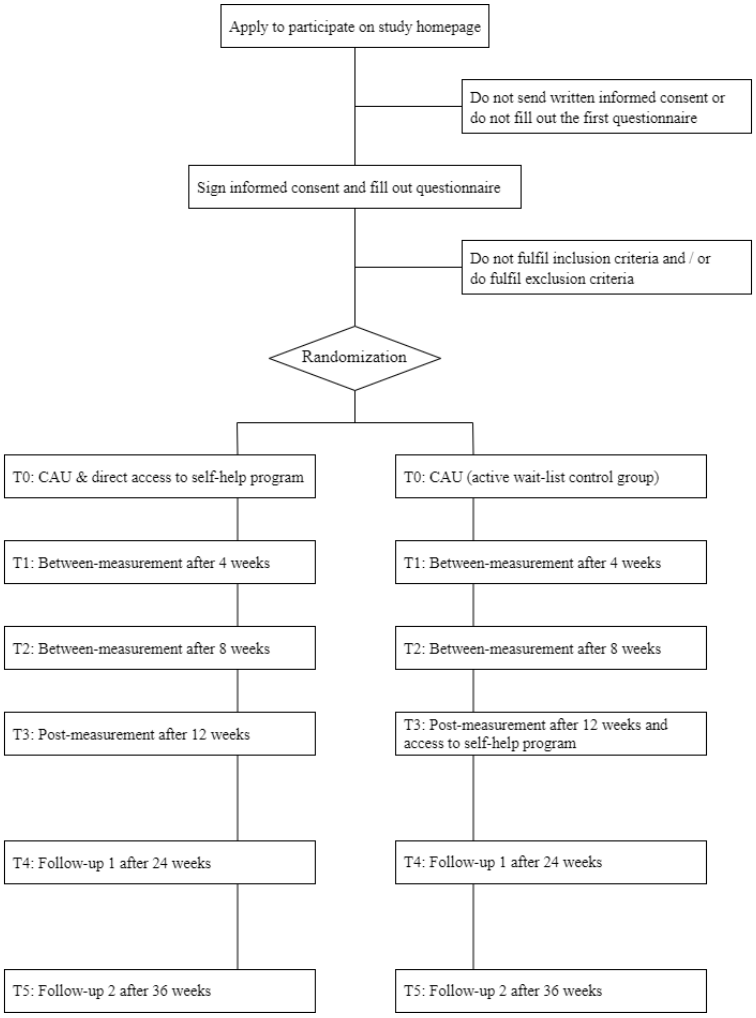
This study is a prospective longitudinal RCT. The study population are German-speaking adults (≥18 years) who suffer from adjustment problems after experiencing an accident between 2 weeks and 2 years before entering the study.

The lower time limit was set in order to reach injured persons as soon as possible after the accident and thereby prevent the development or worsening of psychological distress such as adjustment problems. The upper time limit was set in accordance with the time criterion of a chronic adjustment disorder according to the current version of the International Classification of Diseases (ICD-10 [30]).

Figure 1 displays the study flowchart, illustrating that participants in the intervention group receive direct access, while those in the control group receive access after 12 weeks. All

participants are asked to complete the online assessment at 6 time points. The first questionnaire (premeasurement) serves both as a baseline and as the screening for inclusion and exclusion criteria. There are two between-measurements after 4 and 8 weeks. The postmeasurement takes place after 12 weeks. All participants are asked to participate in the follow-up measurements taking place 24 and 36 weeks after randomization to evaluate the long-term effects of the intervention. Participants who drop out at any point will be asked to participate in any remaining measurements nonetheless.

Figure 1. Flowchart of the SelFIT study design. CAU: care as usual.



Randomization

After receipt of the informed consent and the initial screening, participants are randomized equally (1:1 ratio) into the treatment or the control group. Randomization is stratified by the point value that participants score on the questionnaire used as the primary outcome measure (12-16 points vs ≥17 points) in order to make the two groups comparable regarding their symptom expression on this measure. This is done with a computerized random number generator and randomly permuted block sizes using Randomization.com [31]. Randomization within each stratum uses a 1:1 ratio as well. The allocation schedule is generated by a researcher not involved in the research process and is unknown to the investigators.

Recruitment

Overview

Recruitment takes place via advertising on social media, websites, and internet forums, and with different organizations and self-help groups, as well as through referrals from rehabilitation clinics, psychotherapeutic practices and clinics, physiotherapists, medical doctors, and hospitals. People interested in participating can leave their contact details on the study home page and will then be sent the participant information either by email or by post, according to their choice. After the signed informed consent form is sent to the study team, potential participants are asked to complete the first online questionnaire to check that they do not meet any of the exclusion criteria and meet all the inclusion criteria described below.

Eligibility Criteria

According to the inclusion criteria of this study, all participants must have experienced and be able to specify an accident during the period from 2 weeks to 2 years prior to participation in this study; exceed the cutoff value for at least a mild psychological burden on the 21-item Depression, Anxiety and Stress Scale [32]; be at least 18 years old; provide informed consent; have access to the Internet; have mastered the German language; and be able to specify an emergency address in the event of an acute crisis.

Persons who show severe depressive symptoms (Beck Depression Inventory II score>29) [33], show suicidal tendencies (Beck Depression Inventory II suicide item>1), or have a known diagnosis of a psychotic or bipolar disorder are excluded.

Description of the Intervention

The SelFIT program takes 12 weeks in total. It consists of an introduction, 8 thematic modules, and a conclusion. The thematic modules are described in Textbox 1. Furthermore, the program includes a page with information about the procedure to be followed in emergencies and acute crises as well as a list of suitable contacts in such situations. Multimedia Appendix 1 shows a screenshot of the program's home page.

Participants are encouraged to work on one module per week and to repeat and deepen the various exercises during the last 4 weeks of the program in order to facilitate the transfer to their own everyday life. However, participants are free to choose both the order and speed of processing of the modules themselves. All modules consist of a video, various texts, exercises, and weekly tasks. In addition, participants are asked to indicate which of a list of feelings, moods, and physical conditions they currently experience. This allows them to observe how their well-being changes over the course of the program.

Since the study employs a guidance on demand approach, participants can contact the study team if needed or desired. For this purpose, they can either write an email or use the chat function within the program. In the settings, there is also the option to choose whether participants want to receive a reminder email after a certain period of inactivity. Other than this, contact with the study team, a therapist, or a counsellor is not planned by default.

Textbox 1. Outline of the thematic modules of the SelFIT program.

Module 1: Accidents and their consequences

- Information about psychological and physical consequences of accidents as well as the symptoms of adjustment problems
- Survey of the participant's current situation and well-being

Module 2: Changing perspectives

- Information on automatic and irrational assumptions, chains of thoughts, and the influence of thoughts and assumptions on one's state of mind
- Exercises with the aim of cognitive restructuring

Module 3: Understanding different reactions to accidents

- Information about frequent psychological reactions to accidents
- Exercise to identify physical symptoms of anxiety

Module 4: Activation

- Behavioral activation with suggestions for different types of activation
- Development of a personal activity plan
- Information about the importance of physical activity

Module 5: Self-care

- Information about post-traumatic growth
- Exercises to promote acceptance, gratitude for positive aspects of life and personal resources

Module 6: Finding calm

- Information about sleep and sleep hygiene
- Exercises to promote mental and physical relaxation

Module 7: Addressing painful feelings

- Information about typical reasoning errors
- Information about and exercises for dealing with painful feelings such as guilt, shame, anger, and resentment after an accident

Module 8: Self-efficacy

- Information about attribution styles, self-fulfilling prophecies and self-instructions
- Identification and activation of personal resources
- Exercise to promote self-confidence

Measures

All instruments used over the course of the study are self-report questionnaires that are completed online. Figure 2 gives an overview of all questionnaires with the time points of the assessments. Since the study population is German-speaking, we use the German version for all questionnaires.

Figure 2. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) figure to display the study's schedule of enrolment, interventions, and assessments. BTM: between-measurement. CAU: care as usual.

	STUDY PERIOD						
	Enrolment	Allocation	Post-allocation				
TIMEPOINT	*T0*	0	*T1: BTM-1*	*T2: BTM-2*	*T3: Post*	*T4: Follow-up 1*	*T5: Follow-up 2*
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTIONS:							
SelFIT direct access + CAU			←	—	—	→	
Wait-list control group + CAU						←	— →
ASSESSMENTS:							
Baseline • Depression, Anxiety and Stress Scale • Adjustment Disorder – New Module 20 • Beck Depression Inventory II • Brief Pain Inventory • Treatment Inventory of Costs in Psychiatric Patients • Work and Health Questionnaire • Short Form Health Survey • Bern Embitterment Inventory • Life Orientation Test Revised • Rosenberg Self-esteem Scale • General Self-Efficacy Scale • Emotion Regulation Skills • Demographic variables	X						
Primary Outcome Measure • Depression, Anxiety and Stress Scale			X	X	X	X	X
Further Outcome Measures • Beck Depression Inventory II			X	X	X	X	X
• Adjustment Disorder – New Module 20 • Brief Pain Inventory • Work and Health Questionnaire • Short Form Health Survey • Bern Embitterment Inventory • Rosenberg Self-esteem Scale • General Self-Efficacy Scale • Emotion Regulation Skills					X	X	X
• Treatment Inventory of Costs in Psychiatric Patients							X
• Client Satisfaction Questionnaire • System Usability Scale • Duration and intensity of use					X	X	

Primary Outcome Measure

The primary outcome measure is the short version of the Depression, Anxiety and Stress Scale with 21 items [32]. Each of this questionnaire's three scales contains 7 items assessing symptoms of depression, anxiety and stress on a 4-point Likert scale ranging from 0=never to 3=almost always. The 21-item Depression, Anxiety and Stress Scale is not diagnosis-specific and has proven to be a well-suited measure of psychological

distress in a broad range of clinical and nonclinical samples [34,35]. This is why we use this questionnaire to assess symptoms of psychological distress and adjustment problems.

Further Outcome Measures

Adjustment Problems and Depressive Symptoms

Adjustment problems are also assessed using the Adjustment Disorder–New Module 20 [36]. The questionnaire was designed according to the upcoming ICD-11 symptom definition of adjustment disorder. It consists of 20 items, which are divided into a stressor list and an item list. While the stressor list captures different acute and chronic life events, the item list assesses the symptoms occurring in response to those stressors. In accordance with the ICD-11 definition of adjustment disorder these symptoms are based on the adjustment disorder core symptoms of avoidance, anxiety, impulse disturbance and depressive mood [36].

Depressive symptoms are additionally assessed using the Beck Depression Inventory II [33]. This questionnaire consists of 21 items, which are rated on a Likert scale ranging from 0=not at all to 3=very strong. Item 9 of this instrument is also used to screen for suicidality at all 6 measurement points of the study.

Accident-Related Measures

Regarding the accident, we ask for a short description of the event, the time that has passed since, and its subjectively perceived severity.

Pain due to the accident is assessed by the Brief Pain Inventory [37], which consists of 15 items. After the question of whether there is any pain that exceeds the normal levels expected in everyday life, participants have to indicate where the pain is located and how severe the limitations in various areas of life are due to the pain. We also assess the participants' own perception of their physical attractiveness. Physical attractiveness is a very influential informational cue that is used frequently and consistently [38,39]. It has been shown to play an important role in how a person is perceived and responded to in many areas of life [38]. This includes health and psychological well-being. Bordieri et al [40] found that physical attractiveness influenced how others make attributions concerning the cause and prognosis of someone's disability. Physical attractiveness was also linked to self-esteem [40]. Among the possible consequences of an accident is skin scarring. In most cases, this is perceived as unattractive [41]. Brown et al [41] found that skin scars impact a person's acceptability to others as well as themselves and also have an effect on social functioning and emotional well-being. Thus, participants in this study are asked to rate their own physical attractiveness compared to that of other people their age. They also have to indicate how often they think about being rated by others in terms of physical attractiveness. Furthermore, the participants assess if and how much their own perception of their physical attractiveness has changed since the accident.

Cost-effectiveness Measures

Two questionnaires, each with a different emphasis, are used to assess the cost-effectiveness of the SelFIT program. The costs of health care consumption and productivity loss are assessed using the Treatment Inventory of Costs in Psychiatric Patients [42], a self-report questionnaire with 23 items of varying answer formats. Work-related factors with regard to the consequences of the accident are assessed by means of the Work and Health Questionnaire [43]. This questionnaire consists of 3 different parts with a total of 21 items with varying answer formats. The first part contains 5 items on current work activity, the second part contains 7 items on workload and cooperation, and the third part contains 9 items on health and well-being.

Embitterment and Optimism

We also assess embitterment and optimism. The Bern Embitterment Inventory [44], an 18-item questionnaire with answers ranging from 0=not at all true to 4=exactly true, is used to survey embitterment. Optimism is assessed as a predictor at the baseline measurement with the Life Orientation Test Revised [45], which consists of 10 items with answer categories ranging from 0=strongly disagree to 4=strongly agree.

General well-being and the ability to cope in everyday life are assessed by the Short Form 12 Health Survey [46]. The questionnaire consists of 12 items with different answer designs and options.

Self-esteem, Self-efficacy, and Emotion Regulation Skills

Furthermore, we assess self-esteem, self-efficacy and emotion regulation skills. Self-esteem is measured using the Rosenberg Self-esteem Scale [47]. This scale consists of 10 items with a 4-point scale from 0=strongly agree to 3=strongly disagree.

The General Self-Efficacy Scale [48] serves as a measure to assess perceived self-efficacy, aiming to predict coping with daily hassles and general adjustment after experiencing a stressful life event. The scale comprises 10 items on a scale from 1=not at all true to 4=exactly true. Emotion regulation skills are assessed via the Self-Report Measure for the Assessment of Emotion Regulation Skills [49], a 27-item questionnaire with answers ranging from 0=not at all to 3=(almost) always.

Program-Related Measures

The program-related factors we survey include user satisfaction and program usability. This is assessed using the Client Satisfaction Questionnaire [50,51], an 8-item scale with a 4-tiered answer format varying in its wording. The program's usability is measured with the System Usability Scale [52], which consists of 10 items with answers ranging from 1=do not agree at all to 5=completely agree.

A further program-related factor is adherence, measured by the frequency and duration of use. Those parameters are gathered within the program by means of, for example, the number of log-ins or the percentage of pages and segments that have been accessed and browsed through at least once.

Demographic Variables

Demographic variables obtained from the first online questionnaire include gender, age, family status, and level of income and education. Additionally, participants are asked to indicate whether they have received or currently receive any treatment for mental health issues or physical rehabilitation.

Data Collection and Management

All data is assessed online, either within the program platform or via online questionnaires programmed in Qualtrics [53]. Data integrity is enforced through different mechanisms including referential data rules, valid values, range checks, and consistency checks. The option to choose a value from a list of valid codes and a description of what each code means will be available where applicable. Checks are applied at the time of data entry into a specific field. All data is stored in anonymous form and can only be traced by a code that cannot be linked to the identity of the participant. Data gathered within the program as well as the program itself are stored on a firewall-encrypted backed-up server of the University of Bern. Only researchers directly involved in the study have access to the data, and they are subject to professional discretion.

Power

In order to specify the sample size needed for the planned analyses, we conducted a power analysis based on a probability level of .05 and a power of 0.80 using G*Power (Heinrich-Heine-Universität Düsseldorf) [54]. To test the program's efficacy compared to the control group, we expect small-to-moderate effect sizes between d=0.2 and d=0.35 as well as a correlation between the groups of r=0.4. Those estimates are based on the results of previous web-based interventions for adjustment problems [29].

The a priori power analyses yielded a necessary sample size of 80 (for d=0.35) to 238 (for d=0.2) participants in total for this analysis. Since the program does not include weekly guidance but rather guidance on demand, we expect slightly smaller effect sizes. Based on these calculations and assumptions we decided to target a sample size of N=240 participants.

Statistical Analysis

Statistical analyses will be carried out on the basis of the intention-to-treat approach and therefore will include all randomized participants. We will analyze the extent of the missing data, explore patterns and determine the type of missing data (missing completely at random, missing at random, not missing at random). Missing values will be substituted using multiple imputations. Sensitivity analyses will be conducted for both the data sets with and without the imputed data.

We will use linear mixed models to analyze all continuous outcomes as a change from baseline to compare effects between the two groups and over the different measurement points. In case of a missing at random mechanism, we will conduct multilevel regression analyses, which are less sensitive to missing data. Multiple regression analyses allow us to include several predictors such as time of measurement or group allocation [55].

Furthermore, exploratory analyses will be conducted. One of these will examine the association between adherence and outcome, since a higher adherence has been shown to have a positive effect on outcome [56,57].

All analyses will be conducted using SPSS (IBM Corporation) and R (R Foundation for Statistical Computing).

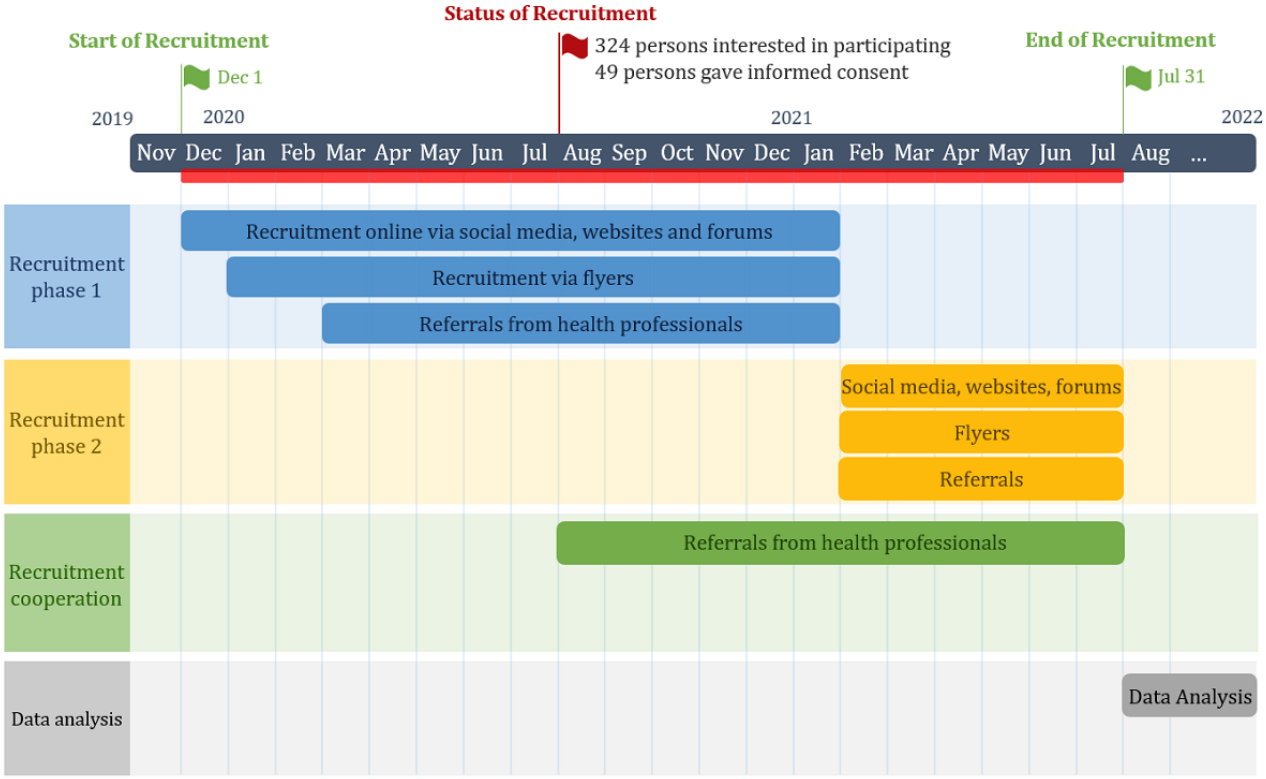
Results

The study is conducted according to the principles of the World Medical Assembly Declaration of Helsinki [58], the Swiss Federal Human Research Act [59], and the Ordinance on Clinical Trials in Human Research [60]. Ethical approval has been obtained from the Cantonal Ethics Committee Berne (BASEC 2018-01059). The study is registered with ClinicalTrials.gov (NCT03785912). Furthermore, the SelFIT program is a CE-certified medical device. Written informed consent is obtained from each participant.

Recruitment, screening, inclusion, and randomization of participants is scheduled to take place between December 2019 and January 2021. Due to the COVID-19 pandemic, recruitment was slowed down. For this reason, the recruitment phase may be extended by 6 months if we are unable to recruit enough participants by the end of January 2021.

As of July 2020, 324 people have shown interest in participating, and 49 people have given their informed consent. We are confident that we will be able to recruit enough people for three reasons. First, a recruitment cooperation with one of the largest rehabilitation clinics for injured persons in Switzerland will start in August. This means a steady influx of participants. Second, all persons who have expressed interest in participating but have not registered are contacted again and asked if they would like to participate in the study. This has proven to be an effective strategy so far. Third, we can extend the recruitment phase if necessary. The project's recruitment schedule is shown in Figure 3.

Figure 3. Gantt chart displaying the study's recruitment schedule and status of recruitment.



Discussion

Principal Findings

Accidents and their consequences often affect not only a person's physical well-being but also their mental health and their professional, personal, and social environment. Thus, accidents often mean a significant change and new challenges for those affected. Adjusting to those changed circumstances can be difficult. This also applies to adjustment efforts when returning to everyday life after rehabilitation is over, for example. A lack of support during this time may lead to the development or worsening of psychological distress such as adjustment problems. Easily accessible treatment options such as the SelFIT program could remedy this situation. For this reason, SelFIT was implemented as a web-based self-help intervention, which allows a high degree of flexibility in terms of time and location and can be used with comparatively little effort. Based on the findings of previous studies on adjustment problems and web-based interventions, SelFIT comprises a guidance on demand approach. This enables users to obtain support when needed with minimal personnel costs. Unlike previous web-based programs on adjustment problems, SelFIT does not address adjustment problems in general. Instead, the focus is specifically on the treatment of psychological distress and adjustment problems after an accident. This allows the content of the program to be matched more specifically to the needs of the participants.

To the best of our knowledge, this combination of web-based delivery, guidance on demand, and focus on the psychological support of injured persons has not yet been done.

Due to this novel approach, SelFIT could also contribute to expanding the scope of therapy options and offers of clinics, practices, or hospitals. Here, the program could serve as a supplement to face-to-face therapy. In addition, SelFIT can also offer extended psychological support, for example after the end of a rehabilitation program in the transition to everyday life at home or as a transitional offer after the end of psychotherapy.

The results of this study will provide insight into the efficacy and cost-effectiveness of the SelFIT program. The analysis of the program's user-friendliness and adherence may provide information for further adaptations to different user needs.

Limitations

Possible limitations of this study include typical challenges of web-based interventions such as the self-selection of participants. This is addressed by recruiting through various channels, such as program referrals from a rehabilitation clinic for injured people, recruitment via social media, and recommendations by physiotherapists. Another potential limitation is participants' physical restrictions due to the accident, which may make it difficult to use a computer or other technical devices. In such a case, access to the program might be limited.

The narrow focus of participants to be included in the study can have disadvantages. Although this allows for more specific tailoring, it makes the target population significantly smaller and recruitment more difficult.

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Authors' Contributions

Initially, this study was conceptualized by TB and HZ. JKH developed the intervention and the design of the study, recruited the participants, and drafted the manuscript. NAB developed the intervention and the design of the study and recruited the participants. The manuscript was reviewed and edited prior to submission, and all authors approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Screenshot of the SelFIT program's homepage.
[PNG File , 1088 KB - resprot_v9i12e21200_app1.png]

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Abbreviations

CAU: care as usual
ICD: International Classification of Diseases
RCT: randomized controlled trial
SelFIT: Selber wieder fit nach einem Unfall (fit again after an accident)
ZIEL: Zurück Ins Eigene Leben (back to your own life)

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Protocol

Using the Online Psychotherapy Tool to Address Mental Health Problems in the Context of the COVID-19 Pandemic: Protocol for an Electronically Delivered Cognitive Behavioral Therapy Program

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Abstract

Background: The considerable rise of mental health challenges during the COVID-19 pandemic has had detrimental effects on the public health sector and economy. To meet the overwhelming and growing demand for mental health care, innovative approaches must be employed to significantly expand mental health care delivery capacity. Although it is not feasible to increase the number of mental health care providers or hours they work in the short term, improving their time efficiency may be a viable solution. Virtually and digitally delivering psychotherapy, which has been shown to be efficient and clinically effective, might be a good method for addressing this growing demand.

Objective: This research protocol aims to evaluate the feasibility and efficacy of using an online, digital, asynchronous care model to treat mental health issues that are started or aggravated by stressors associated with the COVID-19 pandemic.

Methods: This nonrandomized controlled trial intervention will be delivered through the Online Psychotherapy Tool, a secure, cloud-based, digital mental health platform. Participants will be offered a 9-week electronically delivered cognitive behavioral therapy program that is tailored to address mental health problems in the context of the COVID-19 pandemic. This program will involve weekly self-guided educational material that provides an overview of behavioral skills and weekly homework. Participants (N=80) will receive personalized feedback from and weekly interaction with a therapist throughout the course of the program. The efficacy of the program will be evaluated using clinically validated symptomology questionnaires, which are to be completed by participants at baseline, week 5, and posttreatment. Inclusion criteria includes the capacity to consent; a primary diagnosis of generalized anxiety disorder or major depressive disorder, with symptoms that started or worsened during the COVID-19 pandemic;

the ability to speak and read English; and consistent and reliable access to the internet. Exclusion criteria includes active psychosis, acute mania, severe alcohol or substance use disorder, and active suicidal or homicidal ideation.

Results: This study received funding in May 2020. Ethics approval was received in June 2020. The recruitment of participants began in June 2020. Participant recruitment is being conducted via social media, web-based communities, and physician referrals. To date, 58 participants have been recruited (intervention group: n=35; control group: n=23). Data collection is expected to conclude by the end of 2020. Analyses (ie, linear regression analysis for continuous outcomes and binomial regression analysis for categorical outcomes) are expected to be completed by February 2021.

Conclusions: If proven feasible, this care delivery method could increase care capacity by up to fourfold. The findings from this study can potentially influence clinical practices and policies and increase accessibility to care during the COVID-19 pandemic, without sacrificing the quality of care.

Trial Registration: ClinicalTrials.gov NCT04476667; https://clinicaltrials.gov/ct2/show/NCT04476667

International Registered Report Identifier (IRRID): DERR1-10.2196/24913

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KEYWORDS

mental health; COVID-19; depression; anxiety; psychotherapy; cognitive behavioural therapy; online; internet; electronic; mental health care

Introduction

Background and Rationale

The COVID-19 pandemic is a source of high-degree uncertainty, anxiety, and stress, and it is ultimately affecting mental health on a global scale. According to a recent survey, 75% of Canadians have reported feeling anxious, 37% have reported feeling lonely, and 32% have said that they are having a hard time falling asleep because of stressors associated with the COVID-19 pandemic [1]. Previous experience has shown that the psychological scars resulting from public disasters go far beyond the official end of the disaster. For instance, the mental health effects that were observed following Hurricane Katrina lasted for over 4 years after the disaster, with a 35% increase in substance abuse hospitalization in New Orleans [2]. This shows that addressing the mental health aspect of the COVID-19 pandemic is as important as addressing the immediate medical emergency. The increase in demand for mental health care services resulting from the COVID-19 pandemic has come in the backdrop of a system that is already in crisis, which necessitates devising innovative approaches for increasing the current care capacity to cover more patients.

Cognitive behavioral therapy (CBT) could be a promising solution for treating depression and anxiety disorders related to the COVID-19 pandemic. CBT is widely regarded as a first-line treatment for major depressive disorder (MDD) and generalized anxiety disorder (GAD), as supported by randomized controlled trials, meta-analyses, and the recommendations of most clinical guidelines [3-7]. CBT has proven to be effective in relieving depressive and anxiety-related symptoms, improving the overall functioning of patients with such symptoms, and preventing relapses of these conditions [3-5], with long-term effects [6,7]. However, effectively administering CBT through face-to-face or virtual/live (ie, synchronous) methods is very time consuming and costly, and in most cases, such methods are not accessible to many patients. Electronically delivered CBT (ie, nonlive, asynchronous care; e-CBT) could be a viable alternative method for mental health care delivery. E-CBT has proven to be efficacious in treating both anxiety and depressive disorders, with comparable results to in-person therapy [8-11]. E-CBT content can be conveniently accessed anytime and anywhere, thereby providing flexible access to care, even for people who live in remote areas. A major benefit of e-CBT is that by delivering predesigned therapy content, clinicians can skip repeating similar general concepts to multiple patients and reduce their time commitment to a fraction of that in in-person therapy [12,13]. This not only reduces the cost of care delivery, but also allows more people to receive care from existing clinical resources and shortens waiting times. The main disadvantage to using e-CBT as a treatment delivery modality is that some individuals might not have access to the necessary technology (eg, phones, tablets, or laptops) or proper internet connectivity. Furthermore, there are different methods of delivering e-CBT, which range from unguided self-help [14,15] to guided programs that consist of a standardized content delivery modality with support from a mental health professional [12,13,16]. Although these different methods have been shown to be effective to some extent, their efficacy varies depending on the level of care provider engagement during the therapy process [17]. Naturally, as the level of clinical engagement goes higher, so does the cost of therapy, thereby making the therapy less accessible to patients in need. We believe a hybrid solution that combines predesigned content with limited and personalized guidance from a clinician could lower the costs of therapy, increase care capacity, and improve patient outcomes through increased patient engagement. Given the structured nature of CBT, even clinician feedback could follow a predesigned structure to make the process more streamlined.

In this protocol, we aim to develop a scalable online psychotherapy clinic centered around e-CBT to assist patients with stress resulting from the COVID-19 pandemic. The e-CBT program consists of 9 weekly modules that focus on coping skills and building resilience, which are effective in the treatment of mood and anxiety disorders. We will use the Online Psychotherapy Tool (OPTT; OPTT Inc) [18], a secure, cloud-based platform, to interact with patients and deliver therapy. By using the OPTT, all patient information can be kept

secure and confidential, while allowing all clinicians on the treatment team to access their patients' information and communicate with one another through the platform to discuss their patients. We hypothesize that using these psychotherapeutic interventions during the COVID-19 pandemic will improve the quality of life and decrease symptoms of depression and anxiety in the intervention group compared to the control group.

Objectives

The first objective of this study is to design and implement a scalable online psychotherapy clinic and care plan (ie, content, design, and feedback structure plans) to address mental health problems that started or worsened during the COVID-19 pandemic. The second objective is to evaluate the feasibility and efficacy of treating COVID-19–related mental health problems by offering specific e-CBT modules through an online clinic. The third and final objective is to rapidly disseminate the knowledge gained from this study to other practices, thereby facilitating the effective and reliable scaling of this solution across the community.

Methods

Study Design

This clinical trial has a nonrandomized controlled trial design. Participants in the intervention group will be offered a 9-week e-CBT program that is tailored to address mental health problems in the context of the COVID-19 pandemic. Qualitative focus groups will be conducted to gather personal demographic information, as well as information about the feasibility of implementing an online psychotherapy clinic. Additionally, quantitative analyses of online psychotherapy treatment efficacy will be conducted using standardized symptomology questionnaires. All procedures have been approved by the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board.

Participants

Participants (N=80) aged 18-65 years will be enrolled in the study based on referrals from the Hotel Dieu Hospital and Providence Care Hospital outpatient clinics located in Kingston, Ontario, Canada, and self-referrals from social media and web-based communities. Those referred and interested in participating will provide informed consent before being evaluated by one of the psychiatrists on the research team through a secure video appointment. During this appointment, MDD/GAD diagnoses will be made or confirmed using the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). Mini-International Neuropsychiatric Interview, Version 7.0.2 DSM-5 will also be administered by a trained research assistant on the team to confirm the diagnosis. Inclusion criteria includes the capacity to consent; a primary diagnosis of GAD or MDD, with symptoms that started or worsened during the COVID-19 pandemic; the ability to speak and read English; and consistent and reliable access to the internet. Exclusion criteria includes active psychosis, acute mania, severe alcohol or substance use disorder, and active suicidal or homicidal ideation. Additionally, to keep the scope of this study focused on the more common challenges that people face during the pandemic, participants will be excluded if mental health problems are secondary to a medical condition. Moreover, if a participant is currently receiving or has received CBT in any format during the past year, they will be excluded to prevent a possible confounding effect between previous CBT treatment and the e-CBT program.

Participants who are eligible for this study will be offered to join the electronic psychotherapy (e-psychotherapy) group. If individuals in this treatment group have been on pharmacotherapy treatment, their medication from 6 weeks prior to the trial and during the 9 weeks of treatment will not get changed. Individuals diagnosed with MDD or GAD who do not wish to participate in the e-psychotherapy group will continue to receive treatment as usual (TAU) and will be part of the control group. TAU is defined as any lifestyle activities and interventions (ie, medication, psychiatric consultation and referrals, exercise, diet, etc) that participants in either group were receiving prior to joining the trial. These activities and interventions will not be changed throughout the course of participants' participation. Both groups will be stratified by sex, gender, and age.

Procedures

Participants enrolled in the e-psychotherapy group will participate in a 9-week program that will include a combination of CBT, mindfulness therapy, and problem-based therapy. The content of the e-psychotherapy program will be customized to reflect the challenges that individuals may face during the COVID-19 pandemic and developed into interactive and engaging therapy modules. A sample session has been provided by OPTT Inc [19]. All online sessions and interactions will occur through a secure, online platform called the OPTT.

Each participant will be assigned to a therapist on the research team. During each week, the therapist will assign a predesigned therapy module to their patient through the OPTT on a specific day of the week. Participants will have access to the therapy content at any time throughout the week. Each weekly module will focus on a new topic by covering general information on the topic, providing an overview of the skills associated with the topic, and providing homework, which will be due on a specific day of the week. All content and topics that will be covered are designed to mirror in-person CBT programs. Completing each weekly module will require an average time commitment of 40 minutes, which can be completed all at once or in several blocks of time. The homework will be directly submitted through the OPTT to the clinician, who will then provide personalized feedback to the patient.

In order to maintain care and outcome consistency and streamline the process, therapists will use predesigned session-specific feedback templates to respond to each homework submission. This will also help to save time and costs and make the program more scalable. Therapist feedback will generally follow a certain structure. First, the therapist will start off feedback by valuing the participant's time and effort. This will help to establish a rapport between the therapist and the participant. Second, the therapist will summarize the previous sessions' material and remind the participant of what they have learned so far. The information in this section will

differ between sessions, but it will remain constant across participants. Third, the therapist will discuss the participant's homework and provide an evaluation. The therapist will always review the event that the participant used in their homework, so that the participant will know that their therapist has read and paid attention to their unique situation. Fourth, the therapist will discuss what the participant did right and what the participant could have done differently in their homework. Last, the therapist will emphasize their appreciation for the participant's hard work and sign their name. This will ensure that the connection between the therapist and the participant remains personal. Writing feedback using this structure usually does not take longer than 15-20 minutes for an experienced therapist. A more detailed explanation on this structure can be found in Online Cognitive Behavioral Therapy: An e-Mental Health Approach to Depression and Anxiety, a book by Alavi and Omrani [20].

Although the homework and clinician feedback are considered the main means of communication between therapists and participants, participants can also communicate with their therapist through a secure chat function that is found directly within the OPTT. This is mainly used to let participants ask further questions about their care, if anything is not clear. Any technical issues will be handled through the OPTT technical support team, which participants will have access to at all times during the program. The patient care team (eg, the therapist and the psychiatrist) will also be able to securely communicate through the OPTT to make decisions regarding each patient's care path.

The control group will continue receiving TAU for the first 9 weeks of their participation. If control group participants continue to present significant symptoms (ie, <50% reduction in symptoms compared to those in baseline), they will again be offered the option to undergo the e-psychotherapy program or other forms of treatments as deemed necessary.

Online Modules

The modules are designed for individuals who experience symptoms of anxiety and depression in the context of COVID-19 pandemic. We combined our expertise in content development [20] from previous clinical trials, which used a similar approach to address depression [21] and anxiety [12], and certain content from previous therapeutic modules, and adapted them to address COVID-19–related stressors and develop relevant strategies. We then discussed the content with an expert panel of therapists, psychiatrists, and end users to ensure the suitability and efficiency of the content. During this program, therapists will help participants understand that in any given situation, their thoughts, feelings, and actions all interact with and influence one another and help them change their thoughts and actions. The goal of this program is to teach individuals how to identify and change their destructive and disturbing thought patterns, which have a negative influence on behavior and emotions. Through these modules, we will discuss the effect of the pandemic on mood, the basics of CBT, deep breathing techniques, body scan and meditation, the self-care kit, SMART (Specific, Measurable, Achievable, Realistic, and Timely) goals, thinking errors, 5-part models, and thought records. The first 2 sessions will be designed to address symptoms caused by the fear of illness and concerns about personal safety in the context of the pandemic. The rest of the sessions will focus on cognitive and behavioral techniques, problem-solving techniques, and mindfulness practices to help build healthy coping skills that address the uncertainties surrounding the COVID-19 pandemic and the symptoms of depression and anxiety. During this program, we will focus on essential thinking and behavioral skills to help individuals become more engaged in day-to-day activities. We will also work on evaluating negative beliefs and thought processes, as well as their relationship with anxiety/depression. Our goal is to adjust negative thinking so that participants can think about and adapt to the things that are happening to them. This will allow participants to adjust the way they behave, think about their problems in a way that is not as negative, and replace negative thoughts with potentially more positive and productive thoughts and behaviors.

In addition to the content, we pay special attention to the presentation of materials to participants. There are multiple animations and interactive examples that will be provided in each session to keep the participants interested and engaged, such as those in the OPTT Inc sample session [19]. The modules are accessible with any device (ie, desktops, tablets, and cellphones) and compatible across multiple browsers.

Training

All the therapists are research assistants hired by the research team. These therapists have previous training in psychotherapy, and they will receive further training from one of the psychiatrists involved in the study before they interact with participants. Therapists will learn the standard care pathway, aim, and content of each therapeutic session. Moreover, they will be provided with sample homework from patients and asked to provide feedback as practice for each session. As explained earlier, the feedback templates will vary from session to session, and therapists will personalize each template for each patient's homework. Training will be provided through webinars and exercises with feedback. Therapists will also be supervised by the lead psychiatrist on the team, who has more than 10 years of experience in in-person and online psychotherapy. After the feedback is prepared by the therapist, the feedback will be read, edited, and approved by the supervisor before it is submitted to the participant.

During the consent process, participants are informed that this program is not to be used as a crisis resource, as therapists cannot be reached at all times through the OPTT platform. In the case of an emergency (eg, suicidal ideation), therapists will be instructed to direct patients to the proper resources (eg, emergency department, crisis lines, etc) and inform their supervisor about such incidents.

Ethics and Data Privacy

All procedures have been approved by and comply with the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board. Only the care providers involved in the care of the participant will have access to their participant's information. Hard copies of consent forms and participant identity will be securely stored on-site and destroyed

5 years after study completion. Participants will only be identifiable by an ID number on the OPTT platform, and only anonymized data will be provided to the analysis team members.

To ensure data privacy and security, the care platform (ie, the OPTT) was developed so that it complies with the Health Insurance Portability and Accountability Act, Personal Information Protection and Electronic Documents Act, and Service Organization Control-2. All servers and databases are hosted in the Amazon Web Service Canada cloud infrastructure, which is managed by Medstack (Medstack Inc) [22], to ensure that all Canadian provincial and federal privacy and security regulations are met. For privacy purposes, the OPTT will not collect any identifiable personal information or internet protocol addresses from participants. The OPTT will only collect anonymized metadata to improve its service quality and provide advanced analytics data to the clinical team. All data will be encrypted by the OPTT, and no employee will have direct access to participant data. All encrypted backups are to be kept in the Amazon S3 storage that is dedicated to Queen's University, Kingston, Ontario, Canada.

Outcome Evaluation

Primary outcome measures will be anxiety level based on Generalized Anxiety Disorder-7 (GAD-7) Item Questionnaire scores, depression level based on Patient Health Questionnaire-9 Item scores, resilience level based on Resilience Scale-14 Item Questionnaire scores, and quality of life based on Quality of Life and Enjoyment Questionnaire scores. All questionnaires will be collected directly through the OPTT at baseline, prior to week 5, and after the last session.

In addition to these quantitative measurements, qualitative analyses will be performed to evaluate the efficacy and feasibility of providers delivering e-CBT and participants receiving e-CBT. Health care providers will be asked about the feasibility of providing e-psychotherapy and how it compares to in-person psychotherapy in terms of time commitment, feelings of connectedness to the participant, and any perceived benefits and drawbacks to e-psychotherapy. Information on personal, social, and cultural factors (eg, gender, sexuality, background, supportive resources, structural/social barriers, etc) will be extracted from focus groups using an interpretive phenomenological analysis approach. Additionally, participants will be asked about their experiences with using the OPTT and their positive or negative experiences with the e-CBT program. Program adherence and completion rates will also be recorded and reported.

Data Analysis

Initially, all data will be examined for missing, nonsensical, and outlying variables. Missing data will be treated as missing and not imputed. This will be analyzed on a per-protocol basis. Given the likelihood of participant drop out or withdrawal, we have purposely oversampled our study and control groups to obtain meaningful and statistically significant results at the end of the study. Based on our previous experience with CBT and e-CBT in similar patient populations, we anticipate that up to 30% of participants will drop out by the end of the treatment or TAU phases. Using GAD-7 questionnaire scores as the primary outcome means that a 30% change is considered clinically significant. Therefore, a sample size of 40 participants in each arm of the study will be sufficient for detecting significant results (ie, P=.05 and a power of 0.95). In addition, an intention-to-treat analysis will be performed to evaluate completion rates and the clinical effects of participants leaving the trial before completion.

Data collection will occur at 3 separate time points, as follows: at baseline (ie, preintervention), in the middle of the study (ie, week 5), and immediately at postintervention (ie, week 9). Mann-Whitney U tests will be used to compare baseline demographic data between individuals who drop out and those who finish the e-CBT program, and any fundamental differences between completers and noncompleters will be identified. A linear regression analysis for continuous outcomes and binomial regression analysis for categorical outcomes will be performed to identify variables associated with the 2 outcome measures over the 3 measurement time points and to compare the differences between study arms. These analyses will be controlled for demographic variables, such as age and gender.

Results

The study was approved for funding in May 2020. Additionally, ethics approval was received from the Queen's University Health Science and Affiliated Teaching Hospitals Research Ethics Board in June 2020, and the recruitment of participants began in June 2020. Participant recruitment has been based on physician referrals and self-referrals through social media and web-based communities. To date, 58 participants have been recruited (ie, 35 in the intervention group and 23 in the control group). Data collection is expected to conclude by the end of 2020, and analyses are expected to be completed by February 2021. We will share the outcomes of our study as a preprint on bioRxiv to rapidly disseminate our findings. We will also hold multiple online workshops for other clinicians who are interested in implementing this approach. During these workshops, we will provide technical and academic support to other clinicians so that they can deploy this solution in their respective practices.

Discussion

Addressing the extensive mental health problems resulting from the COVID-19 pandemic requires rapid and easily accessible solutions. An online psychotherapy clinic with predesigned therapy modules can be used to rapidly scale up clinical capacity to address mental health problems resulting from the COVID-19 pandemic, while also ensuring a high quality of care. That is why, through this study, we emphasize developing and validating a comprehensive solution (ie, engaging and effective content, feedback templates, and clinician training) that can be easily deployed with minimal resources. We are also planning to disseminate the outcomes of our study through publicly accessible media, so other clinicians can easily access and incorporate this solution into their clinical practices in time to meet their patients' needs. This approach will result in major financial savings for the health care system, as it provides methods for the efficient use of clinicians' time and the equitable and accessible delivery of care to patients.

It should be noted that our current study design has some limitations, such as the nonrandomized design of the study. In order to address these concerns in a structured format, we are using the "guidance for reporting intervention development studies in health research (GUIDED)" framework [23] and "template for intervention description and replication (TIDieR)" [24] to report our protocols and outcomes (Tables S1 and S2 in Multimedia Appendix 1). We are also planning to start a randomized study in January 2021. Additionally, the electronic mode of care delivery might not be suitable for specific subgroups of patients (eg, older adults or patients who lack experience with related technologies). We hope that through our qualitative focus groups, we will be able to identify each of these subgroups and find suitable remedies for future iterations of our study design (eg, changing the module design so that it is user-friendly for older adults).

Delivering care through a digital platform provides new opportunities for tracking behavior in a way that was not possible before [25], such as new methods for tracking sleep patterns and activity level changes across multiple people with mood disorders. Currently, subjective and qualitative descriptions of sleep and activity changes are used for tracking patients' mood changes. However, with the widespread use of wearable devices that can quantitatively track these behaviors, incorporating such devices in patients' care could provide an invaluable source of information for monitoring patient progress.

In order to take advantage of this new avenue, the new randomized study in January 2021 will incorporate the procedure explained above. In this study, each participant will be provided a wearable device that will record their activities and sleep patterns. Data from the wearable devices will be automatically synched and collected with the OPTT platform, and analytical data will be provided to clinicians. An additional session will be added to the current modules to provide information regarding sleep hygiene and the importance of remaining active during the pandemic. Clinicians will also monitor participants' sleep patterns and activities for significant changes (ie, increases or decreases in sleep duration and decreases in activity), provide feedback to the participants, and encourage participants to follow a healthy routine. We believe that this comprehensive plan will significantly boost the positive effect of our e-CBT program.

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Conflicts of Interest

NA and MO cofounded the care delivery platform in use (ie, the OPTT) and have ownership stakes in OPTT Inc.

Multimedia Appendix 1
Reporting Guidelines.
[PDF File (Adobe PDF File), 503 KB - resprot_v9i12e24913_app1.pdf]

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Abbreviations

CBT: cognitive behavioral therapy
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
e-CBT: electronically delivered cognitive behavioral therapy
e-psychotherapy: electronic psychotherapy
GAD-7: Generalized Anxiety Disorder-7
GUIDED: guidance for the reporting of intervention development
MDD: major depressive disorder
OPTT: Online Psychotherapy Tool
SMART: specific, measurable, achievable, realistic, and timely
TAU: treatment as usual
TIDieR: template for intervention description and replication

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Protocol

An Educational Network for Surgical Education Supported by Gamification Elements: Protocol for a Randomized Controlled Trial

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Abstract

Background: Traditionally, medical students have learned surgical skills by observing a resident physician or surgeon who is performing the technique. Due to inconsistent practice opportunities in the clinical setting, a disparity of skill levels among students has been observed. In addition, the poor availability of faculty professors is a limiting factor in teaching and adequately preparing medical students for their clerkship years. With the ongoing COVID-19 pandemic, medical students do not have access to traditional suturing learning opportunities. Didactic courses are available on videoconferencing platforms; however, these courses do not include technical training.

Objective: Our overarching goal is to evaluate the efficacy and usability of web-based peer-learning for advanced suturing techniques (ie, running subcuticular sutures). We will use the Gamified Educational Network (GEN), a newly developed web-based learning tool. We will assess students' ability to identify and perform the correct technique. We will also assess the students' satisfaction with regard to GEN.

Methods: We will conduct a prospective randomized controlled trial with blinding of expert examiners. First-year medical students in the Faculty of Medicine of Université de Montréal will be randomized into four groups: (1) control, (2) self-learning, (3) peer-learning, and (4) peer-learning with expert feedback. Each arm will have 15 participants who will learn how to perform running subcuticular sutures through videos on GEN. For our primary outcome, the students' ability to identify the correct technique will be evaluated before and after the intervention on GEN. The students will view eight videos and rate the surgical techniques using the Objective Structured Assessment of Technical Skills Global Rating Scale and the Subcuticular Suture Checklist as evaluation criteria. For our secondary outcomes, students will anonymously record themselves performing a running subcuticular suture and will be evaluated using the same scales. Then, a survey will be sent to assess the students' acceptance of the intervention.

Results: The study will be conducted in accordance with the Declaration of Helsinki and has been approved by our institutional review board (CERSES 20-068-D). No participants have been recruited yet.

Conclusions: Peer learning through GEN has the potential to overcome significant limitations related to the COVID-19 pandemic and the lack of availability of faculty professors. Further, a decrease of the anxiety related to traditional suturing classes can be

expected. We aim to create an innovative and sustainable method of teaching surgical skills to improve the efficiency and quality of surgical training in medical faculties. In the context of the COVID-19 pandemic, the need for such tools is imperative.

Trial Registration: ClinicalTrials.gov NCT04425499; https://clinicaltrials.gov/ct2/show/NCT04425499

International Registered Report Identifier (IRRID): PRR1-10.2196/21273

(JMIR Res Protoc 2020;9(12):e21273) doi:10.2196/21273

KEYWORDS

distance learning; COVID-19; surgical pedagogy; learning platform; subcuticular sutures; advanced sutures; medical education; peer learning; surgery; medical student; web-based learning; web-based tool; gamification; video

Introduction

The necessity for medical students to develop proper suturing skills to achieve future excellence in surgery is sufficiently important to warrant interest in pursuing educational research with the goal of implementing systematic and effective methods of training [1]. Historically, the traditional methods by which medical students learn basic suturing skills have involved observation and trial during clerkship [2-4]. Currently, several issues pertaining to this practice in medicine have arisen due to the legal ethics involved [5] because both patients and students are at greater risk of injury. Without appropriate preparation, students are at higher risks of making mistakes [1,6]. Poor suturing technique and increased wound tension have been associated with substandard wound adhesion and increased scar formation [7]. The levels of comfort, confidence, and preparedness felt by medical students when performing these medical acts are also less developed [8], which may further adversely affect their performance when treating a real patient.

The academic learning objectives of medical students include several different suturing techniques. The most basic is the simple interrupted suture. A more advanced technique is the running subcuticular suture. All medical students are required to learn these surgical skills during their education, which is a source of anxiety and a challenge for many students.

With the traditional method, student learning depends on circumstances and the random presentation of cases [6]. The benefits of developing basic surgical skills before clerkship have been demonstrated. Early and prolonged exposure to and practice of suturing have been associated with an increased level of confidence relative to suturing a patient [2,4].

Acquiring this skill during preclinical years may increase the level of preparation of students, thereby increasing the professionalism and quality of the medical acts they perform on patients. However, the training in this technique during preclinical years has been limited due to time constraints on faculty staff as well as the cost of using these staff as trainers [9,10].

Several studies support peer-assisted training during preclinical years as a sustainable alternative [9,11-14]. These studies focus on basic surgical skills, such as uninterrupted stitches and knot-tying [15]. Although most studies demonstrate equivalence in acquisition of proficiency whether students are taught by peers or by faculty surgeons [12,13,16-18], it is unknown whether these results can be extrapolated to more advanced suturing skills, such as the vertical/horizontal mattress or running subcuticular sutures. In 2013, a study compared the execution of interrupted and subcuticular sutures among three groups: expert-trained, peer-trained, and self-taught. This study demonstrated that the execution by students in the peer-trained group was equivalent to that of the expert-trained students for both suture techniques [8]. Further studies pertaining to more advanced skills are warranted.

In the pursuit of developing sustainable alternatives in surgical education, several web-based tools have been gaining ground; tools that implement gamification elements are of particular interest, as they may further engage the student during their learning experience [19-21]. Several publications support gamified learning in health education due to its many unique advantages. Innovative platforms have the potential to provide effective, collaborative, inexpensive, and enjoyable opportunities to learn [19,21,22]. The Gamified Educational Network (GEN) is a web-based platform that was developed at Ontario Tech University and permits peer feedback through video assessment. Several educational tools have been developed and tested in surgical training [23-27]; however, the GEN platform enables students to learn a variety of skills without developing incorrect habits while practicing on their own. Students can upload videos of themselves performing a skill and share improvement tips with peers. Long-term retention of a surgical skill is optimal when the training is spread out over time rather than being provided in a single training session in one day [28]. Therefore, this platform offers superior psychomotor skill development by offering students the opportunity to expand the practice time of basic surgical skills beyond the classroom or clinical setting. In this way, students can practice skills and receive direct feedback at home.

During the present worldwide event of the COVID-19 pandemic, medical curricula have been suspended [29-31]. Therefore, offering students access to optimally efficient academic tools at home is of primordial importance [32]. The necessity for video instruction investigations is henceforth essential.

This study has four aims: (1) to evaluate students' ability to identify the correct subcuticular suture method, comparing three web-based learning approaches of self-learning, peer-learning, and peer-learning with expert feedback; (2) to evaluate students' ability to execute a proper running subcuticular suture, comparing three web-based learning approaches of self-learning, peer-learning, and peer-learning with expert feedback; (3) to determine the students' acceptance of GEN to improve the platform as a learning tool; and (4) to develop an innovative

web-based training and teaching method to better prepare students for simulation training and clerkship.

Methods

Study Design

This will be a prospective randomized controlled study with blinding of expert examiners. The study has been registered (ClinicalTrials.gov NCT04425499).

Population

Participants are first-year medical students at Université de Montréal. We decided to target this population because these students do not yet have significant experience with suturing. We will invite the whole cohort (about 300 students) by email.

Eligibility and Ineligibility Criteria

Conditions for Eligibility

Students must be enrolled in their first year of medical school at Université de Montréal.

Conditions for Ineligibility

Students will be ineligible if they have returned after a leave, such as a sabbatical year, sick leave, or maternity leave; have already obtained a medical degree in another country; have studied medicine in another country; or are injured at the beginning of the study.

Participant Recruitment

All students in their first year of medical school will receive an email inviting them to participate in the study. If they agree, they will be required to complete a consent form and provide a mailing address (Qualtrics XM).

All students enrolled in this study will be asked to participate using a personal computer. Students will be advised that participation will require their availability for one to three hours on three consecutive days. They will be advised not to study, practice, or view any external videos pertaining to suturing skills for the duration of the study.

When the students agree to participate, they will receive an email with the GEN platform link.

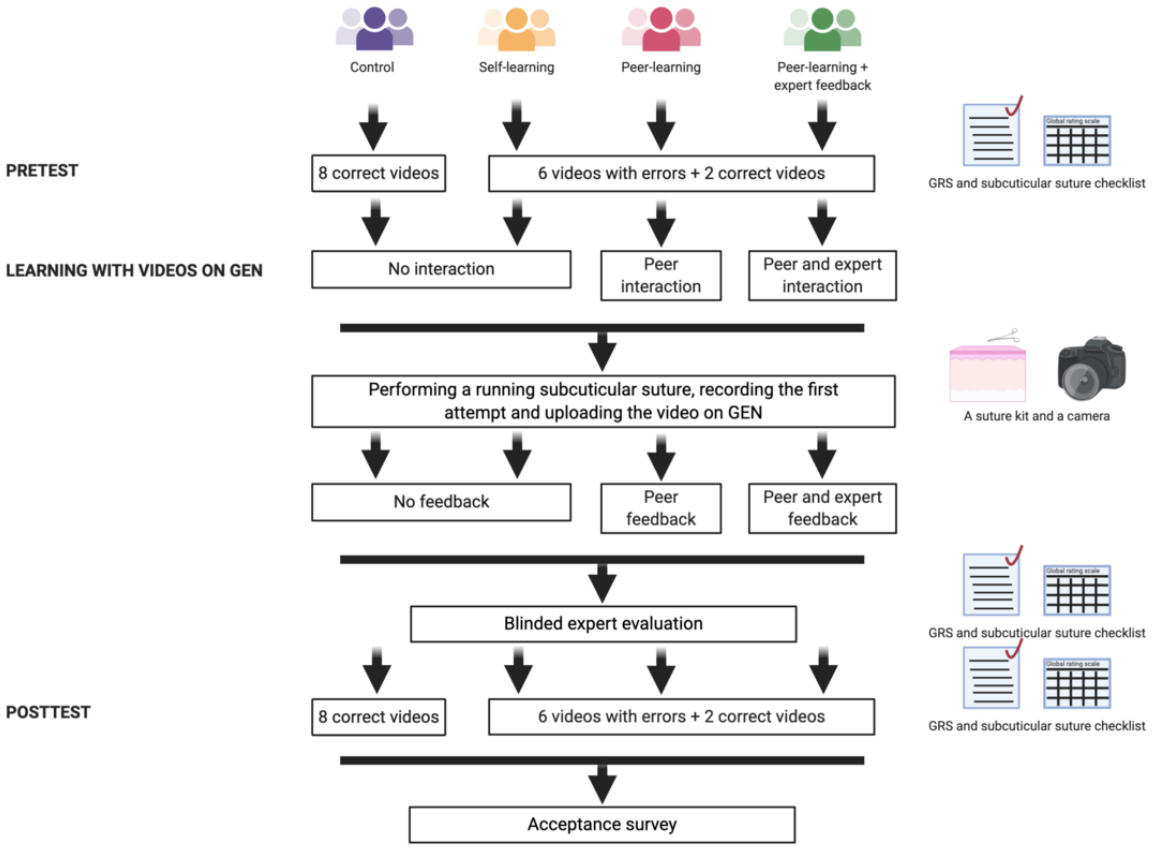
Students' previous experience with suturing will be surveyed, as well as the context of this experience (eg, workshop, former profession).

Upon creation of a new user account on GEN, students will be automatically randomized to one of the four groups and will only have access to the platform set for their study group.

Randomized Groups and Study Intervention

Figure 1 depicts the study intervention.

Figure 1. Study workflow. GEN: Gamified Educational Network; GRS: Global Rating Score.



Group 1: Control Group

On GEN, each student will individually view eight videos of an expert performing a running subcuticular suture correctly as a pretest. The Objective Structured Assessment of Technical Skills (OSATS) Global Rating Scale (GRS) (Table 1) and Subcuticular Suture Checklist (Textbox 1) will be made available beside each video, and students will be required to fill out these assessments for each video. For three days, students will have access to a distinct set of videos on GEN to learn running subcuticular sutures. Three days later, each student will perform a subcuticular suture on a suturing pad and record their first attempt. Then, students will undergo a posttest with the same eight videos shuffled in a different order. The order of the videos will be the same for all students.

The OSATS, developed by the University of Toronto, is an accurate and validated method of assessing surgical skills in an operating room setting [33,34]. It comprises a GRS (Table 1) in which certain skills are graded from 1 to 5 (ie, respect for tissue, time in motion, knowledge of instruments, instrument handling, suture skill, flow of operation, knowledge of procedures, and final product).

The checklist is a list of verifications specific to the technique of interest to ascertain whether every step of the procedure was executed (Textbox 1). The checklist was built and revised by a focus group led by the principal investigator, who is the director of the clerkship surgical rotation in the Faculty of Medicine of Université de Montréal. The focus group was composed of one medical student, one junior surgery resident, and one senior surgery resident.

Table 1. Global Rating Scores of the Objective Structured Assessment of Technical Skills [8,33,34]. The students will be asked to rate the candidate's performance on a scale of 1 to 5, and the total score will be summed.

Skill	Potential scores for observed outcomes		
	1-2	3	4-5
Respect for tissue	Frequently used unnecessary force on tissues or caused damage by inappropriate instrument use	Careful handling of tissue, but occasional inadvertent damage	Consistently handled tissues appropriately with minimal damage
Time in motion	Many unnecessary moves	Efficient time and motion, but some unnecessary moves	Clear economy of movement and maximum efficiency
Instrument handling	Repeatedly makes tentative or awkward moves with instruments	Competent use of instruments, but occasionally awkward	Fluid movements
Suture skill	Awkward and unsure with poor knot tying and inability to maintain tension	Competent suturing with good knot placement and appropriate tension	Excellent suture control with correct suture placement and tension
Flow of operation	Frequently stopped operating, seemed unsure of next move	Demonstrated some forward planning and reasonable progression of procedure	Obviously planned operation
Knowledge of procedure	Inefficient knowledge of procedure. Looked unsure and hesitant	Knew all important steps of procedure	Demonstrated familiarity of all steps of procedure
Final product	Final product of unacceptable quality	Final product of average quality	Final product of superior quality
Overall performance	Very poor	Competent	Very good

Textbox 1. Subcuticular suture checklist. One point is given for each step performed correctly.

Preparation for the technique

☐ The student dons sterile gloves.

☐ The student maintains sterility throughout the procedure.

Appropriate use of suturing equipment

☐ Needles and tissue are always manipulated with equipment and not with hands.

☐ The needle is properly held at a point two-thirds from its tip.

☐ The needle holder is appropriately held with extended index and fourth fingers.

☐ Forceps are properly held with the student's nondominant hand.

Execution of the running subcuticular suture

☐ Orientation of the needle upon insertion is appropriate (at 90º).

☐ A deep dermal suture is performed on the extreme interior part of the wound.

☐ The needle is properly exited between the deep dermal knot and the apex of the wound.

☐ At least three knots are performed, with two loops around the needle holder for the first knot and 1 loop for the remaining knots.

☐ The student alternates directions at 180º angles when tying the knot.

☐ For each subcuticular insertion, the needle is properly inserted in the superficial layer of the dermis.

☐ Each subcuticular insertion is appropriately spaced out.

☐ Each bite is alternated on one side of the wound to the contralateral wound edge.

☐ The surgical threads between each bite are parallel to each other.

☐ A deep knot is performed at the other end of the wound.

☐ Correct final knot technique is performed with the needle holder.

☐ The final knot is exited lateral to the apex.

Best practices

☐ Supination and pronation of wrists is performed.

☐ The needle is protected at the end of the intervention.

☐ The student can view the knot when it is cut and the scissors are held at a 45º angle.

Final knot

☐ Proper tightness of the final knot is obtained.

☐ The thread is cut at an appropriate length.

Overall aesthetics

☐ Proper wound tension is displayed (no overlapping of tissues, no gaps).

Total: ( )

Group 2: Self-Learning

Each student will view eight videos individually and complete the GRS and Subcuticular Suture Checklist for each video as a pretest. Six videos will contain errors and two videos will not. The errors will be technical mistakes in the execution of a running subcuticular suture. Then, for three days, students will have access to a distinct set of videos on GEN to learn how to perform running subcuticular sutures. Three days later, each student will perform a subcuticular suture on a suturing pad and record their first attempt. Finally, students will perform a posttest with the same eight videos shuffled in a different order. The order of the videos will be the same for all students.

Group 3: Peer-Learning

Each student will view eight videos and complete the GRS and Subcuticular Suture Checklist for each video as a pretest. Six videos will contain errors and two videos will not. After this initial test, students will interact with other medical students in their group on the GEN platform anonymously for three days. We will display distinct videos on GEN. Comments will be allowed in an interactive format to encourage exchanges. Students will be required to participate in the discussion of at least two videos. Students will not be able to modify their answers on the initial test. Three days later, each student will perform a subcuticular suture on a suturing pad and record their first attempt. Students will interact on GEN and comment on the videos recorded by their peers. On the third day, the students in this group will perform a posttest with the same eight initial

videos, but shuffled. The order of the videos will be the same for all students.

Group 4: Peer-Learning With Expert Feedback

The details for this group are mostly the same as for group 3; the only difference is that an expert will actively participate in the discussion by commenting on each video on GEN to enhance the students' educational experience. Although the expert will be anonymous, the students will be able to identify them because they will use the name "expert." The expert will answer any questions and comment on the discussion to guide the students.

Study Intervention

In summary (Figure 1), the intervention consists of learning subcuticular sutures on the GEN platform with videos. In groups 1 and 2, there is no peer feedback. In group 3, the participants will learn the suturing skill *on GEN* by collaborating and interacting with each other. They will comment on the videos on GEN (ie, peer feedback). In group 4, the participants will receive peer and expert feedback.

Several gamification elements are integrated into the study to facilitate the interventions. First, the GRS and checklist are installed next to each video; therefore, the students can easily view the videos and properly check every step. Another gamification element in this system is similar to the entertainment, social networking, and news website Reddit, which supports peer-based assessment; peers will be able to comment on the videos, discuss them, and collaborate with each other.

GEN enables the application of a leaderboard. This social comparative feedback component provides learners with information regarding how well they are doing with respect to their peers. This comparative information is provided both individually and in a general context by showing the learner's position on a private individual leaderboard. The learners do not have access to the scores of their peers, avoiding comparisons that could be a detriment to motivation. Learners also obtain access to the number of points they received in each course section through an individual scoreboard.

GEN also provides division of the modules. When the participant has successfully completed one activity, the next activity is unlocked and displayed, much like a video game with successive levels. Moreover, there is a segmented progress bar that allows learners to track their progress in each course and also in each individual course component. As such, the tasks the students are required to complete are clearly displayed, similar to a map, with deadlines; this clearly guides the participants through the activities and completion of the learning material on GEN.

Study Procedure

Objective 1: Evaluate Students' Ability to Identify the Correct Subcuticular Suture Method

We will determine the best learning method in a virtual environment among the three main groups. We will compare groups 2, 3, and 4: self-learning, peer-learning, and peer learning with expert feedback. There will be no crossovers. Students will undergo a pretest and a posttest to assess the effect of the intervention on their ability to identify the correct way to perform subcuticular sutures. We will also use the control group to compare our intervention to the regular web-based learning method, in which students learn alone by watching different videos with no artificial errors inserted. We will analyze the students' scoring of each video with the GRS and Subcuticular Suture Checklist.

Pretest and Posttest

All videos will show an expert performing a running subcuticular suture. The expert will be an experienced faculty surgeon licensed by the Royal College of Canada. The expert will only perform the suture without explanation; there will be no sound accompanying the videos. Among the eight videos displayed to students in groups 2, 3, and 4, six will contain technical errors. We will evaluate the students' ability to identify the errors as they complete the GRS and the Subcuticular Suture Checklist. Participants in groups 2, 3, and 4 will all see the same videos in the same order. The OSATS GRS (Table 1) and Subcuticular Suture Checklist (Textbox 1) will be available beside each video in the pretest and posttest for every student in all four groups.

Errors

Each video with errors will include 1 to 3 errors from the list detailed below:

- The needle holder is held with the thumb and index finger instead of the thumb and fourth finger.
- The thumb is entirely inserted in the ring of the needle holder.
- The needle is not held at two-thirds in the jaw of the needle holder.
- Suturing is performed at an incorrect depth.
- Excessive force is used with the forceps.
- The needle is not inserted at a 90º angle.
- Sutures are at inappropriate distances.
- Extra unnecessary steps are performed.
- The knot is not sufficiently tight.
- Supination and pronation are not properly performed.
- The thread is cut at an inappropriate length after tying the knot.
- The thread is cut without seeing the knot.

Objective 2: Evaluate Students' Ability to Execute a Proper Running Subcuticular Suture

We will determine the best learning method in a virtual environment among the three main groups. We will compare groups 2, 3, and 4: self-learning, peer-learning, and peer learning with expert feedback. There will be no crossovers. Students will receive a suture kit and perform a running subcuticular suture on a synthetic suturing pad. They will record their first attempt and upload it on GEN. One expert will evaluate the students' performance in the uploaded videos using the GRS and the Subcuticular Suture Checklist. The expert will be a faculty surgeon licensed by the Royal College of Canada. The results will not be published on GEN. The expert will be blinded to the study groups. We will require students to set up their camera field identical to that in the expert videos they will watch

on GEN. This will prevent variations in ratings that could occur due to differences in the participants' setups. More specifically, the learners will be instructed to adjust the field of view of the camera as follows:

- Camera location: The camera must face the front and be positioned at a height of 30-50 cm.
- Field of view: The entire simulator must be visible. Instruments and hands (up to the elbows) must be visible at all times. Students must wear gloves and ensure that there are no objects within the camera's field of view that can be used to identify them.
- Resolution and frequency: The camera should be set to 1080p resolution at 24 frames per second.
- Format: The students are asked to ensure that the videos are captured in mp4 or mov file formats.

We will also use the control group to compare our intervention to the regular web-based learning method in which students learn alone by watching different videos with no artificial errors inserted.

The package of the suture kit will contain an instruction to only open the box while recording the video in which the first attempt at suturing is performed. The student must demonstrate that the package is opened only while recording the video to ensure that they do not practice beforehand. Only the suture pad and the student's forearms will be shown in the videos to maintain anonymity. Students will not have access to the uploaded videos of the other students.

Objective 3: Determine the Students' Acceptance of GEN to Improve the Platform as a Learning Tool

At the end of the study, the students will fill out a survey [35] on their experience with the GEN platform as a learning tool (Textbox 2). This survey is anonymous.

Textbox 2. Survey to evaluate the students' acceptance of GEN.

1. In this study, there were four experimental groups, and you were enrolled randomly to one of these four groups. Based on your experiences and interactions within GEN, which group do you think you were enrolled in?

   a. Group 1. Control

   b. Group 2. Self-learning

   c. Group 3. Peer-learning

   d. Group 4. Peer-learning with expert feedback

2. Please rate the level of agreement with the following statements, where 1 means "strongly disagree," 2 means "disagree," 3 means "neutral," 4 means "agree," and 5 means "strongly agree."

   a. I found GEN to be a user-friendly platform.

   b. I found GEN to be a useful platform for improving my suturing skills.

   c. I would recommend GEN to other medical students.

3. Based on your recent experience, please provide a very brief description of features of GEN that you think we should:

   a. Stop (one feature that we should eliminate)

   b. Start (one feature that we should add)

   c. Change (one feature that works but could be improved upon)

   d. Continue (one feature that we should retain and not change)

Questions 4 to 12 are derived from the System Usability Scale [35]. The scale ranges from 1 to 5.

4. Please rate the level of agreement with the following statements, where 1 means "strongly disagree," 2 means "disagree," 3 means "neutral," 4 means "agree," and 5 means "strongly agree."

   a. I would like to use GEN frequently.

   b. I found GEN unnecessarily complex.

   c. I thought GEN was easy to use.

   d. I would need the support of a technical person to be able to use GEN.

   e. I found the various functions in GEN were well integrated.

   f. I thought there was too much inconsistency in GEN.

   g. I would imagine that most people would learn to use GEN very quickly.

   h. I found GEN very cumbersome (awkward) to use.

   i. I felt very confident using GEN.

   j. I needed to learn a lot of things before I could get going with GEN.

5. During the study, did you access any external resources to help you with the material on GEN?

   a. Yes (if yes, please answer question 6)

   b. No (If no, you are finished with the survey))

6. If you did indeed access external material, please list these resources below.

Objective 4: Develop an Innovative Web-Based Training and Teaching Method to Better Prepare Students for Simulation Training and Clerkship

The GEN platform was built by the research group of Dr Adam Dubrowski at Ontario Tech University. In collaboration with this research group, the platform will be further developed for our study. Each study group will have its own sector on the platform. Therefore, students from one group will not have access to the comments and web-based activity of the other groups. The pretest and the posttest performed in objective 1 will be on GEN, as will the videos uploaded by students in objective 2.

Materials

Students will require a computer with internet access and a camera.

The pretest and posttest videos will be recorded beforehand using synthetic suture pads and the following instruments: a needle holder, a sterile suture, forceps, and latex gloves.

All students will receive a suturing kit by mail composed of a synthetic suture pad, a needle holder, a sterile suture (3-0 Vicryl), forceps, and latex gloves.

Sample Size

The experiment is designed so that each of the four groups will have the same sample size. We calculated the sample size based

on our primary objective considering a balanced one-way analysis of variance (ANOVA) model. We used the GRS for the calculation.

In the study by Denadai et al [8], subcuticular sutures were assessed using the GRS among three intervention groups. The difference between the lowest mean and the highest mean was 12.25. In that study, we approximated the mean standard deviation within groups to be 1.45. We chose to set the effect size at 0.8 because we do not know the overall standard deviation for all participants. We set the power to 80% and the significance level to 0.05.

Using RStudio, we obtained a sample size of 13 participants per group and a total sample size of 52. We will include 15 participants in each group (total N=60) to have sufficient statistical power. We will invite the whole cohort of first-year medical students (n=300) and enroll the first 60 students who reply favorably.

Ethics

This study will be conducted following the Declaration of Helsinki on human research. The protocol has been approved by our institutional review board (CERSES 20-068-D). Any amendment to the protocol must be approved by this committee. A consent form will be sent to the students. Participation in this study is voluntary. Students will not be exposed to any risks apart from those inherent in the manipulation of sterile needles. This small risk will be mentioned in the consent form and is considered to be low compared to the benefits of the study.

Students' anonymity will be maintained on the GEN platform throughout the study.

Results

Data Collection

All data will be anonymous, and files will be secured with a password. In objective 1, the results of the GRS and Subcuticular Suture Checklist for all participants will be collected through GEN. In objective 2, the expert evaluating the videos will compile the data in one file that will not be published on GEN. Responses from the acceptance survey will be collected using Qualtrics XM.

Statistical Analysis Plan

First, we will perform descriptive statistical analyses to assess the distributions of the variables of interest and determine the appropriate tests to use as well as the need for a potential transformation. Continuous variables with an asymmetric distribution will be described using median (IQR). Categorical variables will be described with proportions. The remaining variables will be described with mean (SD).

In the following paragraphs, we describe our statistical plan assuming a Gaussian distribution.

Objective 1: We will perform balanced one-way ANOVA to compare mean GRS and Subcuticular Suture Checklist scores among all four groups. First, distinct analyses of the pretest and the posttest scores will be performed. Then, the mean difference between the pretest and the posttest scores will be compared using paired *t* tests if the difference between paired values is consistent.

Objective 2: We will perform balanced one-way ANOVA to compare the performance of students in executing a running subcuticular suture as assessed by the GRS and the Subcuticular Suture Checklist.

Objective 3: We will perform descriptive statistical analyses and correlate the study groups with the Likert scales using the Kruskal-Wallis equality-of-population rank test.

Analysis will be performed in RStudio version 1.2.5033 (RStudio Team) [36] and GraphPad Prism version 8.0.0 for Mac OS X (GraphPad Software) [37]. For each analysis, confidence intervals will be calculated for a 95% confidence level. Statistical hypothesis testing will be performed with an alpha threshold of .05.

Discussion

Significance

In this study, we will compare alternative learning methods of an advanced surgical skill. The role of distant peer-learning with or without the involvement of an expert will help reinvent surgical skill teaching. Also, the interactive aspect of the GEN platform will improve the students' learning experience while reducing their anxiety. Students will be able to share tips and to progress with their team from home. Students participating in this study will have the opportunity to gain suturing knowledge and to help improve surgical education.

This study has potential to create a sustainable educational method for the acquisition of advanced suturing techniques. We will develop a web-based training and teaching method to better prepare students for simulation training and clerkship, especially when there is no access to traditional training methods in the context of the COVID-19 pandemic. Another important advantage is the alleviation of the burden carried by surgical professors, who have a considerable number of responsibilities.

Our goal is to eventually allow students to upload their own videos on GEN and to interact with other students and with an academic surgeon. Learning on GEN with teammates and expert feedback is promising for students, as they can receive accurate feedback with lower risks of acquiring incorrect habits.

Study Limitations

The suturing skills of the students before this study are unknown. However, this factor is controlled because all students will be randomized. Only students in their first year of medical school are eligible to participate the study. At this stage of their education, they have not yet received any training in surgical or suturing skills. However, students who are more interested in surgery and with more experience are more likely to participate. This can lead to small effect differences between groups.

A possible limitation is that students may access external material such as other videos on the web or through practicing on their own. However, we will require students to self-report external material they have used or additional practicing they

performed. These questions will be asked in the poststudy survey. Because the students will be in their first year of medical school, they will have poor suturing knowledge. Further, the students will only have three days to complete the study and learn a practical skill, which limits the time they can spend on external platforms. Therefore, we do not believe that accessing external material will have a considerable impact on the outcomes.

Learning and practicing for three days at home is not directly comparable to the traditional method in which a single surgeon teaches suturing skills for one to three hours at a university. In this study, we aim to compare different web-based learning methods for a specific skill. Learning on GEN cannot replace the traditional method. Rather, we believe that it represents a potential adjunct and an optimal option in the context of the COVID-19 pandemic.

A vast array of gamification elements have been previously published [19-22]. However, we decided to limit the number of gamification elements used in this study and to focus on our primary objective of evaluating procedural knowledge. Further, limiting the number of gamification elements helps simplify distance learning of an advanced suturing skill for novice learners who are not familiar with that skill.

Other groups have used constructs to study distinct outcomes, such as students' fear of making mistakes, perceived knowledge of how to behave, perceived errors committed, and attitudes [38]. These subjective variables would be interesting to assess in subsequent studies as well in the surgical field. We believe that GEN could decrease students' anxiety when learning advanced suturing techniques compared to the traditional method [39]. In our study, we will assess user experience on GEN using the System Usability Scale.

Conflicts of Interest

None declared.

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Abbreviations

ANOVA: analysis of variance
GEN: Gamified Educational Network
GRS: Global Rating Scale
OSATS: Objective Structured Assessment of Technical Skills

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Protocol

An Intervention With Dance and Yoga for Girls With Functional Abdominal Pain Disorders (Just in TIME): Protocol for a Randomized Controlled Trial

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Abstract

Background: Functional abdominal pain disorders (FAPDs) affect many children worldwide, predominantly girls, and cause considerable long-term negative consequences for individuals and society. Evidence-based and cost-effective treatments are therefore strongly needed. Physical activity has shown promising effects in the practical management of FAPDs. Dance and yoga are both popular activities that have been shown to provide significant psychological and pain-related benefits with minimal risk. The activities complement each other, in that dance involves dynamic, rhythmic physical activity, while yoga enhances relaxation and focus.

Objective: This study aims to evaluate the effects of a dance and yoga intervention among girls aged 9 to 13 years with FAPDs.

Methods: The study is a prospective randomized controlled trial among girls aged 9 to 13 years with functional abdominal pain, irritable bowel syndrome, or both. The target sample size was 150 girls randomized into 2 arms: an intervention arm that receives dance and yoga sessions twice weekly for 8 months and a control arm that receives standard care. Outcomes will be measured at baseline and after 4, 8, 12, and 24 months, and long-term follow-up will be conducted 5 years from baseline. Questionnaires, interviews, and biomarker measures, such as cortisol in saliva and fecal microbiota, will be used. The primary outcome is the proportion of girls in each group with reduced pain, as measured by the faces pain scale-revised in a pain diary, immediately after the intervention. Secondary outcomes are gastrointestinal symptoms, general health, mental health, stress, and physical activity. The study also includes qualitative evaluations and health economic analyses. This study was approved by the Regional Ethical Review Board in Uppsala (No. 2016/082 1-2).

Results: Data collection began in October 2016. The intervention has been performed in 3 periods from 2016 through 2019. The final 5-year follow-up is anticipated to be completed by fall 2023.

Conclusions: Cost-effective and easily accessible interventions are warranted to reduce the negative consequences arising from FAPDs in young girls. Physical activity is an effective strategy, but intervention studies are needed to better understand what types of activities facilitate regular participation in this target group. The Just in TIME (Try, Identify, Move, and Enjoy) study

will provide insights regarding the effectiveness of dance and yoga and is anticipated to contribute to the challenging work of reducing the burden of FAPDs for young girls.

Trial Registration: ClinicalTrials.gov (NCT02920268); https://clinicaltrials.gov/ct2/show/NCT02920268

International Registered Report Identifier (IRRID): DERR1-10.2196/19748

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KEYWORDS

dance; functional abdominal pain; functional abdominal pain disorders; irritable bowel syndrome; physical activity; randomized trial; study protocol; yoga

Introduction

Functional abdominal pain disorders (FAPDs) [1,2] affect 13.5% of school-aged children worldwide [3] and are associated with low quality of life [4]. The prevalence is substantially higher among girls (15.9%) than boys (11.5%) [3]. The negative consequences of FAPDs, such as absence from school [4,5], depression [4,6], and high consumption of medical care [7], pose a considerable burden on children and their families. It is common for pain to be sustained throughout the school years [8-11]. Furthermore, somatic symptoms in childhood predict severe mental illness in adulthood [12]. Specifically, FAPDs in childhood can lead to long-term vulnerability to anxiety later in life, even if abdominal pain resolves [13]. Children need early treatment and preventive strategies to address these symptoms [14] regardless of the presence of co-occurring mental health disorders [12].

For almost 90% of children with chronic abdominal pain, no explanatory organic cause can be identified [15], and psychosocial factors contribute to the development and maintenance of the disease [16]. The predisposing factors and pathophysiological mechanisms of FAPDs include visceral hypersensitivity, altered gastrointestinal motility, and changes in intestinal microbiota, as well as stressful events [3,17], mental health issues, and negative experiences, such as bullying [18]. These children are likely to have poor coping strategies for stressful situations [19]. Thus, interventions and therapeutic modalities that address stress reduction are frequently discussed [3].

There is currently no convincing evidence for treatment or symptom relief with pharmaceuticals [17,20-22] or dietary treatment [23]. Nonpharmacological interventions, such as hypnotherapy and different types of cognitive behavioral therapy (CBT), have shown both short- [17,19,24] and long-term pain relief for children with FAPDs [24]. However, many of these interventions are time-consuming or require specially educated staff [17]. Effective strategies for managing FAPDs in children include reducing both parent and child concerns about the seriousness of the condition and, instead of striving for total pain relief, reducing the disability associated with pain [25] and improving the quality of life for the child [25-27].

Physical activity has been shown to be effective in the practical management of FAPDs [18] by distracting from the pain and improving function. Unfortunately, levels of physical activity among young girls is alarmingly low, which calls for action [28]. Dance is a popular physical activity among young girls [29] that can positively influence physical health outcomes [30], motor skills [31], and psychological well-being [32,33]. Through the expressive, creative, and aesthetic aspects of physical activity, dance holds potential to enhance body awareness and improve poor body image, which in turn strengthens self-esteem [34,35]. In a social context, dance is a cost-effective intervention [36] that can reduce somatic and emotional stress-related problems [37], increase self-rated health [38], and enhance self-esteem [39] and feelings of enjoyment and energy [40-42]. For girls aged 8 to 12 years, multicomponent interventions including dance can lead to improvements in psychological well-being, perceived self-efficacy, and physical self-confidence [43]. Although more research is needed, dance has also been proven to help decrease pain, both for young people [44] and adult women [45-47].

Yoga is a psychophysiological practice with a focus on posture, controlled breathing, and attention [48]. For children, yoga has been shown to improve focus and emotional regulation [49] and to effectively reduce anxiety [50,51] and depression [52]. Yoga has also gained popularity in the treatment of pediatric FAPDs [27,53-55]; studies have shown reductions in abdominal pain frequency [56], pain intensity [56,57], and school absence [57]. For children with irritable bowel syndrome (IBS), yoga has been shown to improve quality of life and physical functioning [58,59] and reduce IBS symptoms [58-60], but more research is needed [20].

A combination of physical and mental training has been shown to be beneficial in reducing stress and increasing quality of life [61]. Coupled together, studies indicate a potentially higher effectiveness than one modality alone [61,62]. Choreographed dance routines to popular music combined with calm breathing meditation has been shown to decrease symptoms of depression and anxiety for homeless women [63].

Dance and yoga have been acknowledged in recent research as pain management for young girls [64] and are both noncompetitive activities that can appeal to girls, which in turn can positively impact participation rates [65]. Dance and yoga can complement each other because dance involves dynamic, rhythmic physical activity, while yoga enhances relaxation and focus [66]. Both dance and yoga focus on body awareness, which has been shown to provide significant psychological and pain-related benefits with minimal risk [67,68], and can also meet young people's desire to self-manage symptoms with accessible treatment options and to take a more active role in their own care [69]. However, more controlled trials of nonpharmacological interventions are warranted [70], especially

for stress-modulated conditions in youth [67]. The novelty of the intervention type and the vulnerability of the target group call for extensive investigation, which we aim to accomplish with a longitudinal randomized design and different methodologies. To our knowledge, dance and yoga for children with FAPDs have not previously been studied.

The overall aim of the study is to evaluate the effects of a dance and yoga intervention among girls aged 9 to 13 years with FAPDs.

Methods

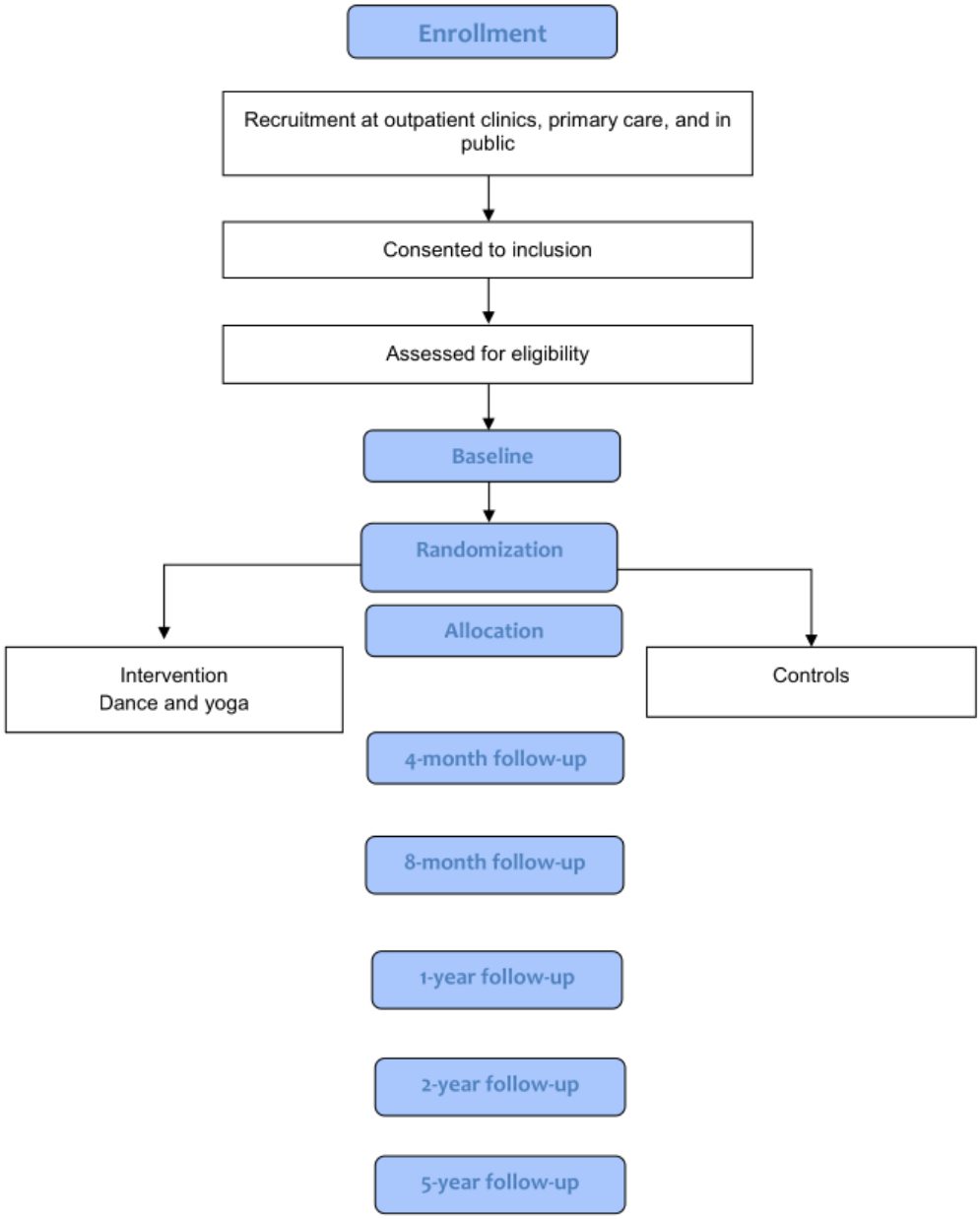
Approval and Registration

The study was approved by the Regional Ethical Review Board in Uppsala (No. 2016/082 1-2) and is registered on ClinicalTrials.gov (NCT02920268). Any protocol modifications will be communicated to relevant parties.

Study Design

This study, called Just in TIME (Try, Identify, Move, and Enjoy), started in 2016 when the first intake was performed and will end in 2023. The study is a prospective randomized controlled trial with 2 parallel groups—an intervention group and a control group—of girls aged 9 to 13 years with functional abdominal pain, IBS, or both. The intervention consists of dance and yoga sessions 2 times a week for 8 months. The control group receives standard care as school health care or primary care. The outcomes are measured at baseline and after 4, 8, 12, and 24 months. A long-term follow-up will be performed 5 years from baseline (Figure 1). At all follow-ups, data are collected for both the intervention and control groups. The trial is being conducted in 2 cities in Sweden.

Figure 1. Flowchart of the protocol.



The study follows the standard methodology of intervention research. This protocol is conducted according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [71], and the description of the intervention follows the TIDieR (Template for Intervention Description and Replication) checklist and guide [72]. The study will be reported according to the CONSORT (Consolidated Standards of Reporting Trials) guidelines [73], COREQ (Consolidated Criteria for Reporting Qualitative Research) [74], and CHEERS (Consolidated Health Economic Evaluation Reporting Standards) [75].

Study Population

According to international guidelines (Rome IV), FAPDs include functional dyspepsia, IBS, abdominal migraine, and functional abdominal pain not otherwise specified with persisting symptoms 2 months prior to diagnosis [1]. The previous term for these diagnoses according to Rome III was abdominal pain-related functional gastrointestinal disorders (FGIDs) [2].

The Rome III criteria provided the current guidelines during the time of the first study inclusion. The study population includes girls diagnosed with functional abdominal pain or IBS according to the Rome III criteria [2] and with persistent pain after examination at the pediatric center. The girls were aged 9 to 12 years during the first year for intake and 9 to 13 years during the second and third intake years.

Inclusion Criteria

Inclusion criteria followed the diagnostic criteria for childhood functional abdominal pain in Rome III [2]: (1) episodic or continuous abdominal pain at least once per week for at least 2 months before diagnosis; (2) insufficient criteria for other FGIDs; and (3) no evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the patient's symptoms.

The following criteria were tested to exclude other illnesses: (1) physical examination including normal growth pattern and (2) laboratory screening, including serological screening with immunoglobulin A antibodies against type 2 (tissue) transglutaminase (TGA-IgA), complete blood cell count, erythrocyte sedimentation rate or C-reactive protein, and urine analysis. A fecal calprotectin test was also included if the girl reported symptoms such as diarrhea.

Diagnostic criteria for IBS in Rome III [2] were used. First, at least once per week for at least 2 months before diagnosis, the patient must have had abdominal discomfort or pain associated with 2 or more of the following at least 25% of the time: (1) improved with defecation, (2) onset associated with a change in the frequency of stool, or (3) onset associated with a change in the form (appearance) of stool. Second, there must be no evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the patient's symptoms.

The following criteria were tested to exclude other illnesses: (1) physical examination including normal growth pattern and (2) laboratory screening including serological screening with TGA-IgA, complete blood cell count, erythrocyte sedimentation rate or C-reactive protein, and urine analysis. A fecal calprotectin test was also included if the girl reported symptoms such as diarrhea.

Persistent pain after examination at the pediatric center was measured with a pain diary at baseline. Girls who reported one or more episodes of pain with a pain score of 4 or higher on the faces pain scale-revised (FPS-r) [76,77] during a full week were eligible for the study.

Exclusion Criteria

The exclusion criteria for this trial were (1) contemporaneous celiac or inflammatory bowel disease; (2) difficulty following oral instructions, such as hearing impairment, mental retardation, or language difficulties; (3) simultaneous treatment with CBT; and (4) severe psychological symptoms for which other treatment is needed.

Recruitment

Participants were recruited from outpatient clinics, primary health care services, and the public.

We recruited participants from the outpatient clinics of the pediatric departments at the university hospitals in Örebro, Karlskoga, and Lindesberg, Sweden. In the second recruitment year, participants were also recruited from the pediatric outpatient clinic in Västerås, Sweden. All girls aged 9 to 13 years (9 to 12 years during the first year of the study) who had visited one of the outpatient clinics during the previous 2 years because of abdominal pain and had received a diagnosis of IBS, functional abdominal pain, constipation, or abdominal pain received an information letter asking whether they wanted to join the study. All participants were found via local diagnosis registries at the included hospitals. After written consent was received from the legal guardians, the diagnosis according to the inclusion criteria was verified in the medical records or by examination by a pediatrician.

In addition, we recruited girls from primary health care services in the region of Örebro and Västerås. Information letters were delivered to potential participants and their legal guardians in primary care, the counselling unit, and school health services. Interested girls and their legal guardians contacted the research team, who distributed an information letter and the consent form. After written consent was obtained, the research team booked an appointment for an examination at the pediatric clinic (Örebro) or research clinic (Västerås).

Information about the study project was provided by several information channels, such as social media, ordinary media, and websites. Interested girls and their legal guardians contacted the research team, who distributed an information letter and the consent form. After written consent was obtained, the research team booked an appointment for an examination at the pediatric clinic (Örebro) or research clinic (Västerås).

Girls and their legal guardians who consented to the study and were eligible for the study according to the inclusion criteria completed the baseline measurement.

Randomization

When the baseline measurement was completed and the eligibility check was accomplished, the sample was randomized into an intervention group and a control group. Randomization was performed by an external statistician using minimization based on pain intensity and age at baseline [78].

Sample Size

The total number of required study participants was calculated for the primary outcome (decreased maximal pain after 8 months). The calculation was based on several assumptions. First, we considered the expected proportion of participants who decreased their maximal pain after 8 months in the intervention group. We estimated that 30% of the intervention group would decrease their maximal pain after 8 months based on previous research with CBT, in which approximately 50% of participants were pain free immediately after the intervention [79]. Second, we calculated the expected proportion of participants whose maximal pain would decrease after 8 months in the control group. In previous CBT studies, approximately 25% of control participants reported being pain free when the intervention ended [79]. Since only girls with a long duration of abdominal pain were included in the present study, we estimated that the placebo effect would be smaller and that 10% of the girls in the control group would report decreased maximal pain at the 8-month follow-up. Third, dropout is a common problem that can bias outcomes. A 20% to 50% dropout rate is commonly reported in studies of participants with long-lasting pain [80]. In the present study, a 20% dropout rate was estimated.

With a power of 80% and a significance level of .05, we calculated the sample size to be N=150 (75 intervention + 75 control participants), including a 20% dropout. To decrease bias, a minimum of 50 participants in each group is recommended in trials studying intervention effects on pain, according to previous literature [80].

Intervention

The description of the intervention follows the TIDieR checklist and guide [72].

Name and Rationale

The intervention is called Just in TIME and addresses the importance of early intervention for this target group. The word “TIME” stands for “Try, Identify, Move, and Enjoy,” which also characterizes the key aspects of the intervention, which aims to decrease FAPDs among 9- to 13-year-old girls through dance and yoga. Essential elements of the intervention included a focus on enjoyment, socialization, and playful creativity in an undemanding environment. We chose a combination of dance and yoga because of experiences from an earlier study [38] that targeted adolescent girls with internalizing problems and evaluated a dance intervention. The study participants appreciated the intervention and rated it to be a positive experience [38], but at the end of the intervention period, they started to request yoga as an add-on at the end of the sessions. They believed that it would be a valuable closure to the session to help them tune in to the relaxation. These requests were a form of evaluation that the research team took into account when designing the current study.

Materials

Informational material was distributed during the training of the intervention providers. It consisted of written course materials and visually recorded practical choreography and sequences, all provided by the intervention coordinator.

Procedures

The intervention was performed as a group activity twice a week after school hours during an 8-month period. The duration of the class was 60 minutes, comprising 30 minutes of dance practice, 25 minutes of yoga including relaxation, and 5 minutes of short reflection (Table 1). Throughout the intervention period, the participants were encouraged to practice their favorite dances, yoga poses, or relaxation techniques at home if they wanted to. Both centers followed the same routine.

Table 1. The 60-minute Just in TIME dance and yoga class.

Minutes	Section	Description
10	Dance: warm-up	The warm-up section aimed to get the participating girls to be active and take part in the social cohesion. It included up-tempo music with prominent drum beats and captivating rhythm. Expansive, easy, accessible movements activated large muscle groups.
20	Dance	The dance choreography section included mostly structured dance as a group under the guidance of an instructor but also included improvisation and playful exploration of movement. The focus was on enjoyment and socialization rather than performance. The intention was to offer an opportunity to experience one's own body in a positive way with popular music in an undemanding and supportive atmosphere as well as to increase heart rate with moderate-to-vigorous physical activity. • Month 1-2: Focus on experiencing joy of movement, feeling safe, and getting to know each other. Dance style: show jazz. • Month 3: Focus on expansive movements, "claiming space," determination, and integrity. Dance style: show jazz and street dance. • Month 4: Focus on body awareness, slow movements, and grace. Dance style: jazz and contemporary dance. • Month 5-6: Focus on increasing energy and working together as a group in the choreography. Dance style: show jazz. • Month 7-8: Focus on enjoyment and meeting variations in the dance movements (high-low, firm-soft, and expansive-small variations). Dance style: show jazz and floor work.
20	Yoga	The yoga section focused on playful movements, such as creative yoga storytelling combined with asanas (body poses), a focus on breathing, and attention. Asanas were performed individually or in pairs and, when appropriate, together as a group. • Month 1-2: *balasana* (child's pose), *marjaryasana* (cat pose) and *bitilasana* (cow pose), *parsva sukhasana* (seated side bend pose), *uttanasana* (standing forward bend), *upavistha bitilasana marjaryasana* (seated cat-cow pose), *jathara parivrtti* (revolved abdomen twist pose) • Month 3: *parivritta sukhasana* (sitting twist pose), *parsvaparvatasana in tadasana* (standing side bend), *uttanasana* (standing forward bend), *sufi grind* (seated torso circles), *paranamuktasana* (knees to chest), *jathara parivrtti* (revolved abdomen twist pose) • Month 4: *virabhadrasana* II (warrior II), *ardha chandrasana* (half-moon pose), *ardha setubandhasana* (half-bridge pose), *adho mukha sukhasana* (easy pose forward bend), *upavistha bitilasana marjaryasana* (seated cat-cow pose), *jathara parivrtti* (revolved abdomen twist pose) • Month 5-6: *vrksasana* (tree pose), *utthita trikonasana* (extended triangle pose), *upavista konasana* (seated wide angle posture), *adhomukha svanasana* (downward-facing dog posture), *balasana* (child's pose), *paranamuktasana* (knees to chest), *sufi grind* (seated torso circles), *jathara parivrtti* (revolved abdomen twist pose) • Month 7-8: extended focus on creative yoga storytelling in group, *phalakasana* (plank pose), *adhomukha svanasana* (downward-facing dog posture), *bhujangasana* (cobra pose), *ardha setubandhasana* (half-bridge pose), *jathara parivrtti* (revolved abdomen twist pose)
5	Relaxation	*Pranayama* (slow deep breathing and attention to the breath), *savasana* (corpse pose), guided relaxation to increase calmness, and lying down with blankets. During the relaxation, a brief massage on the shoulders was offered by the instructors (voluntary).
5	Reflection	Finally, a short voluntary sharing session was held while seated in a circle, highlighting a positive experience during this particular class.

Intervention Providers

Each group included 7 to 14 girls and was under the guidance of 2 instructors, one at a time. The instructors had a profession in either health care or pedagogy, had experience working with young people, and were educated in teaching children or adolescents in dance (instructor training) and yoga (ie, registered yoga teacher 200-hour training). Prior to the start of the intervention, all instructors attended a 2-day course administered by the research team. This course consisted of practical instructions from the intervention coordinator about the dance and yoga session according to the standardized program design, including dance choreographies and yoga sequences adjusted to the target group as well as teaching style (nonjudgmental and supporting approach). Lectures about theories and underlying mechanisms and about guidelines and ethical aspects regarding children with FAPDs were also given.

Modes of Delivery

Various styles of dance with a focus on enjoyment were performed during the intervention period. The yoga practice consisted of both playful movements (such as creative yoga storytelling) and calm physical postures with a focus on breathing and attention, which were performed individually, in pairs, and as a group. The intervention (further described in Table 1) was developed by the intervention coordinator (author AD). To ensure standardization in program delivery across both centers and between instructors over time, booster sessions were given 3 times during the intervention period (in addition to the initial 2-day course). The participants in the intervention were advised to wear practical soft clothes suitable for the activity, and no special shoes were needed.

Locations

The intervention took place in studios located in the center of Örebro and Västerås, Sweden, which were easily accessible by bus or walking. The studios had yoga mats and music equipment.

Frequency and Duration

The 8-month period was chosen because it corresponded to 2 school semesters. No classes were held during holidays; thus, 50 dance classes were held over 25 weeks. The practice can be classified as moderate-to-vigorous physical activity.

Tailoring and Modification

To address modifications, both dance and yoga movements were introduced in steps to include all participants regardless of previous experience. Alternatives were given when needed. No changes were made in the intervention.

Adherence

Adherence to the dance and yoga intervention was noted by the instructors. A strategy to maintain and improve fidelity was to consciously focus on relatedness and provide a feeling of social inclusion, supportiveness, and the chance to meet new friends. To keep the dance and yoga sessions interesting over the time period, a variety of styles and themes were presented, all distributed by the intervention coordinator. The intervention was delivered as planned throughout the 3 intervention years.

Outcomes

This study includes biochemical and physiological measures, questionnaires (for the girls in the study and their legal guardians who answer questions about their daughters as a proxy), and qualitative interviews (with both the girls in the study and their legal guardians) (Figure 2). The questionnaire sessions are performed at the research centers, and the project team provides assistance. To retain as many participants as possible, reminder mail and emails are sent to participants. Notes about participants who discontinue or deviate from the study are made.

Figure 2. Enrollment, interventions, and assessments. An "X" represents a child report and an "O" represents a legal guardian report. The PACES, enjoyment rating scale, and experiences questions were only asked to the girls in the intervention group. BSC: Bristol stool chart; ChilD-S: Children's Depression Screener; CSSI-24: Children's Somatic Symptoms Inventory-24; EQ-VAS: EuroQol visual analog scale; FPS-r: faces pain scale-revised; LH-YP: Life and Health – Young People; PACES: Physical Activity Enjoyment Scale.

	Enrollment	Baseline and allocation	Postallocation				
Time point	**Month –1**	**Month 0**	**Month 4**	**Month 8**	**Month 12**	**Month 24**	**Month 60**
Enrollment							
Eligibility screen	X						
Informed consent	X						
Baseline		X					
Allocation		X					
Interventions							
Intervention: dance and yoga		X	♦	———	♦		
Control: standard care		X					
Assessments							
FPS-r		X	X	X	X	X	X
CSSI-24		XO	XO	XO	XO	XO	XO
Pain drawings		X	X	X	X	X	X
Feces		X		X			
BSC		X	X	X	X	X	X
LH-YP somatic and psychosocial		XO	XO	XO	XO	XO	XO
Self-rated health		XO	XO	XO	XO	XO	XO
ChilD-S		X	X	X	X	X	X
LH-YP mental health		XO	XO	XO	XO	XO	XO
Salivary cortisol		X	X	X			
LH-YP sleep habits		O		O	O		
School attendance		XO	XO	XO	XO	XO	XO
Accelerometer		X		X			
PACES			X	X			
Enjoyment ranging scale			X	X			
Experiences				XO			
Kidscreen		X	X	X	X	X	X
EQ-VAS		X	X	X	X	X	X
Resource use		XO	XO	XO	XO	XO	XO
LH-YP food habits		XO	XO	XO	XO	XO	XO
Covariates		XO					

Primary Outcome Measure

The primary outcome is the proportion of girls in each group who have reduced maximal pain, measured immediately after the intervention (8-month follow-up) with the FPS-r [76,77] in a pain diary in which the girls register their abdominal pain 3 times a day for 1 week. The psychometric features for the FPS-r are reported to be good [77].

Secondary Outcome Measures

Abdominal Pain and Gastrointestinal Issues

Abdominal pain is measured with the pain diaries with the FPS-r [76,77].

Abdominal pain is also measured in the questionnaires with a subscale in the Children's Somatic Symptoms Inventory-24 (CSSI-24) (formerly known as the Children's Somatization Inventory) [81-84]. The CSSI-24 is a valid and reliable instrument that assesses a variety of nonspecific somatic symptoms [81].

Pain drawings are used to elicit information about the location of pain symptoms [85,86]. A growing body of evidence supports pain drawings as an assessment of pain among children [85].

Fecal samples were collected at baseline and at 8 months for measurement of the intestinal bacterial composition. This is an important background variable that can affect how effective the intervention is for a participant and thus has prognostic significance for the treatment outcome [87].

The Bristol stool chart (BSC) is a well-recognized tool designed to classify the form and consistency of feces into 7 categories [88]. It is used in both clinical and experimental fields [89] and has been used to assess the intestinal transit rate. Normal stool consistency is considered type 3 to type 5 on the BSC [90].

Other Somatic Symptoms

Other somatic symptoms are measured with the CSSI-24 [81-83].

Somatic and psychosocial symptoms are also measured with questions from a well-used Swedish survey, Life and Health – Young People (LH-YP) [91]. The questions are in line with the types of questions used in the Health Behavior in School-aged Children study, a cross-national study coordinated by the World Health Organization's Regional Office for Europe [28].

General Health

Self-rated health is measured with a single question: "How do you rate your general health?" The response options range from 1 to 5 (1=very poor, 2=poor, 3=neither good nor poor, 4=good, and 5=very good) [92]. It has been proven to predict mortality and morbidity [93] and to be a valid and reliable item [93,94].

Mental Health and Stress

Depressive symptoms are measured with the Children's Depression Screener (ChilD-S). The ChilD-S is an 8-question validated screening instrument for depressive symptoms designed for children aged 9 to 12 years [95,96]. The recommended cutoff for depression is ≥13 when the child is investigated in psychiatric or psychosomatic care, according to the Swedish translation of the ChilD-S.

The questionnaires also include 8 questions about stress, anxiety, mood, and happiness. These questions are derived from the LH-YP [91].

Stress was also measured with salivary cortisol. Saliva was collected using oral polymer swabs and tubes (Salimetrics LLC). To measure the morning and evening components of the cortisol circadian rhythm, saliva was sampled as soon as possible after awakening while still in bed in the morning and at least 1 hour after last food intake in the evening on a weekday. Collection times were noted. Saliva cortisol has previously been used as a marker of stress for infants, youth, and adults within the research group (eg, with 11- to 12-year-old girls) [97]. The samples were centrifuged and stored at –20 C in the university hospital in Örebro and then sent on dry ice to the laboratory at the university hospital in Linköping, where they will be analyzed using a commercial enzyme immunoassay method (Salivary Cortisol Enzyme Immunoassay Kit; Salimetrics LLC) [98]. The results will then be sent back to Örebro University Hospital for evaluation.

Sleeping Habits

Questions regarding sleeping habits are derived from the LH-YP [91].

School Attendance and Function

School attendance and function are measured with 2 questions created by the research group.

Physical Activity

A direct measurement of physical activity was obtained using accelerometers with 3 axles (GT3X; ActiGraph) [99]. The participating girls were instructed to wear the accelerometer for 7 days while they were awake.

Enjoyment

The validated Physical Activity Enjoyment Scale (PACES) was customized for dance and yoga in this study. PACES was originally developed to measure enjoyment of physical activity and contains 16 items [100,101].

Enjoyment of the intervention was also evaluated with a graphic rating scale [102], which has been proven to have good consistency and stability [103]. The question was "How do you experience dancing/yoga/relaxation while you perform it?" The rating scale ranges from entirely negative to entirely positive.

Experiences

To investigate the girls' experiences of their participation in the intervention and the legal guardians' experiences of how the girls were influenced by participating in the intervention, qualitative interviews were conducted a few weeks after the intervention ended. The interviews were face-to-face, with the girl and her legal guardian interviewed separately, and semistructured. They were conducted by the same team each year for internal consistency. The interviews were based on open-ended questions from an interview guide, and participants were encouraged to speak freely about their experiences. Prompts (eg, "Could you tell me more?") were used to obtain richer material.

Quality of Life

Quality of life (QOL) is measured with the Kidscreen-10 index [104], which is an instrument with good psychometric features that assesses children's and adolescents' subjective health and well-being. It is used in public health and clinical medicine disciplines in multiple countries. An algorithm for mapping the

Kidscreen-10 index onto the Child Health Utility Index 9D (CHU9D) utility scores will be used [105].

QOL is also measured with the EuroQol visual analog scale, which represents health status at the moment of evaluation and ranges from 0 (extremely bad) to 100 (excellent quality of life) [106]. Its validity and reliability are reported to be good [107,108].

Resource Usage

Both the girls and their legal guardians are asked about resource consumption, such as visits to primary care, school health care, and other open care. These questions were created by the research group.

Food Habits

Questions about food habits were derived from the LH-YP [91].

Covariates

To assess covariates, we asked about (1) demographics; (2) parental abdominal and gastrointestinal morbidity; (3) the girl's background, including mode of delivery (caesarean or vaginal), antibiotic consumption early in life, dance and yoga experiences, menarche, etc; and (4) safety at home, in school, during leisure time activities, on social media, and at other places were the girls spend their time.

Analyses

Statistical Analysis

The Just in TIME study follows the intention-to-treat paradigm. Complementary analyses will be performed per protocol and according to the number of sessions the participant attends.

For baseline statistics between the groups, descriptions will be constructed using frequencies and proportions for categorical data and means and standard deviations for continuous variables. Baseline characteristics will be compared using the Fisher exact test for dichotomous outcomes, the Mantel-Haenszel chi-square test for ordered categorical outcomes, and the Mann-Whitney U test or unpaired *t* test for continuous outcomes. A *P* value of <.05 for the 2-tailed test will be considered statistically significant for all outcomes. When deemed necessary, correction for multiple significance will be performed.

The primary outcome analysis will initially be performed using a Fisher exact test to evaluate differences between groups. To analyze the change in scores from baseline between groups for approximately normally distributed variables, a repeated-measures covariance pattern mixed model will be used, adjusting for significant differences at baseline. To identify predictive factors at baseline that might be associated with the primary outcome, a univariable logistic regression analysis followed by a stepwise multiple logistic regression analysis will be performed.

The distribution of continuous variables will be described using the mean and standard deviation or median and interquartile range. Categorical variables will be described with numbers and percentages.

Study participants who choose to leave the intervention before the study is finished are encouraged to complete all assessments. Missing data will be handled with multiple imputations or within the mixed model.

Cortisol Analyses

To study the difference between morning and evening values, the evening-morning cortisol quotients will be calculated by dividing each girl's evening cortisol value by the morning cortisol value. To study potential changes in evening-morning cortisol quotients between baseline and 4 and 8 months, the median change score will be calculated by subtracting baseline cortisol morning samples from 4-month morning cortisol samples and 8-month morning cortisol samples, and the same procedure will be performed for the evening samples.

Feces Analyses

Participants received a kit containing everything needed to perform the fecal test at home. The test was stored in the freezer at home for approximately 1 week and was subsequently delivered to the research team in a small freezer bag. The samples are stored at –80 C at the university hospital in Örebro, and analyses of the intestinal microbiota and short-chain fatty acids will be performed.

Analyses of Physical Activity

The frequency of the accelerometer collecting data will be set to 30 Hz. Data will be processed in ActiLife (version 6.13.4; ActiGraph). Raw data from the accelerometers will be converted to 10-second epochs. Valid wear time will be considered to be at least 480 minutes per day, and minimum valid days will be set to 4 days, including 2 weekdays and 1 weekend day. Total counts per day, sedentary time, and activity of moderate or higher intensity will be measured.

Qualitative Analyses

The interviews will be transcribed verbatim and analyzed with inductive content analysis, as described by Elo and Kyngäs [109]. The analysis process will initially include getting to know the material, generating codes, and identifying categories. Data will be analyzed using the NVivo software program (QSR International) for qualitative data analysis [110]. All of the authors will discuss the coding process until it is agreed upon and the codes will be grouped into subcategories that reflect the core message of the interviews. Thereafter, the subcategories will be abstracted into generic and main categories [109].

Health Economic Analysis

The health economic evaluation will be performed as a cost-utility analysis using individual data [111]. Societal costs (including health care, informal care, and school health care) will be considered. Gained quality-adjusted life-years (QALYs) will be used to measure the effects. QOL will be measured with Kidscreen-10 [104], and an algorithm for mapping the Kidscreen-10 index onto the CHU9D utility scores will be used [105]. Questions about resource use and QOL are asked to both girls and their legal guardians at all follow-ups. Cost-effectiveness ratios will be based on the changes in QALY and net costs for the intervention group compared with the control group. The results will be presented as an incremental cost-effectiveness ratio (ICER), which is expressed as ICER = (Ca – Cb)/(Ea – Eb), where "Ca" is the cost of the intervention,

Cb is the cost of the comparator, Ea is the effectiveness of the intervention, and Eb is the effectiveness of the comparator.

Ethics and Dissemination

The study is conducted in accordance with the standards of Good Clinical Practice and in agreement with the Declaration of Helsinki, and it is approved by the Regional Ethical Review Board in Uppsala, Sweden (No. 2016/082 1-2). Since all participants are younger than 15 years, written informed consent was provided by legal guardians. The information letter included written information about the study, including the purpose and procedures, the voluntary nature of participation, and the option to withdraw at any time. The participants are also guaranteed confidentiality and secured data storage. In addition, all legal guardians and the girls in the study were invited to an information meeting before the start of the study, where verbal explanations of all the procedures were given.

Any adverse events or harm arising from study participation will be reported and managed by the instructors and the research team in accordance with ordinary health care routines. All participants who report 13 or higher on the ChilD-S [95] are offered a clinical evaluation with a psychologist or a psychiatrist and, if needed, are referred to other health care resources, such as the school health service or child and adolescent psychiatry care, without further engagement in the study.

Data are collected in both pen-and-paper and digital formats and securely stored at the University Health Care Research Center. The questionnaire was pretested on an age-appropriate group to determine whether the wording and length of the questionnaire were appropriate for the study's target group. No unauthorized persons have access to the collected data, either throughout or after the conclusion of the study.

All samples collected in this study are registered in a biobank in Region Örebro County and handled according to the current biobank laws and regulations. The samples are coded to protect the study participants' identification. All samples and the code list are stored securely and separately to prevent unauthorized persons from having access to them.

Patient and Public Involvement

A number of girls aged 9 years were involved in composing the questionnaire, selecting research questions, and the developing the intervention. Patients and the public were not involved in the development of the study design, overall measures, recruitment, or conducting of the study. The final results of this study will be disseminated to participants through presentations by the research team at health care and community forums.

Results

Ethical approval was received in March 2016 and the data collection began in October 2016.

In total, 172 participants were recruited in 3 waves and the intervention was performed in 3 periods from 2016 through 2019. In summary, 121 girls were eligible and allocated. A total of 64 participants were allocated to the intervention group, and 57 participants were allocated to the control group. Data collection of the postintervention follow-ups are ongoing and the final 5-year follow-up will be completed by fall 2023. We expect to publish the first results of the study in the beginning of 2021.

Discussion

Considering that FAPDs are prevalent among young girls, cost-effective and easily accessible interventions are warranted to reduce the negative consequences arising from these disorders. Physical activity is an effective strategy, but intervention studies are needed to better understand what types of activities facilitate regular participation for this target group. This study will provide new insights regarding the effectiveness of dance and yoga as an active and health-strengthening intervention for girls aged 9 to 13 years with FAPDs. To our knowledge, this is the first study to investigate the influence of these activities combined in an after-school setting.

Worth mentioning is that the current study cannot determine whether one part of the intervention had a greater effect than another. The aim was to evaluate the combination of dance and yoga and the effect of the entire intervention. The supportive group setting, the instructors, the music, or specific parts of the intervention may influence the health effects in different ways. Additionally, it is possible that behavior change alone (ie, engaging in a new organized activity) could contribute to changes in abdominal pain. As always, when testing complex interventions, there are many factors that can affect the outcomes. However, this is also the fact in clinical and real-life situations, and we have chosen a randomized design to account for confounding factors as much as possible.

Methodological strengths of the study include the randomized controlled design, the preregistration in a clinical trials registry, the long follow-up, and the combination of quantitative and qualitative measures. We also verified the FAPD diagnosis with an examination and laboratory evaluation performed by experienced physicians before including the participants in the study.

Several aspects of our trial design are worth noting as potential limitations. The timing of the intervention period followed the Swedish school year, which meant that we conducted the baseline measurement after the summer holiday, when the symptoms from FAPDs can be lower than at other times during the school year. This may have resulted in somewhat inflated exclusion rates, as some girls did not reach the inclusion criteria at the time point for inclusion. Moreover, due to the age of the target group, we need to rely on legal guardians to assist with data collection, which might influence the outcome. There is a possibility that girls with more engaged legal guardians could be overrepresented in the study groups. Intervention logistics, such as avoiding conflicts between the dance and yoga class and the participants' school curriculum and offering the intervention in an easily accessible studio, are worth considering in future research and in dissemination plans if the activity is being implemented in usual care.

In addition, regarding the biomarker and physiological measures (saliva cortisol, feces, and accelerometer data), we cannot verify

how meticulously the participants followed the prescribed guidelines.

The results from this study will broaden the knowledge of how nonpharmacological interventions can be valuable for overcoming the future challenge of reducing the burden of FAPDs for young girls and their families. Combined dance and yoga could be an example of an easy-access joyful intervention with promise as a complementary treatment.

To conclude, this randomized controlled study with 150 participants will investigate the effects of combined dance and yoga in girls with FAPDs. The primary aim is to study the effects of the intervention on abdominal pain, but several other aspects of FAPDs in young girls will also be studied. The results from this intervention study may provide useful information for caregivers in school health care, primary health care, and pediatric outpatient clinics.

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Authors' Contributions

AP prepared the manuscript, coordinated the study during the first year, and is the corresponding author. AD prepared the manuscript, was responsible for the intervention (intervention coordinator), and coordinates the study. All authors (AP, MM, LE, ME, ULF, EM, SS, and AD) are steering committee members; contributed to the design of the study, the inclusion of study participants, and the writing of the manuscript; and have read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

BSC: Bristol stool chart
CBT: cognitive behavioral therapy
CHEERS: Consolidated Health Economic Evaluation Reporting Standards
ChilD-S: Children's Depression Screener
CHU9D: Child Health Utility Index 9D
CONSORT: Consolidated Standards of Reporting Trials
COREQ: Consolidated Criteria for Reporting Qualitative Research
CSSI-24: Children's Somatic Symptoms Inventory-24
FAPD: functional abdominal pain disorder
FGID: functional gastrointestinal disorders
FPS-r: face pain scale-revised
IBS: irritable bowel syndrome
ICER: incremental cost-effectiveness ratio
LH-YP: Life and Health – Young People
PACES: Physical Activity Enjoyment Scale
QALY: quality-adjusted life-years
QOL: quality of life
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TGA-IgA: immunoglobulin A antibodies against type 2 (tissue) transglutaminase
TIDieR: Template for Intervention Description and Replication

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Protocol

An Intervention to Enhance Social, Emotional, and Identity Learning for Very Young Adolescents and Support Gender Equity: Protocol for a Pragmatic Randomized Controlled Trial

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Abstract

Background: The onset of puberty is a pivotal period of human development that is associated with significant changes in cognitive, social, emotional, psychological, and behavioral processes that shape identity formation. Very early adolescence provides a critical opportunity to shape identity formation around gender norms, attitudes, and beliefs before inequitable gender norms are amplified during and after puberty.

Objective: The aim of the Discover Learning Project is to integrate strategic insights from developmental science to promote positive transformation in social, emotional, and gender identity learning among 10- to 11-year-olds in Tanzania. Through a pragmatic randomized controlled trial, the intervention scaffolds the development of critical social and emotional mindsets and skills (curiosity, generosity, persistence, purpose, growth mindset, and teamwork) delivered by conducting 18 after-school, technology-driven, experiential learning sessions in small, mixed-gender groups.

Methods: The Discover Learning Intervention is a 3-arm randomized controlled trial that will be delivered to 579 participants selected from four public primary schools in Temeke District, Dar es Salaam, Tanzania. Randomization will be done at the individual level into 3 treatment groups receiving incremental intervention components. The treatment components include Discover Learning content curated into child-friendly videos, facilitated discussions, and a parent-child workbook, to be implemented over two phases, each 6 weeks long. A baseline survey will be administered to participants and their parents prior to the intervention. The process will be observed systematically, and data will be collected using surveys, in-depth interviews, observations, and focus group discussions with adolescents, parents, teachers, and facilitators conducted prior, during, and after each implementation phase.

Results: This study builds on formative and pilot studies conducted with the target population to inform the design of the intervention. The results will generate new evidence that will inform strategies for achieving scale in Tanzania and provide insights for replication of similar programs that are invested in gender-transformative interventions in peri-urban, low-resource settings.

Conclusions: The Discover Learning Intervention makes an important contribution to the field of adolescent developmental science as an intervention designed for very young adolescents in a low-resource setting.

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KEYWORDS

developmental science; adolescence; adolescence interventions; gender norms; developmental evaluation; gender; social learning; emotional learning; identity learning; adolescents

Introduction

Overview

The period of developmental changes and rapid growth during adolescence presents a key opportunity to promote positive lifetime health and well-being trajectories that have enduring impact throughout life [1]. Very early adolescence, before the onset of puberty (10-11 years old), is a pivotal transition from childhood into adulthood that can benefit from developmentally informed programming and strategic investment. Changes during this period include rapid physical growth and brain development, sexual maturation, and changes in cognitive, social, emotional, psychological, and behavioral processes. The period of brain development from the onset of puberty may represent a unique combination of stability and plasticity in developing neural networks that facilitate learning and experience [2]. During this distinctive maturational window, adolescents are particularly sensitive to learning opportunities that can shape social, emotional, and identity development [3]. A growing body of evidence indicates that adolescents between the ages of 10 and 14 actively build their identities, establish behaviors, gain social knowledge, and shape their values and beliefs during these years [1,2,4]. Furthermore, very early adolescence is an opportune window to shape identity formation around gender norms, attitudes, and beliefs before inequitable gender norms are amplified during and after puberty.

Brain development during early adolescence is naturally aimed at discovery learning in the social, emotional, and identity learning domains. The onset of puberty is associated with two important maturational changes that impact learning: (1) an increase in the tendency to explore, discover, and seek novelty/excitement; and (2) an increase in natural curiosity to explore and understand one's social world, including social roles, social hierarchies, issues of social acceptance, admiration, and learning to establish individual identity [5]. Early learning experiences during adolescence shape identities in ways that have profound implications for health—especially sexual and reproductive health and vulnerability to gender-based exploitation.

The Lancet Commission on Adolescent Health and Wellbeing report highlighted the need for investment in the largest generation of 10- to 24-year-olds in human history [6]. By 2018, there were approximately 1.24 billion adolescents, representing 16% of the global population [7]. Research indicates that adolescence is a period of vulnerability where physical and mental health problems emerge, which can persist into adulthood [8]. Increases in accidents, suicides, homicide, mental disorders, substance use, eating disorders, sexually transmitted diseases, and unintended pregnancy can lead to lifelong negative trajectories. While interventions have worked to address these risks, they often target older adolescents (aged 15-19 years) and have limited impact on very young adolescents [9,10].

Adolescence in Tanzania

In low-resource contexts, adolescents face additional stress and adverse life experiences. As a result, there has been an increasing focus on the need to target early adolescence to improve health trajectories for sub-Saharan African youth [11]. Evidence suggests that interventions that target very young adolescents can have sustained impacts such as decreasing the spread of HIV/AIDS, decreasing the number of unwanted pregnancies, and improving health and well-being [12-14]. Tanzania is experiencing a surge in the youth population, with about half the population younger than 17.5 years and 47% younger than 15 years [15,16]. The population in those age groups is expected to double by 2055 [7]. The Global Out-Of-School Children Study estimated that approximately 3.5 million school-aged children and adolescents were not in school in 2017 [17], and the results of a child poverty study released in 2016 showed that 74% of children in Tanzania are affected by multidimensional poverty while 29% live in households below the monetary poverty line [18].

Since the introduction of free primary education in 2001, Tanzania has made strides to improve access to education. Between 2004 and 2010, enrolment in secondary education tripled for girls and quadrupled for boys, and by 2011 over 94% of children aged 7 to 13 years were enrolled in school [19]. While the introduction of free primary education has resulted in higher secondary education enrolment, it has also revealed important equity gaps. Only a third of children that start primary school complete the cycle in seven years. The transition rates largely favor boys, with approximately 21% of boys joining secondary schools compared to 16% of girls [20].

In 2016, 1 in 4 adolescent girls aged 15-19 years had begun childbearing, reflecting a 4% increase in teenage pregnancy since 2010 [21]. Unfavorable sexual and reproductive health outcomes for girls have been attributed to the fact that Tanzanian youth face highly contrasting norms around gender and adolescent sexuality. Gender roles are differentiated, with boys allowed more freedom outside the house, whereas girls are perceived to be better suited for home chores [22,23]. A cultural prototype of a chaste female student is highly valued. At the same time, female sexuality is perceived as a resource intended for exploitation, and transactional sex is often considered a young woman's sole commodity. Disparities in enrolment patterns and educational outcomes have led researchers to focus on the role of gender and sexual and reproductive health in education.

Investing in programs for very young adolescents can help address gender inequities through inclusion of gender-transformative content that includes mixed-gender learning in social groups before puberty and sexual debut. Previous studies targeting the sexual and reproductive health of adolescents in Tanzania often focused on later adolescence (ages 15-19 years) and missed the opportunity to shape social, emotional, and identity learning during early adolescence, which can be transformative during later adolescence. More research is needed to understand what impact investment in very early adolescence can have on improving multiple health outcomes as well as transforming gender behaviors, attitudes, and beliefs.

Technology as a Learning Tool

Advances in technology provide an increasingly important social learning context and access to information and new learning opportunities. By 2017, use of mobile phones in Tanzania was at 80% [24]. The changing technological landscape in

low-income countries is a nascent opportunity to advance learning and address inequities in overburdened, underresourced education systems [25]. In Tanzania, one program that has integrated the use of technology in learning is the BridgeIT project, which reaches 80,000 pupils across 150 primary schools [26,27]. Adolescents are often early adopters and are motivated to learn using new technology, particularly those that enable them to gain social support [28]. The natural motivation of adolescents to explore, discover, and master novel and stimulating environments is an opportunity to deliver a high-impact intervention through technological platforms. Small advances have been made toward leveraging technology as a tool for promoting positive social and emotional skills and mindsets among adolescents. Examples of such programs have demonstrated positive impact on mental health and have reduced bullying among adolescents [29,30].

This study explores the design of a social and emotional learning intervention to promote gender equity among very young adolescents. The study hypothesis is that targeting a window of opportunity for very young adolescents (aged 10-11 years) and supporting development of social and emotional mindsets and skills through experiential learning in small, mixed-gender groups will promote social and emotional learning and identity development that has a positive impact on gender equity and associated health outcomes [3]. To test this theory of change, we measure social and emotional mindsets and skills and measures of gender norms, attitudes, and beliefs to capture the positive impact of the intervention on these outcomes. Other objectives of this study are (1) to test the effectiveness of providing learning opportunities that focus on specific social and emotional skills and mindsets (including curiosity, generosity, persistence, purpose, growth mindset and teamwork and gender equity); (2) to evaluate the use of digital technology for social, emotional, and identity learning; and (3) to identify aspects of high-impact learning opportunities with the potential to be scaled in low-resource settings across Tanzania and in similar low-resource contexts.

Methods

Study Location

Discover will be conducted in Temeke Municipality in Dar es Salaam, Tanzania. Temeke District is the largest of Dar es Salaam's three districts. It is unique since it encompasses both metropolitan urban and rural areas. It has a sociodemographic mix of people from all parts of the country. There are 114 primary schools in Temeke with more than 130 pupils per classroom on average. The number of primary school–going children in the municipality is 170,477. Of these, 84,371 are boys and 86,106 are girls [31].

Overview of Discover Learning Project

The primary aim of the Discover Learning Project (*Discover*) is to test an intervention for very young adolescents to promote positive social and emotional skills and mindsets that have the potential to transform gender norms and attitudes. A secondary aim is to better identify effective components of *Discover* that are scalable and require the fewest resources to implement. The study aims are detailed in Textbox 1.

Textbox 1. Discover study design.

Research aims:

Compared to matched controls, do participants in *Discover* show the following?

- Decreased experience of gender inequality
- More positive social relationships with peers and trusted adults
- Enhanced feelings of empowerment and motivation to engage in school and other learning experiences
- More positive attitudes toward and comfort with using technology as a learning tool

A secondary aim is to identify high-impact components for scale at low cost.

Selection of study sites:

- The profile of the schools should be representative of an average school found in Tanzania in terms of socioeconomic status, religion, amenities, etc.
- Schools should be a public day school where a majority of pupils reside within a walking distance from the school.
- Schools should not have had an existing behavioral intervention within the last 7 years targeting the target age group.
- Schools should have a large enough number of 10- to 11-year-olds to obtain sample size required for study.

Participant eligibility criteria:

- Must be a 10- to 11-year-old student in Grade 3, 4, or 5 in any of the 4 selected study sites
- Must have agreed to participate in the study
- Parent must consent to the study and provide written parental permission

The project draws on developmentally informed principles that balance autonomy with adult engagement to scaffold social and emotional learning [32]. The specific target areas of adaptive social and emotional mindsets and skills include growth mindset,

curiosity, generosity, persistence, purpose, prosocial behavior, and teamwork. The study is implemented in small mixed-gender groups by introducing positive, socially scaffolded exploration and use of digital technology. *Discover* integrates insights from developmental science that are matched to developmental changes during early adolescence in three ways:

1. By focusing on social learning in mixed-gender groups. Adolescents have a natural motivation for social status, prestige, and respect. Mixed-gender groups provide opportunities for positive, collaborative, and scaffolded learning that integrate content that recognizes girls and boys as equal in solving problems.
2. By building upon a core concept of discovery learning. Adolescent-driven discovery learning creates opportunities for positive risk-taking that results in healthy, positive, productive, high-arousal learning.
3. By using technology to deliver learning experiences. Technology takes advantage of adolescents' increased tendency to seek novelty, excitement, and mastery and helps them adapt successfully to the increasing influence of technology in the world around them.

The content and activities in *Discover* are focused on enhancing and supporting skills and mindsets that motivate adolescents to feel respected and admired by the adults and peers in their lives [3]. The adaptive areas of social and emotional mindsets and skills include *positive gender norms*—encouraging positive gender norms and exploration of gender identity can disrupt inequitable gender norms and support gender equity; *teamwork*—activities geared toward teamwork can promote positive peer interactions, encourage communication skills, and provide appreciation to and from peers; *growth mindset*—focusing on the potential to develop personal abilities; *curiosity*—curiosity and experimentation are highly arousing and motivate learning; *purpose*—exploring one's purpose can help develop long-term, heartfelt goals; *persistence*—focusing on ways of increasing coping skills for rapid physical, social, and emotional changes that are associated with early adolescence; and *generosity*—encouraging intentional practice of gratitude and kindness in order to foster better interpersonal skills.

Each of these mindsets and skills have been adapted into scripted videos that are culturally sensitive and easy to understand for 10- to 11-year-olds. In addition to watching the videos, the adolescents will be immersed into a series of experiential and interactive learning activities specific to each mindset and skill. A detailed description of each social and emotional mindset and skill and the associated intervention activities can be found in Multimedia Appendix 1.

Intervention Components

The intervention design focuses primarily on increasing positive gender norms and boosting the outcome of each social and emotional mindset and skill among study participants. The intervention includes the following elements.

Youth Sessions

1. Ubongo Kids videos: Students will watch engaging digital learning content developed for children in East Africa by Ubongo Kids.
2. Team building: Students will be placed in small mixed-gender teams for self-guided discussions and activities that are designed to facilitate teamwork and provoke discussions on gender.
3. Reflection: At the end of each session, students will be encouraged to reflect about what they learned during the session as a team as well as reflect on how this might apply to their life.
4. Technology 101: Students will be introduced to the basic components of a tablet and taught how to turn them on and off as well as how to navigate to files and programs.
5. Tablet games: Students will work in pairs on simple games designed with increased difficulty. The games the youth play will be modified versions of Tic-Tac-Toe, Pong, and a mathematical/numeracy game.
6. Community mapping: Students will be taken around their community to help them identify different places in the community that contain resources of importance.
7. Mind mapping: This mapping activity will look at important aspects in a student's life and help them consider their identities and roles as individuals, in their family, and in the community.
8. Kanga project: Youth will be encouraged to think about a value that they or their community have and represent this in a fabric commonly used in East Africa.
9. Parent-child workbook: The workbook will have class activities that youth fill out during the sessions, as well as home activities, which will be simple questions or activities that reflect what they will have learned during the sessions.
10. Community event: At the end of the project, students will present their kanga artwork and gifts in an event that will bring together children and caregivers, members of the local government and ministries, and teachers.

Parent and Caregiver Sessions

For each implementation phase, *Discover* will hold three one-hour sessions every other week over 6 weeks with parents and caregivers. Structured parent sessions are an opportunity for caregivers to ask questions about the intervention or the parent-child workbook. The parent-child workbook is designed to reinforce learning within the home by providing discussion questions and short activities. A community event will be held at the end of each intervention phase that brings together the participant youth, parents and caregivers, members of the community advisory board, members of the local government, and teachers. Students will get a chance to demonstrate the skills they will have learned during the intervention, showcase their kanga (traditional African fabric commonly designed with colorful patterns and messaging), and offer them as gifts to the community.

Research Team Training

Core research team members will complete training on research ethics prior to the study. Their training will include confidential handling of data, obtaining consent and assent from study

participants, and data collection and management. The field research team will be composed of 2 master trainers and 12 community facilitators. Training will be conducted in two phases. First, the master trainers will be trained over two weeks by the *Discover* Project Manager. The training will cover research ethics, gender-transformative content, technology use, and partnering with the community. Second, community facilitators will be trained with support from the master trainers over eight days. During the training, 6 facilitation principles will be adapted to facilitate discovery learning. They are (1) scaffolding learning to create a safe space for learners, (2) emphasis on learning over education, (3) withholding judgment since learning is a nonlinear process, (4) encouraging teamwork and positive group dynamics, (5) disrupting gender norms, and (6) encouraging a growth mindset. Sessions will use a combination of presentations, discussion, practice, and reflection.

Participant Recruitment and Eligibility Criteria

Participants will be recruited from four primary schools from low-income urban neighborhoods of Temeke District. They will be selected based on the following criteria: (1) the school should not have had an intervention within the last 7 years that included a behavior change component, a teachers' capacity-building component on soft skills (eg, positive discipline or facilitation skills), or a gender equity program; (2) the school should be a public/government school; (3) the school should have a large enough number of early adolescents to obtain the sample size required for study; and (4) the school should be representative of an average school in Tanzania in terms of socioeconomic status, religion, amenities, etc. Participants will be eligible if they meet the following criteria: (1) they must be a 10- to 11-year-old student in Grade 3, 4 or 5 in the 4 selected study sites; (2) they must verbally assent to participate in the study; and (3) their caregiver must provide consent for them to participate in the study. The after-school intervention will be conducted with a total of 579 youth. Students will be randomized into Groups A, B, and C. Figure 1 provides an overview of the scheduling of the intervention and research elements. A complete checklist listing the items to address in a trial protocol according to the CONSORT (Consolidated Standards of Reporting Trials) guidelines can be found in Multimedia Appendix 2 [33].

Figure 1. Study recruitment and implementation schedule.

	STUDY PERIOD					
MONTH	***Jun 2019***	***Jul 2019***	***Aug 2019***	***Sep 2019***	***Oct 2019***	***Nov 2019***
ENROLMENT						
Eligibility screen	X					
Informed consent	X					
Recruitment	X					
Allocation	X					
INTERVENTION						
Group A		←	—			
Group B		←	—			
Group C		←	—	—		
ASSESSMENTS						
Youth baseline survey	X	X				
Parent pre-intervention interviews	X					
Youth and facilitator observations		←	—	—		
Youth endline survey				X	X	
Youth focus group discussions				X	X	
Youth in-depth interviews				X	X	X
Parent post-intervention interviews				X	X	
Teacher and facilitator in-depth interviews					X	X

Randomization Procedure

Participating 10- to 11-year-olds from grades 3, 4, and 5 will be identified from each school. At each school, we will hold an event where we line up eligible youth outside their classrooms. A research assistant will hold a box with pencil sharpeners of different colors inside. The box will have a small hole large enough to fit a hand through but small enough that students cannot see the pencil sharpeners. Each youth will select one sharpener at random. Students will be assigned to groups A, B, or C depending on whether they pick pink, yellow, or blue pencil sharpeners, respectively. Youth will then be matched to their selected pencil sharpener with a research assistant holding the same color, and that research assistant will register students to

the assigned group. Table 1 lists the expected results of randomization to the three groups, according to the sample size calculation, and the intervention components that will be administered to each group.

Table 1. Intervention components offered per study arm.

Study components	Group A (n=186)	Group B (n=185)	Group C (n=208)
Number of sessions	6	6	18
Ubongo Kids videos	✓	✓	✓
Mixed gender groups of size	15-26	4-5	4-5
Discussion and activities	✗	Self-guided	Guided by trained facilitators
Parent-child workbook	✗	✗	✓

Study Instruments

A mixed-method approach will be used to capture the innovation process of project implementation. Qualitative methods will be sought to capture perspectives from youth participants, parents and caregivers, and community members. Qualitative tools to be used include in-depth interviews, focus group discussions, and participant and facilitator observations. The mixed-method evaluation design is detailed in Textbox 2.

Textbox 2. Data collection methods.

QUALITATIVE METHODS

Adolescent

- In-depth interviews
- Focus group discussions
- Session materials
- Parent-youth workbook

Parent

- In-depth interviews (pre- & post-intervention)
- Parent session materials

Facilitator

- Session debrief reflections
- Challenges, solutions, and adaptation logs
- In-depth interviews

Participant and facilitator observations

QUANTITATIVE METHODS

Adolescent Survey

- Sociodemographic information
- Social and emotional mindsets and skills
- Discrete choice experiment
- Parent-youth workbook

Youth Surveys

The evaluation surveys for youth in *Discover* have been developed following a review of existing, validated tools that have been previously used in similar low-resource settings and tested through multiple pilot field tests with young adolescents in study sites. The surveys have been adapted through an iterative process following the pilot intervention and through meetings with Tanzanian and US research evaluation team members. Some of the measures that have been adapted include the following: gender equality—Gender Roles, Equality and Transformations [34]; curiosity—the Trait State Curiosity Scale [35]; empathy—the Empathy Questionnaire for Children and Adolescents [36]; growth mindset—Dweck Growth Mindset Questions [37]; and technology use and uptake—Media and Technology Usage and Attitudes Scale [38].

Final survey measures have been reviewed for relevance, cultural meaning, and acceptability by youth. Following this, the survey will be transferred to a tablet-based questionnaire

for use in one-on-one interviews. The survey will be translated and back-translated from English to Swahili. The final *Discover* measures are listed in Multimedia Appendix 3.

Discrete Choice Experiment

We have developed a discrete choice experiment to assess adolescents' gender perceptions, attitudes, and roles. This is a quantitative technique for eliciting individual preferences and hence informing policy, planning, and resource allocation decisions [39]. Typically, in a discrete choice experiment, study participants are repeatedly presented with scenarios on several attributes and asked to state their preference. In our approach, adolescents will be presented with 3-5 scenarios under each attribute and asked to decide whether the scenarios best describe boys, girls, or both boys and girls. The attributes will complement the social and emotional mindsets and skills from our intervention modules. Response options will be presented as cartoon images of boys only, girls only, or both girls and boys; participants will have to pick one image for each scenario.

Qualitative Data Collection

In-depth interviews with youth and parents will be conducted at the start of the program over a period of 6 weeks. Interviews with youth will be conducted by trained qualitative researchers after school hours. Parent interviews will be conducted over the phone at a time preferred by the parent. During classroom sessions, trained observers will keep notes of youth and facilitator engagements. This will be done throughout the project. Upon completion of the project, endline in-depth interviews with youth and parents lasting approximately 30 minutes will be conducted. In-depth interviews will be conducted with all facilitators. Further, focus group discussions will be held with groups of 4-6 youth, and in-depth interviews with teachers will be completed. Recordings of all interviews and focus groups will be transcribed in Swahili and then translated to English by project staff.

Sample Size and Power

The sample size of 579 was chosen to be able to measure the minimum detectable effect of the *Discover* intervention on outcomes of social and emotional mindsets and skills. A sample of 186 students per study group produces an effect size of 0.28 and 80% power, assuming a 1-sided *t* test and α level of .05 to allow for multiple testing across groups. Randomization will be done at the individual level because the research protocol poses minimal risk for contamination. The project does not have a prior estimate of the intracluster correlation coefficient between individuals nested within a school, so we have used 0.39, adapted from similar studies on social and emotional interventions in sub-Saharan Africa [40]. The control groups (A and B) will each have 186 students, and the remaining participants will be in the treatment group (Group C).

Data Analysis

Quantitative statistical data analysis will be conducted using Stata SE 16.0 (StataCorp). For each group, we will test using an intent-to-treat model to determine the effectiveness of each group on (1) social and emotional mindsets and skills outcomes (curiosity, generosity, persistence, purpose, growth mindset, and prosocial behavior) and (2) gender norms, attitudes, and beliefs. Descriptive statistics will be calculated for each measure per intervention group and will be used to check for skewness and data non-normality. The psychometric properties of each measure will be assessed using confirmatory factor analysis to assess the adequacy of factor structures suggested by previous studies. Additional analyses will be conducted using *t* tests and logistic regressions to explore potential confounders of these relationships such as age, gender, and assigned facilitator. Validated measures will be used for structural equation modelling to test the relationships between intervention groups on social, emotional, and identity learning measures. For each model tested, structural equation modelling will be used to test (1) overall fit, (2) the significance of structural paths, and (3) the amount of variability of the latent variables accounted for by observed variables. Model fit will be assessed by using goodness-of-fit indices including the chi-square, the root mean square error of approximation [41], the comparative fit index [42], the Tucker-Lewis index [43], and the standardized root mean residual.

Qualitative data analysis will be conducted in ATLAS.ti (ATLAS.ti Scientific Software Development GmbH). After completion of interviews and focus groups, a Tanzanian translator will complete translation from Swahili to English. The translations will be cross-checked by researchers in Tanzania. Transcripts will be coded using grounded theory methodology, and content analysis will be performed to identify key themes. Quotes will be selected as exemplars of these themes. Additional qualitative materials include participant observations, facilitator debrief reflections, parent session notes, and teacher interviews. Each of these documents will be translated from Swahili to English by the research team and summarized, and key themes will be extracted. Artifacts from youth will be collected throughout the intervention implementation to serve as exemplars of curriculum implementation.

Availability of Data and Materials

The data sets that will be generated or analyzed during this study will not be made publicly available due to the sensitive age of the study participants (10- to 11-year-olds) at baseline but may be available from the corresponding author on reasonable request. The author will vet requests to be certain that appropriate institutional review board (IRB) approvals and data safety guidelines are in place before distribution.

Results

This project was funded in November 2016 by the Bill and Melinda Gates Foundation. The University of California, Berkeley Committee for Protection of Human Subjects IRB approved this study (CPHS Protocol Number: 2017-01-9464; date: July 11, 2019). The primary local partner, Health for a Prosperous Nation, obtained ethical clearance for these research activities from the National Institute of Medical Research, the local IRB in Tanzania (Ref. NIMR/HQ/R.8a/Vol. IX/ 2491; date: May 15, 2019). In addition, the project sought and secured support from all local partners, Temeke Municipal Council and the Ministry of Education in Tanzania. Screening and enrolment

of participants was done in June 2019. Data for the baseline survey was collected in July 2019.

The first phase of the intervention was delivered starting in the month of July 2019 for a period of 6 weeks to 579 participating 10- to 11-year-olds. Throughout the course of the intervention, systematic observations were carried out. Follow-up data was collected in the months of October and November 2019. The first phase of the intervention closed out in November 2019. At the time of writing this paper, data analysis had not yet been concluded. The second phase of the intervention kicked off with enrolment of participants in July 2020. This phase of the study targets the same participants from phase I and expects to reach 500 participants. The baseline survey will be conducted from August to September 2020. The intervention will be delivered remotely via technology for ten weeks from September 2019. The key findings from this phase of the project and the longitudinal data collected will be submitted for publication in peer-reviewed literature and presented at national and international conferences.

Discussion

Findings from *Discover* will provide evidence of the impact of the different components of a developmentally informed social, emotional, and identity learning intervention for very young adolescents by comparing outcomes in groups A, B, and C and emergent themes from interviews and focus groups. Synthesis of quantitative and qualitative results will allow for identification of the highest impact components and resources required for the intervention. Results from structural equation modelling will be used to create a testable model of the relationships between social, emotional, and identity development on gender equity outcomes. These results will be used to develop a scalable, low-resource intervention program. This study tests the translation of developmental science principles to youth programs. In addition, findings have the potential to be replicated in other low-resource contexts. This study has some limitations. Randomization of adolescents will be done at the individual level and not the school level to maximize participation. Findings from the intervention will therefore apply to the individual level but cannot be extrapolated to the community level. Despite efforts to ensure intervention groups receive the package of components pertinent to that group, there is a possibility that some adolescents will discuss their group's activities with friends and siblings, and therefore groups may become aware of intervention components received by other groups. The findings from this study will contribute to the evidence base on development science for very young adolescents. Further, the study design, methods, and evaluation will be useful for other studies that are invested in gender-transformative interventions through support of social and emotional learning. *Discover* will identify the impact of different intervention components that can be leveraged to replicate and scale up similar programs in peri-urban, low-resource settings.

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Authors' Contributions

The original *Discover* study design was conceived of and designed by MC, RD, and CS. Recruitment of participants, management, and project implementation will be performed by CS. Development of survey instruments and evaluation was done by MC and SL. Manuscript preparation was carried out by MC and SL. All authors have contributed critically and significantly to drafting a final manuscript. All authors approved the final version. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. The funding body has no role in the design of the study, in collection, analysis, and interpretation of data, or in writing the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Social emotional mindsets and skills targeted by Discover.
[PDF File (Adobe PDF File), 132 KB - resprot_v9i12e23071_app1.pdf]

Multimedia Appendix 2
CONSORT Checklist.
[PDF File (Adobe PDF File), 65 KB - resprot_v9i12e23071_app2.pdf]

Multimedia Appendix 3
Measurement scales used in Discover.

[PDF File (Adobe PDF File), 132 KB - resprot_v9i12e23071_app3.pdf]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials

IRB: institutional review board

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Protocol

Efficacy and Safety of Inhaled Ciclesonide in Treating Patients With Asymptomatic or Mild COVID-19 in the RACCO Trial: Protocol for a Multicenter, Open-label, Randomized Controlled Trial

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Abstract

Background: Currently, there are no specific effective treatments for SARS-CoV-2 infection; however, various COVID-19 treatment options are under investigation. It is vital to continue investigating the landscape of SARS-CoV-2–induced pneumonia and therapeutic interventions.

Objective: This paper presents the protocol for a randomized controlled trial that aims to compare the pneumonia exacerbation rate between ciclesonide (ALVESCO; Teijin Pharma Limited) administration and symptomatic treatment in patients with COVID-19 and to determine the efficacy of ciclesonide. The secondary objectives are to investigate the safety of ciclesonide administration, changes in clinical and laboratory findings, and the number of viral genome copies of SARS-CoV-2 over time between the 2 groups.

Methods: In this investigator-initiated, exploratory, prospective, multicenter, parallel-group, open-label, randomized controlled trial, a total of 90 patients diagnosed with COVID-19 will be recruited from 21 hospitals in Japan based on specific inclusion and exclusion criteria. Participants will be randomized either to the ciclesonide group, which will receive a 400-µg dose of ciclesonide 3 times per day over a 7-day period, or to the symptomatic treatment group. Both groups will receive antitussives and antipyretics as required. Data collection for various parameters will be conducted on days 1, 2, 4, 8, 22, and 29 to record baseline assessments and the findings over an extended period. Computed tomography images taken prior to drug administration and 1 week following treatment will be compared, and efficacy will be confirmed by checking for pneumonia exacerbation. Primary endpoint analysis will be performed using the Fisher exact test to determine statistically significant differences in the pneumonia exacerbation rate between the ciclesonide and symptomatic treatment groups.

Results: The first trial participant was enrolled on April 3, 2020. Recruitment is expected to be completed on September 30, 2020, while follow-up assessments of all participants are expected to be completed by October 31, 2020. The study results will be published in a peer-reviewed scientific journal.

Conclusions: The RACCO (Randomized Ciclesonid COVID-19) study will provide definitive comparative effectiveness data and important clinical outcomes data between the ciclesonide and symptomatic treatment groups. If the hypotheses that pneumonia exacerbation rate reduction is more significant in the ciclesonide treatment group than in the symptomatic treatment group and that ciclesonide is safe for use are valid, ciclesonide will serve as an important therapeutic option for patients with COVID-19.

Trial Registration: Japan Registry of Clinical Trials jRCTs031190269; https://jrct.niph.go.jp/en-latest-detail/jRCTs031190269

International Registered Report Identifier (IRRID): DERR1-10.2196/23830

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KEYWORDS

COVID-19; SARS-CoV-2; proposed therapy; therapy; drug; treatment; protocol; randomized controlled trial; intervention

Introduction

Background and Rationale

An outbreak of severe respiratory illness occurred in Wuhan, China at the end of December 2019. The World Health Organization and China were alerted by an increase in the number of patients with pneumonia of unknown etiology. In January 2020, it was reported that a novel type of coronavirus, SARS-CoV-2, was responsible for the outbreak [1]. Three months later, almost half a million cases of this contagious infection had been identified across 197 countries [2], and on March 11, 2020, the World Health Organization declared the COVID-19 outbreak as a pandemic [3].

While most COVID-19 cases result in mild symptoms, some cases progress to pneumonia, acute respiratory distress syndrome, and death [4,5]. The case fatality rate reported across various countries, settings, and age groups is highly variable, but ranges from less than 1% to 19% [6]. Among hospitalized patients, the case fatality rate has been reported to be greater than 10% in some centers [7].

There is currently no specific effective treatment for SARS-CoV-2 infection, but various options and strategies for treating COVID-19 are under investigation worldwide [8]. Lu et al [9] reported that antiviral molecules, nucleoside analogs, neuraminidase inhibitors, therapeutic peptides, RNA synthesis inhibitors, anti-inflammatory drugs, and Chinese traditional medicine could be therapeutic options for SARS-CoV-2 infection. Currently, the standard treatment methods for clinicians only involve symptomatic treatment; therefore, it is vital to continue investigating the landscape of SARS-CoV-2–induced pneumonia and therapeutic interventions. The asthma drug ciclesonide (ALVESCO) is a pressurized metered-dose inhaler that uses the glucocorticoid ciclesonide and originates from Nycomed. It is now developed, manufactured, and marketed by numerous pharma companies worldwide, including Covis Pharma, Takeda, Sunovion Pharmaceutical, and Teijin Pharma [10]. Teijin Pharma in Japan developed ciclesonide for adult bronchial asthma in April 2007, and it was approved for child doses in January 2011. This drug acts by reducing the swelling of the airways in the lungs in order to make breathing easier. After the oral inhalation of ciclesonide, a prodrug is enzymatically hydrolyzed in the lungs to an active metabolite (ie, des-ciclesonide). Des-ciclesonide has an anti-inflammatory effect and binds to glucocorticoid receptors, thereby controlling chronic inflammation in the air ducts [11].

Preclinical data [12] have suggested that ciclesonide could potentially treat COVID-19, since it has been shown to suppress the replication of human coronaviruses (eg, Middle East respiratory syndrome–related coronavirus) in cell cultures [13] and exhibit strong antiviral activity, even against SARS-CoV-2 [12]. Additionally, a recently published case series [14,15] showed that treatment with this drug has led to favorable outcomes in 3 patients with confirmed COVID-19 [14,15]. These case reports from Iwabuchi et al [14,15] indicated that the ideal administration period should be in the early intermediate stage of infection or in the initial stage of pneumonia, prior to the worsening of symptoms. Covis Pharma has launched a phase III clinical trial in the United States to evaluate its asthma drug, ciclesonide (ALVESCO), for its ability to treat nonhospitalized, symptomatic patients with COVID-19 aged ≥12 years. As of May 22, 2020, the drug is currently being investigated for the treatment of COVID-19 in several countries, such as Australia, South Korea, Sweden, the United Kingdom, and the United States [10], and the results are not yet available.

More studies on ciclesonide are required to assess its efficacy and safety in treating patients with COVID-19. This prospective randomized controlled trial in Japan aims to investigate the efficacy and safety of ciclesonide in treating patients with COVID-19 during the early stages of SARS-CoV-2 infection. The accumulation of findings from this study will be significant for the treatment of COVID-19.

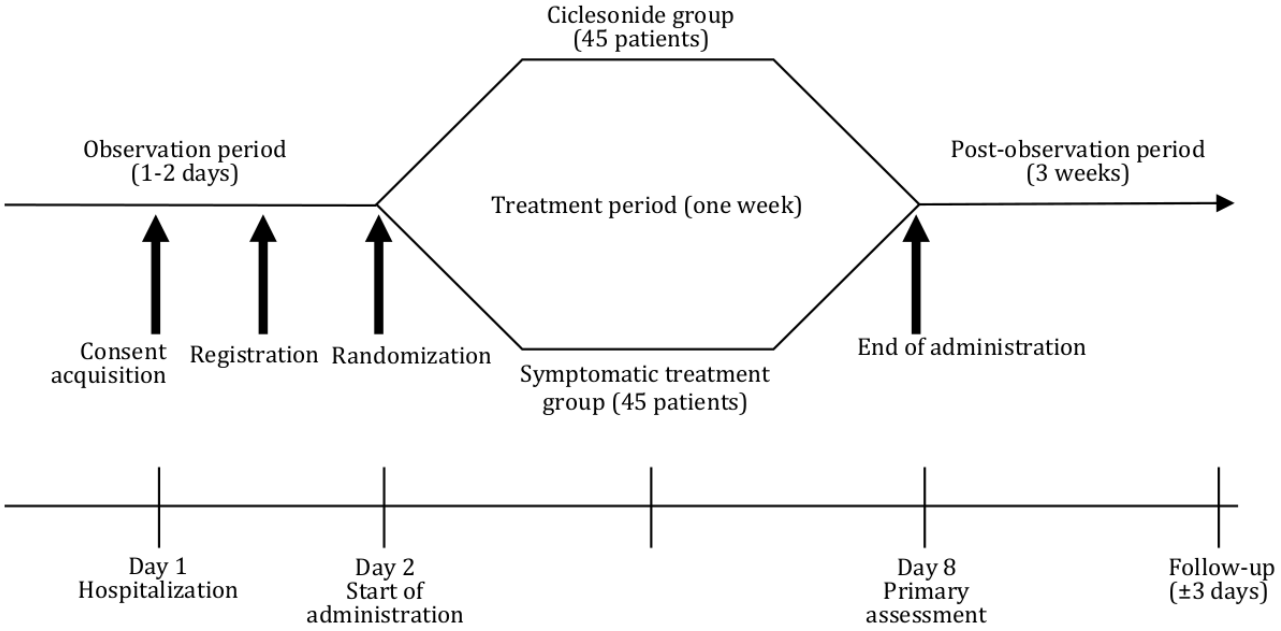
Objectives

The primary objective of the RACCO (Randomized Ciclesonide COVID-19) trial is to compare the pneumonia exacerbation rate between the ciclesonide and symptomatic treatment groups, which consist of patients with COVID-19, and to determine the efficacy of ciclesonide. The secondary objective is to investigate the safety of ciclesonide administration by comparing the rate of adverse events between both groups. In addition, changes in clinical and laboratory findings and changes in the number of copies of the viral genome over time will be monitored between the 2 treatment groups.

Trial Design

This is an investigator-initiated, exploratory, prospective, multicenter, parallel-group, open-label, randomized controlled trial. Figure 1 describes and outlines the design in more detail. The first trial participant was enrolled on April 3, 2020. Recruitment is expected to be completed on September 30, 2020, while the follow-up of all participants is expected to be completed by October 31, 2020.

Figure 1. Trial design and outline.



Methods

Ethical Approval

This study is being conducted in compliance with the Declaration of Helsinki 2013; Clinical Trials Act; Clinical Trials Act Enforcement Regulations; 2018 Ordinance of the Japanese Ministry of Health, Labor, and Welfare; and Japanese Good Clinical Practice (GCP). In the Japanese GCP, principal investigators in all participating institutions serve as the study sponsor for investigator-initiated, registration-directed trials, and hospital directors take responsibility for the study conduct. Prior ethical approval for the protocol and the informed consent document was obtained from The University of Tokyo, Clinical Research Review Board (Approval No CRB3180024), and each participating hospital investigator received permission from the administrator to conduct the study, after which the representative physician submitted the explanatory and consent documents to the Ministry of Health, Labor, and Welfare in Japan. This trial is registered and recorded in the Japan Registry of Clinical Trials (jRCT; jRCTs031190269), and research only commenced after the jRCT release.

Study Setting

The main study site is the Center Hospital of the National Center for Global Health and Medicine, Tokyo, Japan, but several other hospitals are participating in this trial. A total of 90 patients diagnosed with COVID-19 were recruited from 22 hospitals in Japan. Textbox 1 lists the medical institutions participating in this trial.

The sample size for the RACCO trial (N=90) is based on a statistical minimum number of patients required for each treatment arm, to control for pneumonia onset and the final number of patients who will undergo the full analysis and complete the study. The sample size calculation is outlined under the Statistical Methods section.

Textbox 1. Participating medical institutions.

Names of the implementing medical institutions

- Center Hospital of the National Center for Global Health and Medicine
- The University of Tokyo Hospital
- Toho University Omori Medical Center
- Showa University Hospital
- International University of Health and Welfare Narita Hospital
- International University of Health and Welfare Mita Hospital
- Atsugi City Hospital
- National Hospital Organization Higashisaga Hospital
- National Hospital Organization Numata Hospital
- Iizuka Hospital
- National Hospital Organization Nishisaitama-chuo National Hospital
- Daini Osaka Police Hospital
- National Hospital Organization Nara Medical Center
- Sapporo City General Hospital
- National Hospital Organization Kokura Medical Center
- Yoshida Hospital
- Ome Municipal General Hospital
- National Hospital Organization Kyushu Medical Center
- National Hospital Organization Fukuyama Medical Center
- Kanagawa Prefectural Hospital Organization Kanagawa Cardiovascular and Respiratory Center
- National Hospital Organization Osaka National Hospital
- The Fraternity Memorial Hospital

Recruitment

Strategies have been implemented to ensure maximum enrollment at each site. Each study site has a target number of patients to enroll. Furthermore, our study period includes the following: the registration period, which lasts from March 30 to September 30, 2020; the observation period, which lasts from March 30 to October 31, 2020; and the implementation period, which lasts from March 30 to October 31, 2021.

Eligibility Criteria

Our inclusion criteria for study participants are as follows: (1) provided written consent for research participation; (2) aged ≥20 years at the time of consent acquisition, regardless of sex; (3) tested positive for SARS-CoV-2 based on polymerase chain reaction (PCR) results or the loop-mediated isothermal amplification method (4) had no clear indications of COVID-19–induced pneumonia on simple chest images; (5) hospitalized during the trial drug administration period (ie, 1 week); and (6) had the ability to receive ciclesonide inhalation using an inhalation-assisting device.

Our exclusion criteria for study participants are as follows: (1) a medical history of ciclesonide hypersensitivity; (2) the presence of an infectious disease or deep-seated mycosis other than COVID-19, for which there is no effective antibacterial agent; (3) the presence of chronic respiratory diseases, such as chronic bronchitis; (4) current treatment with inhaled or oral steroids; (5) a history of a continuous fever of ≥37.5°C that lasted for over 7 days; (6) current treatment with agents that have potential therapeutic effects against COVID-19 and may affect the efficacy assessments, including remdesivir, lopinavir/ritonavir compound drugs, favipiravir, interferon, and hydroxychloroquine; and (7) conditions deemed unsuitable for research by the principal physician or subphysician.

Informed Consent

Physicians trained in GCP will determine participants' eligibility, discuss the trial with the patients, and seek their informed consent. Explanatory and consent documents approved by the authorizing clinical study examination committee and authorized by the Minister of Health, Labor, and Welfare will be provided to the research participants, and sufficient written and verbal explanations will be provided in order to avoid forceful or unfair influences. Consent from research participants will be obtained by having them sign and date the consent document.

Patient Registration and Allocation Method

After obtaining written consent from the research participants, the principal physician or subphysician will confirm whether a research participant is suitable for the trial by verifying the

inclusion and exclusion criteria, promptly performing electronic data capture (EDC)-based patient registration, and acquiring the allocation results.

A stratified block randomization method will be used to allocate participants into 2 groups, the ciclesonide group and symptomatic treatment group. Allocation adjustment factors include the numbers allocated to each facility, fever temperature (ie, over or below 37.5°C), and age (ie, over or under 60 years). Allocation results will be displayed on the EDC system after inputting and confirming the allocation adjustment factors into the EDC system.

The principal physician or subphysician will commence research treatment in accordance with the allocation results. Research participants will be issued a research ID that is specific to the proposed research.

Interventions

Participants will be randomized to 1 of the 2 treatment groups. In the ciclesonide group, a 400-μg dose of ALVESCO, which is manufactured by Teijin Pharma Limited, Japan, will be administered to patients with asymptomatic or mild COVID-19 3 times per day over a continuous 7-day period. The patients will also receive antitussives and antipyretics as needed. In the symptomatic treatment group, only antitussives and antipyretics will be administered to the patients as needed.

Ciclesonide has not been approved for COVID-19 treatment in Japan or internationally, and is used only for research purposes.

Criteria for the Discontinuation of Treatment/Intervention

The representative physician will review the continuation of research implementation when the following events occur: (1) when important information relating to the trial drug quality, efficacy, and safety; factors that may affect the research implementation or continuation; and other factors that affect the effective implementation of the research is obtained; (2) when research subject incorporation and the attainment of the predicted number of participants becomes difficult; (3) when research objectives are achieved during intermediate analysis prior to reaching the predicted number of participants or completion of the predicted period; (4) when the authorizing clinical study examination committee instructs a revision of the research proposal and when this revision is difficult to incorporate; (5) when the authorizing clinical study examination committee issues a suspension; and (6) when serious or continuous violations of the clinical research methods, enforcement regulations, or this research proposal are noted.

Strategies to Improve Adherence to Intervention

A face-to-face initiation meeting was held prior to the commencement of the trial at each site. Site investigators and research staff engaged with their multidisciplinary teams and provided training.

The principal physician or subphysician will provide guidance for research participants prior to the start of research. Research participants will be shown an inhalation guidance video beforehand and will be guided on how to use the AeroChamber Plus (Trudell Medical UK Limited) in order to increase respiratory efficiency. Furthermore, an asthma diary will be distributed to the patients in advance. Patients are to confirm that the inhalant has not yet been administered, and the patient will be instructed to check the confirmation column after inhalation.

Relevant Concomitant Care Permitted or Prohibited During the Trial

The following drugs are prohibited during the research implementation period (ie, from consent acquisition to the final observation date): (1) orally or intravenously administered systemic adrenocortical steroids, (2) inhaled steroids other than inhaled ciclesonide, and (3) drugs that may have therapeutic effects against COVID-19 (eg, remdesivir, lopinavir/ritonavir compound drugs, favipiravir, interferon, and hydroxychloroquine).

Provisions of Posttrial Care

The expected research participation period will last for approximately 1 month, after consent acquisition (ie, 1 week for the protocol treatment period and 3 weeks for the follow-up period). Research participants will be hospitalized during the treatment period, and outpatient follow-up observations will be permitted following the end of the protocol treatment period. In cases where the research participants experience adverse events linked to the treatment, follow-up examinations are to be conducted until the principal physician or subphysician has ensured the safety of the research subject.

Outcomes

Primary Outcome Measure

The primary outcome is the pneumonia exacerbation rate within 7 days after ciclesonide inhalation. Computed tomography (CT) images taken prior to drug administration and 1 week following treatment will be compared, and efficacy will be confirmed by checking for pneumonia exacerbation. Pneumonia exacerbation will be independently diagnosed by 2 radiologists, who will only refer to the CT images. An exacerbation of pneumonia will be diagnosed if evidence of exacerbation is present on the day 8 CT image compared to the day 1 CT image.

Secondary Outcome Measures

Secondary outcome measures include changes in clinical findings, laboratory findings, and the number of quantified SARS-CoV-2 viral genome copies over time. Clinical findings include the following: body temperature, malaise/appetite, oxygen therapy conditions, respiration rate, oxygen saturation, systolic blood pressure, heart rate, level of consciousness, hospital discharge, ventilator use, extracorporeal membrane oxygenation use, presence of intensive care unit management, and miscellaneous combined medicine conditions.

Laboratory findings include the following: albumin level, lymphocyte count, C-reactive protein level, D-dimer level, leukocyte count, hemoglobin level, platelet count, blood sedimentation, bilirubin level, aspartate transaminase level, alanine transaminase level, lactate dehydrogenase level, γ-glutamyl transpeptidase level, alkaline phosphatase level,

creatine kinase level, creatinine level, blood urea nitrogen level, sodium level, potassium level, glutamic acid level, and procalcitonin level.

The safety endpoint will be based on adverse event frequency/percentage.

Participant Timeline

Figure 2 and Table 1 show the schedule of enrollment, interventions, and assessments. Data collection will occur at screening (ie, day 1), day 2 (ie, randomization period), and days 4, 8, 15, 22, and 29.

Figure 2. Participant timeline, enrollment, interventions, and assessments.

Category	Screening period		Administration period			Observation period			Suspension
Time period	Hospitalization date		day 1	day 3	day 7	14 days after the start of administration	21 days after the start of administration	28 days after the start of administration	
Day	Day 1		Day 2	Day 4	Day 8	Day 15	Day 22	Day 29	
Allowable range	-Day 3-0		±Day 1	±Day 1	±Day 1	±Day 3	±Day 3	±Day 3	±Day 1
Written consent acquisition	✓								
Background confirmation		✓							
Trial drug administration			←	—	→				
Subjective symptoms and objective symptoms		✓	←	—	→	✓	✓	✓	✓
Adverse event observation			←	—	—	—	—	—	→
Vital signs		✓				✓	✓	✓	✓
Body weight measurement		✓			✓				

Table 1. Assessment details and days of implementation.

Assessment	Screening period	Administration period	Observation period	Suspension
Hematologic test[a]	Day 1	Days 4 and 8	Day 15: implemented as an outpatient examination when the research subject has been discharged. Days 22 and 29: unnecessary when the research subject has been discharged.	Unnecessary when the research subject has been discharged
Biochemical blood inspection[b]	Day 1	Days 4 and 8	Day 15: implemented as an outpatient examination when the research subject has been discharged. Days 22 and 29: unnecessary when the research subject has been discharged.	Unnecessary when the research subject has been discharged
Infectious disease inspection[c]	Day 1	Not implemented	Not implemented	Not implemented
Coagulation test[d]	Day 1	Days 4 and 8	Day 15: implemented as an outpatient examination when the research subject has been discharged. Days 22 and 29: unnecessary when the research subject has been discharged.	Unnecessary when the research subject has been discharged
Coronavirus inspection[e]	Day 1	Day 8	Day 15: implemented as an outpatient examination when the research subject has been discharged.	Implemented when suspended before Day 8
Image inspection[f]	Day 1	Day 8	Day 15 Days 22 and 29: unnecessary when the research subject has been discharged.	Implemented when suspended before Day 8
Peak flow measurement[g]	Day 1	Performed daily	Days 15, 22, and 29	Not implemented
Questionnaire[h]	Day 1	Subjective symptoms recorded daily	Day 15: implemented as an outpatient examination when the research subject has been discharged. Days 22 and 19: obtained by phone when the research subject has been discharged.	Obtained by phone when the research subject has been discharged
Comprehensive assessment by the physician	Day 1	Day 8	Day 15: implemented as an outpatient examination when the research subject has been discharged. Days 22 and 29: unnecessary when the research subject has been discharged.	Unnecessary when the research subject has been discharged
Confirmation of combined drug usage conditions[i]	Not implemented	Information on the presence of concomitant medications collected daily	Days 15, 22, and 29	Not implemented

[a]Leukocyte count, neutrophil count, lymphocyte count, hematocrit level, hemoglobin level, platelet count, and blood sedimentation are to be measured for the hematologic tests.

[b]Albumin, bilirubin, aspartate transaminase, alanine transaminase, lactate dehydrogenase, γ-glutamyl transpeptidase, alkaline phosphatase, creatinine kinase, creatinine, blood urea nitrogen, sodium, potassium, C-reactive protein, glutamic acid, and procalcitonin levels are to be measured for biochemical blood inspections.

[c]Hepatitis B surface antigens, hepatitis B core antibodies, hepatitis C virus antibodies, and HIV antibodies are to be measured for infectious disease inspections.

[d]Prothrombin time, activated partial thromboplastin time, fibrinogen level, and D-dimer level are to be measured for coagulation tests.

[e]For coronavirus inspections, SARS-CoV-2 real-time polymerase chain reaction samples are to be collected with nasal swabs and measured on the day of and 8 days after hospitalization, and serum SARS-CoV-2 antibodies are to be measured on the day of and 8 days after hospitalization.

[f]Chest computed tomography scans are to be taken on the day of and 8 days after hospitalization, and simple chest radiographs are to be taken 4, 8, 15, 22, and 29 days after hospitalization. In addition, image inspections will be conducted as necessary when symptom exacerbation is suspected. Simple chest radiographs on days 22 and 29 will not be taken if the research subject is already discharged. Computed tomography is to be performed when pneumonia worsens within 8 days of hospitalization and when the research is suspended.

[g]Peak expiratory flow is to be measured every morning with a peak flow meter during hospitalization and recorded in a diary.

[h]To be conducted prior to assessment by the physician (eg, before the examination).

[i]Information on drug and treatments other than the trial drug are to be collected.

Data Collection Items and Management

With regard to research subject demographics and background medical information, the following demographic and medical data will be collected: sex, birth date (ie, age), initials, nationality, ethnicity, height, smoking history (ie, presence/absence, the number of cigarettes per day, and the number of years of smoking), complications, medical history,

history of present illness, drug allergies, COVID-19 onset date, PCR positivity date, level of consciousness, hospitalization conditions, ventilator use, extracorporeal membrane oxygenation use, oxygen therapy conditions, physical activity conditions, the presence of intensive care unit management, and miscellaneous combined drug conditions. With regard to subjective and objective symptoms, data on physical findings confirmed through visual, tactile, auditory, and percussion inspections will be collected.

With regard to adverse event observation, in cases where adverse events are confirmed in the research subject, the following information will be confirmed, and the content will be recorded in the clinical record and case report: adverse event name, extent, severity assessment, causal relationship, onset time, outcome, and elimination period.

With regard to vital signs, the following data will be collected during resting conditions: blood pressure, pulse rate, respiratory rate, body temperature, and oxygen saturation. In terms of body weight measurements, body weight and body mass index will be recorded.

Details for blood sample collection are found in Textbox 2.

Textbox 2. Blood sample collection and analysis.

Hematologic test

- The following were measured at each implementing institution: leukocyte count, neutrophil count, lymphocyte count, hematocrit level, hemoglobin level, platelet count, and blood sedimentation.

Biochemical blood inspection

- The following were measured at each implementing institution: albumin level, bilirubin level, aspartate transaminase level, alanine transaminase level, lactate dehydrogenase level, γ-glutamyl transpeptidase level, alkaline phosphate level, creatinine kinase level, creatine level, blood urea nitrogen level, sodium level, potassium level, C-reactive protein level, glutamic acid level, and procalcitonin level.

Infectious disease inspection

- The following were measured at each implementing institution: hepatitis B surface antigen level, hepatitis B core antibody level, hepatitis C virus antibody level, and HIV antibody level.

Coagulation test

- The following were measured at each implementing medical institution: prothrombin time, activated partial thromboplastin time, fibrinogen level, and D-dimer level.

Coronavirus inspection

- Nasal swabs will be taken to test for SARS-CoV-2 infection via real-time polymerase chain reaction. Samples will be temporarily stored at each participating medical institution (ie, stored at below −80°C for blood serum), collected by the National Center for Global Health and Medicine, and quantified at the Tokyo Metropolitan Institute of Public Health.
- Serum samples will be taken to test for the presence of SARS-CoV-2 antibodies. Samples will be temporarily stored at each implementing medical institution (ie, stored at below −80°C for blood serum) and quantified at the National Center for Global Health and Medicine.

The following will be performed for image inspection: high-resolution CT on days 1 and 8, and chest radiography on days 1, 8, 15, 22, and 29.

With regard to peak expiratory flow, measurements will be performed every morning with a peak flow meter and recorded in a diary.

A questionnaire assessment using a 10-stage assessment scale for appetite, fatigue, and cough will be issued on days 1-8, 15, 22, and 29. This questionnaire is to be administered prior to the physician-based assessment (eg, diagnosis) to eliminate bias. The subphysician is not to behave in a manner that induces answers from respondents, and the respondent who is handed the questionnaire must respond to it individually.

A comprehensive assessment is to be conducted by the physician. For this assessment, a 3-stage assessment for general patient conditions is to be conducted on days 8 and 15, relative to day 1. The confirmation of combined drug use conditions will begin on the start date of drug administration and continue until the administration period is complete. Trial drug/combined drug administration conditions will also be recorded.

Discharge outcomes are to be recorded.

Data input into the case report and inquiry responses are to be conducted through the EDC system (REDCap [Research Electronic Data Capture]). A manual with details on inputting data, such as input methods and duration, has been created. Chest CT images and simple chest radiographs taken when research is suspended due to pneumonia onset within 7 days of administration will be sent to the Center Hospital of the National Center for Global Health and Medicine by CD-ROM.

Adverse Event Reporting

The incidence of adverse events, including abnormal variations in clinical inspection values and physiological function inspections, will be recorded. Adverse event incidence duration/elimination duration, extent, treatment, outcomes, severity assessments, correlation with medicinal drugs, and predictability are to be recorded in the diagnostic record and case report.

Adverse event extent will be determined based on certain criteria. Mild adverse events refer to conditions in which continued drug administration is possible with no treatment. Moderate adverse events refer to conditions in which continued drug administration is possible with some form of treatment. Severe adverse events refer to conditions in which drug administration is or should be suspended.

Adverse event severity will be determined using the following criteria: (1) death, (2) conditions that may lead to death, (3) conditions for which hospitalization at a medical institution is necessary or hospitalization duration must be extended for treatment (4) disorders, (5) conditions that may lead to disorders, (6) conditions that are severe according to criteria 1-5, and (7) congenital illnesses or abnormalities due to prior generations. All conditions that are not considered severe will be categorized as nonsevere.

Serious Adverse Events and Disease Reporting

The following procedures will be undertaken when illnesses occur in the present research. With regard to illnesses, this study will use certain definitions relating to disease.

- The term “disease” was defined as an illness, disability, mortality, or infectious disease caused by the implementation of the clinical research, as well as clinical inspection value abnormalities or symptoms. “Disease” was also defined as adverse events that have a causal relationship with the proposed research that cannot be refuted.
- The term “predictability” refers to diseases with incidence tendencies (eg, research subject drug-based disease incidence, the number of incidents, incidence frequency, and incidence conditions) in the disease report that can be predicted from research proposals or documents, explanations, and attached documents that include a summary of the drug. Incidence tendencies that can be predicted will be indicated as “known,” and those that cannot be predicted will be indicated as “unknown.” As a general principle, drugs that have already been approved for research subjects will use the attached documentation as the decision criteria.
- The term “causal relationship” refers to diseases that have a causal relationship with the proposed research that cannot be refuted. At the very least, the correlation with the research subject drug will be determined as a logical possibility, using the GCP ordinance as a guide.

During the implementation of the proposed research, adverse events will be reported in accordance with national guidelines.

Plans for the Assessment and Collection of Outcomes

Participants will be assessed, enrolled, randomized, and followed up. Clinical and laboratory data will be collected by study staff.

Plans to Promote Participant Retention

It has been anticipated that participants will be in the hospital during the treatment phase. Subsequent outpatient visits to the study site will be performed and timed with routine clinic appointments, as per the protocol.

Data Management

The EDC system, REDCap, will be used for the collection of trial data. An input manual with details on the input methodology will be created. Chest CT images and chest radiographs taken when the research is suspended due to pneumonia onset are to be sent to the Center Hospital of the National Center for Global Health and Medicine by CD-ROM.

Confidentiality

Any information that may identify a participant will be excluded from publicly presented data. Furthermore, all study-related information will be stored securely at each study site. All copies of clinical records, reports, data collection documentation, process documentation, and administrative forms will be identified through coded identification. Additionally, the principal physician will retain the stored records that relate to the proposed research for 5 years following the day the proposed research is completed.

Storage of Biological Specimens

Serum and nasal swabs are to be stored in a freezer at a temperature of below −80°C.

The samples from the collaborating research implementing medical institutions will be sent to the National Center for Global Health and Medicine. Serum SARS-CoV-2 antibody values will be measured at the National Center for Global Health and Medicine laboratory, and SARS-CoV-2 PCR assays will be performed at the Tokyo Metropolitan Institute of Public Health. All samples will be stored for 5 years following the day the proposed research is completed.

Statistical Methods

Sample Size

The sample size for the RACCO trial will be 90 patients (ie, n=45 for the ciclesonide group and n=45 patients for the symptomatic treatment group) to control for pneumonia onset and allow for the full analysis of study participants to complete the study.

Based on our experience, 35% of patients who have tested positive for COVID-19 without pneumonia symptoms will have pneumonia during the follow-up period. The necessary number of cases for a 2-sided α-level of 10% and power of 80% for cases with incidence percentages of 30%, 35%, 40%, and 50% in the standard treatment group and incidence percentages of 5%, 10%, 15%, and 20% in the trial treatment group are shown in Figure 3.

The effect of controlling the pneumonia onset percentage to 25% would mean that the drug is clinically effective. The numbers highlighted in grey in Figure 3 are the sample sizes necessary for detecting effects with a power of 80% in cases where a 25% pneumonia onset control is present. For example, if the pneumonia onset percentage of the standard treatment and trial treatment groups were hypothetically set to 35% and 10%, respectively, the required sample size would be 84. Factoring in cases where consent may be withdrawn during the trial or participants drop out, the target number of cases for the present

research will be set at N=90. The target number of cases will be specified for each implementing medical institution.

Figure 3. Sample size calculation. Numbers highlighted in grey represent the sample sizes necessary for detecting effects with a power of 80% in cases where a 25% pneumonia onset control is present.

		Trial treatment group			
		5% incidence, n	10% incidence, n	15% incidence, n	20% incidence, n
Standard treatment group	30% incidence, n	72	116	216	502
	35% incidence, n	56	84	134	244
	40% incidence, n	44	64	94	148
	50% incidence, n	32	40	54	74

Analysis Sets

This study will contain the following 3 analysis sets: the full analysis set, the per protocol set, and the safety analysis set. The full analysis set has been defined as research participants who have been registered in the proposed research, have been randomized, have had their baseline CT image data acquired, and have no serious protocol violations.

The per protocol set has been defined as research participants from the full analysis set after removing cases with the following serious protocol violations: selection criteria violations, exclusion criteria violations, prohibited drug violations, prohibited treatment violations, and a medicine administration compliance of below 90%.

In the safety analysis set, all participants will be analyzed.

Statistical Methods for Primary and Secondary Outcomes

Analyses are to be conducted after drug administration to all patients has been completed and the data have been finalized. For all efficacy assessments, the full analysis set analysis will be set as the primary analysis, and the per protocol set analysis will be conducted as a reference. A safety analysis will also be conducted using the safety analysis set.

The distribution of research subject background data and the summary statistics in each analysis set will be calculated for each group. For nominal variables, category frequency and percentage will be shown for each group. For continuous variables, the summary statistics (ie, number of cases, average value, standard deviation, minimum value, median value, and maximum value) will be calculated for each group.

Intergroup comparisons will be performed with the Pearson Chi-squared test or Fisher exact test for nominal variables. The 2-tailed Student *t* test or Wilcoxon signed-rank test will be used for continuous variables. The significance level will be set at 10% for both sides.

Primary Endpoint Analysis

The primary objective of this study is to verify if the pneumonia exacerbation rate outcome on day 8 in patients with COVID-19 in the ciclesonide administration group is significantly increased compared to that of the symptomatic treatment group.

The primary endpoint analysis will be performed using the Fisher exact test to determine statistically significant differences in pneumonia exacerbation percentages between the ciclesonide and symptomatic treatment groups. The 90% and 95% confidence intervals will be calculated, along with the risk ratio. Secondary analysis will involve identical analyses on the group of patients who do not show evidence of clear pneumonia on simple chest radiographs, but have evidence of pneumonia on chest CT images, and another group of patients whose pneumonia was not observed on chest CT images.

A subgroup analysis based on the following classifications will be conducted: fever presence (ie, over or below 37.5°C), age (ie, over or under 60 years), smoking history (ie, present or absent), and implementing medical institution.

The significance level will be set at 10% for both sides.

Secondary Endpoint Analysis

A secondary endpoint analysis will be conducted with the aim of supplementing the primary analysis results. The significance level of hypothesis testing will be set at 5% for both sides, and the 95% confidence interval for both sides will be calculated.

Pneumonia Exacerbation

The number and percentage of cases divided among 3 assessment levels, including remission or stabilization cases, potential exacerbation cases, and clear exacerbation cases, will

be calculated, and intergroup comparisons will be conducted using the Mantel test.

Change in the Quantity of the Virus Genomes

Quantified virus genomes at each assessment time point, quantified antibody values, and related changes will be calculated for each group and illustrated over time. Furthermore, the average difference between groups and the 95% confidence intervals will be calculated, and intergroup comparisons will be conducted.

Body Temperature, Respiratory Rate, Oxygen Saturation, Systolic Blood Pressure, and Pulse Rate

The recorded metrics of each assessment criterion at each assessment time point will be calculated for each group, and changes over time will be illustrated. The least mean square and 95% confidence interval at each assessment time point, as well as the least mean square difference and 95% confidence interval, will be calculated. The amount of change from day 1 will be used as the result variable by using mixed models for repeated measures (MMRMs), and intergroup comparisons will be conducted.

Fever Duration

The recorded fever temperature for the number of days in which a fever of at least 37.5°C was present during the trial period will be calculated, and intergroup comparisons will be conducted using a 2-tailed *t* test.

Symptom Changes

Recorded symptom scores (ie, malaise/appetite scores) at each time point will be calculated, and changes over time will be illustrated. The least mean square and 95% confidence interval at each assessment time point, as well as the least mean square difference and 95% confidence interval, will be calculated. The amount of change from day 1 will be used as the result variable by using MMRMs, and intergroup comparisons will be conducted.

Changes in Inspection Findings

Recorded metrics for the continuous values obtained through clinical inspection will be calculated at each time point. Furthermore, the least mean square and 95% confidence interval at each assessment time point, as well as the least mean square difference and 95% confidence interval, will be calculated. The amount of change from day 1 will be used as the result variable by using MMRMs, and intergroup comparisons will be conducted.

For categorical variables obtained from inspection findings, the number and percentage of each criterion at each time point will be calculated, and intergroup comparisons will be conducted using a Mantel test.

Oxygen Therapy

The number and percentage of research participants who underwent oxygen therapy during the trial period will be calculated for each group and compared using the Fisher exact test. Furthermore, the average oxygen therapy duration and its 95% confidence interval will be calculated for each group, and intergroup comparisons will be conducted using a 2-tailed *t* test.

Hospital Discharge

The number and percentage of research participants who are discharged from the hospital will be calculated for each group, and comparisons will be performed using the Fisher exact test. Furthermore, a Kaplan-Meier curve for the time until hospital discharge will be calculated.

Peak Expiratory Flow Measurement

Recorded statistics for peak expiratory flow at each time point will be calculated for each group, and changes over time will be illustrated. Furthermore, the least mean square and 95% confidence interval at each assessment time point, as well as the least mean square difference and 95% confidence interval, will be calculated. The amount of change from day 1 will be used as the result variable by using MMRMs, and intergroup comparisons will be conducted.

Comprehensive Assessments by Physicians

The number and percentage of research participants at the 3 comprehensive assessment levels will be calculated for days 8 and 15, and intergroup comparisons will be conducted using the Fisher exact test.

Safety Analysis

The safety endpoints include adverse event incidence and rates. The 95% confidence intervals for determining binomial distribution accuracy will be calculated for the estimated rates that relate to the incidence number and presence of adverse events. Intergroup comparisons will be conducted using the Pearson Chi-squared test or Fisher exact test. The significance level of hypothesis testing will be set at 5% for both sides.

Recorded metrics that are calculated for continuous data, such as clinical inspection criteria and vital signs, and suitable methods (eg, number and percentage) will be used as categorical variables for each group.

Interim Analysis

An intermediate analysis will be conducted after 50% participant enrollment has been achieved to determine whether the primary objective has been attained. If the trial treatment group shows significantly higher efficacy results than the standard treatment group (ie, efficacy suspension), or if the trial treatment group shows significantly lower efficacy results than the standard treatment group and drug superiority cannot be verified, even with the continuation of treatment (ie, inefficacy suspension), the independent monitoring committee will advise on the suspension of the study in order to prevent the continuation of treatment in the disadvantaged treatment group. In order to ensure an α error of 10% in the overall trial, the Lan and DeMets α spending function will be used to adjust for the redundancy of inspections in the intermediate and primary analyses, and the statistical significance of primary endpoint differences between groups will be studied. The O'Brien and Fleming-type α spending function will be used. A Bayesian predictive power based on a noninformative prior distribution will be used for inefficacy suspension determination in the proposed study.

Methods for Additional Analysis

Additional analyses will be conducted after the completion of the additional period and the finalization of the cases, from which data are obtained and presented in a statistical report for the representative physician.

Methods for Handling Missing Data

Questionable issues will be resolved after discussion between the representative physician and the statistical analysis manager. Missing values are not to be filled out, and details on the handling of outliers and abnormal values are to be regulated in the statistical analysis plan.

Oversight and Monitoring

Quality control for ensuring compliance will be performed through monitoring by the Central Coordinating Unit of the Clinical Research Promotion Center at the Tokyo University Hospital. A monitoring plan has been created and approved by the representative physician and the authorizing clinical study examination committee. The principal physician who receives the monitoring reports is to notify the representative physician about the applicable report content as necessary.

No audit has been scheduled, and audits will only be conducted if serious problems are identified in the monitoring reports or if there are any events that impact patient safety.

All documents relating to the research are directly accessible for inspection.

Composition of the Data Monitoring Committee

An independent Data and Safety Monitoring Board (DSMB) has been formed, and it consists of members with no financial or scientific conflicts of interest in this study. The DSMB chair is a clinician with extensive experience in respiratory medicine, DSMBs, and clinical research. The DSMB statistician is an experienced statistician. The other member of the DSMB is an experienced respiratory clinician. The committee's remit is to protect the safety of trial participants by monitoring intermediate safety and operational data during trial implementation, and to provide suitable advice and suggestions to ensure the ethical and scientific validity of the study.

Dissemination Plans

At 1 year after trial registration, the representative physician will report on the progress of this randomized controlled trial to the manager of the implementing medical institution and the Ministry of Health, Labor, and Welfare. A comprehensive report will be submitted at the end of the study.

Trial findings will be communicated at national and international scientific meetings by publications in a scientific journal. In addition, results will be disseminated to trial participants, study staff, clinicians, and patient groups via direct approaches and a variety of traditional and electronic media, including newsletters.

Compensation Criteria

The principal physician, subphysician, and implementing medical institution must conduct suitable diagnoses and treatment and provide clinical care and other measures to ensure that the research subject is receiving the necessary care.

The representative physician has been enrolled in a clinical research insurance plan that includes compensation for the death or physical impediment of the research subject and medical expenses and care needed for the treatment of the health hazards in the research subject, in accordance with the payment conditions of clinical research insurance. The principal physician and subphysicians are also enrolled in a medical professional liability insurance plan.

Results

The first trial participant was enrolled on April 3, 2020. Recruitment and registration are expected to be completed on September 30, 2020, while the follow-up of all participants is expected to be completed by October 31, 2020.

Discussion

Preclinical data [12] have shown that ciclesonide can suppress the viral replication of coronaviruses in cell cultures [12,13], suggesting that ciclesonide can potentially be used to treat COVID-19. This multicenter, prospective, open-label randomized controlled trial has been designed to determine the efficacy and safety of ciclesonide in treating patients with asymptomatic and mild COVID-19. The rationale for choosing such patients was based on the findings of Iwabuchi et al [14,15], who indicated that the ideal ciclesonide administration period should be in the early intermediate stage of infection or the initial stage of pneumonia, prior to the worsening of symptoms.

The eligibility criteria in this study were designed to enroll study participants who had been diagnosed with SARS-CoV-2 infection without pneumonia and were not on any concomitant or prior medication that could affect the efficacy assessments. The trial processes of this study have been designed to be integrated within medical care at the participating hospitals, thereby enabling physicians to easily enroll participants without the need for a large research staff to compliment and implement the treatment, and learn more about the disease. Most of the clinical data will be routinely collected, except for SARS-CoV-2 antibody and viral genome quantification data. Trial staff have also been trained to adhere to the protocol.

There are some limitations that need to be considered. First, a placebo is not available because of the rights to the drug. Second, since this is an open-label study, there is potential for bias in the assessment. To avoid this, the primary endpoint analysis will be performed by a blinded independent radiologist. Third, ciclesonide is a steroid, and it is difficult to distinguish between its antiviral and anti-inflammatory effects.

Other trials that involve ciclesonide are in progress or in planning. Covis Pharma has launched a phase III clinical trial in the United States to evaluate the asthma drug, ciclesonide (ALVESCO), in treating nonhospitalized patients with symptomatic COVID-19 aged ≥12 years. In this US trial, participants will be given 320 μg of ciclesonide (ALVESCO) via metered-dose inhaler twice daily, along with standard supportive care or a placebo and standard supportive care. The primary endpoint of the Covis Pharma trial is the percentage of

patients who were admitted to a hospital or died by day 30 [16]. The accumulation of findings from the RACCO study together with those from the other trials will be significant in developing interventions and treatments for COVID-19.

In conclusion, the RACCO study is an ongoing open-label randomized controlled trial that will provide the most definitive comparative effectiveness data to date and other important clinical outcomes data from the ciclesonide and symptomatic treatment groups. If the hypotheses that pneumonia exacerbation rate reduction is more significant in the ciclesonide treatment group than in the symptomatic treatment group and that ciclesonide is safe for use are valid, ciclesonide will provide an important therapeutic option for patients with COVID-19 that can be rapidly implemented in clinical practice.

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Conflicts of Interest

None declared.

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Abbreviations

CT: computed tomography
DSMB: Data and Safety Monitoring Board
EDC: electronic data capture
GCP: good clinical practice
jRCT: Japan Registry of Clinical Trials
MMRM: mixed model for repeated measures
PCR: polymerase chain reaction
RACCO: Randomized Ciclesonide COVID-19
REDCap: Research Electronic Data Capture

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Protocol

A Patient-Centered Asthma Management Communication Intervention for Rural Latino Children: Protocol for a Waiting-List Randomized Controlled Trial

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Abstract

Background: Rural Latino children with asthma suffer high rates of uncontrolled asthma symptoms, emergency department visits, and repeat hospitalizations. This vulnerable population must negotiate micro- and macrolevel challenges that impact asthma management, including language barriers, primary care access, parental time off from work, insurance coverage, distance from specialty sites, and documentation status. There are few proven interventions that address asthma management embedded within this unique context.

Objective: Using a bio-ecological approach, we will determine the feasibility of a patient-centered collaborative program between rural Latino children with asthma and their families, school-based nursing programs, and primary care providers, facilitated by the use of a smartphone-based mobile app with a Spanish-language interface. We hypothesize that improving communication through a collaborative, patient-centered intervention will improve asthma management, empower the patient and family, decrease outcome disparities, and decrease direct and indirect costs.

Methods: The specific aims of this study include the following: (1) Aim 1: produce and validate a Spanish translation of an existing asthma management app and evaluate its usability with Latino parents of children with asthma, (2) Aim 2: develop and evaluate a triadic, patient-centered asthma intervention preliminary protocol, facilitated by the bilingual mobile app validated in Aim 1, and (3) Aim 3: investigate the feasibility of the patient-centered asthma intervention from Aim 2 using a waiting-list randomized controlled trial (RCT) to investigate the effects of the intervention on school days missed and medication adherence.

Results: Mobile app translation, initial usability testing, and app software refinement were completed in 2019. Analysis is in progress. Preliminary protocol testing is underway; we anticipate that the waiting-list RCT, using the refined protocol developed in Aim 2, will commence in fall 2020.

Conclusions: Tailored, technology-based solutions have the potential to successfully address issues affecting asthma management, including communication barriers, accessibility issues, medication adherence, and suboptimal technological interventions.

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KEYWORDS

asthma; mHealth; mobile app; Latino; pediatrics; family-centered care; school nursing; rural health; RCT; mobile phone

Introduction

Background

Rural Latino children with asthma and their families may experience unique, multilevel barriers to effective asthma management, contributing to disparate health outcomes and broader health disparities. Children with asthma insured by Medicaid disproportionately represent emergency department (ED) visits, including repeat visits [1], and are more likely to require repeat hospitalizations for uncontrolled asthma symptoms [2]. Patients and families who are able to address environmental triggers, address medication adherence, and access timely primary care visits have fewer exacerbations requiring emergency interventions, resulting in significantly reduced direct and indirect costs, fewer lost school days and workdays, and improved quality of life. Evidence suggests that Latino people are more likely to access and use mobile health (mHealth) apps, especially if the app contains a Spanish-language interface [3]; however, there are no asthma management apps currently available in Spanish.

Barriers and Solutions to Effective Asthma Management

Communication With and Between Health Care Providers

Sporadic availability of language interpreters, especially in rural areas and in systems with limited resources, often results in providers "getting by" with problematic solutions, such as child interpreters or overestimating their ability to communicate in the target language [4]. Beyond the obvious communication challenges that participants in language discordant interactions can encounter, parents report significant issues in conflicting management styles and communication between health care providers [5], causing parents to become frustrated with their child's care [6].

Continuity of Care

Parents express a preference for primary care management of their child's asthma, and patients who have primary care appointments soon after an asthma exacerbation requiring an ED visit are less likely to require a repeat ED visit during the following month [7]. However, there are real and perceived barriers experienced by these families, including the inability to schedule urgent visits or parental work demands [5]. Further, continuity of care and primary care access may be compromised due to insurance status [8]. The vast majority of patients do not follow up after suffering an asthma exacerbation requiring emergency intervention, even when they have insurance and an identified primary care provider (PCP) [9].

Lack of Adherence to Medication

Latino patients are less likely to take asthma medications as prescribed when compared to non-Latino White people [10]. Cost, access challenges, and knowledge deficits contribute to suboptimal medication adherence, often related to difficulty obtaining the appropriate medications and devices, such as spacers or nebulizer machines, due to lack of insurance coverage or cost. Knowledge deficits (eg, parental beliefs that prolonged use of asthma medication can cause weakening of the lungs, bone density loss, medication dependence, or cardiac complications) and parental perceptions regarding the necessity of their child's asthma medication can negatively influence preventative therapy adherence [11].

Fragmented Technological Interventions

Technological interventions, including mobile apps to assist the patient with asthma management, are readily available for use on smartphones. However, few apps incorporate functions associated with improved patient outcomes [12]. For example, some asthma apps offer the ability to track medications and asthma symptoms but do not allow the correlation and sharing of data. There are no apps available currently that (1) allow secure storage and correlation of medication administration, symptoms, and exacerbations requiring medical intervention, (2) allow health care providers to access the patient data to examine trends over time, and (3) are available in Spanish.

School Nursing Programs

School nursing programs have the potential to positively impact childhood chronic disease management, including asthma, as approximately 90% of elementary and secondary school–age children are enrolled in public schools in the United States [13]. School-based educational programs have been shown to increase parents' knowledge regarding environmental triggers for their children's asthma [14,15], but school-based services often do not meet National Heart, Lung, and Blood Institute asthma management guidelines [16]. In addition, while educational programs delivered by school nurses are effective in improving patient asthma knowledge, these nurses face their own unique barriers, including time to attend educational programs and provide case management for the students with asthma, specific knowledge deficits, and having confidence in their ability to independently implement asthma programs [17]. The challenges school nurses face in caring for their students with asthma are compounded when parents have limited English proficiency. However, a clear understanding of how existing relationships and systems can be leveraged and coordinated has the potential to streamline the disease management process and effectively address outcome disparities among rural Latino children with asthma.

Contribution of Proposed Project to Advancing Scientific Knowledge and Public Health

Overview

The proposed feasibility study is supported by a K23 award; this type of award provides individuals who have a clinical doctoral degree with an intensive, supervised, patient-oriented research experience. This study addresses a gap in our current understanding of best practices for asthma management in vulnerable populations. While the majority of the 56 million US Latino people live in urban areas, this population is increasingly moving to nontraditional, rural settlement areas such as South Carolina. Latino children born in rural areas are significantly more likely to be poor, have limited access to services, and live in substandard housing associated with migrant farming [18]. My previous research has identified unique barriers impacting asthma management in rural Latino children,

including parental documentation status, access to transportation, and distance to specialty sites [19]. My focus on a targeted, patient-controlled intervention taking multilevel pressures into account may reduce the disparities suffered by this vulnerable population.

Innovation

Innovative aspects of this project include the bio-social-ecological framework, the patient-centered and collaborative approach, and the utilization of bilingual technology. The bio-ecological perspective guiding the research addresses the *specific challenges rural Latino children and their families face* when managing asthma care embedded in a complex interaction of environments, agencies, and systems. The research incorporates patient-centered and community-based collaboration, building on a patient- and family-directed collaboration, rather than an institutionally situated intervention, and leveraging existing systems such as school nursing programs. Bilingual technology addresses language discordance. The app does not translate; rather, the parent and caregiver interface is in Spanish and input is securely transmitted to the school nurse and accessible in English. The use of the Spanish-language version of *AsthmaMD* (AMD-Sp), a free asthma management app, will facilitate day-to-day communication between the school nurse and the parent or caregiver, minimizing the daily need for an interpreter.

Theoretical Framework

My preliminary studies and proposed study are guided by a bio-ecological conceptualization of the complex interactions and intersections of multilevel factors with childhood asthma management in a specific vulnerable population group: rural Latino children with asthma. I will use Bronfenbrenner's Process-Person-Context-Time model to organize the study approach, intervention design, and data analysis (see Table 1) [20]. The concepts in this model allow for identification and examination of relevant variables that contribute to poorer health care outcomes (eg, communication issues within and between patients and system representatives, where people live, health care accessibility, socioeconomic status, demographics, individual knowledge, and how people and environments change over time).

Table 1. Bronfenbrenner's Process-Person-Context-Time model and ecological levels.

Ecological level	Associated factors
Microsystem	Patient: knowledge deficits and medication adherence
	School nurse: knowledge and informational deficits
	Primary care provider: knowledge and informational deficits
Mesosystem	Interactions between the patient and family and school nurses
	Interactions between the patient and family and provider
	Interactions between the provider and school nurses
Exosystem	Effects of transportation issues
	Effects of work attendance constraints
	Effects of documentation status
Chronosystem	Knowledge change over time
	Medication adherence over time
	Biophysical measures over time
	Emergency department visits (retrospective and prospective)
	Sustainability of program after feasibility study is complete

Preliminary Studies

The first preliminary study was *Patterns of communication technology utilization for health information among Hispanics in South Carolina: Implications for health equity* [19]. This cross-sectional, descriptive study examined patterns of technology use and health care information seeking and service access among South Carolina–based Latino people with limited English proficiency. Data were collected in two waves; 361 Latino people completed surveys. Self-reported accessibility and utilization of cell phones increased (89% in 2011 to 96.6% in 2015-2016), supporting the feasibility of using a technology-based approach in this proposal.

The second preliminary study was *Exploring app features with outcomes in mHealth studies involving chronic respiratory diseases, diabetes, and hypertension: A targeted exploration of the literature* [21]. This review identified 27 studies that utilized mobile apps in the management of selected chronic diseases: diabetes, hypertension, and asthma. The use of at least one of four specific app features was associated with improved patient outcomes; the app proposed for the study, *AsthmaMD*, contains two of these features, including clinical data shared with health care providers through interoperability and incorporation of an evidence-based clinical decision support system.

The third preliminary study was *Urban-rural differences in school nurses' asthma training needs and access to asthma resources* [22]. This survey study was conducted with school nurses in South Carolina, including those in the Lancaster County School District (LCSD), which had 100% participation rate. At the time, only 16% of participants were implementing an asthma program in their school, yet the vast majority (87%) of nurses expressed a desire for further asthma training programs.

The preliminary data from these studies substantiate the uptake of technology by rural Latino people, as seen by improved patient compliance with certain features of apps that are contained in the *AsthmaMD* app and an increase in school nurses' willingness to participate in the study.

Methods

Study Overview

This project received funding from the National Heart, Lung, and Blood Institute of the National Institutes of Health (NIH) (2017-2022). Guided by a bio-ecological theoretical framework, the primary goal of this research is to develop and evaluate a patient-centered collaborative intervention between rural Latino children with asthma and their families, school-based nursing programs, and PCPs, facilitated by the use of a smartphone-based Spanish-language mobile app. The three specific aims are as follows:

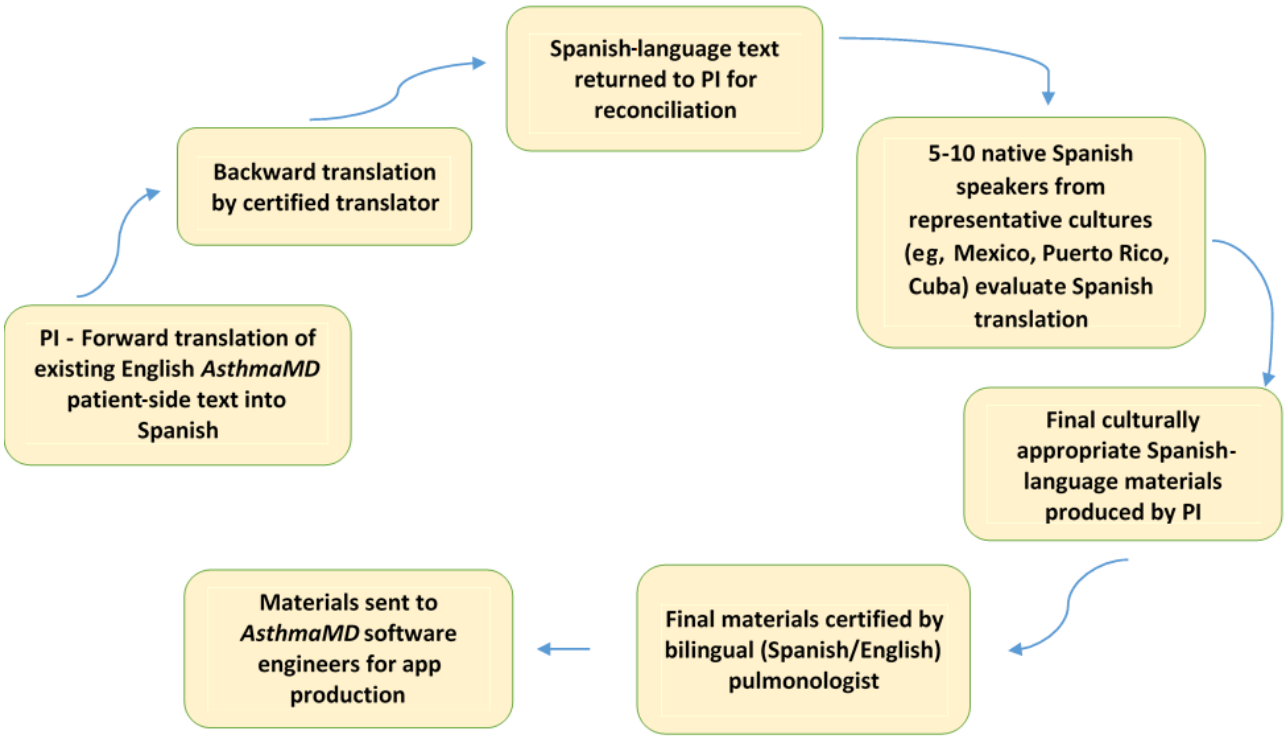
1. Produce and validate a Spanish translation of an existing asthma management app and evaluate its usability with Latino parents of children with asthma.
2. Develop and evaluate a triadic, patient-centered asthma intervention preliminary protocol, facilitated by the bilingual mobile app validated in Aim 1.
3. Investigate the feasibility of the patient-centered asthma intervention from Aim 2 using a waiting-list randomized controlled trial (RCT) to investigate the effects of the intervention on school days missed and medication adherence.

Aim 1: Produce and Validate a Spanish Translation of the App

Overview

Figure 1 shows the systematic translation process of an existing asthma management app, *AsthmaMD*. We will create a Spanish-language version of *AsthmaMD*, AMD-Sp, a free asthma management app, and will evaluate its usability with Latino parents of children with asthma. Users of the existing *AsthmaMD* app are able to (1) track their maintenance and rescue medications as well as set medication administration reminder alerts, (2) produce an asthma action plan, (3) note asthma symptoms and exacerbations, including ED visits, and (4) share this information with health care providers securely. An unpublished analysis by *AsthmaMD* developers demonstrated that English-speaking adult users with higher app engagement had improvement in their pulmonary function measurements by a minimum of 10% after 6 months of usage. Three independent certified translators will render the English app text into Latin American Spanish, as the population targeted in this study is primarily of Mexican origin, using methods adapted from Squires et al [23] (see Figure 1). *AsthmaMD* software engineers will use the certified, translated materials to produce AMD-Sp for the iOS platform. The state of South Carolina has a contract with Verizon Wireless that will allow me to minimize the costs associated with the hardware (ie, iPhones) and data plans necessary to implement the intervention.

Figure 1. Systematic translation process of an existing asthma management app. PI: principal investigator.



Participant Recruitment

Once developed, I will recruit a convenience sample of 5 limited English–proficient Latino parents or caregivers of children with asthma to use the app for a week. They will examine the app for learnability, memorability, number of errors made in use, and satisfaction [24]. I will employ a usability heuristic to identify potential problems [25]. Participants will receive a US $25 cash incentive on return of the phone.

App Refinement

We will consider modification of app software as needed at each step of the evaluation, including translation, usability, and protocol development.

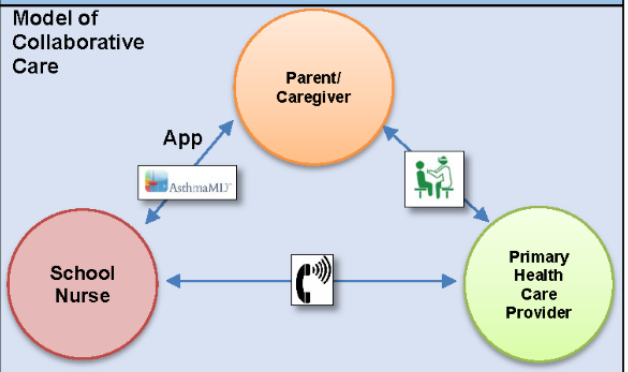
Aim 2: Develop and Evaluate the Preliminary Protocol for a Triadic, Patient-Centered Asthma Intervention

Overview

The goal of this aim is to develop a pragmatic, acceptable, and financially sustainable *model of collaborative care* intervention (see Figure 2) facilitated by the Spanish-language mobile app validated in Aim 1. I will utilize the data from my study *Experiences of rural Southeastern Latino parents of children with asthma* to identify patient and family issues of importance to this collaboration. To situate the collaboration, I will utilize the analysis of relevant South Carolina epidemiological data to account for macrolevel issues that may impact the collaboration. Once developed, evaluated, and refined, the protocol generated by Aim 2 will be used in Aim 3.

Figure 2. Preliminary protocol. ED: emergency department; NHLBI: National Heart, Lung, and Blood Institute; PCP: primary care provider.

School Nurse Responsibilities | Parent/caregiver Responsibilities | Primary Health Care Provider Responsibilities

Intervention Steps	Rationale
With assistance from the bilingual research assistant, parent/caregiver will: • Enter child's information into app, which then generates asthma action plan • Set up repeating, daily medication reminders • Attach medication counters to inhalers if needed	Interactivity with the research assistant increases study engagement/participant retention • Assures accuracy of information loaded into app • Assures information loaded into app is entered correctly • Objective means of determining medication adherence
School nurse reviews asthma action plan with primary health care provider via existing communication school district protocols	App-generated asthma action plan is consistent with NHLBI guidelines
Asthma action plan is approved by primary health care provider and documented in patient chart	All participants in the study are operating from the same, current information
Parent/caregiver prospectively and daily uploads medication administration and daily symptom information for 2 weeks	Early evaluation and troubleshooting of app facilitated communication. Bilingual research assistant will recontact parent/caregiver in 48 to 72 hours to reinforce training
Protocol Implementation	
Parent/caregiver uses app to: • Record medication administration (inhaled steroids, rescue inhalers, oral medications) and daily symptoms • Record asthma exacerbations managed at home as well as exacerbations requiring outpatient and/or emergency department intervention • Transmit information securely via app daily to school nurse	Model of Collaborative Care 
Parent/caregiver will communicate any nonemergent questions or concerns to the school nurse with assistance from the bilingual research assistant, who will be available via phone/text	
School nurses will review all data transmitted by the parent/caregiver to the school-based computer (asthma symptoms and medication adherence trends, as well as asthma exacerbations) daily	
School nurse will contact the primary health care provider for: • Deviations in the asthma action plan • An ED visit noted for further orders or to facilitate setting up a clinic follow-up visit • Asthma symptoms noted by the child's teacher	Allows the nurse and primary health care provider to collaborate and adjust maintenance medications if indicated, or set up an outpatient clinic visit
School nurse will perform any physical assessments as indicated after collaboration with the PCP (eg, pulse oximetry, lung sounds, respiratory rates)	
School nurse will contact the family by phone with assistance of the bilingual research assistant for additional training if weekly review reveals no information input in the app	
Primary health care provider will be available weekly and as needed to the school nurse, and to review asthma action plan	
Primary health care provider will facilitate appointment availability as indicated by the school nurses' assessment and recommendation	

Participant Recruitment

Overview

Five triads of participants will participate in the preliminary protocol. First, I will arrange a meeting with clinic and school representatives to develop an acceptable communication protocol between these institutions. As a former full-time, and now part-time, employee I have an established relationship with the largest pediatric primary care facility in Lancaster, South Carolina, which has a large Latino patient base, as well as with the LCSD. The director of student services, along with the director of nursing services, has already made a commitment to this study. Participants include three distinct groups, listed in order of recruitment: (1) a PCP, (2) Latino children with asthma and their parents or caregivers, and (3) school nurses. SPH and DHM will guide me in subject recruitment [26] as discussed in the following sections.

Primary Care Provider

A local pediatrician who has practiced primary care pediatrics in Lancaster County for over 15 years has agreed to participate; her consent will be obtained prior to initiating the identification of potential Latino children participants.

Latino Children With Asthma and Their Parents or Caregivers

I will purposively recruit a convenience sample of 5 Latino children with asthma, along with their parents or primary caregivers who have limited English proficiency; who reside in Lancaster County, South Carolina; and who are patients at the local pediatrician's clinic. The pediatrician will assist in the identification of appropriate participants, and I will also utilize Spanish-language recruitment flyers to be placed at the outpatient clinic. Once participants are identified and express interest in participating in the study, a bilingual research assistant will contact them personally to give an overview of the study and obtain consent (parents) and assent (child), as well as appropriate Health Insurance Portability and Accountability Act (HIPAA) and medical records release forms. Inclusion criteria are as follows: (1) children who self-identify or family-identify as Hispanic or Latino, (2) school-aged (5-12 years) children who attend school within the LCSD, (3) children who have received a diagnosis of asthma from a health care provider and are taking a controller medication, and (4) parents' or primary caregivers' (eg, grandparents and extended family) language of preference is Spanish.

School Nurses

The LCSD includes 21 schools serving 11,500 students. Each of these schools has at least one dedicated nurse: a licensed practical nurse or a registered nurse. Once patient participants are identified, I will contact the nurses at the school they attend to review the study and obtain their consent to participate. Once the participants have been enrolled, they will participate in targeted training, as described in the following sections.

Training

Primary Care Provider and School Nurses

I will conduct one-on-one sessions with the PCP and school nurses to explain how the patient enters information (ie, medication administration and symptoms) into the app. For the school nurses, I will demonstrate how to access the digitally encrypted information using their site-based computers, which are available at all LCSD schools, as well as provide a short manual of instructions that will include screenshots and frequently asked questions.

Parents and Caregivers of Latino Children With Asthma

An iPhone 5 will be provided for each participant, to be returned at the conclusion of the study. The phone will have AMD-Sp installed. They will review the information on the phone data plan, how to use the iPhone, and how to enter information into the app. At the completion of Aim 2, parents and guardians will receive US $100 cash per family.

Intervention: Developing a Model of Collaborative Care

Overview

The intervention development stage will begin after completion of the initial educational activities. Enrolled participants will be followed over 3 months using the preliminary protocol (see Figure 2), with the understanding that this protocol is adaptable and flexible as the study progresses.

Parents and Caregivers of Latino Children With Asthma

As each subject is recruited and enrolled, a bilingual research assistant will conduct a training session with the child as well as with the parent or caregiver in Spanish. They will also be given a short instruction manual, in Spanish, with screenshots and frequently asked questions.

Data Collection, Analysis, and Protocol Refinement

Formative Data Collection for All Participants

Demographic information will be obtained from all enrolled participants: school nurses, parents and caregivers, children, and health care providers.

Quantitative Data Collection

We will perform medication counts monthly; asthma medications that do not have counters or individual vials, such as some metered-dose inhalers, will be fitted with a PuffMinder, a digital inhaler dose counter. These results will be compared to the self-report medication adherence information entered into the app by the parent or caregiver.

Qualitative Data Collection

Postintervention data regarding the experiences of the participants in this collaborative intervention will be obtained through a postintervention focus group facilitated by the principal investigator (PI) with the PCP and school nurses; in addition, five interviews will be conducted by a bilingual research assistant with the Latino families. These focused, semistructured encounters will be guided by open-ended questions detailed in interview guides to be developed. Audio data will be digitally recorded, then transcribed in Spanish by Verbal Ink; data will be managed with the NVivo 10 platform (QSR International) [27]. A qualitative, descriptive, thematic analysis approach will inform the transcript analysis. The data analysis will be conducted by the PI with input from DHM, who has an extensive background in qualitative research. She

and I will be responsible for the iterative process of data analysis, and will conduct open and focused coding as well as thematic analysis [28].

Potential Limitations and Solutions

The results from Aims 1 and 2 will be used to refine the intervention for Aim 3. For example, if we find that the PCP prefers to communicate with the school nurses via secure email instead of by phone, we will adjust the procedures. If the school nurses have issues accessing the data, I can offer additional training. As self-reports of adherence may be inflated, we will compare medication counts with information entered into the app by the parent or caregiver. Finally, even though AMD-Sp is easy to use and will require approximately five minutes of the parent's or caregiver's time to log symptoms and medication adherence information, if the parent or caregiver is having difficulty using the technology, my bilingual research assistant will provide additional support. I will be tracking app usage for the first week of each new enrollee to discuss concerns and strategies. We are aware of the possibility that these participants may have some unknown difficulties. If this preliminary step reveals this to be an issue, we can consider simple modifications to the study plan, such as the use of a short messaging service (ie, text messaging, which is associated with improved chronic disease management) in lieu of the app.

Aim 3: Investigate the Feasibility of the Patient-Centered Asthma Intervention

Overview

With the results from Aim 2, I will refine the collaborative intervention and produce the protocol to be utilized in Aim 3. Using a waiting-list RCT, I will then evaluate the feasibility and acceptability of the intervention, including dosing, fidelity, recruitment, and retention [29], and investigate the effects of the intervention on school days missed and medication adherence.

Participant Recruitment

Participant recruitment will occur on a rolling basis and will follow the same procedure as noted in Aim 2, except that 20 Latino families will be recruited, following the same inclusion and exclusion criteria, for this arm of the study. Participant responsibilities will also remain as noted in Aim 2, unless there is a need to modify them based on the qualitative results from Aim 2. As the families are enrolled in the study, they will be randomly assigned to either the intervention group or the waiting-list control group. After the initial 10 intervention group participants complete the 6-month data collection period, the 10 waiting-list control group participants will then proceed with the 6-month intervention. In addition to Dr Ambati, there are additional pediatricians and nurse practitioners at the primary care clinic site, as well as other pediatric providers in the area served by the LCSD. An invitation to participate will be extended to them as well. Participant training will follow the procedures outlined previously. At the completion of the study, parents and guardians will receive US $100 cash per family.

Intervention

The refined protocol developed at the end of Aim 2 will be used to direct the intervention stage of Aim 3; it is anticipated that the steps will be similar. Participants will be followed for 6 months.

Data Collection

Anticipated quantitative data that will result from Aim 3 include the information entered into the app by the parent or caregiver, which are then encrypted and transmitted to the school nurse. These data will include selected NIH and Agency for Healthcare Research and Quality standardized asthma outcomes [30], including the primary outcome measures of medication adherence information (ie, asthma medication ratio [31], which is predictive of childhood asthma ED visits and hospitalizations) and school days missed. This school district requires HIPAA waivers to allow communication between school nurses and local health care providers and will be able to provide information on recorded school absences once informed consent forms are obtained. Secondary outcome measures include frequency of rescue inhaler use, as well as asthma exacerbations, outpatient clinic visits, and ED visits (see Table 2). Lung capacity will be obtained using spirometry pre- and postintervention [32] to obtain relevant lung function variables, such as FEV1 (forced expiratory volume in 1 second) and FEV1/FVC (forced vital capacity). Measures from the control group will include medication counts, number of asthma exacerbations, ED and outpatient clinic visits, and spirometry measures on enrollment, during the intervention phase, and again at the end of the intervention.

Table 2. Outcome measures and their details.

Outcome variable	Description	Source of data	Type of measure
Medication adherence—asthma medication ratio (primary outcome)	Medication administration data uploaded to the app	Parents	Continuous
Medication adherence—asthma medication ratio (primary outcome)	Medication counts performed monthly by the principal investigator	Principal investigator	Continuous
School days missed	School absences secondary to asthma symptoms	Nurses	Continuous
Asthma exacerbations	Number of asthma exacerbations uploaded to the app	Parents	Continuous
Frequency of rescue inhaler use	Albuterol usage for wheezing episodes	Parents	Continuous
Emergency department visits	Number and dates of emergency department visits uploaded to the app	Parents	Categorical
Outpatient clinic visits	Number and dates of outpatient clinic visits uploaded to the app	Parents	Continuous

Data Security

Biometric data are shared by the parent with the school nurse and PI through the AMD-Sp app by selecting and sending all uploaded information directly to the designated recipients. The app will be password protected to prevent unauthorized access to the information in case of phone loss [33].

Power Analysis

Formal power analyses are not presented for this study, because (1) we do not have useful effect size estimates and (2) the resources available for K23 research virtually insure an underpowered research design. Our sample of 20 (10 in each group) thus represents far less than .80 power. We will have power to detect an effect size of 1.16 in the mean asthma medication ratio between the intervention group and control group; the power to detect a large effect size (0.80) is .53 [34,35]. Our goals are to arrive at effect size estimates for future work.

Statistical Analysis

The main analysis for Aim 3 will be to compare the average adherence between the case and control groups. This comparison will be made via PROC REG in SAS, version 9.4 (SAS Institute) [36]. We will also compare mean rates of the asthma medication ratio using the Wilcoxon rank-sum test. A 1-sided *P* value of .05 will be considered significant for all analyses. I anticipate that the results will support the rationale for an RCT focused on a scalable, multisite, multicounty version of this intervention, with state-level stakeholders such as Select Health, at the conclusion of this study.

Results

The University of South Carolina Institutional Review Board reviewed the study protocols for Aims 1 and 2 and these were approved after expedited review. The mobile app translation, initial usability testing, and app software refinement were completed in 2019. Analysis is in progress. Preliminary protocol testing is underway; we anticipate that the waiting-list RCT, using the refined protocol developed in Aim 2, will commence in fall 2020.

Discussion

This collaborative mHealth intervention study addresses a gap in our current understanding of best practices for asthma management in specific vulnerable populations. Tailored, technology-based solutions have the potential to successfully address issues affecting asthma management, including communication barriers, accessibility issues, medication adherence, and suboptimal technological interventions.

Conflicts of Interest

None declared.

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Abbreviations

AMD-Sp: Spanish-language version of AsthmaMD
ED: emergency department
FEV1: forced expiratory volume in 1 second
FVC: forced vital capacity
HIPAA: Health Insurance Portability and Accountability Act
LCSD: Lancaster County School District
mHealth: mobile health
NIH: National Institutes of Health
PCP: primary care provider
PI: principal investigator
RCT: randomized controlled trial

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Protocol

COVID-19 Misinformation Prophylaxis: Protocol for a Randomized Trial of a Brief Informational Intervention

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Abstract

Background: As the COVID-19 pandemic continues to affect life in the United States, the important role of nonpharmaceutical preventive behaviors (such as wearing a face mask) in reducing the risk of infection has become clear. During the pandemic, researchers have observed the rapid proliferation of misinformed or inconsistent narratives about COVID-19. There is growing evidence that such misinformed narratives are associated with various forms of undesirable behavior (eg, burning down cell towers). Furthermore, individuals' adherence to recommended COVID-19 preventive guidelines has been inconsistent, and such mandates have engendered opposition and controversy. Recent research suggests the possibility that trust in science and scientists may be an important thread to weave throughout these seemingly disparate components of the modern public health landscape. Thus, this paper describes the protocol for a randomized trial of a brief, digital intervention designed to increase trust in science.

Objective: The objective of this study is to examine whether exposure to a curated infographic can increase trust in science, reduce the believability of misinformed narratives, and increase the likelihood to engage in preventive behaviors.

Methods: This is a randomized, placebo-controlled, superiority trial comprising 2 parallel groups. A sample of 1000 adults aged ≥18 years who are representative of the population of the United States by gender, race and ethnicity, and age will be randomly assigned (via a 1:1 allocation) to an intervention or a placebo-control arm. The intervention will be a digital infographic with content based on principles of trust in science, developed by a health communications expert. The intervention will then be both pretested and pilot-tested to determine its viability. Study outcomes will include trust in science, a COVID-19 narrative belief latent profile membership, and the likelihood to engage in preventive behaviors, which will be controlled by 8 theoretically selected covariates.

Results: This study was funded in August 2020, approved by the Indiana University Institutional Review Board on September 15, 2020, and prospectively registered with ClinicalTrials.gov.

Conclusions: COVID-19 misinformation prophylaxis is crucial. This proposed experiment investigates the impact of a brief yet actionable intervention that can be easily disseminated to increase individuals' trust in science, with the intention of affecting misinformation believability and, consequently, preventive behavioral intentions.

Trial Registration: ClinicalTrials.gov NCT04557241; https://clinicaltrials.gov/ct2/show/NCT04557241

International Registered Report Identifier (IRRID): PRR1-10.2196/24383

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KEYWORDS

COVID-19; misinformation; infodemic; infodemiology; trust; trust in science; protocol; intervention; health information; prevention; behavior

Introduction

COVID-19 and Misinformation

The COVID-19 pandemic has significantly affected the United States in numerous ways, both directly and indirectly. As of July 17, 2020, the number of daily new cases per 100,000 people was sharply increasing at a rate that exceeded corresponding increases in testing numbers across various states in the country [1]. The same day, the death toll due to COVID-19 in the United States was 133,600 [2], but this number did not reflect the anticipated lag time between diagnosis and fatality. In addition, there has been extensive disruption of most major societal structures, including economic and educational systems during the pandemic [3]. From July 10 to July 17, 2020, alone, the Centers for Disease Control and Prevention (CDC) reported 133 news stories about major social impact due to COVID-19 [4].

Behavioral preventive measures continue to be an effective primary public health tool for addressing challenges during the pandemic [5-7]. However, adherence to behavioral recommendations to prevent COVID-19 spread has been inconsistent, especially in the United States, with documented instances of refusal among lawmakers [8], airline passengers [9], general consumers [10], and churches [11], among others. As COVID-19 cases and related fatalities continue to rise, it is critical to identify the factors underpinning refusal to undertake basic preventive measures against disease transmission and adopt suitable measures to address them.

In addition to the spread of COVID-19, researchers have reported extensive proliferation of misinformation and conspiracies about the disease [12-14]. Intensive efforts have been made to delineate the accuracy of information about COVID-19 shared on social media (ie, by using natural language processing) [15]. However, numerous governmental and scientific organizations have simultaneously issued inconsistent and contradictory guidance about preventive measures such as face masks, further complicating the issue [16]. Although differential but reasonable interpretations of extant data and modification of recommendations in response to new data are expected of the scientific process, public correspondence, including that via official channels, has suggested otherwise. This oversaturation—with different sources of information of varying quality being constantly disseminated—adds considerably to the complexity of COVID-19 prophylaxis and may have real-world consequences. For example, one can identify specific, problematic behavioral outcomes that can be conceptually mapped to believing particular misinformed COVID-19 narratives (eg, 5G wireless, Bill Gates vaccination, and restriction of liberty) [17].

Research on misinformation and conspiracy theories, in general, has suggested that political orientation [18], religious commitment [19], and cognitive sophistication [20] are core factors associated with such beliefs. However, emerging research and commentary specific to COVID-19, including our own study, have indicated strong associations between trust in science and political and religious factors, as well as the belief in misinformed narratives and support for public health prevention efforts [17,21-24].

COVID-19 Nonpharmaceutical Preventive Behaviors

Extant cross-sectional research investigating COVID-19 nonpharmaceutical preventive behaviors (NPBs) has frequently identified that unchangeable factors or hard-to-change factors serve as significant predictors, such as political beliefs [25,26], choice of news channel [27], age, and sex [28]. Single studies have reported that COVID-19 conspiracies may mediate between vertical individualism (believing that people are autonomous and unequal) and social distancing [29] and that beliefs about the efficacy of NPBs increase voluntary preventive compliance [30]. Other studies have also indicated that self-efficacy and perceived severity might be associative factors of NPBs [31,32].

Thus far, only 2 experimental studies on COVID-19 misinformation and NPBs have been conducted. One study focused on the likelihood of sharing false narratives on social media and found that sharing misinformation is a function of inattention, but this study did not examine trust or beliefs [33]. The other study focused on trust in science and examined political orientation as a moderating variable, using support for social distancing as the outcome, but this study did not address misinformation [23]. To our knowledge, our proposed study will be the first experimental study to examine improving trust in science as a means of reducing the likelihood of believing scientifically implausible narratives about COVID-19 and increasing intentions to engage in COVID-19 NPBs.

Specifically, we will expand on current knowledge by assessing whether exposure to a brief informational statement (in the form of an infographic) about the scientific process can increase trust in science, reduce the likelihood of believing scientifically implausible narratives about COVID-19, and increase intentions to engage in recommended COVID-19 NPBs. Given the scale and scope of the pandemic, an intervention with a small effect size, if feasible to deploy within the cost-effective US social media infrastructure, would have the potential to save lives through increased adherence to NPBs. However, it is important not to rush the deployment of brief social media campaigns without careful research and planning to verify efficacy, given that such campaigns could have iatrogenic effects even when designed by scientists and media experts [34,35]. This echoes the recent findings by Lane and Fauci [36], who remind researchers even in the context of a pandemic, it is important to generate scientifically sound evidence.

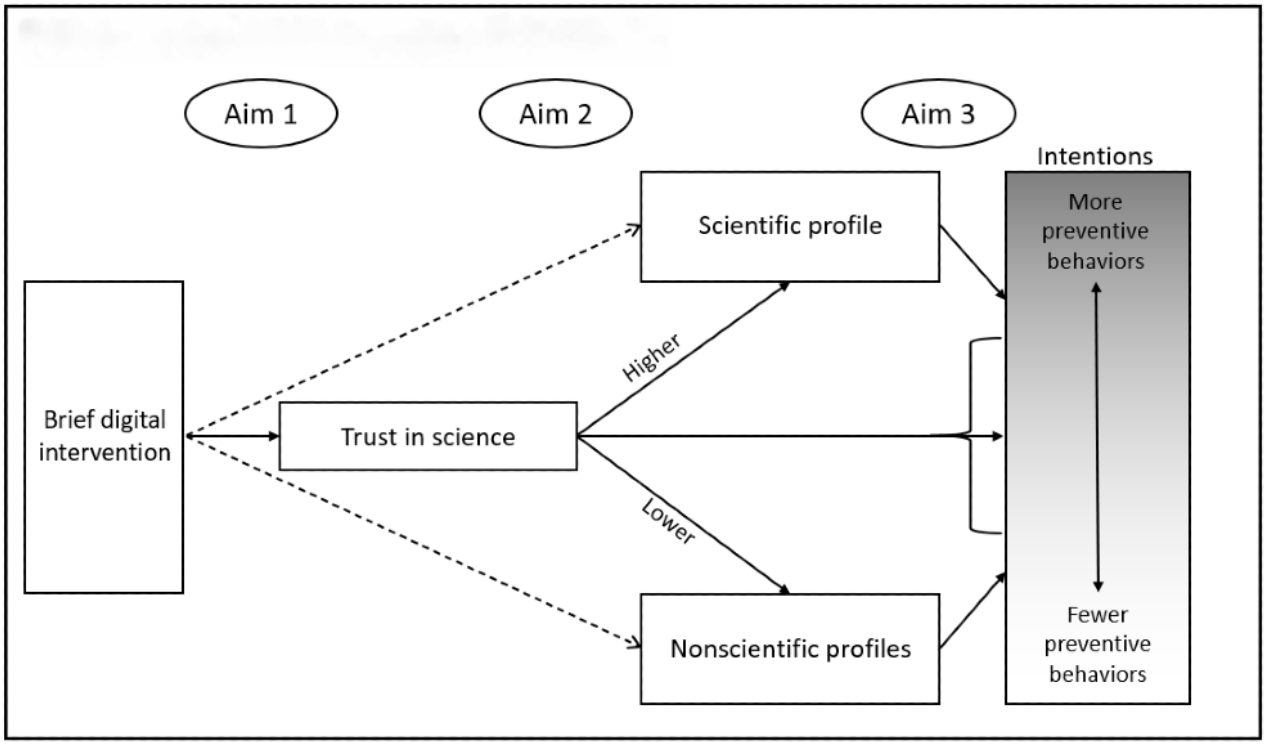
Conceptual Framework for the Proposed Study

Our prior research on COVID-19 misinformation identified 4 different COVID-19 belief profiles [17]. The "scientific" profile was the most common (~70% of the respondents), comprising individuals who reported high believability for a statement about the zoonotic origin of COVID-19 and low believability for misinformed narratives. The other 3 "nonscientific" profiles were not named and were instead numbered alongside conceptual descriptions. Profile 2 (~8% of the respondents) comprised individuals who reported high believability for all narratives, including the zoonotic statement and misinformed statements. Profile 3 (~12% of the respondents) comprised individuals who reported moderate believability for all narratives, and the lowest believability for the zoonotic statement of any profile (although it was still reasonably high, with a mean score of 4.59 on a scale of 1-7). Finally, Profile 4 (~10% of the respondents) was similar to Profile 2, except for a comparatively lower endorsement of the narrative that 5G networks caused the spread of COVID-19. Trust in science (a scale variable, scored from 1 to 5, and computed from a 21-item questionnaire) [37] was substantively associated with different profile memberships, after controlling for political orientation, religious commitment, race and ethnicity, gender, age, and education level. Compared to the scientific profile, each 1-point decrease in trust in science was associated with 5 (for Profile 3) to 14.3 (for Profiles 2 and 4) times higher adjusted odds of belonging to nonscientific profiles [17]. Therefore, we speculate that intervening at the level of trust in science will potentially nudge some individuals into the scientific profile.

However, whether trust in science will further affect individuals' intention to engage in preventive NPBs via mediated beliefs in misinformation remains to be clarified. To the extent that some common narratives suggest that COVID-19 does not pose a serious health threat [17], such narratives may reduce the magnitude of "perceived severity" based on the health belief model. It is also notable that cross-sectional studies have suggested an association between perceived severity, self-efficacy, and COVID-19 NPBs in Turkey and Kenya [31,32].

Separately, a complex network analysis in the United Kingdom and Netherlands found that COVID-19 NPBs are most closely related to normative beliefs held by family and friends, along with the beliefs that preventive measures work [38]. Given the emerging conspiratorial narrative that face masks are an attempt to exert social control and do not actually prevent COVID-19 transmission, it is plausible that such narratives also affect the perceived efficacy of common NPBs. More direct, yet anecdotal findings in support of this mediated relationship include documented incidences of this type of misinformation being explicitly stated by individuals who publicly refuse to engage in NPBs [39-41]. Finally, in the only causal finding, Koetke et al [23] reported that trust in science exerted a direct influence on the intention to practice social distancing, but their work focused on political ideology, not misinformation, as a mediating variable. A similar associative finding by Chambon et al [38] suggested that "trust in authorities" was moderately associated with an increase in NPBs. A depiction of the overall conceptual framework of study variables is illustrated in Figure 1.

Figure 1. Conceptual framework of study variables.



Study Aims and Hypotheses

This study will accomplish the following 3 aims:

Aim 1

We aim to assess the effect of a brief informational infographic about the scientific process on trust in science. *We hypothesize*

that exposure to such an intervention will have a moderate, positive effect on trust in science.

Aim 2

We aim to assess the effect of a brief informational infographic about the scientific process on the likelihood of believing scientifically implausible narratives about COVID-19. *We hypothesize that exposure to such an intervention will have a small, negative effect on the likelihood of believing implausible narratives, as evidenced by profile membership, and that this will be partly mediated by trust in science.*

Aim 3

We aim to assess the effect of a brief informational infographic about the scientific process on behavioral intentions to engage in recommended COVID-19 NPBs. *We hypothesize that exposure to such an intervention will have a small, positive effect on behavioral intentions to engage in recommended COVID-19 NPBs that will be partly mediated by misinformation profile membership.*

Methods

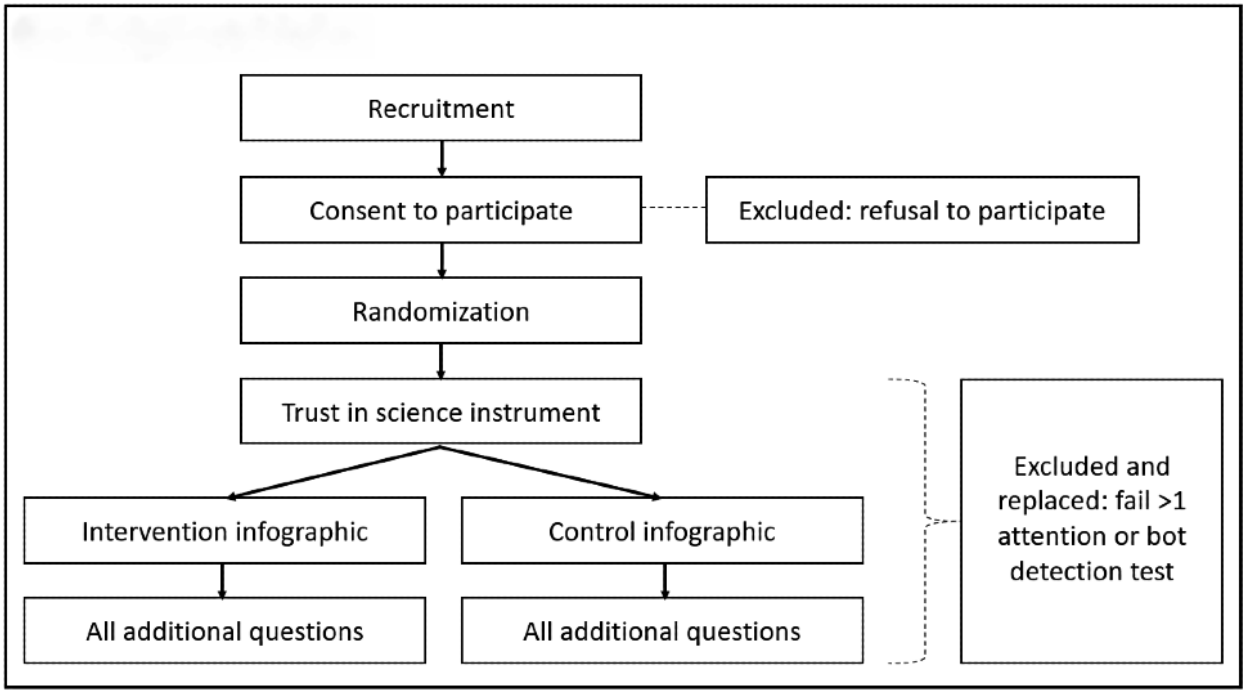
Ethics Approval and Consent to Participate

This study has been approved by the Indiana University Institutional Review Board (IRB), protocol #2008571490. Participants in both the pilot test and the main study will digitally indicate their consent to participate after reviewing a study information sheet.

Trial Design

We propose a single-stage, randomized, superiority trial comprising 2 parallel groups allocated with a 1:1 ratio. The study design and workflow involving participants is shown in Figure 2. The comparator in this study will be a control ("placebo") infographic that is completely unrelated to science (eg, an infographic about cats) but is developed using the same communication and graphical style. The full trial, including presentation of the intervention or control condition, will be embedded within the data collection platform and will be completed in a single sitting.

Figure 2. Study design and workflow.



Study Setting

Participants will be recruited using the data collection platform Prolific, which is one of two primary online crowdsourced research platforms (the other is Amazon's Mechanical Turk, or mTurk). Evidence suggests that both platforms replicate known experimental outcomes when studies are structured correctly and that the platforms compare favorably to a university-recruited subject pool [42,43]. Prolific also has the ability to collect a nationally representative sample for the United States by age, sex, and race and ethnicity, thereby improving generalizability of findings [44]. Prolific outperforms mTurk with regard to the number of accessible participants (>40,000 vs 15,000-30,000), responsiveness, diversity, and quality of participants [43,45]. Recent studies, including studies on COVID-19 perceptions, have successfully used nationally representative samples from Prolific [46].

Eligibility Criteria

For inclusion in the study, participants must be identified by Prolific as part of a nationally representative sample. Only participants aged 18 years or older and residing in the United States will be considered. Individuals who decline to digitally sign the informed consent document will be excluded from the study and replaced by other eligible individuals. Based on best practice recommendations for crowdsourced digital research, attention checks and screens for "bots" and international users with virtual private networks to mimic US internet protocol addresses will be embedded within the instruments, and failure of more than one attention check, or any bot or location check

will result in subject exclusion and replacement [47]. Attention checks will be located prior to randomization in Qualtrics, a cloud-based survey tool, so replacements will be randomized with the same allocation ratio and will be drawn in a manner that preserves the representativeness of the sample.

Study Intervention

Infographic Design

The primary intervention in this study will be an infographic that is designed to build trust in the scientific process. Infographics are preferable to narratives or text because they focus on visuals as part of the storytelling process and facilitate cognitive information processing, knowledge absorption, and enhanced persuasion [48-50]. The infographic design used in this study will follow best practices in health communication. The message communicated will be simple and jargon free. The infographic will comprise visuals of individuals (scientists), charts, text, and numerical data [48]. Attention will be paid to the images used, color, frames, representation, and composition (eg, how the elements in the infographic are organized to show their relationship to each other) [49]. The design process will be completed in the following 2 stages (note that these are development stages, not trial stages).

Stage 1

Sample concepts and messaging will be created based on the core constructs underlying the trust in science inventory [37]. The messages will assume divergent approaches to clarify what science is, how the scientific process operates, and how science is a self-correcting process. This content may focus, for example, on how the self-correcting elements of science serve to enhance people's quality of life (eg, addressing items 1 and 21 from the inventory [37]). In such a case, the accompanying visuals might demonstrate a flat earth progressing to a globe, and then to a picture of the earth captured from a space station. These messages will be informally discussed by the authors' nonscientific social network in preparation for a formal pilot study.

Stage 2

In collaboration with professional graphic designers, the study team will design 5 infographics for the pilot testing. At present, we plan that each infographic will use an "internet comic" style of presentation that will be familiar to most participants to express core concepts underlying trust in science. The infographics will each be presented to 20 mTurk users (using the same procedures to screen for respondent quality as the overall study). Enrolled participants (N=1000) will first complete the trust in science inventory, and they will then be randomly assigned to view one of the infographics, following which they will be required to complete the inventory again. Participants will also be asked to qualitatively describe the meaning conveyed through the infographic (an open-ended question) [51] and will be asked to indicate how believable they find the infographic using a validated modification of the narrative believability scale (nbs-12) [52]. In this manner, the best-performing infographic, based on the judgment of the study team, will be used for the intervention arm of the experiment, and will be made available as a supplemental file alongside the published results. This decision will be made based on qualitative response, believability, and any observed effect on trust in science (although in the latter case, the pilot sample is not sufficiently powered to test a hypothesis, so we will consider the data broadly within the context of the other metrics).

Participants will be required to pause for at least 60 seconds while viewing the infographic (ie, the button to proceed forward will be hidden). The control infographic will be completed by the same designers but will be a placebo (ie, it will be a summary of basic information about a neutral topic, such as cats). It will mention neither science nor scientific processes.

Primary Study Outcomes

Trust in Science

Participants' "trust in science" will be measured both before and after they view the intervention or placebo using the 21-item scale developed by Nadelson et al [37]. Our previous research has found that this scale is highly reliable for diverse, online, and crowdsourced respondents [17,21].

Believability Profiles

Next, participants' "believability profiles" will be computed via a latent profile analysis of the believability measures described below, which will be administered after the infographic is viewed. The measures and approach used to conceptualize believability of misinformation were developed and first used in our recent study on COVID-19 narratives [17]. As in the original study, we will not prespecify the existence of certain profiles, although we do expect to identify similar profiles in this study (potentially with differences introduced by the additional metrics described subsequently).

Response options for all believability measures will use well-established semantic differential responses for believability of different statements (eg, as used by Herzberg et al [53]), ranging from 1 ("extremely unbelievable") to 7 ("extremely believable"). The original measures [17] assessed the believability of 4 statements related to COVID-19 that were derived from common pieces of misinformation (as of April 2020), as identified by a team at Cornell University [54]. For instance, one of the statements was, "The recent rollout of 5G cellphone networks caused the spread of COVID-19." Another statement asked subjects about their believability of a particular statement reflecting scientific consensus (ie, the zoonotic origin of the virus). Our ability to use latent profile analysis to generate plausible and conceptually meaningful subgroups with a good model fit points toward a certain degree of validity of these questions. This is noteworthy especially given the existence of a latent profile that generally believed the scientific consensus explanation and no other narrative (which would be less likely with invalid questions). Therefore, in this study, we will assess participants' believability of the following 6 statements, which include slightly modified versions of the 4 above-referenced statements, as well as 2 new statements based on scientific findings clarifying emergent, persistent misinformation about the use of face masks to prevent COVID-19 spread [55-57]:

- "The rollout of 5G cellphone networks caused the spread of COVID-19."

- "SARS-Cov-2, the virus that causes COVID-19, likely originated in animals (like bats) and then spread to humans."
- "Bill Gates caused (or helped cause) the spread of COVID-19 in order to expand his vaccination programs."
- "COVID-19 was developed as a military weapon (by China, the United States, or some other country)."
- "The number of deaths from COVID-19 has been exaggerated as a way to restrict liberties in the United States."
- "Wearing a face mask for COVID-19 prevention can cause oxygen deficiency or carbon dioxide intoxication."
- "Face masks are probably not helpful in reducing COVID-19 spread in a community."

Behavioral Intentions

Participants' behavioral intentions will focus on the following specific recommendations current proposed by the CDC [58]:

- Wash your hands often (or use a hand sanitizer that contains at least 60% alcohol).
- Avoid close contact (stay at least 6 feet from other people).
- Cover your mouth and nose with a mask when around others.
- Cover coughs and sneezes.
- Clean and disinfect frequently touched surfaces daily.
- Monitor your health daily.

Each recommendation will be placed into a behavioral intention questionnaire format to assess self-reported likelihood of behaviors using a guide published by Azjen who proposed the Theory of Planned Behavior [59]. For example, "I intend to clean and disinfect frequently touched surfaces daily for the next month," with response options ranging from 1 ("likely") to 7 ("unlikely"). These questions will be administered after the infographic is viewed.

Covariates

We will also collect the following additional variables to serve as covariates in the models based on other factors suspected to influence trust in science, believability of misinformation about COVID-19, and/or behavioral intentions regarding NPBs.

- Political orientation and religious commitment, using the scales from our previous works [17,21]
- Race and ethnicity, gender, age, and education level
- Whether the respondent has been diagnosed with, or believes they have had, COVID-19 [60]
- Perceived severity and self-efficacy regarding COVID-19, based on the health belief model and that used by Yıldırıma & Gülerc [31] (which was derived from similar work related to SARS)
- Normative beliefs about friends' and family's COVID-19 behaviors (single item from Chambon et al [38])

Sample Size

We will recruit 1,000 individuals using Prolific, which is the maximum sample size permitted for a nationally representative sample via this platform. This sample size will give allow us to detect small (Cohen's d=0.18) differences between both groups with 80% power. This effect size would be more than sufficient for both analysis types, that is, LMM (linear mixed models) and path analyses, thus accounting for power and other sample size considerations common to path analysis (eg, overspecification) [61].

Recruitment

Participants will be recruited via the Prolific platform to ensure a nationally representative sample of the US is composed with regard to age, sex, and race and ethnicity. To ensure compliance with institutional review board requirements, the questionnaires and procedures (including the study information sheet) will be hosted securely within Indiana University's Qualtrics platform. Prolific will refer the sampled individuals to the Qualtrics system. Thereafter, we will randomly generate a unique identification for each Qualtrics user and ask the participants to enter it into Prolific to verify that they have completed the survey. We anticipate the survey will take no more than 15 minutes to complete; compensation will be set by Prolific to be equitable but noncoercive for research. The proposed methodology mirrors the protocol we successfully used with mTurk in our previous works [17,21].

Allocation of Interventions

The allocation sequence will be managed using the Randomizer tool in the Qualtrics platform [62] to ensure a 1:1 allocation of participants to intervention (1) and control (0) arms, each comprising 500 participants. Allocation will occur after consent has been processed. Furthermore, the procedure is automated, thereby ensuring allocation concealment.

Although this is, in practice, a double-blind study since participants will be unaware that they are randomized and all study mechanics will be processed using a computer, analysts will not be blinded to the meaning of the assignment variable. However, 2 independent consultant analysts have been retained to verify all results and subsequent interpretation.

Data Collection and Management

All data will be collected and stored using the QualtricsXM (Qualtrics) digital platform. This platform enables direct exporting of data to a variety of formats (eg, Excel and SPSS). To promote data quality, respondents will be required to respond to all items on each page of the survey before proceeding to the next part of the study, which would ensure there are no missing data from completed cases. While excellent participant retention is expected since the study (including intervention) is brief and occurs contemporaneously, some participants may decide to quit prior to completion. If a participant has provided any data beyond the study information sheet, the case will be analyzed according to the study arm to which it was assigned, with missing data managed as described in Statistical Analysis (eg, intention-to-treat). However, this will not apply to participants who are excluded due to failed quality checks (see Eligibility Criteria) because these are designed to filter for cases that were not eligible but were enrolled in the study inappropriately (eg, "bots" or individuals who mask their global location with a virtual private network).

Statistical Analysis

Missing Data and Data Quality

Missing data will be addressed using either full information maximum likelihood or Markov Chain Monte Carlo multiple imputation strategies [63]. In case there is a violation of missing at random in preliminary analyses (which is unlikely), we will incorporate strategies representing the missingness. We will further explore data quality in terms of outliers, measurement error, non-normality, and variance heterogeneity. Robust methods of analysis (eg, Huber-White robust standard errors) will be used, as appropriate [64]. For all multi-item measures, we will evaluate reliability prior to computation of the variable.

Analyses

The following analyses will be performed for the 3 aim statements:

Aim 1: We will use an LMM to examine the effect of the intervention on trust in science, controlling for specified covariates (see Covariates).

Aim 2: We will first examine the profiles of believability in our control and intervention group using latent profile analyses [65,66]. After determining the number of classes and identifying scientific versus nonscientific profiles, we will conduct path analyses linking the brief digital intervention to believability profiles and the mediator (trust in science).

Aim 3: We will first examine the outcome variables for Aim 3—intention to engage in NPBs. Although we expect these intention-based items to function as a monotonic scale that can be collapsed into a single variable, we will need to conduct exploratory factor analysis to determine whether this is the case. The number of factors identified will affect how this outcome is treated in the subsequent part of Aim 3.

We will also examine the mediation effect of believability profiles on the association between behavioral intentions, trust in science, and the primary outcome for Aim 3 (ie, intention to engage in NPBs) in the post-test. Next, we will conduct path analyses linking the brief digital intervention to believability profiles and the mediators (trust in science and believability profiles), and behavioral intentions in the post-test.

For both Aims 2 and 3, we will use model fit statistics (eg, root mean square error of approximation, comparative fit index, and Tucker-Lewis Index) and examine specific indices of ill fit (eg, modification indices). To increase power and maintain Type I error, we will adapt the posterior probability method (eg, partial *P* value) for formal mediation analyses with intervening variables [67]. We aim to elucidate key mediational chains between our mediators (ie, trust in science and believability classes), predictors (ie, behavioral intervention statement), and outcome (ie, intention to engage in NPBs) through this design, instead of simply looking at the link between the intervention and intention to engage in NPBs.

Results

This study was funded in August 2020, approved by the Indiana University Institutional Review Board on September 15, 2020, and prospectively registered with ClinicalTrials.gov. We expect the infographics to be finalized in early December 2020 and plan to run the pilot test in the same month. The entire experiment should be completed, and the results published, in 2021. This protocol was submitted as prepared for review in a grant format to the Indiana Clinical and Translational Sciences Institute in June 2020. Aside from stylistic modifications made in transforming the grant into a paper, and in addressing grant reviewers' and manuscript reviewers' comments, the protocol reflects the originally proposed work.

Discussion

Next Steps

The primary purpose of this study is to test an actionable, brief digital intervention that can modify trust in science and thereby mitigate belief in misinformation and increase behavioral intentions to engage in NPBs. Thus, if any hypotheses are validated, the primary next step will be to disseminate this information and coordinate use of the infographic. Two articles published in *Nature* [68,69], (including one by that journal's editorial board), acknowledged the need for researchers to honestly and transparently address COVID-19 misinformation, and to specifically look into trust, but the cited research primarily examined networking and spread dynamics, not prevention.

Data Monitoring, Interim Analyses, and Auditing

This study will not have a data monitoring committee because data collection will be automated, stored, and archived. Moreover, no harms are anticipated to occur as a result of the experiment. No interim analyses are planned. Data and analyses will be reviewed by all members of the study team as well as by independent statistical consultants.

Study Limitations

This study has several limitations that might affect its conclusions. First, the data are based on self-reporting. For believability and trust in science, this is a less substantive issue; however, it is potentially subject to social desirability bias, which we will attempt to minimize. Although extant behavior models like the Theory of Planned Behavior [59] indicate that intentions are direct antecedents to behavior, we cannot be certain that intentions will result in actual behavior. Nevertheless, measuring this would be beyond the scope of this protocol. Second, we are unable to control the conditions in which people will participate, but we will incorporate attention checks throughout the process. Furthermore, prior studies have been able to replicate known experimental findings using crowdsourced digital participants, suggesting that the undue influence of inattention can be minimized [42,43]. Third, this experimental approach is likely subject to a Type II error because a real-life application of this process would entail repeated exposures over time, whereas this approach tests the effect of a single exposure. Fourth, other variables that might influence behavioral intentions also likely exist, but by recruiting a large sample and randomizing participants, we will be able to more cleanly isolate the differences attributable to the intervention.

Finally, generalizability to individuals who do not have internet access or who are unable to participate in online surveys might be limited. However, regarding the concern about access, it is noteworthy that approximately 90% of US adults used the internet in 2019, with higher percentages reported for younger adults and lower percentages, for older adults. Of note, 73% of individuals aged >65 years reported they had internet access in 2019 (although it began trending sharply upward in 2018) [70]. Furthermore, as noted throughout our proposal (and in academic papers published since submission [71]), social media remains a primary source of misinformation about COVID-19. Considering that the online data collection platform introduces bias as a result of internet access, we speculate that controlling for age (which we already do) may attenuate this concern to an extent, in addition to the fact that the intervention itself is designed for distribution on social media.

Regarding the latter point (opt-in participation), we acknowledge that individuals who opt into survey completion may differ systematically in one or more ways from those who do not. However, the data collected through platforms like Prolific are of good quality and have replicated results of multiple established experiments, thereby reducing concerns about the influence of opt-in participation on the results. Further, studies on similar crowdsourced survey platforms such as mTurk have found that the study participants are similar to the overall US population with regard to a number of different characteristics. However, they also found that survey takers are younger and are more educated, on average, than the US population as a whole [72-74]. Both variables (ie, age and education level) will be controlled in our study's analyses. This further mitigates concerns that the participants recruited by Prolific are systematically different from those that might be enrolled in a similar experiment in other circumstances.

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Authors' Contributions

JA and YX developed the idea for the study. JA, YX, and ET conjointly prepared the protocol. YX and LG prepared the analysis plan. All authors reviewed and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Review of original grant submission (Reviewer 1, scores redacted by funder).
[PDF File, 115KB - researchprotocols_v9i12e24383_fig.pdf]

Multimedia Appendix 2
Review of original grant submission (Reviewer 2, scores redacted by funder).
[PDF File, 111KB - researchprotocols_v9i12e24383_fig.pdf]

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Abbreviations

CDC: Centers for Disease Control and Prevention
LMM: linear mixed model
mTurk: Amazon Mechanical Turk
NPB: nonpharmaceutical preventive behavior

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Protocol

An Autonomy-Supportive Online Decision Aid to Assist Smokers in Choosing Evidence-Based Cessation Assistance: Development Process and Protocol of a Randomized Controlled Trial

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Abstract

Background: Decision aids (DAs) may be used to facilitate an autonomous, informed decision to cease smoking and promote the uptake of evidence-based cessation assistance (ie, behavioral support, nicotine replacement therapy, or prescription medication). However, knowledge is lacking regarding their effective elements and (cost-)effectiveness.

Objective: We describe the development process of an online DA (called "VISOR") that helps smokers to choose evidence-based cessation assistance. Additionally, we provide a description of the protocol of an ongoing randomized controlled trial in which the DA containing an explicit value clarification method (VCM) and tailored advice is compared with a DA without an explicit VCM and tailored advice.

Methods: The development of "VISOR" was based on the International Patient Decision Aid Standards guidelines. Viewpoints of end users (collected through 20 interviews with smokers) and clinical and scientific experts (assessed using 2 Delphi studies with 24 scientists and 38 clinicians) were assessed regarding cessation tool decision making and preferred DA content. These findings, together with principles from the Self-Determination Theory, served as input for the development of the online DA. A first DA prototype was alpha-tested in September 2019 and beta-tested for usability in December 2019; feedback was incorporated and resulted in a final version. The final DA contains (1) an information section, (2) an optional knowledge quiz, (3) a brief smoking assessment, (4) intuitive decision, (5) intermediate advice, (6) an explicit VCM, (7) tailored advice, and (8) access information. A randomized controlled trial is currently being conducted to assess the DA's (cost-)effectiveness compared to a DA that does not include the explicit VCM and the tailored advice; specifically, the DA's effect on smoking abstinence, uptake of evidence-based cessation assistance, smoking abstinence mediated through uptake of evidence-based cessation assistance, and decisional conflict are investigated. Participants are randomly allocated to receive access to 1 of the 2 DAs and are asked to complete 5 questionnaires (including the baseline questionnaire) over a period of 12 months. To evaluate the effects of the DA on the outcome measures, logistic and linear regression analyses as well as mediation analyses will be carried out. An economic evaluation will be performed to assess the cost-effectiveness.

Results: Data regarding the effect of the VISOR DA are currently being collected, and data collection is expected to be concluded in 2021.

Conclusions: By making use of an iterative process that integrated different stakeholders' perspectives (including end users), we were able to systematically design an evidence-based DA. The study will contribute to the current knowledge regarding smoking cessation DA application, the added value of explicit VCMs, and the effect of behavioral and informed decision-making outcomes.

Trial Registration: Netherlands Trial Register NL8270; https://www.trialregister.nl/trial/8270

International Registered Report Identifier (IRRID): DERR1-10.2196/21772

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KEYWORDS

digital health; decision making; decision support technique; decision aids; smoking; smoking cessation; informed decision making

Introduction

Smoking continues to kill, both on a global level [1] and in the Netherlands [2]. According to predictions, more than 8 million deaths per year will be caused worldwide by tobacco use by 2030 if evidence-based smoking cessation interventions are not put into use [3]. One way to reduce tobacco-related deaths is to promote the uptake of evidence-based cessation assistance, such as pharmacological support (eg, nicotine replacement therapy [NRT]) [4] and behavioral support (eg, counselling) [5]. Unlike non-evidence–based cessation assistance, such as acupuncture [6], evidence-based cessation assistance can greatly increase successful smoking cessation [7]. However, uptake of evidence-based cessation assistance is low in the Netherlands [8]. And, even if people are interested in using evidence-based cessation assistance, they still have to choose between the multitude of options that exist in order to make an informed decision. Making an informed decision requires people to gather and review information regarding cessation assistance options and weigh up all the advantages and disadvantages of those options [9]—tasks that can be difficult for unsupported lay people [10].

Decision aids (DAs) are interventions that are specifically designed to help users with those difficult decisional processes. DAs aim to facilitate informed decision making between different health or health care options by providing information and helping users to become aware of their own values in relation to those options [9]. Often, DAs are used when people have to choose between different medical treatment options or if they are considering whether to participate in a screening program [9]. However, a systematic review regarding DAs for smoking cessation has also shown positive results in terms of increased quit attempts [11]. Insights from the Self-Determination Theory (SDT) also suggest that the offering of choice (as DAs explicitly do) enables individuals to engage in long-term behavior change, such as smoking cessation, by supporting their need for autonomy [12,13]. Nonetheless, only one DA for smoking cessation has previously been developed and tested in the Dutch setting [14]. And, while this DA was effective in promoting quit attempts and smoking abstinence, no effects were found regarding the use of cessation assistance [14]. As increased cessation assistance uptake could further improve cessation outcomes [7], we propose several limitations of the earlier DA that might need to be overcome to increase cessation assistance uptake and subsequent smoking cessation behavior. First, the earlier DA was paper-based and sent to people by mail, thereby limiting widespread dissemination. Offering a smoking cessation DA online could potentially reach many more people [15], especially given that the Dutch are likely to search for health-related information online nowadays [16]. Second, offering the DA online allows for a more flexible and interactive design that can be particularly interesting for people with a high need for autonomy [17]. And third, the aforementioned DA did not explicitly include methods that help users to become aware of their own values, even though explicitly including smokers' values in their decisional process could potentially improve cessation assistance uptake rates [18,19].

So-called value clarification methods (VCMs, also referred to as value clarification exercises) can support users to "evaluate the desirability of options or attributes of options within a specific decision context, in order to identify which option he/she prefers" as defined by the International Patient Decision Aid Standards (IPDAS) [20]. The underlying belief is that users with clarified values (ie, users who know what is important to them) will be more likely to choose an option that reflects their own preferences, which is regarded as a prerequisite of high-quality decision making [9,20]. VCMs can either be explicit or implicit; the former refers to methods that involve the user actively engaging in an activity (eg, scoring certain statements), while the latter refers to the provision of information that is specifically linked to the decision at hand (similar to the aforementioned paper-based DA [14]), with the underlying belief that users will engage in cognitive processes themselves to reach a decision [21]. There is some evidence that shows that explicit VCMs are more effective than implicit VCMs (in terms of decisional processes) [22], especially in the long run [21] and when people are supported in understanding the implications of their clarified values for the decision [23,24]. One way to help users understand these implications is to show participants which options fit their clarified values [23] (ie, tailored advice following the VCMs based on the answers that were provided). Interestingly, the feasibility study of a digital DA for smoking cessation that did include an explicit VCM has shown promising results, both in terms of evidence-based cessation assistance uptake and smoking cessation outcomes [25]. Thus, explicit VCMs could potentially be used to enhance the effectiveness of DAs for smoking cessation. However, the feasibility study's design (pretest and posttest assessment without a control group) limits the interpretability of the feasibility study's findings [25], and it remains unclear whether

such an explicit VCM results in significant changes in cessation rates and decisional outcomes.

Based on these limitations and the existing literature, an online DA, called "VISOR," containing an explicit evidence-based VCM and tailored advice was developed that helps smokers to choose evidence-based cessation assistance tools. This DA was systematically developed and is currently being tested in a national randomized controlled trial (RCT) for its effect on individual decisional processes and smoking cessation attempts, as well as smoking abstinence compared to a DA without the explicit VCM component. Specifically, we aim to test the following hypotheses.

$H_{1a/b/c}$ is that a DA with an explicit VCM and tailored advice will lead to a statistically significant increase in smoking abstinence after 1 month (H_{1a}), 6 months (H_{1b}), and 12 months (H_{1c}) compared to a DA without an explicit VCM and tailored advice: direct effect on smoking abstinence.

$H_{2a/b/c}$ is that a DA with an explicit VCM and tailored advice will lead to a statistically significant increase in evidence-based cessation assistance use after 1 month (H_{2a}), 6 months (H_{2b}), and 12 months (H_{2c}) compared to a DA without an explicit VCM and tailored advice.

$H_{3a/b}$ is that the positive effect of a DA with an explicit VCM and tailored advice (vs a DA without an explicit VCM and tailored advice) on smoking abstinence after 6 months and 12 months will be at least partially mediated by the use of evidence-based cessation assistance at 1-month (H_{3a}) and 6-month (H_{3b}) follow-ups, respectively: indirect effect on smoking abstinence.

H_4 is that a DA with an explicit VCM and tailored advice will lead to a statistically significant decrease in decisional conflict (state of uncertainty about which course of action to take) right after the DA compared to a DA without an explicit VCM and tailored advice.

In addition, it will also be tested whether the DA is more cost-effective compared to a DA without the explicit VCM component. This paper aims to thoroughly describe the DA "VISOR," its development process, and the study protocol to test its (cost-)effectiveness.

Methods

An RCT is being conducted and will be reported in line with the CONSORT-EHEALTH checklist [26]. Participants are randomly allocated to receive access to either a DA with an explicit VCM and tailored advice (intervention group) or a DA without an explicit VCM and tailored advice (control group). Study materials (such as questionnaires, but not the DA) will be made available on the open science framework website, in line with recommendations in the field of behavioral science [27].

The study does not fall under the scope of the Medical Research Involving Human Subjects Act as indicated by the Medical Ethics Committee Zuyderland, the Netherlands (16-N-227). The development of "VISOR" and the accompanying studies are funded by the Dutch Cancer Society, UM2015-7744.

Study Population

Recruitment is predominantly conducted online to reflect the online nature of the DA. We make use of various methods: Mainly, we are recruiting participants through project social media accounts (eg, [28]) and paid social media advertisements. We decided to make use of 4 big social media platforms (ie, Facebook, Instagram, Twitter, and LinkedIn) as they cater to different target groups [29]. In addition, our recruitment messages are being shared on the social media accounts of the project members and their institutions. Also, we promote the RCT through the project's website, and we asked various relevant Dutch institutes and organizations (eg, the Dutch institute for addiction and mental health and municipal health services) to promote the study. Finally, we advertise the study in online newspapers. All recruitment materials include a link to enroll in the RCT, if possible, to simplify the process for potential participants as much as possible. Study inclusion criteria are: (1) participants are currently smoking, (2) participants are motivated to stop smoking within 6 months, (3) participants are 18–100 years old, (4) participants are able to understand Dutch, and (5) participants have access to the internet and have the necessary internet literacy skills to use the intervention. People are excluded if they only use e-cigarettes; however, dual users can participate. The rationale behind the inclusion and exclusion criteria is described in Table 1.

Table 1. Overview of the randomized controlled trial inclusion and exclusion criteria, including rationale.

Criteria	Rationale
Inclusion criteria	
Participants are currently smoking	To test the primary hypothesis that the DA will have a positive effect on smoking cessation, it has to be tested among smokers
Participants are motivated to stop smoking within 6 months	As smokers unmotivated to quit cannot be expected to be willing to consider the use of cessation assistance
Participants are 18–100 years old	As the DA was developed for adults
Participants are able to understand Dutch	To ensure that participants understand all provided information
Participants have access to the internet and have the necessary internet literacy (skills) to use the intervention	As the DA is fully online, participants need both access to the internet and the necessary internet literacy (skills) to access and use the DA
Exclusion criteria	
Participants exclusively use e-cigarettes	As there is no consensus on whether cessation assistance tools can be used to cease e-cigarette use

Required Sample Size

The power calculation was based on the dichotomous outcome measure of smoking abstinence (primary outcome: 7-day point prevalence abstinence). The only previous RCT in the Netherlands testing the effect of a DA for smoking cessation on this outcome measure showed a significant effect (20.2% vs 13.6%) at 6 months [14]. To be able to significantly (α=.05; β=.20) detect the same effect in a 1-sided test, 398 smokers per arm are necessary at the end of the trial (796 in total). Considering 50% attrition over the intervention period, we aim to include 1592 smokers at baseline.

The Intervention

Initial DA Development

The development process of the DA was based on the IPDAS guidelines for DA development [30]. In line with these guidelines, both end users' (ie, smokers) and clinicians' needs were assessed. In addition, we asked scientific smoking cessation experts for extra input as smoking cessation is often done without consulting clinicians — especially in the Netherlands [8]. In the end user needs assessment, 20 interviews were conducted to assess end users' needs regarding potential cessation assistance's characteristics that should be described in the DA and DA functions (eg, a knowledge quiz). The input of the experts was gathered through 2 Delphi studies (24 scientists and 38 clinicians completed the final round). The input of these 3 qualitative studies was used to inform the design and content of the DA, supplemented by the IPDAS background papers (eg, [31]) as well as other relevant literature in the field (eg, [23]) and in consultation with established experts in the field. The SDT served as the theoretical framework. After this, a first prototype was developed that was alpha-tested in September 2019 with potential end users (n=3) and Dutch smoking cessation experts (n=8). During the alpha test, participants were asked to focus on the content of the DA. The end users alpha-tested parts of the DA, while the smoking cessation experts tested the whole first version. Before the beta test, the DA was evaluated by 1 of the co-authors (JR) with regard to the comprehensibility of the text for people with limited health literacy. On the basis of that evaluation, some sections and sentences were rephrased or simplified.

Usability Testing

In December 2019, after the alpha test, the DA was beta-tested among 15 experts and end users: 5 smoking cessation counselors, 5 eHealth experts (of whom, 2 had digital DA experience), and 5 potential end users (ie, people motivated to stop smoking). Respondents were given access to the DA to assess the DA's usability using the heuristic evaluation method (smoking cessation counselors and eHealth experts) and the think-aloud method (potential end users) [32].

Using the heuristic evaluation method, smoking cessation counselors and eHealth experts were asked to evaluate the DA against a list of recognized usability principles: (1) use simple and natural dialogue, (2) speak the user's language, (3) minimize memory load, (4) be consistent, (5) provide feedback, (6) provide clearly marked exits, (7) provide shortcuts, (8) provide good error messages, (9) prevent errors, and (10) provide help and documentation. The smoking cessation counselors and eHealth experts were asked to use predetermined scenarios (eg, whether cessation attempts have been undertaken before) during the evaluation.

With the think-aloud method, end users were asked to complete the DA while verbalizing their thoughts. The think-aloud method is considered particularly useful in understanding processes of cognition and is considered to be of high value in evaluating an intervention's design on usability flaws [32].

Data gathered through these tests were compared and compiled into a summary describing the usability flaws of the DA. Based on these results, adjustments to the DA were identified, which can be seen in Textbox 1.

Textbox 1. Overview of alterations to the decision aid (DA).

- More information was added on how to use the DA: for example, “Now click on 'next' to start with the information.”
- The language and complexity level have been simplified.
- Certain subparts (eg, results of the knowledge quiz) were rewritten in a more positive tone.
- Content was shortened if possible (eg, by combining pages or by removing too many details).
- Some content was added (eg, required duration of prescription medication use).
- More visuals were added (eg, icon arrays to showcase cessation assistance’s effectiveness).
- Information regarding cessation assistance’s effectiveness was adapted to make it more accessible.
- The order of the given information was changed (eg, information regarding non-evidence–based cessation assistance was moved to the beginning as testers found it confusing that this information was mentioned only at the end of the information section).
- A function was added to enlarge visuals and tables.
- The layout was changed to make the DA more accessible to users with visual impairments (eg, we added more lines and changed the color of the text).
- All abbreviations were removed, as were references to terms that were used in other parts of the DA.
- All hyperlinks were removed.
- Two possible options (ie, combination of behavioral support and nicotine replacement therapy; combination of behavioral support and prescription medication) were added.
- A ranking of the evidence-based cessation assistance tools based on the value clarification method was added.

Description of the DA

An interactive Dutch DA with an explicit VCM and tailored advice that facilitates the process of choosing an evidence-based cessation assistance was developed. The DA follows a stepwise approach and is designed to encourage a decision that is autonomous and consistent with participant’s values and smoking behavior. The DA consists of 8 sequential sections: (1) information section, (2) optional knowledge quiz, (3) brief smoking assessment, (4) intuitive decision, (5) intermediate advice, (6) explicit VCM, (7) tailored advice, and (8) access information.

In step 1, the information section explains the decision at hand, as well as all the available cessation assistance in the Netherlands. The following topics are addressed: (1) smoking cessation with and without evidence-based cessation assistance, (2) non-evidence–based cessation assistance, and (3) evidence-based cessation assistance.

For the first topic, differences in smoking cessation outcomes are described between people using and not using evidence-based cessation assistance using simple frequency formats (eg, “By using one or more of these stop methods, 15 out of 100 people are still smoke-free after one year.”).

For the second topic, a list of various non-evidence–based cessation assistance tools (ie, acupuncture, laser therapy, hypnotherapy, mindfulness, smartphone apps, self-help books, and e-cigarettes) are described, and a remark is made that the use of these tools is not advised.

For the third topic, evidence-based cessation assistance is described (Table 2), including behavioral support in general, in which users can choose to read more detailed information about all possible options (ie, face-to-face counseling, counseling over the phone, group coaching, and eHealth); NRT in general, in which users can choose to read more detailed information about all possible options (ie, nicotine patches, nicotine gum, nicotine lozenge, nicotine mouth spray, and nicotine inhaler); prescription medication in general, in which users can choose to read more detailed information about all possible options (ie, varenicline, bupropion, and nortriptyline); and cessation assistance during pregnancy and breastfeeding. Users can compare all cessation assistance options using an option grid and are informed about combinations of multiple cessation assistance options. In addition, costs and reimbursement are described, and sources used to inform the information section content (ie, reports, scientific manuscripts, websites) are provided.

Table 2. Overview of cessation assistance characteristics included in the decision aid (DA).

Cessation assistance characteristic	Rationale for inclusion in the DA	This characteristic is included in the statements (VCM[a]) for:
Effectiveness of the cessation assistance options	During the interviews with potential end users, this was both the most mentioned characteristic and considered the most important characteristic.	Behavioral support, prescription medication
Probability of nausea and dizziness when the cessation assistance option is used Probability of mood changes when the cessation assistance option is used Probability of headaches when the cessation assistance option is used Probability of sleeping problems when the cessation assistance option is used Probability of other side effects that are very likely to occur when the cessation assistance option is used	Probability of side effects was the third most often mentioned characteristic during the interviews with potential end users and was also considered to be of importance by the clinicians. The first 3 side effects were specifically named as important by potential end users, while the fourth was added, as this is a common side effect. Other side effects were included if they are regarded as being very likely to occur.	Nicotine replacement therapy, prescription medication
Extent and type of contact someone has with a professional when the cessation assistance option is used	Both scientists and potential end users indicated that this was of great importance. Clinicians indicated that required contact with a health care professional was of great importance.	Behavioral support
How the cessation assistance option is used	This was integrated after it had been decided that Dutch health insurance companies would cover evidence-based cessation assistance use, as that left too few features to distinguish between the different nicotine replacement therapies and prescription medication.	Nicotine replacement therapy, prescription medication

[a]VCM: value clarification method.

In step 2, users can choose to complete the knowledge quiz or skip the knowledge quiz and proceed to the following step. If they complete the knowledge quiz, they will receive the results, see the correct answers to the questions that they answered incorrectly or could not answer (seeing the correct answers can also be skipped even if a respondent opts to do the knowledge quiz), and proceed to the following step.

The brief smoking assessment in step 3 consists of 2 closed (yes/no) questions: "To ensure that our advice suits you best, we would like to ask you if you smoke more than 10 cigarettes (or other tobacco products) on a normal day?" and "To ensure that our advice suits you best, we would like to ask you if you have ever made one or more smoking cessation attempts in the past that were unsuccessful?"

In step 4, an intuitive decision occurs between different clusters of cessation assistance tools: behavioral support; NRT; combination of behavioral support, NRT, and prescription medication; combination of behavioral support and NRT; combination of behavioral support and prescription medication; other, non-evidence–based cessation assistance; and no cessation assistance at all.

In step 5, intermediate advice is provided for users to reevaluate their intuitive decision in step 4 when they chose behavioral support only or NRT only, while also affirming at least 1 of the 2 questions in step 3 (indicating that they smoke more than 10 cigarettes on a normal day or have made one or more smoking cessation attempts in the past): They are advised to consider using a combination of behavioral and pharmacological cessation assistance tools. Intermediate advice is also given to users who chose non-evidence–based cessation assistance or no cessation assistance at all regardless of their answers in step 3: They are advised to consider using one or more evidence-based cessation assistance tools.

The explicit VCM in step 6 is provided for users that chose evidence-based cessation assistance tools in steps 4 or 5; users are asked to rate certain statements regarding cessation assistance characteristics (eg, "I prefer a stop method that works better, even if that means that I have to leave the house."). These statements are also described in Table 2. Users only rate statements for options that belong to the cluster of cessation assistance options they selected in the previous step.

Step 7 is tailored advice based on the explicit VCM and an optional ranking of all options. The advice is given only when it is possible to give clear advice (ie, if users' scores do not suggest that more than 2 cessation assistance tools are suitable based on their indicated values).

Step 8 involves accessing information on how to obtain the chosen cessation assistance (eg, nicotine patches).

Above and beyond these 8 steps, framing throughout the DA is positive and autonomy-supportive [33] (in line with the SDT as theoretical framework) to support users' need for autonomy (eg, we refrained from using fear appeals [34] and controlling language [12,33]). We also clearly communicate that users can make their own choice at the end and included "cues" to support

this process (again in order to support users' need for autonomy; eg, by stating that the advice is only a recommendation and not a command and that it might be a good idea to discuss this with either the social environment, a health care provider, or both). A flow chart of the DA can be seen in Figure 1. The digital DA is hosted by the Dutch company OverNite Software Europe BV, and we make use of their product "TailorBuilder" [35]. Translated screenshots of different sections can be seen in Figure 2 (example of the information section) and Figure 3 (example of the explicit VCM).

Figure 1. Sections of the decision aid. VCM: value clarification method.

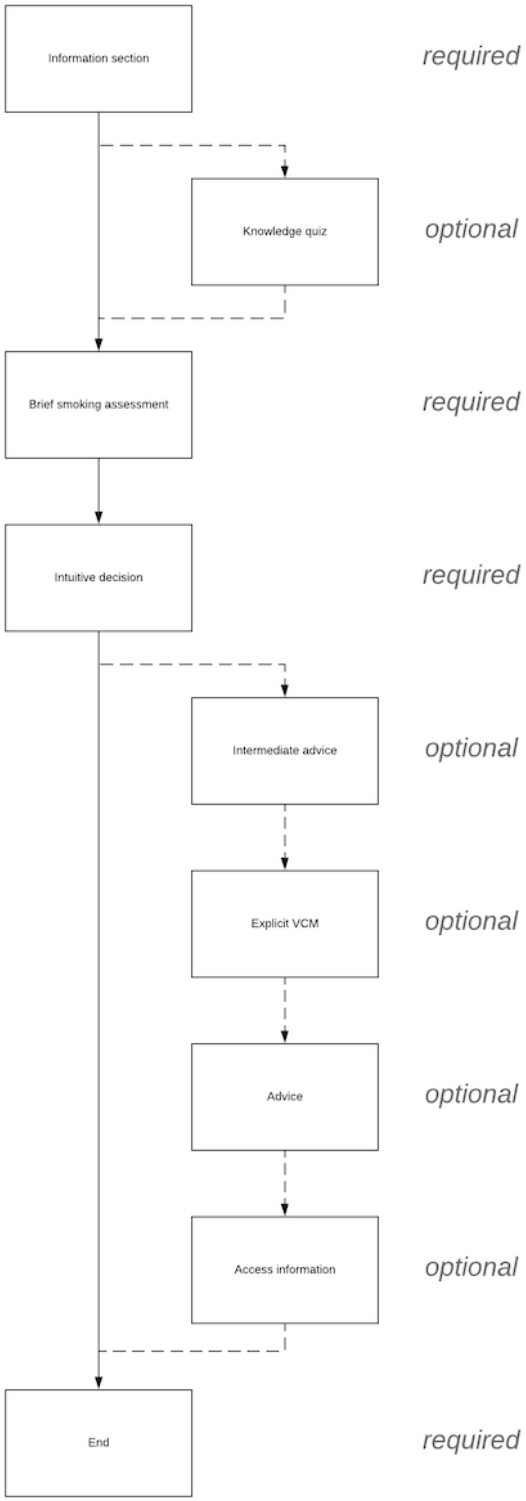
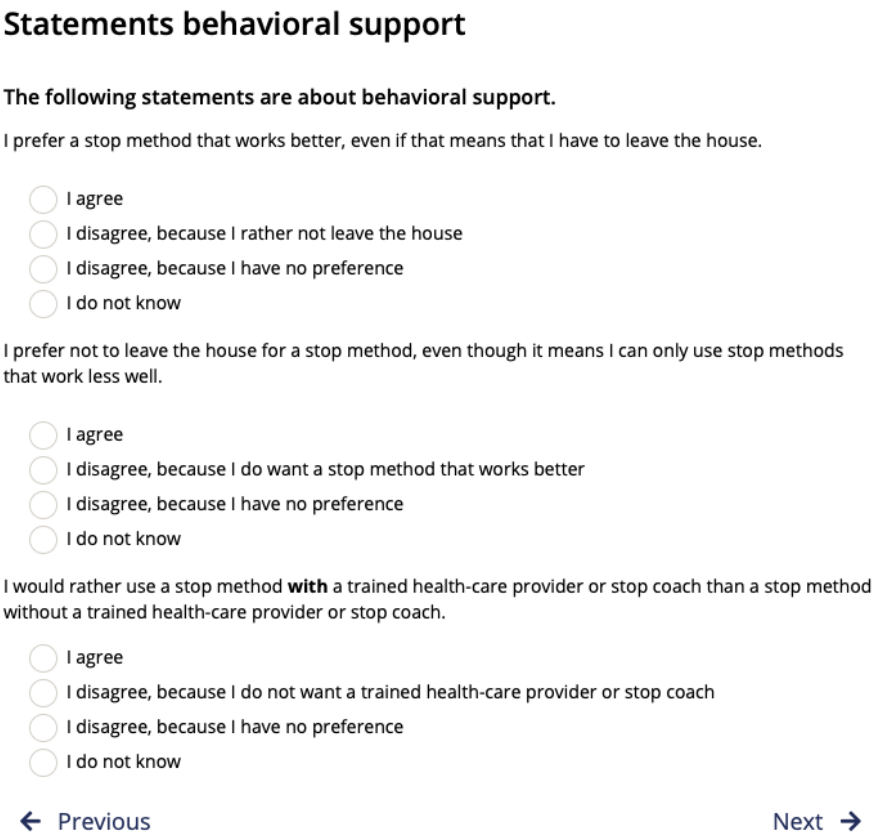


Figure 2. Screenshot of the information section in the decision aid (original text translated from Dutch).

Figure 3. Screenshot of the value clarification method (VCM) in the decision aid (original text translated from Dutch).



Theoretical Background of the Different Sections

An information section was predominantly included as relevant knowledge is needed to engage in high-quality decision making [36] and as it is regarded as an active ingredient by the IPDAS [37,38]. Given this fact, and as potential end users indicated that they would like a knowledge quiz within the DA, a knowledge quiz was included at the end of the information section. Users are thus able to check for themselves if they have the necessary knowledge to engage in the decision process and can obtain additional information if desired. The content of the information section was mainly based on Dutch guidelines (eg, [39]), supplemented by various Cochrane reviews (eg, [40]),

online information from the Dutch National Health Care Institute [41], and the Dutch Medicines Evaluation Board [42].

An intuitive decision to limit the choice set for the explicit VCM was included to both prevent choice overload [43] and to include intuitive decision-making processes in the DA. Choice overload describes a scenario in which the difficulty of the decision to be made is greater than the cognitive means of the person faced with the decision, due to too many options. Many DAs focus on a rather small set of available options [44] (eg, deciding between intensive or less intensive aftercare after breast cancer treatment [45]); yet, a cessation assistance DA has to include more options to present all available possibilities. Considering that the comparison of too many characteristics of too many options can lead to choice overload, which can in turn lead to worse decisional outcomes [43], in step 4 of the DA we decided to have users intuitively choose to go on with a limited choice set (eg, only behavioral support). Another benefit of this approach is that users are encouraged to make use of both deliberative and intuitive decision-making processes. While many DAs focus on facilitating deliberation, de Vries et al [36] have argued that combining those 2 strategies can lead to improved decisional outcomes. Importantly, however, users receive information about all possible options before they intuitively make a first, broad decision as knowledge is regarded as a necessary prerequisite for high-quality intuitive decision making [36].

As the Dutch smoking cessation guideline indicates that a combination of both behavioral and pharmacological support should be considered if smokers smoke >10 cigarettes per day or if many of their past cessation attempts failed [39], users that indicated in step 3 that this applies to them are provided with information on the improved effectiveness of a behavioral and pharmacological combination. Of course, even then, they can autonomously decide to continue with another cessation assistance set — in line with their preference and the SDT. In case smokers choose to use either no cessation assistance or no evidence-based cessation assistance, they are also reminded that evidence-based cessation assistance will probably lead to more successful cessation outcomes, but if they choose not to change their mind, they are directed to the last step (ie, access information) if they decided to use no cessation assistance or directly to the end if they decided to use no evidence-based cessation assistance.

We decided to use an explicit VCM in the intervention group as VCMs are regarded as active ingredients by the IPDAS [20,37], and while conflicting evidence exists [46], an overwhelming amount of research has shown that interactive methods to clarify people's values seem to result in better decisional outcomes [22], especially in the long run [21] and if people are supported in understanding the implications of their clarified values [23,24]. This is why we decided to integrate individual tailored advice that is supplemented with information on how to obtain the different cessation assistance options to remove barriers for the users.

Study Comparator Group

Participants in the control group receive the same DA without an explicit VCM and tailored advice; thus, the DA includes the following steps: (1) information section, (2) optional knowledge quiz, (3) brief smoking assessment, (4) intuitive decision, (5) intermediate advice, and (8) access information. Steps 6 and 7 are skipped. The only other difference is that participants in the control group are not immediately directed towards the end after they have chosen to use no evidence-based cessation assistance to also provide them with a chance to reevaluate their choice. More information about the individual steps can be found under "Description of the DA."

Trial Flow and Measurement Instruments

As participants register for the study via an online form, which includes their provision of informed consent and the creation of an account, participants are automatically randomized into 1 of the 2 groups (intervention or control group), allocating approximately 50% of respondents to either group. After this, they are asked to fill in the first part of the baseline questionnaire (t=0) consisting of 22-94 items (depending on the respective answers; eg, if the participants state that they have never attempted to cease smoking, no follow-up questions are posed), in which general demographic information (eg, age), smoking behavior, nicotine dependence, productivity loss, health care utilization, quality of life, and stages of decision making are assessed. Participants are excluded from the study if they indicate that they are <18 years old, do not smoke, are not motivated to stop smoking within 6 months, or only use e-cigarettes. Participants immediately receive access to 1 of the 2 DAs after being randomized, as this process is fully automated. After having accessed the DA, the second part of the baseline questionnaire is made available (t=1). The second part consists of 53-56 items regarding stages of decision making, the decision, the decision-making process, knowledge, perceived autonomy support, perceived competence, user evaluation, and recruitment channels.

One month after the baseline questionnaire (t=2), users are asked to fill in a short follow-up questionnaire consisting of 14-21 items regarding cessation assistance utilization, smoking cessation status, stages of decision making, and knowledge.

After 6 months (t=3) and 12 months (t=4), users are asked to fill in a longer follow-up questionnaire that consists of 16-88 items relating to cessation assistance utilization, smoking abstinence (7-day point prevalence abstinence and prolonged abstinence), and questions regarding smoking behavior for those that did not achieve smoking abstinence. Health care utilization, productivity losses, quality of life, and decisional regret are also assessed (again). During t=4, 2 qualitative items are included to assess users' experience of having used the DA during their cessation attempt.

All included measures are based on our theoretical background (ie, SDT [47,48]), the IPDAS guidelines on establishing effectiveness of DAs [49], Dutch guidelines on health economic evaluation [50], and expert knowledge regarding smoking cessation outcomes [51,52]. For a more detailed overview of all included constructs, measurements, and their respective sources, see Table 3.

Table 3. Overview of included constructs, measurements, and sources.

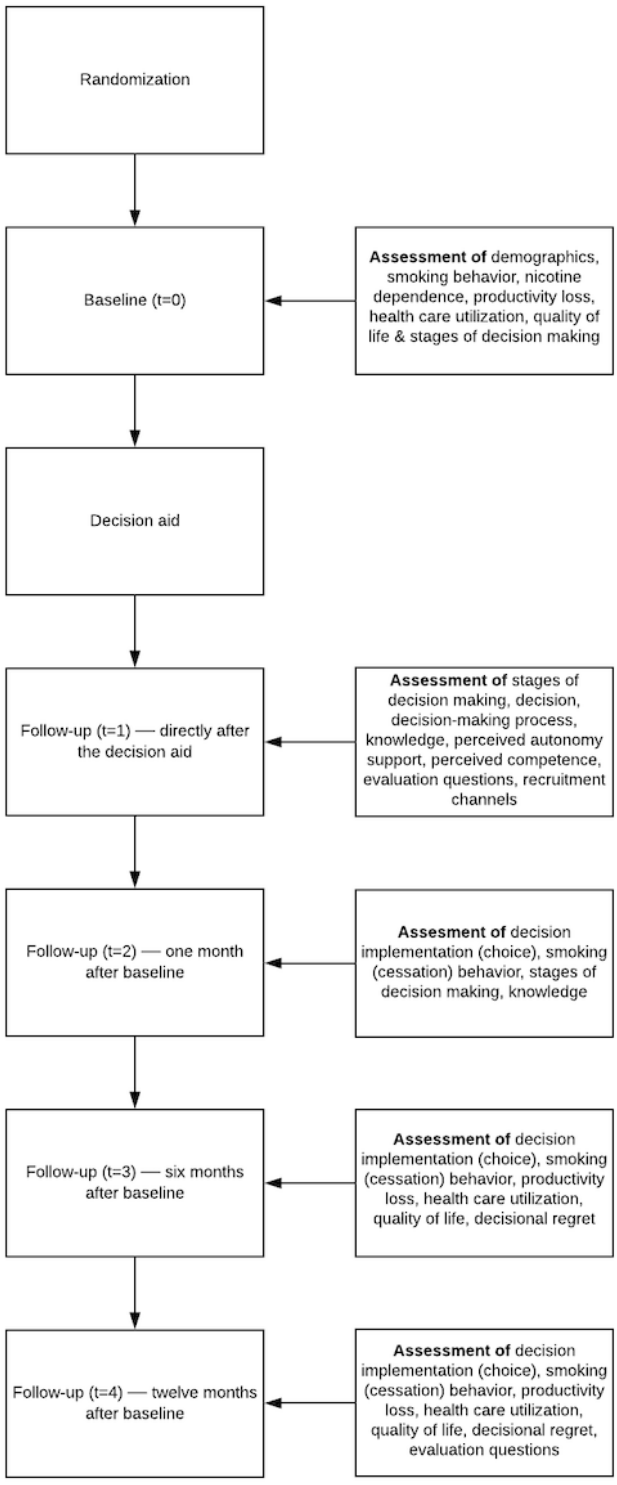
Constructs	Measurements and sources	Purpose
Baseline (t=0): directly before the decision aid		
Demographics	Age, gender, education [52]	Sample description, attrition analyses, covariate(s) in (main) analyses
Smoking behavior	Smoking status, motivation to quit, type of tobacco products, amount of tobacco consumption, amount of past cessation attempts, and cessation assistance utilization in the past 6 months [52]	Sample description, attrition analyses
Nicotine dependence	Revised Fagerström Test for Nicotine Dependence (FTND-R) [53]	Sample description, attrition analyses, covariate in (main) analyses
Productivity loss	iMTA Productivity Cost Questionnaire (iPCQ) [54]	Economic evaluation
Health care utilization	Contacts with health care professionals (plus frequency) in the past 6 months, cessation assistance utilization (plus frequency) in the past 6 months [55]	Economic evaluation
Quality of life	ICEpop CAPability measure for Adults (ICECAP-A) [56]	Economic evaluation
Stages of decision making	Stage of Decision Making [57]	Sample description, attrition analyses, process information, covariate in (main) analyses
Follow-up (t=1): directly after the decision aid		
Stages of decision making	Stage of Decision Making [57]	Sample description, process information
Decision	Decision after having used the decision aid (DA), not yet implemented	Sample description, process information
Decision-making process	Decisional conflict scale [58], first item from the Preparation for Decision Making Scale [59]	Hypothesis testing, H_4 (decisional conflict scale [58]); process information and additional studies (see "Data Analysis")
Knowledge	Self-developed knowledge scale [60]	Additional studies (see "Data Analysis")
Perceived autonomy support	The Virtual Care Climate Questionnaire [47]	Additional studies (see "Data Analysis")
Perceived competence	Perceived competence scale [48]	Additional studies (see "Data Analysis")
Evaluation questions	Regarding attention, clarity, satisfaction, and one open question	Process information
Recruitment channels	N/A[a]	Recruitment monitoring and analyses
Follow-up (t=2): 1 month after baseline		
Decision implementation	Implemented decision (choice) after having used the DA	Hypothesis testing, H_{2a} and H_{3a}
Smoking (cessation) behavior	Prolonged abstinence; 7-day point prevalence abstinence; for users that did not successfully stop: type of tobacco products and amount of tobacco consumption [52]	Hypothesis testing, H_{1a} (7-day point prevalence abstinence [52]); additional studies (see "Data Analysis")
Stages of decision making	Stage of Decision Making [57]	Sample description, process information
Knowledge	Self-developed knowledge scale [60]	Additional studies (see "Data Analysis")
Follow-up (t=3): 6 months after baseline		
Decision implementation	Implemented decision (choice) after having used the DA	Hypothesis testing, H_{2b} and H_{3b}
Smoking (cessation) behavior	Prolonged abstinence; 7-day point prevalence abstinence; for users that did not successfully stop: type of tobacco products and amount of tobacco consumption [52]	Hypothesis testing, H_{1b} and H_{3a} (7-day point prevalence abstinence [52]); additional studies (see "Data Analysis")
Productivity loss	iPCQ [54]	Economic evaluation

Constructs	Measurements and sources	Purpose
Health care utilization	Contacts with health care professionals (plus frequency) in the past 6 months, cessation assistance utilization (plus frequency) in the past 6 months [55]	Economic evaluation
Quality of life	ICECAP-A [56]	Economic evaluation
Decisional regret	Decision regret scale [61]	Additional studies (see "Data Analysis")
Follow-up (t=4): 12 months after baseline		
Decision implementation	Implemented decision (choice) after having used the DA	Hypothesis testing, H_{2c}
Smoking (cessation) behavior	Prolonged abstinence; 7-day point prevalence abstinence; for users that did not successfully stop: type of tobacco products and amount of tobacco consumption [52]	Hypothesis testing, H_{1c} and H_{3b} (7-day point prevalence abstinence [52]); additional studies (see "Data Analysis")
Productivity loss	iPCQ [54]	Economic evaluation
Health care utilization	Contacts with health care professionals (plus frequency) in the past 6 months, cessation assistance utilization (plus frequency) in the past 6 months [55]	Economic evaluation
Quality of life	ICECAP-A [56]	Economic evaluation
Decisional regret	Decision regret scale [61]	Additional studies (see "Data Analysis")
Evaluation questions	Regarding perceived decision support	Process information

[a]N/A: not applicable.

Participants are invited to fill in each follow-up questionnaire if they made use of the entire DA, even when they skipped one of the other follow-up questionnaires. To avoid high drop-out rates, participants receive either 1 automatic reminder after a week (if they have not filled in the follow-up questionnaires at all) or 2 after 2 days and a week (if they already started filling in at least parts of the follow-up questionnaires). Participants that started using either the DA or started filling in the baseline questionnaire (t=0) without finishing it also receive 2 automatic reminders (after 2 days and a week). In addition, participants who took part in the last measurement receive €10 (US $11.84). A visual representation of the trial flow can be seen in Figure 4.

Figure 4. Trial flow.



Data Analysis

Assessment of the Scale Quality

Before conducting any analyses, we will assess the scale quality of all measurement instruments where appropriate, following the 2 steps proposed by Crutzen and Peters [62]: (1) conformation of intended structure of the measurement instrument by means of exploratory factor analyses and (2) calculation of omega [63] as a less biased alternative to (Cronbach) α. Compared to α, omega has more realistic assumptions regarding variances of and covariance between items [64]. $Omega_{hierarchical}$ is based upon the sum of the squared loadings of items on the general factor and reduces the risks of misjudging the internal consistency of scientific scales [65]. Values will be calculated with R [66], making use of the integrated development environment RStudio [67].

Analysis of Primary and Secondary Outcomes

To assess the effects of the DA on dichotomous and continuous (primary and secondary) outcome measures, logistic and linear regression analyses will be conducted, respectively. Mediation analyses will be conducted to determine whether the effects of the DA on smoking abstinence are mediated through cessation assistance use. All analyses will include covariates that were selected a priori (as recommended by Gruijters [68] and De Boer et al [69]), if these are also associated with the 3 outcome measures as described in our hypotheses (ie, smoking abstinence, evidence-based cessation assistance use, and decisional conflict) within our sample. Demographic factors (ie, age, gender, and education) were selected for all 3 outcome measures. The Revised Fagerström Test for Nicotine Dependence was also selected for the smoking-related outcome measures, whereas stage of decision making was selected for decisional conflict. More information on the rationale for selecting those covariates can be found in Multimedia Appendix 1. Results will be reported from both the fully adjusted as well as crude analyses [68]. These analyses as well will be done with R [66], making use of the integrated development environment RStudio [67]. To test the robustness of the results, all analyses will be conducted according to 3 different approaches (if applicable): analyses based on (1) worst case scenario (dropout respondents are considered not to have changed), (2) multiple imputations, and (3) complete cases only. We will also test whether selective dropout has occurred in order to subsequently minimize the bias that this can cause.

Economic Evaluation

An economic evaluation will be performed from a societal perspective with a time horizon of 12 months. Both a cost-effectiveness analysis and a cost-utility analysis will be conducted. For the cost-effectiveness analysis, 2 incremental cost-effectiveness ratios will be calculated, based on the cost per abstinent respondent and the cost per individual who uses evidence-based cessation assistance. For the cost-utility analysis, an incremental cost-utility ratio will be calculated, based on the ICEpop CAPability measure for Adults, as proposed by Smit et al [70]. Uncertainty will be accounted for by bootstrapping and several univariate and multivariate sensitivity analyses. Cost-effectiveness acceptability curves will be constructed, showing for varying willingness-to-pay thresholds the probability that the DA with an explicit VCM and tailored advice is cost-effective compared to the DA without an explicit VCM and tailored advice.

Additional Studies

An additional study using the data collected during the RCT as described in this protocol will be conducted in the future to test the cognitive processes (eg, the clarification of one's values) that may underlie the effects of the DA on primary (ie, smoking abstinence) and secondary (eg, decisional regret) outcomes activated by the DAs by making use of Structural Equation Modelling in R [66] with the lavaan package [71].

Results

The RCT started in January 2020, and at this writing, 1248 users created an account, of which 519 finished the DA. Data collection is ongoing and will be conducted until September 2021.

Discussion

This paper describes the systematic development of an autonomy-supportive DA to assist smokers in choosing evidence-based cessation assistance and the intended study design to test its (cost-)effectiveness. In order to systematically develop an evidence-based online DA for a lifestyle behavior, we applied the IPDAS development process guideline [30]. The DA described in this article does not require the assistance of a health care professional and is intended for all adults that want to quit smoking in the near future (ie, within the coming 6 months). Therefore, we explicitly try to reach a broad range of potential users by focusing our recruitment strategy on social media platforms and other, more traditional media outlets. This enables us to reach a target group interested in making a decision on smoking cessation support independently from more traditional channels, such as their health care provider. This is especially interesting, as Dutch smokers often do not engage in smoking cessation discussions with their health care provider and instead most often turn to the internet for smoking cessation advice [8]; therefore, we believe this recruitment strategy is most suitable for reaching this rather general target group and could expose an additional group of smokers motivated to quit to evidence-based cessation assistance.

The results of this RCT can be used to improve our understanding of decision-making processes (especially in the context of smoking cessation) and to provide new insights into effective elements of DAs, to support not only informed decision making but also subsequent behavioral change. Formative studies (ie, the aforementioned interviews and beta/usability tests) have shown that potential end users are interested in the DA as they want to achieve long-term behavior change (ie, smoking abstinence). However, most RCTs testing the effects of DAs focus on decisional outcomes alone [9]. Our RCT will thus be of added value to the field and might provide unique insights that have remained unexplored so far.

Furthermore, if the DA will be proven to be (cost-)effective, it can be implemented nationwide and will thus help to reduce tobacco-related diseases and deaths. Two of 3 unique characteristics of this DA that were mentioned in the Introduction to overcome the limitation of the paper-based DA that was tested in the Netherlands before [14] could make a nationwide implementation particularly interesting: The online nature will (1) allow for a wider reach and (2) enable a more flexible and interactive approach.

Potential Strengths of the Study

The study shows several potential strengths. First, we are conducting an RCT to assess the DA's impact on behavior change and decision-making outcomes, with randomization being done automatically. The fact that participants are being

blinded (as the control group receives a DA as well) further strengthens this study. DAs aimed at smoking cessation with explicit VCMs have been tested before, but without following an RCT protocol (eg, [25]). Testing the DA in a longitudinal RCT design will allow for stronger conclusions about the DA's impact. Following participants for a longer period of time is especially interesting as explicit VCMs have been shown to result in long-term benefits but not necessarily in short-term benefits [21].

Second, recruited end users are only included if they are motivated to stop smoking in the near future, meaning they actually have to decide how they wish to stop smoking. A previous study that tested the effects of an explicit VCM found no effects [46]; however, they made use of a hypothetical decision, which hampers interpretation of their findings. As both primary (ie, smoking abstinence) and secondary (eg, decisional conflict) outcomes relate to "real-life" phenomes and affect, testing the DA in a nonhypothetical and "natural" context will also allow for stronger conclusions about the DA's impact.

Third, and as previously mentioned, the DA is tested not only for outcomes at the decisional level but also at the behavioral level. Above and beyond this, the DA will also be tested regarding its cost-effectiveness. This is especially interesting as experts strongly urge to test eHealth applications not only for their effectiveness but for their cost-effectiveness as well [72]. However, these practices are not commonly applied. Testing the DA's cost-effectiveness will enable decision makers to make evidence-based recommendations regarding the widespread implementation of the cessation assistance DA — which is particularly interesting given the scarcity of health care resources.

Potential Limitations of the Study

The study also has a few potential limitations. First, as it was decided to include 2, and not 3, study arms in our RCT, it will not be possible to assess the effects of the explicit VCM and the tailored advice separately. However, including a third arm would have required an even bigger sample, which was deemed not feasible.

Second, the online nature of both the DA and our recruitment strategy exclude potential participants that either have no access to the internet or lack the digital skills needed to use the DA. However, given that the Netherlands is 1 of the 2 countries with the highest percentage of households with internet access in the European Union [73], we expect this to be a relatively minor limitation.

Conclusion

DAs that assist smokers in choosing evidence-based cessation assistance offer a potential approach to both counteract the public health effects of smoking and facilitate individual's smoking cessation attempts. However, knowledge regarding effective elements and (cost-)effectiveness is lacking. Our study is therefore expected to contribute significantly to the current knowledge regarding smoking cessation DA application, the added value of explicit VCMs within such DAs, and the effect on behavioral and informed decision-making outcomes.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Selection of covariates.
[DOCX File , 21 KB - resprot_v9i12e21772_app1.docx]

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Abbreviations

DA: decision aid
FTND-R: Revised Fagerström Test for Nicotine Dependence
ICECAP-A: ICEpop CAPability measure for Adults
iPCQ: iMTA Productivity Cost Questionnaire
IPDAS: International Patient Decision Aid Standards
NRT: nicotine replacement therapy

RCT: randomized controlled trial
SDT: Self-Determination Theory
VCM: value clarification method

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Protocol

Increasing HIV Testing and Viral Suppression via Stigma Reduction in a Social Networking Mobile Health Intervention Among Black and Latinx Young Men and Transgender Women Who Have Sex With Men (HealthMpowerment): Protocol for a Randomized Controlled Trial

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Abstract

Background: Stigma and discrimination related to sexuality, race, ethnicity, and HIV status negatively impact HIV testing, engagement in care, and consistent viral suppression (VS) among young Black and Latinx men who have sex with men and transgender women who have sex with men (YBLMT). Few interventions address the effects of intersectional stigma among youth living with HIV and those at risk for HIV within the same virtual space.

Objective: Building on the success of the HealthMpowerment (HMP) mobile health (mHealth) intervention (HMP 1.0) and with the input of a youth advisory board, HMP 2.0 is an app-based intervention that promotes user-generated content and social support to reduce intersectional stigma and improve HIV-related outcomes among YBLMT. The primary objective of this study is to test whether participants randomized to HMP 2.0 report improvement in HIV prevention and care continuum outcomes compared with an information-only control arm. We will also explore whether participant engagement, as measured by paradata (data collected as users interact with an mHealth intervention, eg, time spent using the intervention), mediates stigma- and HIV care–related outcomes. Finally, we will assess whether changes in intersectional stigma and improvements in HIV care continuum outcomes vary across different types of social networks formed within the intervention study arms.

Methods: We will enroll 1050 YBLMT aged 15 to 29 years affected by HIV across the United States. Using an HIV-status stratified, randomized trial design, participants will be randomly assigned to 1 of the 3 app-based conditions (information-only app-based control arm, a researcher-created network arm of HMP 2.0, or a peer-referred network arm of HMP 2.0). Behavioral

assessments will occur at baseline, 3, 6, 9, and 12 months. For participants living with HIV, self-collected biomarkers (viral load) are scheduled for baseline, 6, and 12 months. For HIV-negative participants, up to 3 HIV self-testing kits will be available during the study period.

Results: Research activities began in September 2018 and are ongoing. The University of Pennsylvania is the central institutional review board for this study (protocol #829805) with institutional reliance agreements with the University of North Carolina at Chapel Hill, Duke University, and SUNY Downstate Health Sciences University. Study recruitment began on July 20, 2020. A total of 205 participants have been enrolled as of November 20, 2020.

Conclusions: Among a large sample of US-based YBLMT, this study will assess whether HMP 2.0, an app-based intervention designed to ameliorate stigma and its negative sequelae, can increase routine HIV testing among HIV-negative participants and consistent VS among participants living with HIV. If efficacious and brought to scale, this intervention has the potential to significantly impact the disproportionate burden of HIV among YBLMT in the United States.

Trial Registration: ClinicalTrials.gov NCT03678181; https://clinicaltrials.gov/ct2/show/study/NCT03678181.

International Registered Report Identifier (IRRID): DERR1-10.2196/24043

(JMIR Res Protoc 2020;9(12):e24043) doi:10.2196/24043

KEYWORDS

HIV; mHealth; smartphone; men who have sex with men; racism; transgender; Hispanic Americans; mobile phone; African American

Introduction

Background

Young Black and Latinx men who have sex with men and transgender women who have sex with men (YBLMT) have the highest rates of new HIV diagnoses compared with non-Hispanic White peers of the same age [1], even when engaging in fewer individual-level risk behaviors [2-4]. YBLMT face multiple stigmas, racism, and discrimination related to their sexual orientation, gender, race, ethnicity, and HIV status that constrain options for building healthy relationships and supportive networks; this contributes to social isolation, inhibiting protective behaviors (eg, consistent condom use, uptake of pre-exposure prophylaxis [PrEP], and adherence to antiretroviral therapy [ART]) [5-9]. These stigmas and discriminatory practices are institutionalized and perpetuated in the systems and environments of daily life, posing barriers to engagement in care such as regular HIV testing, PrEP and ART persistence, and attending HIV care appointments [10-17]. Stigma- and discrimination-related stressors have additive or multiplicative negative physical, social, and mental health effects at the individual, interpersonal, community, and structural levels [18-23].

Although a growing number of interventions aim to address individual- or community-level HIV stigma [24,25] or consider YBLMT intersecting identities [26-30], few focus on addressing intersectional stigma as a primary mechanism for improving HIV prevention and care [31]. Furthermore, most stigma-focused interventions are delivered in person, are not tailored for the unique developmental stages of youth and young adulthood, and focus on either HIV-positive or HIV-negative populations [27,28,32-36]. The social and logistical requirements of attending in-person interventions may not fit the realities of YBLMT, particularly if they are geographically isolated [37] or have perceived discrimination or experienced microaggressions within the health care system [15,38,39]. Segmenting participants by HIV status could further polarize individuals in the community, reinforcing rather than reducing HIV-related stigma [40,41]. The biomedical advances of PrEP and Treatment as Prevention and the *undetectable equals untransmittable* (U=U) movement necessitate more inclusive, accessible intervention approaches [42].

As a strengths-based approach, social networks hold the potential power to resist stigma and improve HIV prevention and care continuum for YBLMT [43-47]. Networks also offer a unique way to understand how stigma norms and beliefs are reinforced or deconstructed. Understanding these processes within networks is important because of the critical roles of connectivity and collective identity in resilience [48-50]. A smartphone-delivered intervention that draws on the strengths of social networks could alleviate barriers to access in-person interventions, facilitate more open dialogue addressing intersectional stigma, and encourage HIV testing and care through supportive interactions with peers across the country [51-56]. Widespread access to smartphones among YBLMT in the United States makes this modality an ideal approach for increasing intervention access and reach [37,57].

A number of mobile health (mHealth) interventions are currently being developed or adapted for YBLMT [54,58-63]; however, few explicitly address the influence of intersectional stigma on HIV care outcomes or take an inclusive approach across HIV status. To address these gaps and barriers, we created an intervention strategy focused on fostering community, providing resources, and amplifying the existing strengths and assets of YBLMT [13,49,64]. The original HealthMpowerment (HMP) intervention and mHealth platform (HMP 1.0) was designed and delivered as a 3-month intervention to increase safer sex behaviors; foster community among YBLMT; and remove logistical, financial, and psychosocial barriers to intervention engagement [58]. The HMP 1.0 intervention yielded significant reductions in condomless anal intercourse (CAI) in a randomized controlled trial (RCT) conducted in the southeastern United States [58]. The social support features of HMP 1.0 were the most frequently used intervention components, and engagement

with these features was associated with improved HIV care outcomes [31]. We also found associations between engaging with stigma-related content and both psychosocial and physical health outcomes [31,65-67].

Objectives

Building on the success and lessons learned with HMP 1.0, and with the input of a youth advisory board (YAB), we rebuilt the intervention platform to reflect participant feedback and advances in technology and design. The HMP 2.0 platform maintains strong social and informational support features and enhanced intervention components. Content focuses on fostering stigma amelioration with the goals of strengthening the continued engagement of YBLMT in HIV testing for those who are HIV negative and sustained viral suppression (VS) for youth living with HIV. Our study will also address a gap in knowledge regarding how participant engagement with mHealth interventions is linked to HIV prevention and care outcomes [68-70]. We will use paradata metrics (data automatically collected as users interact with mHealth interventions such as time stamps in system logs to quantify time spent using the intervention) to gauge how intersectional stigma- and HIV-related outcomes differ based on participants' frequency of use (exposure), amount of time spent (engagement), and types of intervention components used (usage) on the app [71].

This intervention trial is built on the scientific premise that network interventions can support behavior change [21,22,43,45,46,72,73]. Given that YBLMT widely use web-based networking sites and apps to socialize with peers [51,53,74-76], HMP 2.0 promotes social support by creating a connected virtual community [56]. We hypothesize that compared with YBLMT assigned to an information-only app condition, YBLMT assigned to an intervention arm of HMP 2.0 will report greater changes in stigma-related measures (eg, anticipated stigma, internalized stigma) and be more successful at buffering the negative sequelae of intersectional stigma and circumventing barriers to successful engagement in the HIV prevention and care continuum [46,77]. As the structural (eg, size, density) and interactional (eg, relational roles between ties; frequency and reciprocity between actors) components of a network also affect behaviors [78-85], we will compare efficacy and engagement levels between 2 types of recruitment networks: a researcher-created network and a peer-referred network. We hypothesize that participants assigned to the peer-referral network condition will have greater success in eliciting peer social support, engaging with the intervention, and achieving the desired stigma- and HIV-related outcomes than participants in the researcher-created network condition.

Methods

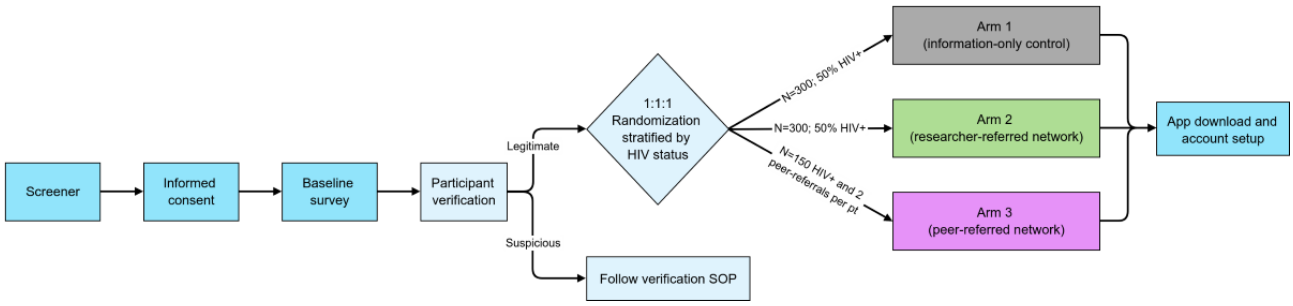
Timeline

This project began in September 2018. The initial period of study start-up activities (eg, obtaining institutional review board [IRB] approvals, hiring and training staff, rebuilding the intervention platform structure, developing the study protocol and study-specific procedures, recruiting YAB members) lasted until September 2019. October 2019 to June 2020 consisted of working with the research team, technology partner, and YAB members to update and expand intervention content; finalize and program all study tools; create HIV and viral load self-testing multimedia support materials and shipping procedures; establish robust recruitment, retention, and engagement plans; and optimize the functionality and usability of the intervention platform and administrators' data management dashboard. Recruitment began in July 2020 and is anticipated to complete between June and September 2022. Final participant follow-ups will end by September 2023 followed by data analysis, and the study results will be disseminated in 2024.

Study Design

The study design is a 3-arm, 12-month prospective RCT enrolling a total of 1050 men who have sex with men (MSM) and transgender women (TW) across the United States. The research team will recruit and enroll 750 participants; the remaining 300 will be referred by enrolled participants. Of the 750 researcher-recruited participants, 300 will be HIV negative and 450 will be HIV positive. Participants' self-reported HIV status at baseline will be used for allocation in our HIV-status stratified randomization procedure (Figure 1). Researcher-recruited participants who self-reported as HIV negative or serostatus unknown will be randomized (1:1; n=150 per arm) into either the information-only control arm (arm 1) or the researcher-created network (arm 2). Researcher-recruited participants who self-report as HIV positive will be randomized across all 3 study arms (1:1:1; n=150 per arm). Researcher-recruited HIV-positive participants randomized to the peer-referral network arm (arm 3; n=150) can then invite peers to participate in the intervention. Up to 2 eligible referred peers may enroll per arm 3 researcher-recruited participant. These peers will be directly assigned to study arm 3 (not randomized); referred peers who enroll may not subsequently refer other peers. We estimate that approximately half of the participant-referred enrolled peers will be HIV negative or sero-unknown (Figure 1).

Figure 1. HealthMpowerment intervention enrollment and randomization procedural flow diagram. SOP: standard operating procedure.



Study assessments will be administered at baseline, 6, and 12 months. An abbreviated version of the study assessment is administered at months 3 and 9. Consistent with best practices, we will use validated measures developed as part of the US National Institutes of Health Adolescent Medicine Trials Network for HIV/AIDS Interventions studies [86].

HMP 2.0 Intervention

Theoretical Foundations

The theoretical foundation of HMP 2.0 builds on the intervention's original behavior change theory—the Integrated Behavior Model [87]—and increases the salience of stigma-related beliefs, norms, and attitudes through new intervention content and activities, as informed by the Conceptual Framework for HIV-Related Stigma, Engagement in Care, and Health Outcomes (the *Stigma Framework*) [88]. Structural stigma and intersectionality are overarching phenomena of the Stigma Framework. Stigma, racism, and discrimination are manifested in the social and institutional structures (eg, laws, policies, norms) that create and perpetuate disadvantage for marginalized groups [89]. Intersectionality theory proposes that the social categorizations of marginalized identities (eg, gender, sexuality, race) are not distinct but rather work together to produce and reproduce inequities [90-93]. These contexts are central to HMP 2.0's intervention approach on the premise that stigma and discrimination shape the health and health care experiences of YBLMT and should thus be a primary target of intervention.

The Stigma Framework reflects the foundational HIV stigma work [94-96] categorizing 4 types of stigma: discriminatory events and experiences (enacted stigma), perceptions of society's stigmatizing attitudes (community stigma), expectations of future discrimination (anticipated stigma), and acceptance of negative societal attitudes as part of one's own beliefs (internalized stigma) [88]. The HMP 2.0 intervention features tailored content and study measures across these 4 dimensions of stigma and also categorizes a fifth dimension of *challenging stigma*, that is, the acts of naming, confronting, resisting, or otherwise countering stigmatizing experiences, beliefs, narratives, practices, and perceptions [13,65]. In the HMP 1.0 trial, 75% of all participant-contributed stigma-related content could be categorized as *challenging stigma*, underscoring its importance within this virtual space [67] and its potential role in fostering resilience and resisting stigma and discrimination [50,65]. In applying the Stigma Framework, we categorize these 5 dimensions of stigma across content about race and ethnicity, gender, sexuality, and HIV.

Finally, the Stigma Framework proposes 4 types of mechanisms operating between stigma and engagement in care and HIV-related outcomes: interpersonal factors, psychological resources, mental health, and stress processes. Psychological resources include the "tools, skills, and personal identities that individuals use to cope with stressful life events" [88]. Stigma is negatively associated with these factors [97] and they may also act as buffers along the pathway to HIV-related outcomes [44]. Mental health refers to the relationship between stigma and depression and anxiety [98]. Finally, stress processes consider the biological pathways that are activated and may have a direct or mediated impact on HIV-related outcomes. A scientific premise of HMP 2.0 is that because of multiple stigmas and discrimination, stress processes are constantly activated among YBLMT. The intervention content and community-focused design aims to raise awareness of these stressors among participants, reinforce and model positive coping strategies, and ameliorate and discourage negative coping.

HMP 2.0 incorporates interpersonal-level components through its social support and social networking approach. Analyses will employ a network dynamics perspective and explore how stigma processes operate in interactions between individuals on the intervention. Psychological resources support a range of prohealth behaviors and constructs, including adherence self-efficacy, self-esteem, and coping skills. HMP 2.0 includes a substantial focus on mental health and wellness resources, activities, and discussion. A care navigator provides tailored referral support through the app.

YAB

Youth involvement is vital when designing and executing a youth-focused HIV intervention [5,7,10]. Alongside the research team, we convened a YAB that includes members recruited nationally through social media (Instagram, Facebook, Twitter, and Craigslist), the Adolescent Medicine Trials Network for HIV/AIDS Interventions, and community contacts with groups that serve Black or Latinx queer communities. The YAB members are diverse in terms of age (21-29 years), race and ethnicity (3 Latinx members, 6 Black members, and 1 Black Native American member), HIV status (not reported for confidentiality), sexual orientation (not reported for confidentiality), and gender identity (8 cisgender men and 2 TW). States currently represented include Georgia, Louisiana, Michigan, New York, North Carolina, and Pennsylvania.

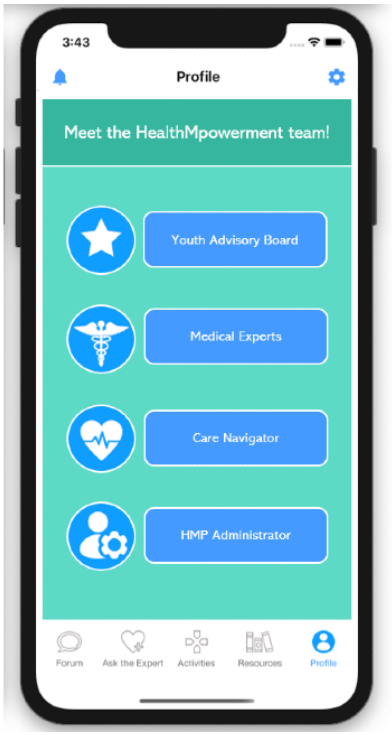
During intervention development, YAB members met biweekly with a designated research team member (YAB coordinator), either one-on-one or through group sessions, and provided iterative feedback as intervention functionality and content were updated, study protocol decisions were considered, and study materials and tools were developed. YAB members provided written and oral feedback; study staff took detailed notes during group discussions. Members reviewed forum topics and prepopulated comments and the organization and content of the Resources section for readability, comprehension, and relevance. They also identified gaps in content and suggested edits for language, tone, and imagery. Differences in opinions and perspectives emerged; however, none were divisive. Recognizing that these differences would also likely be reflected among study participants, the research team attempted to incorporate these multiple perspectives into intervention design and content. When relevant, the team gave greater weight to options that had a stronger evidence base or were more technologically feasible. Detailed descriptive processes regarding the YAB are planned for a YAB-focused paper, including YAB co-authorship.

During the active intervention (July 2020 to June 2023), YAB members will contribute on the forums in both intervention arms (2 and 3). Their HMP usernames will be preceded with

"YAB" and feature a distinct avatar icon (Figure 2) and they will help monitor the forums for ideas for new content and flag any posts that do not follow the HMP 2.0 community guidelines of mutual respect. Interested YAB members will receive additional training to support writing new content for the intervention and analyzing the participant-contributed forum conversations. YAB members are considered integral members of the study team and receive a stipend commensurate with their time contributed each month. In addition to their monthly stipend, YAB members work with a YAB coordinator to create personalized professional development plans.

Development activities range from resume and interview preparation to connecting and networking with professionals in their fields of interest. The YAB coordinator also identifies shared interests among the group and facilitates opportunities for group professional development.

Figure 2. Screenshot of all icons for HealthMpowerment (HMP) 2.0 nonparticipant roles.



Intervention Components

Intervention Features

Table 1 presents brief descriptions of the core components of HMP 2.0 aligned with the theoretical underpinnings for addressing stigma and changing behavior. Modifications to the intervention were guided by the HMP 1.0 trial evaluation [65-67], the Stigma Framework developed by Turan et al [88], the YAB study, and advances in the science of HIV prevention, care, and health communication (eg, PrEP, U=U).

Table 1. HealthMpowerment 2.0 core components, scientific rationale, and measurement metrics.

Features	Description	Scientific rationale (measurement metrics)
Base app components for all study arms 1, 2, and 3		
Resource center	• Multimedia resources and information on health and wellness, stigma, resilience, and life skills—tailored for YBLMT[a], inclusive learning styles and health literacy • Robust management system to create and tailor new content and activities	Content corresponds to and extends the HMP[b] 1.0 intervention and aligns with the Integrated Behavior Model (number of articles read and total time spent)
Test kit ordering	• Ability to order and track HIV self-test kit and viral load self-collection test • HIV test result image upload to app triggers care navigator follow-up	Provides an opportunity to get tested by reducing barriers to in-person testing (number of test kits ordered and results uploaded to app or received by laboratory)
Care navigator	• Facilitates referral and linkage to HIV services in the participant's local community • Follows up on unreported HIV test results and all shared unclear and positive results • Supports app engagement and retention • Troubleshoots and triages participant questions within the app to medical, study, and technology teams	Increases intervention tailoring and linkage to care for nonclinic-based study. Provides equipoise and reduces risk of social harms for remote study with HIV at-risk minors. Supports use of self-testing and self-collection for youth (number of questions asked, content of questions, and participant satisfaction)
Interactive app components for intervention arms 2 and 3		
Profile	• Personalized, anonymous username, avatar, brief bio, badges earned, and activities completed	Personalization, gamification, and cues to action incentivize engagement (number of times visited and profile sections completed)
Activities	• Activity templates include quizzes, self-assessments, goal setting, choose-your-own-adventure, sorting, and matching	Interactive features will enhance learning, skill building and coping skills (number of activities done and total time)
Ask an expert	• HIV, STI[c], sex questions answered by board-certified physicians • Care navigator directs participants to on- and off-app follow-up resources	Provide evidence-based answers to participants' health questions (number of questions asked, total time, and content of questions)
Forums	• Start or add to existing discussions, upload images, videos, memes, etc • Favorite posts and follow others • Staff monitor and add to forum posts and include polls to encourage dialogue	Forum topics correspond to Stigma Framework constructs. Peer support for resilience and behavior change (number of posts, comments, and likes; total time; content of posts)
Gamification	• Sophisticated tracking of app use to trigger behavior-specific rewards • Badges awarded for tracked events	Gamification features incentivize continued engagement (number of log-ins and badges earned)
Peer network referral features for intervention arm 3 only		
Peer referral center	• Unique referral code provided to share with peers • Participant can track how many of their referred peers have successfully enrolled and then link to their in-app profiles	YBLMT widely use networking sites and apps to socialize with peers. Structural and relational aspects of social networks affect decision making and behaviors (number of peers referred and enrolled, characteristics, eg, size, density, and diversity of intervention networks)

[a]YBLMT: young Black or Latino men who have sex with men and transgender women.

[b]HMP: HealthMpowerment.

[c]STI: sexually transmitted infection.

HMP 2.0 App Intervention Study Arms

Information-Only Control Group (Arm 1)

The information-only control group (arm 1) features a streamlined version of the intervention app that provides all the informational content of the Resources section (Figure 3), HIV or viral load test kit ordering and tracking (Figure 4), and access to the care navigator. Our design of the control arm balances equipoise with the research study design; in the HMP 1.0 trial, information-only control arm participants also experienced a statistically significant intervention benefit [58]. We have considered this effect in our sample size calculations.

Figure 3. Example informational article screenshots from HealthMpowerment (HMP) 2.0 resources feature.

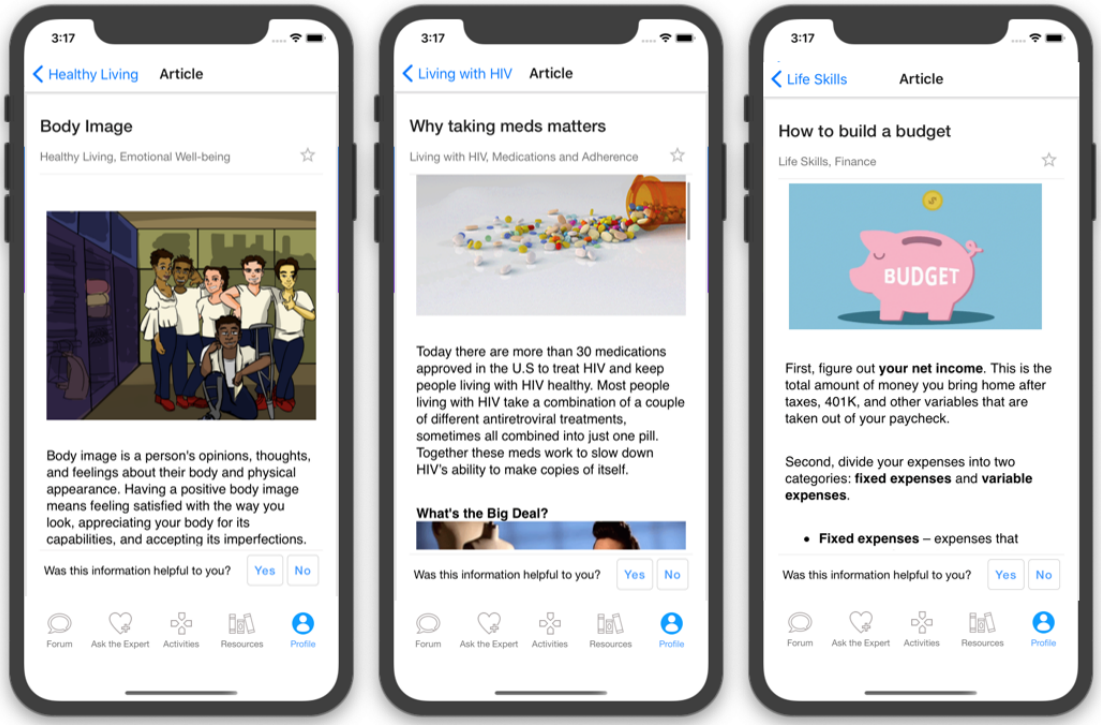
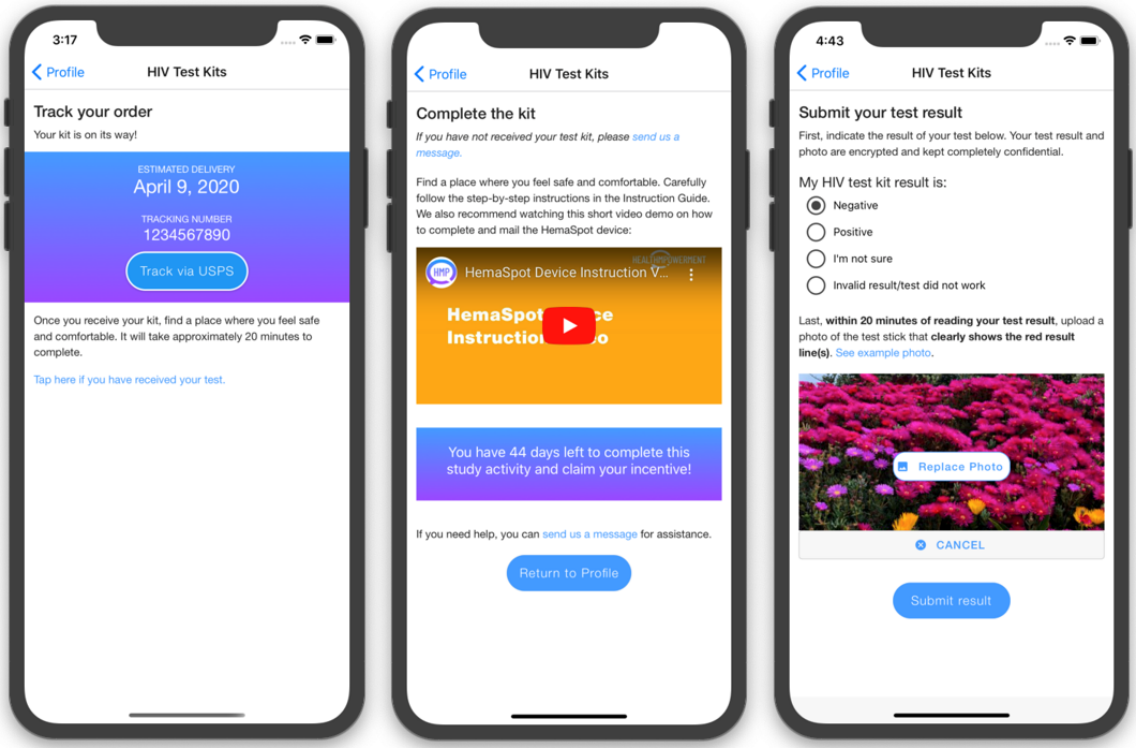


Figure 4. Example screenshots of the HealthMpowerment (HMP) 2.0 HIV and HemaSpot self-test kit features.



Researcher-Created Network Intervention (Arm 2)

Eligible, enrolled participants who are randomized to the researcher-created network intervention (arm 2) will have access to all features of HMP 2.0 (Table 1). These features include those described earlier and forums where participants can start or contribute to conversation threads and polls (Figure 5); an anonymous question and answer platform (Ask an Expert) where participants submit questions that are answered by a health care provider (Figure 6); a profile page that participants can personalize (Figure 7); an activity center supporting interactive learning, skill building, goal setting, and decision making (Figure 8); and a badge center with reward levels for all forms of engagement within the app (Figure 9).

Figure 5. Example Forum conversation screenshots from HealthMpowerment (HMP) 2.0 intervention arms feature.

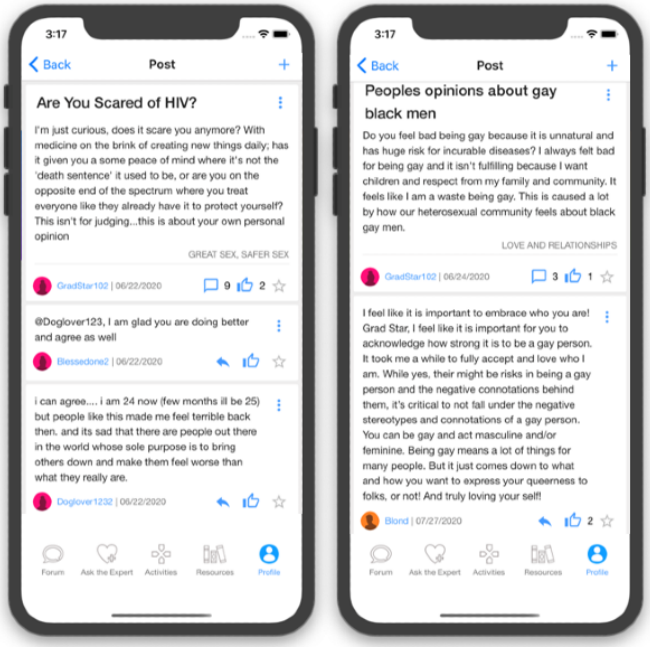


Figure 6. Example Ask the Expert screenshots from HealthMpowerment (HMP) 2.0 intervention arms feature.

Figure 7. Example screenshots from avatar and personalized profile for HealthMpowerment (HMP) 2.0 intervention arms.

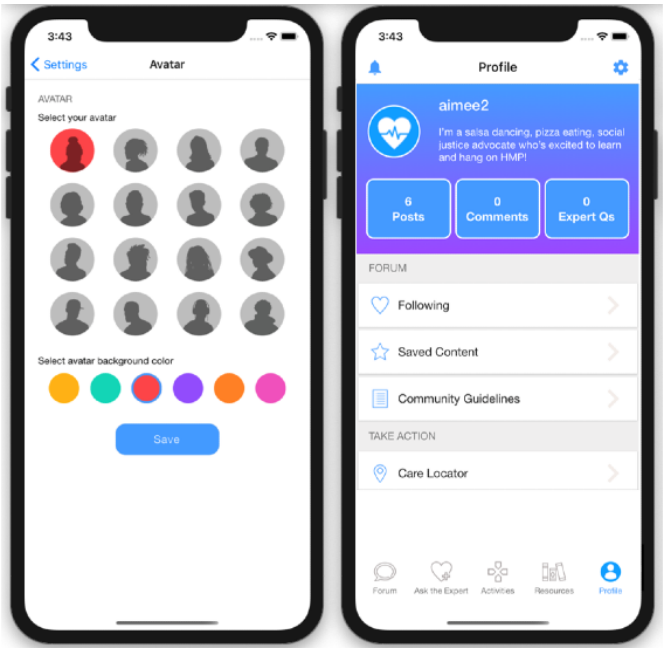


Figure 8. Example screenshots of decision-making activities in the HealthMpowerment (HMP) 2.0 intervention arms.

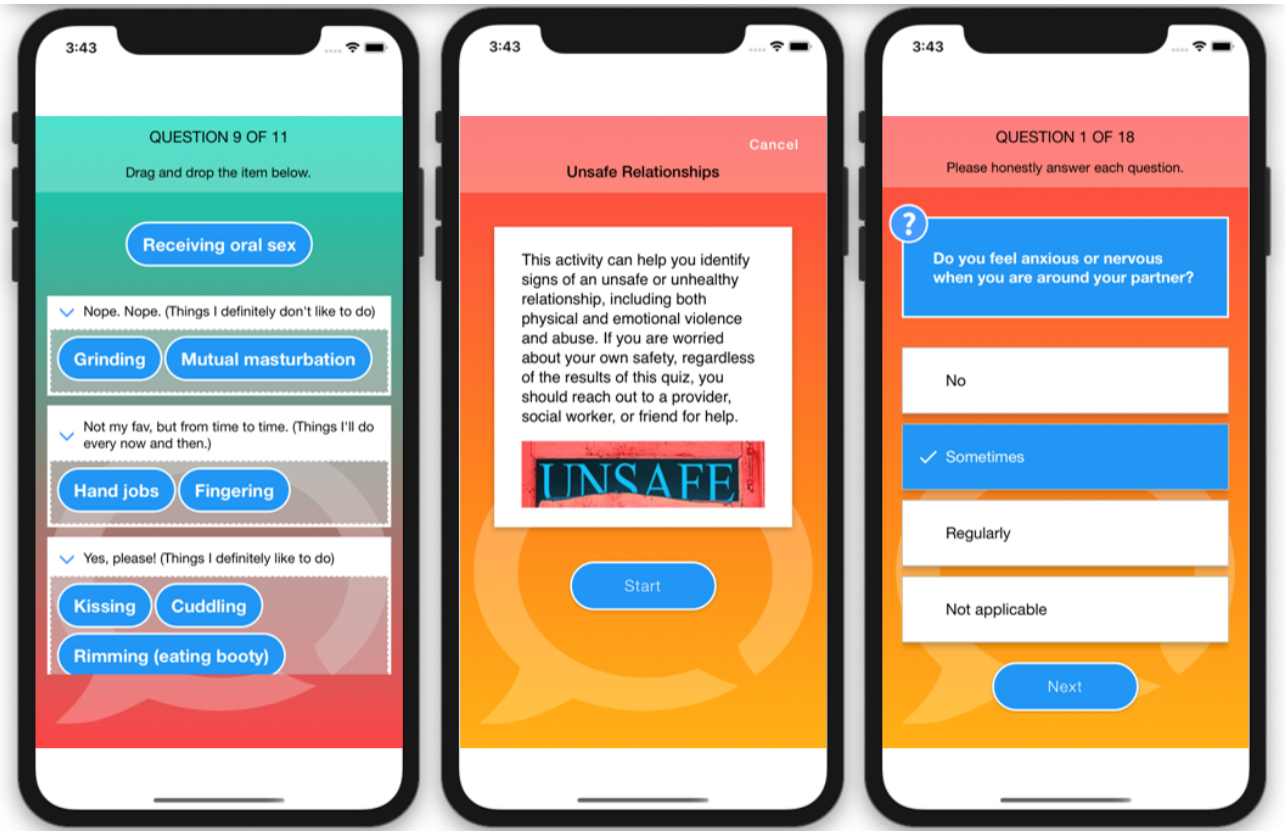
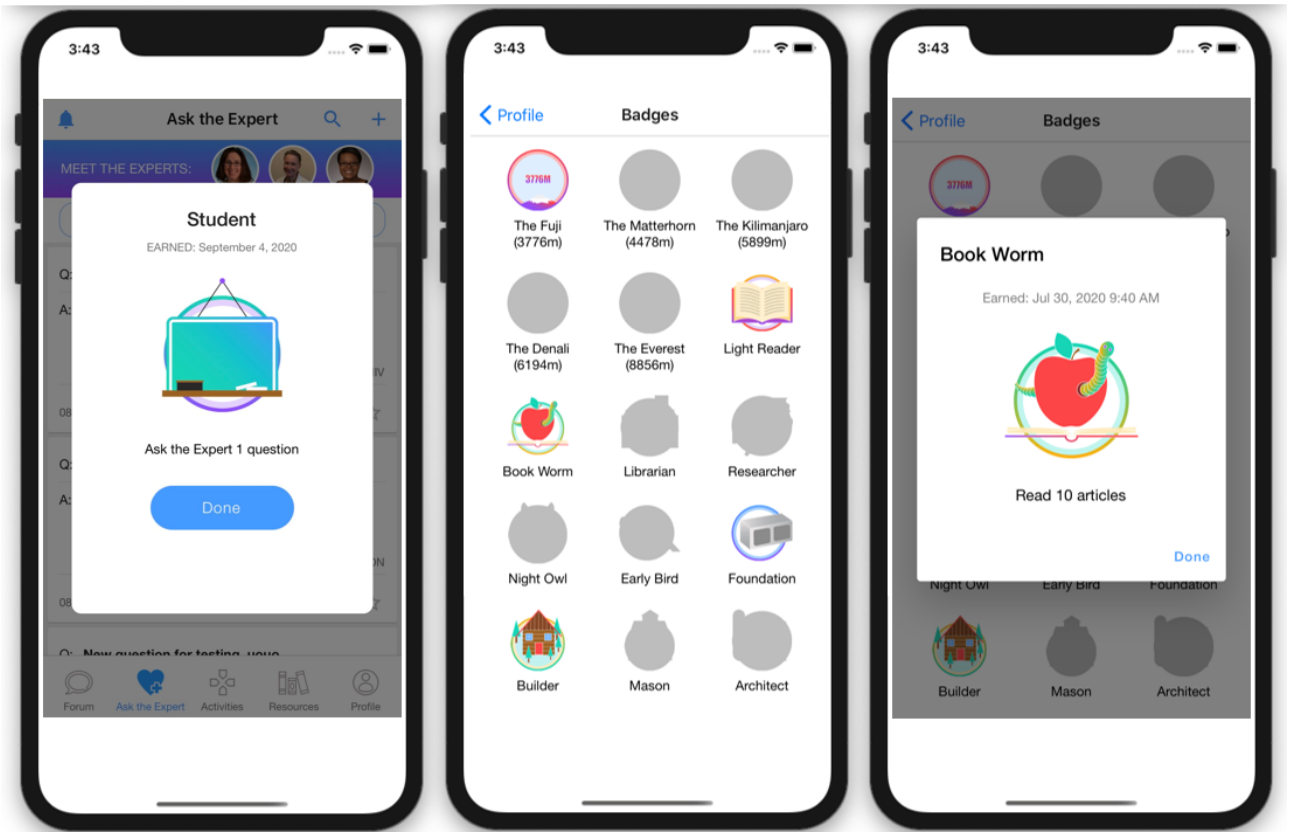


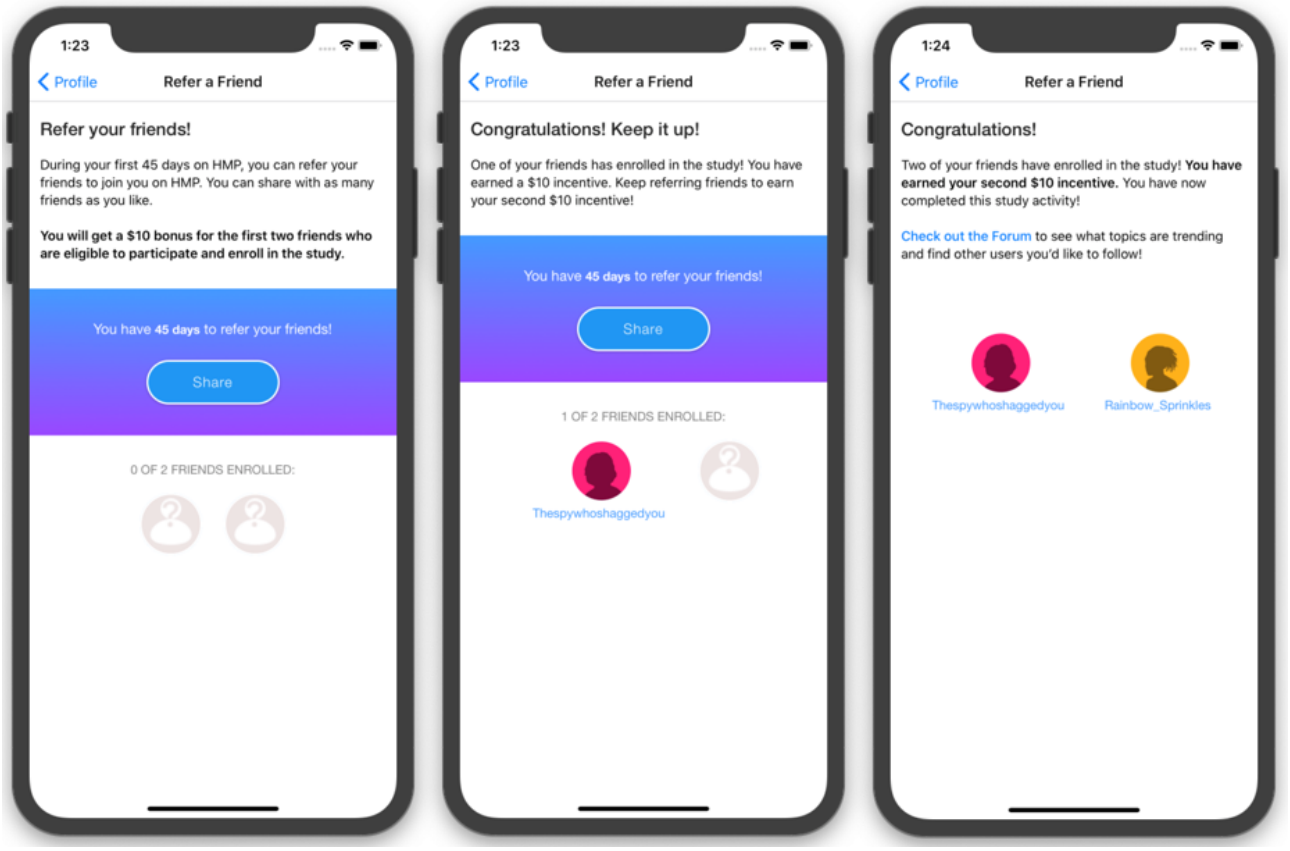
Figure 9. Examples of badges HealthMpowerment (HMP) 2.0 intervention arms participants can earn within the app.



Peer-Referred Network Intervention (Arm 3)

Participants randomized to arm 3 will be enrolled into a separate, parallel version of the HMP 2.0 full-feature intervention with access to all the features described for arms 1 and 2. However, participants in arm 3 can also share a customized invitation for peers to join the study (Figure 10) [99]. Participants may continue to send invitations to peers up until their 90th study day or until 2 of their referred peers have screened eligible and enrolled in the study. At that point, the participant's app will display a message to them that they have reached their peer referral quota and their referral button will be deactivated. In the app, participants in arm 3 can see the usernames of their referred peers but no other information about these individuals. Enrolled peers will see the username of their referrer but will not be eligible to refer peers themselves.

Figure 10. Example screenshots of peer referral feature from HealthMpowerment (HMP) 2.0 intervention arm 3.



HMP 2.0 Care Navigator

HMP 2.0 provides all study arm participants access to a trained care navigator who will use existing web-based databases of resources to connect participants to trusted HIV testing and care services in their communities as needed and auxiliary resources such as behavioral health services, housing assistance programs, and food assistance programs. Within the study intervention arms (2 and 3), the care navigator will also monitor the forum and Ask an Expert health care provider platform. During all study years, the care navigator will work closely with the YAB to elicit additional content to support emerging stigmas, service-related needs, and concerns among YBLMT that can be integrated into the intervention.

Home Collection of Blood and Saliva for Viral Load and HIV Testing

At baseline, 6, and 12 months, HIV-positive participants, across all study arms, who provide valid mailing addresses will be sent a HemaSpot-HF kit (Figure 11). The kit contains (1) one HemaSpot-HF device (Figure 12) and an instructional booklet on how to properly collect a blood specimen (eighth-grade reading level) with a link to a web-based step-by-step video; (2) a return envelope addressed to the lab with postage; (3) a lab sheet that includes the participant's unique identification number; and (4) all materials needed to collect the blood specimen in a safe and sanitary way: alcohol pads, 2 retractable 18-gauge fingerstick safety lancets, gauze pads, adhesive bandages, and a biohazard bag.

Figure 11. Image of participant informational package insert depicting the HemaSpot-HF blood collection kit contents.

Figure 12. Two HemaSpot-HF blood collection devices (open and closed).

HemaSpot-HF was developed to address technical issues associated with using traditional filter cards for dried blood spot collection [100]. Research by our team members found that men living with HIV are willing and able to collect their own blood specimens using HemaSpot-HF and may prefer this option over blood draws at clinic-based study visits as it offers convenience and privacy [101,102]. HemaSpot-HF is a small plastic device, about the size of a credit card and 0.25 inches deep. Specimens can be stored at room temperature, making HemaSpot-HF amenable to home self-collection. After blood collection (3-5 drops) with a single-use retractable safety lancet, HemaSpot-HF can be closed and shipped immediately because a desiccant in the kit quickly dries the sample inside the cartridge. Participants mail their completed kits directly to the study laboratory using a prepaid return envelope. Laboratory staff will track and store packages and test samples in batches

according to their internal protocol. Participants will be informed that testing is for research purposes only and that the results of their HemaSpot-HF viral load test will not be returned to them given that we cannot guarantee clinically accurate results for individual participants because of time lags from shipment and batched specimen processing. Study staff will recommend that participants visit their regular HIV care providers or work with care navigators to access providers to obtain current HIV viral load test results.

Self-reported HIV negative or status unknown participants across all study arms can request up to 3 in-home OraQuick (R) HIV tests (oral self-swab) [103] over the course of the 12-month study. Kit requests are made via the app and are sent in a discreet, unmarked box. These rapid tests are optional and help to maintain equipoise with the viral load collection procedures with HIV-positive counterparts in the trial. We will ask participants to take a picture of their test stick that shows their test result and then upload it securely through the intervention app. In post hoc analyses, we will compare those who request home test kits with those who report traditional testing in the follow-up assessments. If a participant reports a new HIV-positive result (whether through home test kit testing results, through an HIV status change in their follow-up surveys, or by notifying the study team), the care navigator will reach out to them following a prespecified protocol to support them in making an appointment for confirmatory testing and linkage to local HIV care.

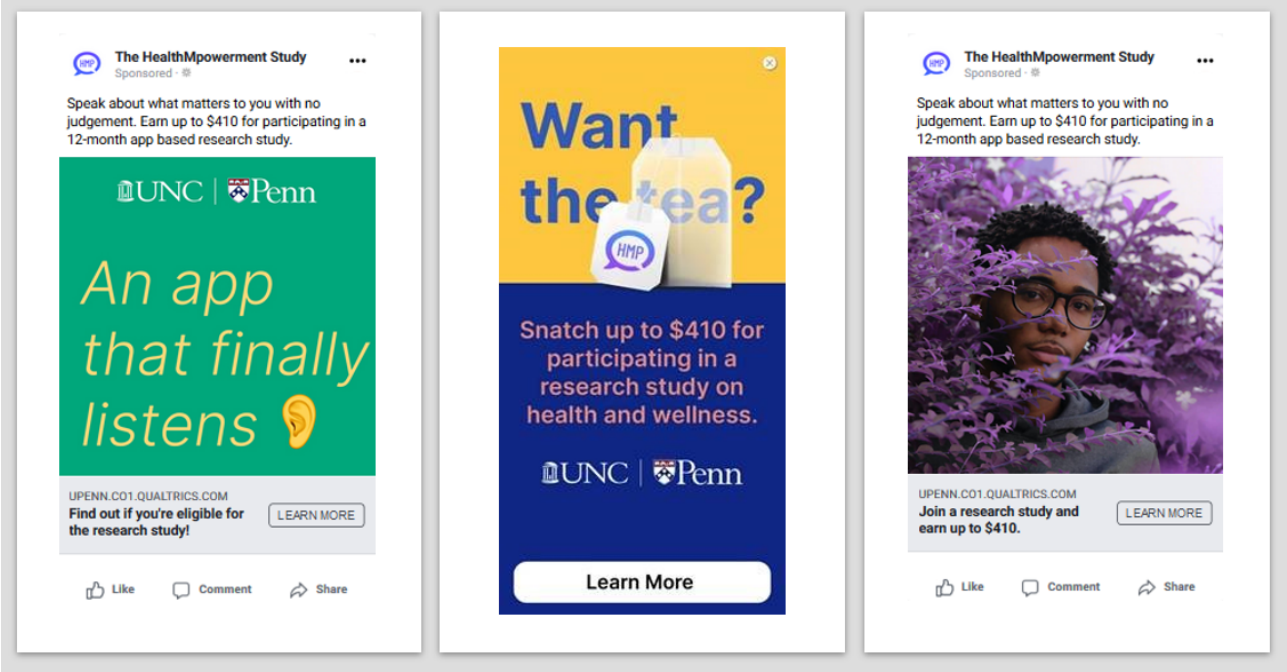
Participants and Enrollment Procedures

Eligible participants will be those assigned male sex at birth (no restrictions on current gender identity), aged 15 to 29 years (inclusive) at the time of screening, identify as Black, African American, Latinx or Hispanic, be a resident of the United States (verified by zip code), report at least one episode of CAI with men or TW in the previous 6 months or recruited from a partner-seeking app (eg, Grindr, Jack'd), and report having regular access to a smartphone device to access the HMP 2.0 app. Individuals who are recruited by participants assigned to the peer-referred intervention arm (arm 3) will have comparable eligibility criteria, with the exception that referred peers can identify as any race or ethnicity. Those who report testing HIV positive and having hemophilia or are currently taking anticoagulant medications will be excluded because of the risk of harm posed by the self-collected blood sampling.

The decision to include MSM and TW and Black and Latinx participants in the same study was decided early in the study design after much thought. We recognize that the experiences of stigma and discrimination manifest differently among MSM and TW communities, Black and Latinx populations, and communities living with, or affected by, HIV. Consistent with our intersectional framing, we value and acknowledge that the resultant combinations of these subgroups are even more different. In our formative study, however, we discovered that sharing these diverse experiences can bring people together to talk about these experiences and engage in inclusive dialogue that fosters support. Creating a space for open dialogue and learning facilitates individuals' learning from each other's differences and working through issues of stigma and discrimination they may be experiencing within the lesbian, gay, bisexual, transgender, queer community. Furthermore, some youths may still be establishing and learning about their various identities; HMP provides a safe space for broader exposure and learning, including welcoming youths who are uncertain about their sexual orientation or gender identity. Therefore, we decided that the benefits of being more inclusive in the context of this intervention outweighed the drawbacks of being more limited or targeted. All study arms have tailored content inclusive of variety in gender identity, gender expression, and sexual orientation. Similarly, the YAB and study team were attentive to include imagery and visual representations in the app that depicted diversity of gender, race and ethnicity, culture, and sexual expression. Participant avatar options feature a range of colors, hairstyles, and face shapes (Figure 7).

We will reach the study population using targeted advertisements based on sociodemographic characteristics on social media sites, including Facebook, Tumblr, Instagram, Black Gay Chat Live, Jack'd, Grindr, and Scruff, and through clinic referrals and participant repositories. Recruitment sites and materials have been developed alongside our YAB. Each study advertisement includes a unique link for interested individuals to complete the study screener, where they may verify their eligibility or contact the study team by email or a toll-free number (Figure 13).

Figure 13. Example Facebook social media study advertisements for HealthMpowerment (HMP) 2.0 trial.



We aim to enroll approximately 20 to 30 participants per month; this staggered design will allow time for the social networks to develop within the intervention. We will monitor recruitment and enrollment efforts weekly, including examining which specific study advertisements and recruitment methods (eg, social media, clinic referrals, participant repositories) generate the most enrolled participants and the characteristics of the enrolled sample. This will allow us to adapt our recruitment strategies as needed to ensure a diverse sample across age and geographic area.

The web-based, self-administered study screener explains the HMP 2.0 trial, the screening process, and confidentiality and privacy of all personal information and collects consent to complete screening. Data from those who screen eligible are reviewed biweekly for signs of fraud [104]. Individuals who pass these data checks are invited to enroll in the study. The enrollment procedures begin with an electronic informed consent form. Consented participants are then directed to a 45-min baseline survey and subsequently allocated to 1 of the 3 study arms using our HIV-stratified randomization procedure. Participants who are ineligible or do not consent are thanked and rerouted to a public site (eg, Google). A second data quality check is completed comparing select baseline and screener responses, and those who pass are sent a unique access code and directions for downloading the study app from either the Google Play or Apple app store (Figure 1).

Sample Size

We will enroll a total of 1050 participants from across the United States. Our sample size calculations were on the basis of pairwise HIV-stratified comparisons of the 3 groups in terms of the proportion of successful engagement using a two-sided significance level of 0.05, adjusted by the number of comparisons using a Bonferroni adjustment (significance level is 0.017 for 3 comparisons) and a minimum power of 80%. To achieve 80% power to detect a minimum effect size (odds ratio [OR] 1.9) of successful engagement in care between the 3-arm trial while maintaining the overall type I error rate at 5%, we will require at least 450 HIV-negative and 450 HIV-positive participants to detect a 17% difference. In the event of a 20% loss to follow-up, we will have sufficient power to detect an OR 2.1 (18% difference) at α=.017. Participants may continue the study even if they miss an assessment intermittently. We will compare those who completed different follow-up surveys with those who did not on key baseline predictors to check for possible sampling bias. Our analysis will use intent to treat as appropriate. The primary outcome for the proposed trial is stratified by HIV status and defined as successful engagement in care. We define power as identifying the difference in the proportions of YBLMT with sero-specific engagement in HIV care within 12 months of each of the 2 intervention arms (arm 2 researcher-created network and arm 3 peer-referred network) compared with the control arm (arm 1 information-only control), and between the 2 intervention arms 2 and 3. We have not set stratifications by gender, sexual orientation, race or ethnicity—it is set only by HIV status. We are proactively recruiting through transfocused health and community–based organizations and networks, and recruitment materials contain a variety of body images and expressions of gender and sexuality. On the basis of prior studies, we anticipate having at least 10% of our sample to identify as transgender. We will compute a post hoc power analysis to calculate the observed power to provide context for our findings for any subgroup analyses.

We will also select a purposive subsample of 45 enrolled participants (5 from the control arm; 20 from each intervention arm) across different demographic and intervention engagement profiles to complete qualitative evaluation interviews via a Health Insurance Portability and Accountability Act–compliant videoconferencing platform. A study team member will conduct interviews following a semistructured guide focused on overall intervention satisfaction, the intervention's perceived impact on stigma and HIV outcomes, and participants' evaluations of

the social networking features (intervention arms only). Control arm participants are included in the interviews, as we expect the information-only intervention will also show a modest impact. Half of the interviews will be conducted at month 6 and half at month 12 to better understand intervention use over time and to reduce *survivor's bias* of only interviewing participants who are retained for 12 months. Interviews will last 30 to 45 min, will be audio recorded with the participant's consent, and will be transcribed.

Randomization

Participants will be allocated to the 3 study arms using a computer-generated block randomization, with stratification by HIV status. For the HIV-negative stratum (n=300, 2 treatment groups), the randomization scheme consists of 18 blocks of 8 subjects and 26 blocks of 6 subjects. Similarly, for the HIV-positive stratum (n=450, 3 treatment groups), the randomization scheme consists of 20 blocks of 9 subjects and 45 blocks of 6 subjects.

Engagement and Retention

In the HMP 1.0 trial, participants who remained more engaged in the intervention had greater improvements in study outcomes [58]. Thus, HMP 2.0 uses multiple strategies to promote sustained participant engagement. First, we expanded the most highly rated and frequently used features of HMP 1.0 (Forum, Ask an Expert, Resources, and Quizzes). Second, we converted the points-based reward system (which was not highly rated by participants) to a system where participants earn virtual badges for completing activities and meeting milestones within the app. We have used a similar badge system within 2 other intervention apps that young MSM have rated with high acceptability [105,106]. Third, we will follow a schedule of releasing new content onto the app each week, including activities, polls, articles, and regular YAB posts. Each month, we will also send an electronic *newsletter* tailored for intervention arms 2 and 3 that highlights new content, poll results, spotlight profiles for YAB and study staff, and the month's most popular app discussions and articles. For overall study retention, we will follow a protocol schedule of connecting with all participants via push notifications, in-app notifications, text messages, emails, and phone calls. These will consist of preprogrammed prompts triggered after 14, 30, and 60 days of no app log-in or missed study milestone, and tailored communications from study staff.

Incentives

Depending on the participant's study arm and the activities they complete, they may receive between US $390 and US $410 in e-gift cards for participating in all aspects of this study (Table 2). All participants can receive up to US $280 in e-gift cards for completing surveys at baseline, 3, 6, 9, and 12 months, with a US $50 bonus for completing at least 4 of the 5 surveys. On the basis of HIV status, participants may complete up to 3 in-home HIV tests or HIV viral load kits. Participants will receive US $20 for each (US $60 total over the 12-month study period) if they report the result of the HIV in-home test or if they complete and return the HIV viral load kits. Peer referral group participants (arm 3) can receive up to US $20 for referring eligible friends to the study: US $10 for each friend that is referred and enrolled in the study within the first 45 days. A subsample of 45 participants who are selected to complete a qualitative evaluation will receive a US $50 incentive. Incentives for completing an HIV self-test were kept intentionally low (US $20) to reduce the influence of the financial incentive driving the behavior. A critical component of the intervention is raising health awareness and individual empowerment for one's sexual health and behaviors; thus, the incentive is a nudge to repeat the desired behavior every 3 months and is not the primary motivator.

Table 2. Schedule of HealthMpowerment 2.0 randomized controlled trial study incentives (US $).

Activity	Eligible participants	Baseline	3 months	6 months	9 months	12 months	≥4 surveys bonus
Complete survey	All	50	35	50	35	60	50
Return HemaSpot kit	HIV positive	20	N/A[a]	20	N/A	20	N/A
Upload HIV test result[b]	HIV negative and unknown	20	N/A	20	N/A	20	N/A
Referred peer enrolls[c]	Arm 3	20	N/A	N/A	N/A	N/A	N/A
In-depth interview	Subset of 45 across all arms	N/A	N/A	50	50	50	N/A

[a]N/A: not applicable (not all incentives are relevant for all study time points).

[b]HIV self-tests may be ordered any time during the 12-month window, up to 3 times, at least three months apart.

[c]US $10 per enrolled peer for up to 2 peers. Peer enrollment must be completed within the first 90 days following the referring participant's enrollment.

Outcomes

Primary Outcomes

Following our theoretical premise that similar stigma-related barriers impact both HIV prevention and care behaviors, we aimed to define a primary outcome of engagement in care with parallel behaviors across HIV status. For HIV-positive participants, we define successful engagement in HIV care as consistent VS across the 12-month trial (per Institute of Medicine guidelines [107]). We will ask self-reported recent (past 3 months) VS status at baseline and each follow-up assessment. Completed HemaSpot-HF kits will provide viral load biomarker data for baseline and months 6 and 12. For HIV-negative or sero-unknown participants, we define successful engagement in care as participation in routine HIV testing (2 or more HIV tests at least three months apart, per United States Centers for Disease Control and Prevention guidelines [108]). We will also examine the proportions of

participants who complete at least one HIV test in the 12-month period and assess whether this is an appropriate parallel measure based on self-reported risk behaviors. Additional analyses will assess appointment and medication adherence (HIV-positive participants), uptake and maintenance of PrEP (HIV-negative participants), and testing and diagnoses for sexually transmitted infections.

Mediators of Intervention Effects

The secondary objective is whether participant engagement mediates the intervention effects observed in stigma and HIV care outcomes. Temporal engagement will be measured by examining participants' number of log-ins to the app and total length of time in the app as calculated by time stamps at each log-in and logout or app timeout. We will also calculate scores for all intervention arms participants on the basis of their levels of *active* (posting and commenting) and *passive* (reading) engagement. Active engagement scores will be calculated by assigning one point for each instance a participant posted or commented on site content. Passive engagement scores will be calculated using paradata to determine the number of times they read content and then assigning one point per read. Aggregate engagement scores for each participant will be included as indicators and latent factors, as appropriate, in our analyses. This strategy will allow us to examine how different forms of engagement (eg, temporal engagement, active engagement, passive engagement) influence our study outcomes. The core measures of app engagement are included in Table 1.

An additional mediation analysis of interest is how changes in stigma and improvements across the HIV care continuum vary between the researcher-created versus peer-referred social network intervention conditions.

Covariates

We will measure the following constructs as potential predictors or moderators: sociodemographics (race, ethnicity, education, employment, place of birth, housing status, and history of incarceration, sexual identity, and *outness* to social network), substance use, psychological distress (depression and anxiety symptoms), intervention acceptability and use over time, use of technology and social media, and eHealth literacy [109]. These measures are included in Table 3.

Table 3. Study measures for HealthMpowerment 2.0 randomized controlled trial.

Variables and scale	Items
Primary outcomes	
Viral suppression (HIV+)	2
Consistent HIV testing (HIV−)	2
Secondary outcomes	
Appointment adherence [110]	2
Wilson adherence scale (HIV+) [111]	3
PrEP[a] uptake (HIV−) [112]	8
STI[b] testing and infections	3
Experienced stigma	
Enacted or personalized HIV stigma scale, adapted [113,114]	12
Gender minority stress and resilience-rejection subscale [115]	6
Every day discrimination scale [116,117]	20
Internalized stigma	
Negative self-image HIV stigma scale, adapted [114]	7
Internalized homophobia scale—revised [118]	4
Anticipated stigma	
Anticipated HIV stigma scale, adapted [114,119]	8
Every day discrimination scale [116,117]	20
Challenging stigma	
Sense of community and self-identity	20
Stigma resistance scale, adapted [120]	16
Contextual mechanisms	
Social support (select PROMIS[c] measures) [121]	8
Social isolation (select PROMIS measures) [121]	8
Depression (PHQ-8[d]) [122]	8
Anxiety (GAD[e]-7) [123]	7
Medication adherence self-efficacy (HIV-ASES[f]) [124]	9
Self-esteem [125]	10
Covariates	
Demographics and socioeconomic characteristics	25
Substance use (ASSIST[g]) [126]	4
PrEP use	5
Sexual behavior [127,128]	35
Technology use [129,130]	24

[a]PrEP: pre-exposure prophylaxis.

[b]STI: sexually transmitted infection.

[c]PROMIS: patient-reported outcomes measurement information system.

[d]PHQ-8: eight-item patient health questionnaire.

[e]GAD: generalized anxiety disorder.

[f]ASES: adherence self-efficacy.

[g]ASSIST: alcohol, smoking, and substance involvement screening test.

Statistical Analysis

Quantitative Evaluation

Clinical and demographic characteristics will be described for the entire sample and by treatment group. We will use both graphical (box-plots and histograms) and descriptive (mean, SD, IQR for continuous variables, and frequency distribution for categorical variables) approaches to describe our sample.

These will be compared with treatment groups using the analysis of variance or Kruskal-Wallis test for continuous variables and chi-square test for categorical variables. We will conduct primary analyses of our successful engagement in care outcome (month 12 status) using logistic regression models to compare each active intervention treatment group (arms 2 and 3) with the control group (arm 1) in pairwise comparison tests at an adjusted significance level of 0.017 to reduce type I errors in our 3-arm trial. This approach allows us to also test for differential efficacy between the 2 intervention conditions (ie, does the peer-referral intervention arm 3 outperform the researcher-created intervention arm 2?).

We will use the general framework of generalized linear mixed models [83,84,131] to model these longitudinal outcome trajectories [132-134]. Given that some of our outcomes are binary, some count and some continuous traits will be treated differently (identity for continuous outcome, logit for binary outcome, and natural log for count outcomes). Logistic regression analyses will be stratified by serostatus. The regression will be run with group assignment only in the model. Among HIV-positive participants, we will examine how intervention conditions influence YBLMT's likelihood of consistent VS over 12 months. We will also test intervention effects on retention in care per Institute of Medicine guidelines (ie, proportion of HIV-positive participants who obtain at least two viral load tests [at least three months apart] within 12 months). For HIV-negative participants, we will compare the proportion of participants who obtain at least two HIV tests (at least three months apart) within 12 months across arms. Estimates will be calculated and presented with corresponding 95% exact binomial CIs.

Building on our theoretical framework, we will use structural equation modeling to test whether engagement with researcher- and participant-generated stigma content predicts changes in stigma-related outcomes over time (eg, decreases in anticipated HIV stigma) and changes in HIV care outcomes over time (eg, repeat HIV testing; consistent VS). In these HIV-stratified analyses, we will use latent class analysis to characterize participants' engagement in the site. We will estimate the independent contributions of passive and active engagement on both stigma and HIV outcomes and how cumulative engagement in stigma-related discussions influences these outcomes. Key sociodemographic predictors will be included as covariates (eg, age, time since diagnosis). We will also conduct exploratory stratified analyses by race, ethnicity, and gender.

Qualitative Evaluation

Expanding on the procedures developed and successfully employed in HMP 1.0 [92], we will conduct a mixed methods analysis of participant-contributed content to the forums. All content and associated paradata of each post will be captured by the intervention database. We will use qualitative data analysis software to catalog and code all instances of stigma-related content and characterize their potential contributions to HIV risk and care behaviors. First, 2 coders will independently identify all posts that contain stigma-relevant content. Next, they will conduct a content analysis to categorize the nature of the coded stigma content as enacted, community, anticipated, internalized, or challenged stigma. Coding discrepancies will be reviewed and resolved by a third analyst. Ongoing analysis progress will be discussed during biweekly YAB meetings and feedback sought on YAB members' interpretations of participant forum conversations and emergent themes. The final coded data set will be used for qualitative analyses and publications, and to create variables that quantify participants' engagement with each type of stigma-related domain. These data will be used to examine how frequency of engagement with stigma content is associated with changes across HIV outcomes directly and through proposed mediators (eg, social support and isolation, substance use, depression). We successfully used this methodology and established analytic protocols to carry out these procedures [66,67,92].

For the qualitative analyses of the 45 interviews, we will create a codebook of *a priori* and emergent themes, including operational definitions of all codes and sample quotations, to illustrate how to apply each code. Two study team members will use the codebook to independently code the data, whereas a third team member will review these coded sections and resolve discrepancies. We will use qualitative data analysis software and matrices to assist with theme identification, coding textual data, and describing relationships among codes (via code co-occurrence and memoing functions) [135]. Analysis results will be used in conjunction with participants' survey responses, biological outcomes, and usage profiles to present a mixed methods intervention results analysis.

Results

IRB Approval and Trial Registration

The research and ethics presented in this study were approved by the IRB of the University of Pennsylvania (829805) as the IRB of Record. Reliance agreements between the University of Pennsylvania, the University of North Carolina Chapel Hill, Duke University, and SUNY Downstate have been completed. A certificate of confidentiality was obtained from the National Institute of Child Health and Human Development, and a waiver of parental consent or assent was obtained for participants aged 15 to 17 years. This study is registered on ClinicalTrials.gov (NCT03678181).

Recruitment and Enrollment

Study recruitment began on July 20, 2020. As of November 20, 2020, 3780 participants had completed screeners, yielding 830 eligible participants. Among the 218 participants who went on to complete the baseline survey, 94.0% (205/218) have enrolled and been randomized to a study arm, representing 19.52% (205/1050) of the total target enrollment. Enrolled participants are geographically diverse, representing all 50 contiguous United States and Washington DC, vary in age (36/205, 17.6% aged

15-19 years; 55/205, 26.8% aged 20-24 years; and 114/205, 55.6% aged 25-29 years), and 18.5% (38/205) report an HIV-positive status at baseline. Recruitment is anticipated to last through September 2022, with final study follow-up to be completed by September 2023 and results to be available in 2024.

Discussion

Trial Innovations

There is a great need and potential to develop, implement, and scale up HIV prevention and care interventions for YBLMT. Implementation barriers and facilitators and analyses from this study will inform the design of mHealth engagement strategies for connecting with YBLMT across the HIV continuum. Our results will further the field's understanding of how engagement with an mHealth intervention that builds on the networks of YBLMT impacts and curtails the role of intersectional stigma in well-being. We are also testing several remote health service intervention components among young people (mail-based self-collected viral load via finger prick, HIV self-testing via oral swab, remote care navigation to confirmatory testing, PrEP, and HIV care) that have previously been tested among an older age range of predominantly White MSM.

Principal Contributions to the Field

These results will be critically important to the field with the exponential expansion of telehealth and at-home, self-administered biomarker specimen collection and testing. Our projects' tools and framework may inform future mHealth and stigma reduction initiatives for YBLMT.

Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

ART: antiretroviral therapy
CAI: condomless anal intercourse
HMP: HealthMpowerment
IRB: institutional review board
mHealth: mobile health
mPI: multiple principal investigator

MSM: men who have sex with men
NIMH: National Institute of Mental Health
OR: odds ratio
PrEP: pre-exposure prophylaxis
RCT: randomized controlled trial
TW: transgender women
U=U: undetectable equals untransmittable
VS: viral suppression
YAB: youth advisory board
YBLMT: young Black and Latinx men who have sex with men and transgender women who have sex with men

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Protocol

Effects of Unfiltered Cigarettes on Smoking Behavior and Toxicant Exposure: Protocol for a Randomized Crossover Clinical Trial

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Abstract

Background: Plastic filters on cigarette butts are a widespread source of nonbiodegradable, toxic environmental waste. State and local legislation to ban the sale of single-use cigarettes may be considered to prevent this waste, but scientific evidence on the impact of switching smokers to unfiltered cigarettes on smoking behavior and toxicant exposures is needed to inform this policy. We have designed an open-label, randomized, 9-week, crossover clinical trial of adult filtered-cigarette smokers who switch to unfiltered cigarettes.

Objective: Our objective is to understand the impact of switching smokers of filtered cigarettes to unfiltered cigarettes on smoking behavior and toxic exposures.

Methods: This trial involves a 1-week baseline period; a 2-week period of smoking filtered or unfiltered cigarettes, where groups are randomly assigned; a 3-week washout period; another 1-week baseline period; and a 2-week crossover period of smoking the opposite condition (ie, filtered or unfiltered cigarettes) for a sufficient sample size of 40 participants. We will determine changes in (1) observed topography (ie, puff count, interpuff interval, and puff volume) and cigarettes smoked per day, via butt counts and self-report, (2) expired carbon monoxide and excretion of urinary cotinine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, and volatile organic compounds, and (3) participants' knowledge and attitudes toward unfiltered cigarettes, satisfaction with smoking, and intention to quit if they were not able to smoke filtered cigarettes.

Results: This study was funded in June 2018 and approved by the relevant Institutional Review Boards in July 2018. This study has enrolled 37 participants as of October 2020. Data analysis is currently underway, and trial results are expected to be published in spring 2021.

Conclusions: This pilot proof-of-principle study will inform the design of a larger, future research project that can provide robust scientific evidence on our research question. Such a large study could inform possible state or local legislation to ban the sale of single-use filtered cigarettes in order to mitigate the environmental impact of discarded single-use plastic filters.

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KEYWORDS

nicotine; tobacco; topography; exposure; policy; environmental

Introduction

Background and Rationale

Cellulose acetate (ie, plastic) filters on cigarette butts are a widespread source of nonbiodegradable environmental waste that may be toxic to marine organisms, aquatic environments, and possibly to human and animal health [1-4]. Cigarette butts are, in fact, a major littered item found during beach and urban cleanups each year throughout the world and adversely affect storm water drainage, beaches, neighborhoods, and other natural environments [5]. There is a widespread perception among smokers and nonsmokers that filters provide a *safer* cigarette [6]. In response to the expanding evidence in the 1950s regarding risks for lung cancer and other serious illnesses due to smoking, the tobacco industry sought to address or at least obfuscate these risks through the development of cigarette *filters*. This terminology suggested purification or reduction of smoking risks to the consumer [6]. It is clear that consumers responded to the marketing blitz around filters and the perceived risks of smoking such that today more that 99% of commercially sold cigarettes in the United States are filtered [7].

Most smokers and nonsmokers do not know that the filters attached to almost all cigarettes sold in the United States are made of nonbiodegradable plastic. In addition, cigarette filters have also been deemed "unproved in reducing harms to the average smoker" by the US Surgeon General and the National Cancer Institute [7,8]. Data comparing the relative risks of smoking among age-matched cohorts of smokers across 50 years show that overall mortality, as well as the smoking-attributable risks for morbidity and mortality from lung cancer, heart disease, and chronic obstructive pulmonary disease, increased over the years during which filters became standard issue as part of manufactured cigarettes [9,10]. State and local governments have jurisdiction to ban the sale of various tobacco products, and in 2019-2020, the California Assembly considered, for environmental reasons, a bill to ban the sale of single-use filtered cigarettes [11]. Additional scientific evidence on the human consequences of removing single-use filters from cigarettes is needed to understand what, if any, health and behavioral impacts may result from a sales restriction to eliminate cellulose acetate–filtered cigarettes from the tobacco market.

Study Objectives

This is a pilot study that will inform a possible larger clinical trial. The research question for the overall project is as follows: *What is the impact of switching smokers of filtered cigarettes to unfiltered cigarettes on smoking behavior and toxic exposures?* The specific aims are as follows:

1. Determine smokers' satisfaction and attitudes toward smoking cigarettes if they were to switch from smoking filtered to unfiltered cigarettes.
2. Measure changes in smoking topography (ST) (ie, puff count and puff volume) and cigarettes smoked per day, via butt counts and self-report, among smokers who change to unfiltered cigarettes for 2 weeks compared with these measures while smoking filtered cigarettes.
3. Measure changes in urinary cotinine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), and volatile organic compound (VOC) excretion among smokers who smoke unfiltered cigarettes for 2 weeks compared to smoking filtered cigarettes.

Study results may inform proposed state or local legislation to ban the sale of single-use filtered cigarettes in order to eliminate the environmental impact of improperly discarded, poorly degradable plastic cigarette filters as toxic waste.

Overview and Trial Design

While the risks of smoking any type of tobacco product are now clear to the public, there has never been a clinical trial comparing changes in biochemically measured exposures, perceptions, topography, and other behavioral elements of cigarette smoking when switching from filtered to unfiltered cigarettes (ie, there have been no studies reported in PubMed or ClinicalTrials.gov as of October 2020). If large-scale trials were needed to definitively answer concerns that policy makers, smokers, and the general public have regarding any potential adverse effects of eliminating filtered cigarettes from the market, it would be important to ascertain the practicality and validity of measures used for such trials. General perceptions of filtered cigarettes and their safety, palatability, and composition have been measured through national panel surveys (publication in progress), but actual changes among smokers switching between filtered and unfiltered cigarettes can only be measured in a clinical trial. Further, to eliminate exposure bias, a trial in which the order of exposure is randomized is most appropriate.

We have completed an open-label, randomized, 9-week, two-sequence, two–treatment condition, crossover clinical trial of 37 adult filtered-cigarette smokers who switch to unfiltered cigarettes. We will evaluate this pilot study's approach as to its applicability for a follow-up research project with a larger sample size.

This approach uses a crossover design, which allows participants to be their own matched control, hence removing participant-level variability [12]. Cigarette smoking is the *chronic* condition in this trial that persists throughout the washout periods, with changes measured against the chronic condition, not against a nonsmoking condition. This design is often used in clinical trials particularly when evaluating interventions to treat or control chronic diseases such as asthma, for which there is large variability across measures within participants. In this pilot trial, we are measuring changes in smoking behavior due to changes in the product smoked, while not assuming any change in the underlying condition of smoking; this study design then accounts for participant-specific variability. Participants were instructed to resume pretreatment activity (ie, smoking filtered Camel or Pall Mall cigarettes) during the washout period during which there were no study measurements. We assumed 3 weeks to be sufficient to *wash out* the effect of exposure to the study cigarettes during the active treatment period [13].

We collected behavioral data via validated computer-based surveys at baseline, intervention, and postintervention time points to assess changes in knowledge and attitudes regarding

smoking of filtered and unfiltered cigarettes. We used a handheld smoking device, the Clinical Research Support System (CReSS) Pocket (Borgwaldt KC), to measure ST over five, daily, 8-hour periods per week; participants took home the device, and measurements were recorded in a naturalistic setting. The rationale for five, 8-hour, ST monitoring periods was based on our aim to measure ST during a representative period for naturalistic smoking. Findings from previous studies using ST measures have not differed between direct and indirect observations [14-16]. Although slightly greater ST variability has been reported between individuals smoking with a CReSS device compared to normal smoking, many studies report consistent within-participant comparisons [14,16,17]. Thus, we were not concerned that smoking outside of the monitoring window would differ from measurement periods. This device enables convenient recording of ST throughout the day and over weeks with time- and date-stamped data; it thus allows evaluation of changes in frequency and characteristics of smoking patterns under different treatment conditions. Participants collected and returned cigarette butts each week, and they self-reported the number of cigarettes smoked per day [18]. We measured exhaled carbon monoxide (CO) weekly, and we collected urine samples at baseline, before and after the washout period, and at the end of the study to measure creatinine-normalized cotinine, NNAL, and VOC excretion.

Methods

Our study protocol followed the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (see Multimedia Appendix 1 for the SPIRIT checklist).

Study Setting

The study was conducted in San Diego, California, United States; participants were screened remotely by Institution A and attended the smoking laboratory facility at Institution B in person. All biologic data and other measurements were collected and analyzed at either Institution A or B.

Eligibility Criteria

Inclusion Criteria

Participants met all of the following criteria: aged 21-65 years; smokers of 5 or more cigarettes per day (CPD) on 25 or more days per month for 1 year or more; smokers of Camel or Pall Mall filtered cigarettes for at least two weeks prior to enrollment, and willing to continue using this brand during the study; fluent in English; have regular telephone access; and have transportation to attend all scheduled visits. Participants must have primarily (ie, ≥50% of the time) smoked cigarettes, allowing for secondary use of other tobacco products. We verified their regular smoking status upon enrollment with an expired CO level of at least 10 ppm [19]. Because we expected to be able to detect changes in our primary outcomes at lighter levels of smoking [20,21], we included light smokers in the study.

Exclusion Criteria

Participants were excluded if they were currently in a smoking cessation program or participating in another clinical trial; were using nicotine replacement therapy or medication that aids smoking cessation in the past month, including Zyban (bupropion), Catapres (clonidine), Pamelor (nortriptyline), or Chantix (varenicline); or were trying to quit or reduce smoking patterns in the past month. Women who were pregnant, breastfeeding, or planning to become pregnant in the next six months were excluded. Medical exclusion criteria included any of the following:

1. Self-reported uncontrolled diabetes mellitus or presence of any cardiovascular issue in the past 30 days, including heart attack, stroke, severe angina (ie, chest pain), hypertension, ischemic heart disease, vascular disease, or any other cardiovascular disease.
2. Presentation to the enrollment visit with a systolic blood pressure greater than 160 mm Hg or a diastolic blood pressure greater than 105 mm Hg, as verified by two consecutive blood pressure readings.
3. Self-reported hospitalization for psychiatric issues.
4. Being mentally or physically unfit to participate in the study.
5. Current dependence on a substance other than nicotine.

Informed Consent and Ethics Approval

Informed consent was ensured during the smoking laboratory visit by trained research assistants. All consent statements were recorded in person. Participants were informed during the consent process that they may withdraw from the study at any time for any reason. Participants were also provided with information on the purpose of the study, study objectives, and how study success will be measured. The study was approved by the Human Research Protection Program from San Diego State University (approval number HS-2018-0152).

Intervention Description

The first week involved baseline measurements of smoking behavior and urinary biologic markers. The next 2 weeks (Weeks 2 and 3) involved filtered- or unfiltered-cigarette smoking treatments, followed by a 3-week washout period (Weeks 4-6). Week 7 involved a postwashout, repeat baseline period. The crossover condition was implemented in Weeks 8 and 9. Study cigarettes were provided during the two treatment periods (ie, 4 weeks total). ST was measured on 5 days of smoking over 8-hour periods per day during the two baseline weeks (ie, enrollment and postwashout) and during the 4 weeks of switching trials; expired CO, weight, and survey measures were assessed at all visits.

Study Cigarettes

Two brands of cigarettes are currently available as filtered and unfiltered: Camel and Pall Mall. Participants were provided supplies of one of these two brands throughout the study period based on their preference. After baseline measurements at the beginning of Week 2, we randomly assigned participants to smoke 2 weeks' worth of filtered or 2 weeks' worth of unfiltered study cigarettes. We supplied study cigarettes according to the average cigarettes smoked per day for the previous week plus 10%. For example, a participant who reported smoking 10 CPD in the previous week would be provided with a supply of cigarettes that would allow 11 CPD for the entire 2-week trial.

Although it is possible that changes in CPD might result from increased supplies, participants were encouraged to smoke as normally as possible and to return any unused study cigarettes in order for us to measure changes in CPD resulting from switching.

Encouraging Adherence

To support participants' adherence to the interventions, study staff reviewed relevant expectations in detail for participants at each laboratory visit. A reminder card with the week's instructions and next laboratory appointment was provided as well as a troubleshooting guide for operation of the CReSS Pocket device. Incentive payments were provided for returning cigarette butts as well as for correct usage of the CReSS device.

Outcome Measurements

Knowledge and Attitudes Toward Unfiltered Cigarettes

Participants were asked at enrollment and at the final visit to what extent they believed that the filter on their brand of cigarettes (1) protects them from health problems caused by smoking and (2) makes smoking more pleasurable. Response options included the following: not at all, a little, quite a bit, and a great deal. In addition, they were asked "If filtered cigarettes were no longer available, what, if anything, would you change about your smoking patterns?" Response options included the following: increase number of cigarettes I smoke, nothing, cut back, and try to quit smoking altogether [22]. Participants were also asked about the purpose of filters on cigarettes, with the following response options (more than one answer was accepted): making cigarettes safer to smoke, making it easier to begin smoking, making it more pleasurable to smoke, selling more cigarettes, making cigarettes cheaper, and other. Finally, participants were asked what filters are made of, with the following response options (more than one answer was accepted): cotton, food starch, asbestos, plastic or cellulose acetate, and other [23,24].

Questions at enrollment and the final visit also covered the following: possible environmental consequences of smoking (eg, whether discarded butts are a problem for the environment and what should be done to prevent these consequences), if they had previously smoked unfiltered cigarettes, and what they would do if filtered cigarettes were no longer available for purchase.

At each lab visit, participants smoked a cigarette and answered questions from the Cigarette Evaluation Scale [25]. These questions included the following: Was it satisfying? Did it taste good? Did it make you dizzy? Did it calm you down? Did it help you concentrate? Did it make you feel more awake? Did it reduce your hunger for food? Did it make you feel nauseous? Did it make you feel less irritable? Did you enjoy the sensations of the smoke in your throat and chest? and Did it immediately reduce your craving for cigarettes? Each item was rated on a numbered 7-point Likert scale, ranging from 1 (not at all) to 7 (extremely). Subscales included Smoking Satisfaction, Psychological Reward, Aversion, Enjoyment of Respiratory Tract Sensations, and Craving Reduction. Response order was the same for all scales.

Intention to Quit

Participants were asked at each visit "What best describes your intentions to stop smoking completely, not even a puff?" Response options included the following: never expect to quit, may quit in the future but not in the next six months, will quit in the next six months, and will quit in the next 30 days [13]. In addition, they were asked whether they have currently set a limit for how many cigarettes they smoke per day to decrease health risks from smoking [26].

Nicotine Dependence

The Fagerström Test for Nicotine Dependence [27] was administered at enrollment and at the final visit, and a single-item index of addiction to cigarettes (0-100) [28] was established at every visit. The Brief Wisconsin Inventory of Smoking Dependence Motives was also assessed at enrollment (ie, baseline) and at the final visit [29].

Cigarettes Per Day: Self-Report and Butt Count

Standard survey questions measured how many days in the past month (enrollment [ie, baseline] visit), past week (weekly visits), and past 2 months (final visit) participants have smoked, as well as how many CPD they have smoked on those days (all study visits). In addition, participants returned their cigarette butts in a sandwich-size Ziploc bag or glass jar each week to provide a validation of their self-report. While these butts were disposed of as toxic waste in approved containers, a small portion were retained for future analyses. Previous studies have included butt counts with reliability set at 75% of returns [30]. We excluded butt count data from participants who did not return 75% of butts and provided incentive payments for returning cigarette butts at this level.

Smoking Topography

Behavioral adaptations were measured by ST, including puff number per cigarette, average puff duration (seconds), average interpuff interval (seconds), average flow rate (mL/s), and average and total volume (mL) [14]. We used the portable CReSS device to measure topography over five, daily, 8-hour periods per week: at baseline (Week 1), during the initial switch (Weeks 2 and 3), at postwashout baseline (Week 7), and again after the crossover switch (Weeks 8 and 9). Participants were trained in the use of the device by the study team at the initial lab visit in a specialized facility designed with proper ventilation to accommodate indoor smoking research. Multiple days of measurement allowed for assessment of reliability and sensitivity of topography changes as a function of the filtered and unfiltered cigarette switch. Topographic measures by CReSS have been compared to direct observation via video recordings [15]. One limitation of the CReSS device is inconsistent methodology and guidelines in calibration settings and standard usage, as well as established acceptable ranges of ST variables (eg, peak flow rates, interpuff interval, etc). However, past studies have mainly used manufacturer guidelines with added modifications and/or adaptations [31], and these were recommended in a recent review [32]; there are no changes in recommendations for newer devices.

Expired Carbon Monoxide

Expired CO provides a measure of exposure to tobacco smoke and other air pollutants. An expired CO breath test was conducted at each visit with the coVita Micro+ Smokerlyzer device (Bedfont) to assess expired CO levels.

Cotinine

Cotinine is the main proximate metabolite of nicotine. Urinary cotinine was measured at each visit by liquid chromatography–mass spectrometry (LCMS) [33] and normalized for urinary creatinine. The correlation between urinary and plasma cotinine is improved by adjusting the urinary cotinine levels for urinary creatinine concentration, which takes into account the variations in urinary dilution between samples [34].

Tobacco-Specific Nitrosamines

Tobacco-specific nitrosamines are carcinogens found in tobacco and tobacco smoke. Excretion of the carcinogen biomarker NNAL, which will be normalized for urinary creatinine, will be measured by LCMS [23] in urine samples. In addition, carcinogenic VOCs, excreted as mercapturic acids, will be measured from urine samples. Both are useful biomarkers of changes in exposure to tobacco smoke [35,36]. These metabolites, along with expired CO, provide biomarkers of exposure, thus creating a battery that reflects risks for smoking-induced diseases [37] that may vary between filtered and unfiltered cigarette smoking.

Safety Monitoring Questions

Respiratory effects were assessed at every visit by asking participants about shortness-of-breath episodes or awakening from sleep due to breathing difficulties during the past 2 weeks (yes/no). Nicotine toxicity was assessed at every visit by asking whether the following symptoms were experienced in the last 2 weeks: nausea and/or vomiting, nervous irritability beyond normal day-to-day stresses, tremors, rapid heart rate, nightmares, and chest pains (yes/no). Blood pressure was also monitored at every visit.

Criteria for Discontinuing or Modifying Allocated Interventions

Serious adverse events will result in discontinuation of the intervention; these are defined as any of the following:

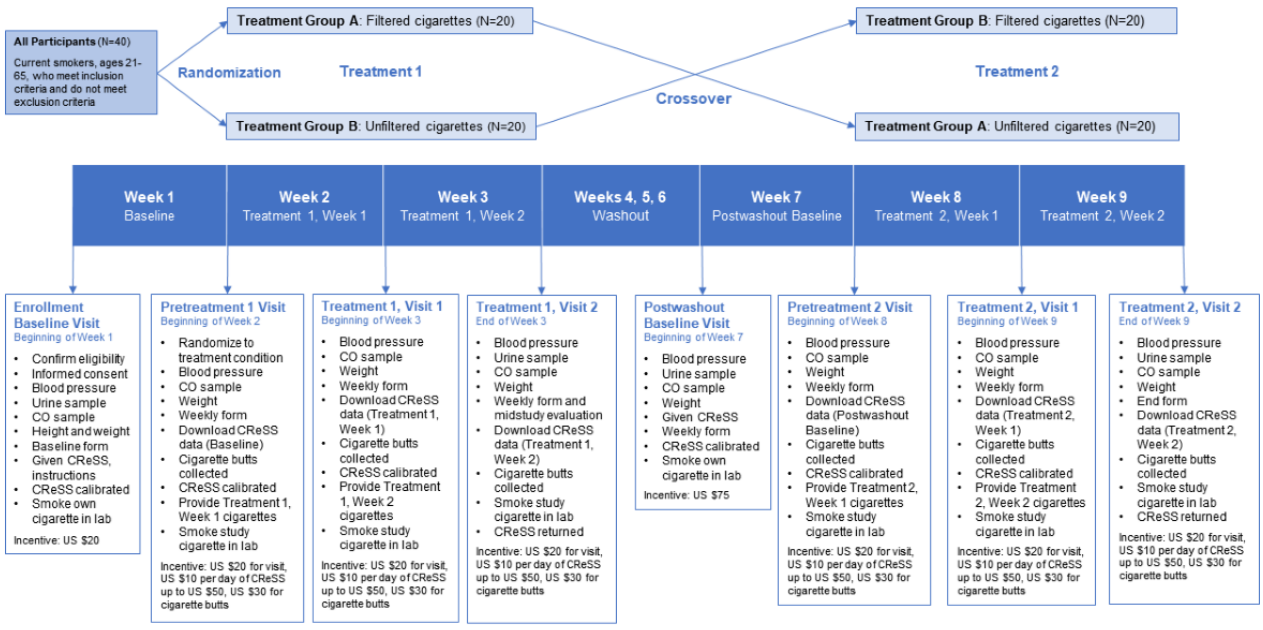
1. Events that have resulted in death.
2. Events that are life threatening.
3. Events that require inpatient hospitalization.
4. Events that result in persistent or significant disability or incapacity.
5. Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Study personnel will notify the principal investigator (PI) of any serious adverse events immediately after first awareness of the problem. The PI will immediately report serious adverse events to the Institutional Review Board (IRB) and the Data Safety and Monitoring Board (DSMB).

Participant Timeline

There will be a 1-week baseline period; a 2-week period of smoking filtered or unfiltered cigarettes, which will be determined at the time of randomization; and a 3-week washout period. This will be followed by a postwashout baseline week and a crossover to 2 weeks of smoking the opposite condition (see Figure 1).

Figure 1. Study design diagram of the randomized crossover clinical trial of unfiltered cigarettes. CO: carbon monoxide; CReSS: Clinical Research Support System.



Sample Size

The study sample size is 40 participants, sufficient to detect moderate within-subject effect sizes (f=0.35) with a moderate correlation between repeated measures (r>0.50). This two-by-two crossover design has statistical power of 80% for a sample size of 20 in each group to detect an effect size of 10% change in average number of cigarettes smoked per day. We tried to recruit at least 10 participants of non-White ethnicities. If participants prematurely discontinued from the trial prior to crossover, we attempted to recruit replacements from the eligible pool or advertise for new participants. We recruited 20 women out of the 40 participants and randomized by sex. Sex stratification is of interest because men and women may metabolize smoke differently due to differences in body size and differences in cigarette preference and behavior. Any woman who becomes pregnant during the trial will be excluded from further participation [38].

Recruitment

Recruitment was accomplished using a combination of Craigslist postings, newspaper ads, and paper flyers, which are approaches that have been successfully used in previous studies by the study team [39,40]. Prospective participants responded to advertisements via telephone or email to learn more about the study and to coordinate a time for phone screening to determine eligibility. Former participants in studies conducted at Institution B who have expressed interest in being contacted for future studies were contacted and invited to complete the screening questionnaire.

Assignment of Interventions: Allocation

Once a participant was deemed eligible for the trial remotely by Institution A, trial personnel at Institution B followed up with the participant to schedule the initial trial appointment (ie, the enrollment, or baseline, visit). Participants who did not meet the eligibility criteria were not included in the trial. Recruitment and enrollment was a continuous process (ie, up to 10 participants at a time), which enabled us to utilize topography devices and lab facilities most efficiently. Randomization, stratified by sex, was based on a table of random numbers, and records were placed in sealed envelopes. A total of 20 participants were assigned to be first switchers following their enrollment (ie, baseline) visit at Institution B. These participants were then tested on individualized schedules (ie, not as a group), with each participant committing to 9 weeks of trial time, including a washout period at midtrial. All subjects had first smoked filtered Camel or Pall Mall cigarettes for at least two weeks prior to beginning the trial, according to the inclusion criteria. This standardized their exposure to a brand that was used as an unfiltered variety in the trial.

Assignment of Interventions: Blinding

Investigators were masked to group allocation, but participants and research staff knew their exposure assignment due to the difficulties of blinding cigarettes that were filtered versus not filtered. DSMB members were unblinded to group allocation if needed.

Plans for Assessment and Collection of Outcomes

There were eight scheduled lab visits, each with an incentive for attendance (see Participant Retention and Complete Follow-Up section). As shown in Table S1 in Multimedia Appendix 2, these visits were to occur weekly at baseline (Week 1), during the first 2 weeks of cigarette use (Weeks 2 and 3), during the postwashout baseline (Week 7), and during the second 2 weeks of cigarette use (Weeks 8 and 9). During each visit, participants were tested for expired CO, had blood pressure and weight measurements performed, and completed surveys (see Table S1 in Multimedia Appendix 2). At Weeks 1, 3, 7, and 9, participants provided a urine sample to measure normalized cotinine and carcinogen biomarkers. All collected urine samples were stored in a –80 °C freezer. Specimens were transported from Institution B to Institution A for laboratory testing.

During visits 2-4 and 6-8, participants visited the Institution B smoking laboratory facility with their topography device, cigarette butts, and unused cigarettes (left only on Weeks 3, 4, 7, and 8). Data from the topography device were downloaded so that the number of cigarettes logged in as smoked on the CReSS device could be compared to the total number of cigarettes or butts returned, as well as the number self-reported cigarettes smoked per day. Those deemed compliant with study procedures were paid for their time and supplied with another weeks' supply of condition-assigned cigarettes. During visit 8, the same procedure was to be followed, except that it would be the final visit and no additional study cigarettes would be provided. Due to the COVID-19 pandemic, some of these procedures were curtailed and moved to remote follow-up.

Participant Retention and Complete Follow-Up

Adherence to using the topography device was incentivized by paying participants US $10 per day for each day up to 5 days per week of use, checked at each lab visit. Compensation was provided for collecting and returning cigarette butts at US $30 per week for each week of participation. These payments, combined with payment for attending the laboratory visit (ie, US $20), totaled US $100 for all visits that were to occur during the 9 study weeks. For the postwashout baseline session, the compensation was US $75. The reimbursement schedule was reviewed with the participant at each visit (see Table S2 in Multimedia Appendix 2). In addition, weekly visit reminder cards were sent home with participants, which outlined next appointments and visit expectations (eg, collect all butts and use device for 5 days).

Data Management

Study data were collected and managed using REDCap (Research Electronic Data Capture) tools that are hosted through Institution A. REDCap is a secure, web-based application that is designed to support data capture for research studies. All of the data collected were anonymized and password protected. Data were entered by trained study staff shortly after collection. All REDCap data are stored securely on a server at Institution A.

Confidentiality

Confidentiality of data was assured by assigning code numbers to each participant survey. Participants' identities are not linked to their responses. Any documentation of participant identities is kept in a locked filing cabinet located at the Institution A study office. Data are only accessible to personnel involved with this research, with access to servers limited by the research facility being locked at all times. All study information is maintained on secured computers and a password-protected laptop. The files on the laptop will be password protected for added security. The Institution A campus data network is protected by a perimeter firewall, and the network within the campus network is further protected by another institutional firewall.

Statistical Methods

Primary and Secondary Outcomes

Descriptive statistics will be used to analyze baseline data to assess any imbalances between groups in baseline demographics and prerandomization characteristics. Stratified analyses and analyses of covariance will be performed to control for any baseline imbalances. To account for the crossover design and repeated measures, linear mixed-effects models with fixed effects for period and exposure sequence (ie, filtered then unfiltered or unfiltered then filtered) and with random effects for sex and participant will be used to analyze continuous outcomes and changes from baseline. Log transformation of nonnormal continuous measures will be performed when necessary. If data do not fit a linear model, generalized models will be considered. Model variance will be fit using a compound symmetry correlation structure with default degrees of freedom, which assumes constant variance between periods, with alternative covariance structures explored in the event of nonconvergence. For analysis of ordinal questionnaire data, we will assess for exposure and period effects using ordinal repeated-measures models with fixed effects for exposure sequence and period and with random effects for sex and participant. Prespecified cutoffs and thresholds for biomarkers and topography variables will be chosen based on a comprehensive literature review prior to conducting any analysis. Normalization and sensitivity analysis will be performed, if required. Changes in means for each continuous measure between participants and between weeks within treatment conditions will be calculated. Mean differences between exposure arms for these continuous measures will also be compared. *P* values and 95% confidence intervals will be reported when providing results from fitted models. All analyses will be performed using SAS 9.4 (SAS Institute) [41]. Noncomplier and dropout data will be utilized in mixed methods models up to the point of dropout and noncompliance for an intent-to-treat analysis. A completer-only (ie, per-protocol) analysis will also be run as a secondary analysis.

Missing Data

Missing data were to be minimized or avoided through extensive training of clinical research staff and repeated efforts to contact trial participants to obtain protocol-specified data. In the event of missing data, sensitivity analyses will be performed, including a completer analysis and multiple imputation approaches.

Oversight and Monitoring

Safety Monitoring Plan and Adverse Event Reporting and Harms

This study was registered at ClinicalTrials.gov (NCT03749876). A DSMB charter was established outlining the board members' responsibilities, meeting structure, deliverables, timeline, and membership requirements. A written schedule of their individual activities, phone numbers, and copies of their informed consent forms were provided to them. The DSMB members with relevant expertise who are not involved in this study included a physician, a clinical pharmacologist, and a health behavioral scientist appointed from Institution A or from other collaborating institutions. Data on serious adverse events, including severity, outcome, and management, were included in individual participant files and in aggregate form by treatment group and were reviewed weekly. These data were provided blinded to the DSMB in a detailed report by an Institution A research assistant. Potential problems reportable to the DSMB included self-reported health issues, such as respiratory problems, addiction or dependence, or nicotine toxicity signs and symptoms. In the event of concerns, the DSMB would notify the PI, and the medical consultant was to be promptly consulted. The PI would assess the potential risks to the participant regarding continuation of the trial and report back to the DSMB on findings; the DSMB would then decide if the trial should continue or if the participant should be excluded.

Although smokers will be switching to unfiltered cigarettes for this trial, a 2-week trial period is highly unlikely to provide any differential short- or long-term risks to participants who smoke unfiltered cigarettes. The targeted cigarette brands are commercially available to the population already and, hence, do not constitute a new product test. In addition, a physician-member of the research team will be on call to answer queries from the field staff regarding problems or questions from participants regarding switching to unfiltered cigarettes.

Auditing

All research staff received human subjects research training and appropriate training in recruitment, data collection, and management. Study progress was tracked with regular monitoring by the PI with study and clinic personnel, monthly research team meetings, and regular reviews with individual staff to ensure that study targets were being met.

Protections Against Risk

We measured biomarkers of carcinogen and nicotine exposures in order to assess the potential for long-term risk differences for unfiltered-cigarette versus filtered-cigarette smoking. In addition, because secondhand smoke is considered a risk exposure, and because this exposure is due to a combination of expired and side-stream smoke, this exposure to participants or their close contacts should be unaffected by the presence or absence of a filter.

We only recruited current smokers for this study, all of whom were also informed about the health consequences of smoking

in the consent procedures. We trained study staff to be nonjudgmental toward smokers, to reassure them of anonymity in reporting findings, to reinforce the scientific value of this study, and to provide feedback after completion of the study. Both excluded individuals following the screening process as well as trial participants were referred for smoking cessation support to the state smoking cessation helpline. Any individuals deemed to have become ineligible, or those, for example, seeking to quit smoking, were provided with referrals and allowed to discontinue the trial.

Protocol Amendment Procedures

Any modifications or amendments to the study protocol were reviewed as a study team, discussed with the DSMB, and ultimately shared for approval by the IRB at Institution A prior to implementation.

Dissemination Plans

This project is expected to result in a number of oral presentations of interest to local, state, and national stakeholders regarding possible regulatory actions on the sale of filtered cigarettes. In addition, results of this study will be published and presented at national and international meetings, such as those of the Society for Research on Nicotine and Tobacco, the American Public Health Association, the National Conference on Tobacco or Health, and joint scientific meetings of the Tobacco-Related Disease Research Program and California Department of Public Health.

Availability of Data and Materials

The data sets used and/or analyzed during this study are available from the corresponding author on reasonable request.

Results

This study was funded in June 2018 and was approved by the relevant IRBs in July 2018. This study has enrolled 37 participants as of October 2020. Data analysis is currently underway, and results are expected to be published in spring 2021.

Discussion

This project will provide preliminary scientific evidence of the individual consequences of removing filtered cigarettes from the commercial tobacco market and how larger clinical trials of switching to unfiltered cigarettes may be undertaken. Outcomes and changes due to smoking unfiltered cigarettes include smokers' satisfaction, attitudinal changes, changes in ST, changes in the number of cigarettes smoked per day, changes in exhaled CO, and changes in urinary cotinine and tobacco carcinogens. This is critical information that may be needed to inform and advance state or local legislation to ban the sales of filtered cigarettes. Such legislation would reduce the environmental impact of nonbiodegradable cigarette butt waste due to the cellulose acetate filter, although there might still be some environmental contamination from butt remnants. It is unknown whether eliminating filtered cigarettes from the tobacco product market will change smoking behavior, such that smokers will be more likely to quit or reduce cigarette consumption. Given that filters are essentially a marketing tool and not a health protective device, cigarette marketing success is likely to be reduced without this tool. If unfiltered cigarettes are less palatable than filtered cigarettes, it is likely that fewer cigarettes will be smoked and fewer children will become addicted. This study will provide missing information as to how smokers might react to no longer being able to smoke filtered cigarettes. If information about the lack of health protection of filters and their environmental impact becomes more widespread, fewer smokers may choose to smoke filtered cigarettes. The preliminary findings this study could be addressed in larger clinical trials in order to have a more substantial impact on tobacco product regulatory science more generally.

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Authors' Contributions

TN and KP conceived the original study design. EO and KP updated and developed the study design with contributions from TN and DR. CB and EC created the study forms, protocols, and tools with support from EO and KP. KP drafted the manuscript and subsequent versions with substantial contributions from EO and TN. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[DOCX File , 14 KB - resprot_v9i12e19603_app1.docx]

Multimedia Appendix 2
Study measures and time points, participant activities, and reimbursement schedule.
[DOCX File , 26 KB - resprot_v9i12e19603_app2.docx]

Multimedia Appendix 3
Peer-review report by the Tobacco-Related Disease Research Program (TRDRP).
[PDF File (Adobe PDF File), 274 KB - resprot_v9i12e19603_app3.pdf]

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Abbreviations

CO: carbon monoxide
CPD: cigarettes per day
CReSS: Clinical Research Support System
DSMB: Data Safety and Monitoring Board
IRB: Institutional Review Board
LCMS: liquid chromatography–mass spectrometry
NNAL: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
PI: principal investigator
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
ST: smoking topography
VOC: volatile organic compound

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Protocol

Exploring Interactive Survivorship Care Plans to Support Breast Cancer Survivors: Protocol for a Randomized Controlled Trial

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Abstract

Background: Breast cancer is the most common form of cancer among American women, accounting for 23% of all cancer survivors nationally. Yet, the availability of adequate resources and tools for supporting breast cancer survivors has not kept up with the rapid advancement in treatment options, resulting in unmet supportive care needs, particularly among low-income and minority populations. This study explores an alternative means of delivering breast cancer survivorship care plans (SCPs), with the aim of improving survivor morbidity, patient knowledge, and self-management of treatment-related symptoms, as well as addressing inconsistencies in follow-up care visits.

Objective: The overall goal of this study is to improve the uptake of SCP recommendations via an educational intervention for breast cancer survivors, to improve treatment-related morbidity, patient knowledge, self-management, and adherence to follow-up visits. The specific aims of the study are to (1) evaluate the feasibility of the online SCP, and (2) assess the impact of the online SCP on survivorship outcomes.

Methods: We will enroll 50 breast cancer survivors who have completed initial breast cancer treatment into a 2-armed, randomized, waitlist-controlled pilot trial, and collect data at baseline and 6 months. For the first aim, we will use mixed methods, including surveys and personal interviews among the intervention group, to determine the feasibility of providing an online, interactive SCP (called ACESO) based on the survivors' online user experience and their short-term adoption. For the secondary aim, we will compare the 2 groups to assess the primary outcomes of survivor knowledge, self-efficacy for self-management, perceived peer support, and adherence to SCP-recommended posttreatment follow-up visits to oncology and primary care; and the secondary outcomes of treatment-related morbidity (body weight, fatigue, depression, anxiety, sexual function, distress, and sleep quality). We assess these outcomes by using measurements from validated instruments with robust psychometric properties.

Results: We have developed and refined the online breast cancer survivorship plan, ACESO, with consultation from breast cancer oncologists, nurses, and survivors. Approval for the study protocol has been obtained from the Institutional Review Board. An advisory board has also been established to provide oversight and recommendations on the conduct of the study. The study will be completed over a period of 2 years.

Conclusions: The results of this pilot study will inform the feasibility and design of a larger-scale pragmatic trial to evaluate the impact of an online breast cancer SCP on treatment-related morbidity and self-efficacy for self-management.

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KEYWORDS

breast cancer; cancer survivorship; self-management; patient education

Introduction

Breast cancer is the most common form of cancer among American women, accounting for 23% of all survivors nationally [1]. Owing to improvements in advanced screening and cancer therapies, breast cancer patients are experiencing better prognosis and higher survival rates than ever before. Yet, the availability of adequate resources and tools for supporting breast cancer survivors has not kept up with the rapid advancement in treatment options, resulting in unmet supportive care needs [2,3]. A survivorship care plan (SCP) [4], an integral element of cancer survivorship planning, is a document provided to patients completing initial cancer treatment that contains a summary of treatments, a schedule of recommended follow-up visits, and general information on treatment-related side effects. However, for breast cancer survivors, SCPs in their current form, as a static paper document, provide little-to-no benefit over standard patient discharge procedures [5]. Furthermore, despite the inclusion of SCPs in standard oncology practice, the lack of evidence supporting improved health outcomes [6,7] may be attributed to them being passive and generic in nature, as well as their reliance on the patient to proactively check, analyze, interpret, and retain the information they contain on a routine basis [8-10]. Moreover, there is limited research studying the role of eHealth literacy among survivors. Survivors are able and willing to use online computer applications that generate customized survivorship information [11]; however, prior research shows that eHealth literacy is associated with access to digital resources and level of education [12]. Recommendations by the National Cancer Institute (NCI), the American Cancer Society (ACS), and the Institute of Medicine (IOM) [13] have all emphasized the need to evaluate SCPs and explore new delivery models. Therefore, examining alternative means of delivering SCPs to improve both survivor and provider outcomes warrants further investigation.

With consultation from experts, including survivors and providers, we designed and developed a prototype of an interactive and personalized online breast cancer survivorship tool called ACESO (After-Cancer Education and Support Operations). ACESO aims to enhance the continuity of care for breast cancer survivors and improve their follow-up experiences, especially as they deal with posttreatment challenges such as comorbidities and side effects of treatment [14]. By transforming the conventional, paper-based SCP into a personalized and interactive survivorship resource, ACESO enables 2-way interaction with the SCP by allowing patients to use the built-in tool to track survivor symptoms and quality-of-life observations, and in return, to receive timely and customized educational alerts and individual reminders for follow-up visits. Moreover, it provides an online platform for breast cancer survivors to connect and interact with peers on survivorship topics and develop a peer support network.

This study's overall goal is to improve the uptake of SCP recommendations via an educational intervention for breast cancer survivors, with the aim of improving treatment-related morbidity, patient knowledge, self-management, and adherence to follow-up visits. The specific aims are, firstly, to assess ACESO's feasibility. Based on results from our preliminary study [14], breast cancer survivors reported high usability and perceived usefulness of ACESO. We will use mixed methods, including surveys and personal interviews, to determine the feasibility of providing an online, interactive SCP (ACESO) based on the online user experiences and short-term adoption of 25 participants. Secondly, we aim to evaluate the extent of ACESO's impact on breast cancer survivorship. We will enroll 50 breast cancer survivors who have completed initial breast cancer treatment (radiation, chemotherapy, or surgery) into a 2-armed, randomized, waitlist-controlled pilot trial, with SCP only as the control, and ACESO with SCP as the intervention. The primary outcomes will be (1) survivor knowledge, (2) self-efficacy for self-management, (3) perceived peer support, and (4) adherence to SCP-recommended posttreatment follow-up visits to oncology and primary care; the secondary outcome will be treatment-related morbidity (body weight, fatigue, depression, anxiety, sexual function, distress, and sleep quality). Outcome measurements will be collected at baseline and at 6 months. We hypothesize that ACESO users will show greater improvement across the primary and secondary outcomes than the waitlist control group.

Methods

Study Design

We will utilize a mixed-methods approach to evaluate the survivor experience and the impact of an interactive SCP tool in this 2-armed, randomized, waitlist-controlled pilot trial using a pretest and posttest design. Study design and reporting will be in accordance with the Consolidated Standards of Reporting Trials (CONSORT) eHealth checklist. We will randomly allocate breast cancer survivors to either the ACESO (intervention) or the waitlist control group. We will measure study outcomes at baseline and at 6 months.

Sample Size

We will seek to enroll 50 breast cancer survivors into the study; 25 will be randomly assigned to the waitlist control group and 25 will be randomly assigned to the intervention (ACESO) group. When a paired *t* test with a significance level of 0.05 is used, our sample size is estimated to achieve over 85% power in detecting an increment of 5.97 (9.70%) in self-efficacy for self-management scores in the intervention group. Our calculations are based on prior studies evaluating the impact of online interventions on self-efficacy for self-management among cancer patients [15,16]. Allowing for a 10% attrition rate, we estimate that we will obtain complete data on 22 participants in each group.

Recruitment and Setting

We will recruit 50 patients completing primary invasive breast cancer treatment (radiation, chemotherapy, or surgery) from a breast cancer surgical oncology clinic located in the Southeastern United States to participate in this proposed study. The clinic served approximately 1160 patients in 2019; therefore, it will provide access to a large and diverse pool of prospective participants for successful recruitment. To be included, patients must (1) be diagnosed with breast cancer at the age of 21 years or older; (2) be within 3 months of

completing initial treatment for localized breast cancer (ie, total or partial mastectomy, radiotherapy, or chemotherapy; patients still undergoing hormone therapy will be eligible to participate); (3) not have a history of any other form of cancer; and (4) have the ability to read and write at eighth-grade level English. There are no inclusion or exclusion criteria that are based on gender or race; however, we anticipate the recruitment of mostly (n=50) female breast cancer survivors. Initial contact takes place at the clinic, where the patient population is predominantly female and reflective of the racial and ethnic diversity of the county where the clinic is located; this is demonstrated in our expected enrollment table (Multimedia Appendix 1). Certain groups, including Native Hawaiian and American Indian groups, account for less than 1% of the population (per 2018 census data) of the county where the clinic is located; as such, every effort will be made to include participants from these groups, but given the relatively smaller sample size (n=50) of this feasibility pilot study, it is not deemed likely.

Study Procedure

Our anticipated study timeline is presented in Multimedia Appendix 2. An informational flyer containing a description and contact information for the research study will be enclosed with the SCP provided to each patient at the clinic. The study coordinator will meet with interested patients after the completion of their SCP clinic visit. Prospective participants will be screened to verify that they meet the inclusion criteria. Eligible patients will be provided with detailed study information, and informed consent will be obtained. Enrolled participants will immediately complete an online, self-administered survey using a provided web-enabled device to collect baseline measurements before randomization. To ensure accuracy, the nurse-trained study coordinator will assist all participants in completing the final section of the survey using their conventional SCP to enter details regarding their breast cancer diagnosis, treatment history, and schedule of SCP-recommended follow-up visits. All participants will be emailed a link to complete the online postintervention survey 6 months from the enrollment date. All surveys will be administered using REDCap (Research Electronic Data Capture) [17]. The study protocol has been approved by the Institutional Review Board and will be registered at clinicaltrials.gov prior to commencing the study activities.

Randomization

Upon obtaining baseline measures, the biostatistician will use SAS software (version 9.4; SAS Institute) to perform a stratified blocked randomization [18] with randomly permuted block sizes. Survivors will be randomly allocated to either the waitlist control group or the intervention (ACESO) group, with a 1:1 ratio (N=50). Stratification will be based on breast cancer diagnosis (ie, breast cancer staging and hormone receptor status) and type of breast cancer treatment (radiation, chemotherapy, surgery, and hormone therapy) because they are both associated with the occurrence and severity of treatment-related symptoms and overall quality of life [19-24]. The study navigator will subsequently implement the group allocations and contact patients via an email and follow-up phone call within 3 business days to explain group assignments and assist with the setting up of participant user accounts, usernames, and passwords (for the intervention group). To protect participant confidentiality and privacy, we will encrypt all usernames, passwords, and email addresses used on the website. Participants will be advised to change their assigned password to their own chosen password during the first login. The study navigator who is aware of group assignments will be sequestered from other research assistants and will not administer study surveys or interviews.

Waitlist Control

The proposed study evaluates an education-based intervention on psychosocial outcomes and will employ a waitlist control condition [25]. Participants assigned to this group will continue to receive usual care and be notified that they are on a waiting list to receive the intervention. The oncology clinic currently provides SCPs to all its patients after treatment completion as part of usual care. However, the paper-based document provides generic information that is not customized for individual patients. Moreover, it does not provide self-tracking of symptoms and quality-of-life indicators affecting breast cancer survivors, and lacks any resources that provide peer support to survivors. After the completion of posttest measures, all participants in the waitlist control group will be provided access and invited to use ACESO.

Intervention

Participants in this group will also receive the conventional SCP as part of usual care, in addition to access to the ACESO website. After randomization, a nurse-trained study navigator will assist patients with creating and setting up their user accounts, as well as entering their breast cancer diagnosis, treatments, and recommended follow-up schedule data as indicated in their conventional SCP into ACESO. Participants in the intervention group will receive basic training on how to use ACESO and will be familiarized with its features and functions. Participants in this group will use ACESO for (1) logging observed survivor symptoms; (2) built-in self-tracking and charting of treatment-related morbidity (weight, fatigue, depression, anxiety, sexual function, distress, and sleep quality; Table 1 [26-38]); (3) personalized, risk-adapted, and customized educational alerts and tips for symptom management, based on treatment history and self-reported symptoms; (4) email reminders for scheduling SCP-recommended follow-up visits a week prior to a visit due date; (5) monthly reminders and instructions to perform breast self-examinations; (6) an online discussion forum for communicating with other participants in this group about survivorship related topics; and (7) access to a list of evidence-based survivorship resources from NCI and ACS.

Table 1. Timing and structure of study outcomes at baseline and 6-month postintervention.

Study outcomes and measurement instruments	Study group	Measure at baseline	Measure at 6 mths	Data source	Cronbach alpha (α)
Aim 1: Assess ACESO's feasibility					
Patient experience of ACESO: online user experience scale	Intervention	No	Yes	Patient	.88
Posttest participants' experience interview	Intervention	No	Yes	Patient	N/A[a]
Adoption: login frequency, average session duration, days of use, visits by page, discussion forum participation (number of original posts; reply posts)	Intervention	No	Yes	Automated tracking on website	N/A
Aim 2: Evaluate the extent of ACESO's impact on breast cancer survivorship					
Primary outcome: treatment-related morbidity					
Self-efficacy for self-management (Patient Activation Measure)	Control & intervention	Yes	Yes	Patient	.87
Patient knowledge (WiSDOM-B[b])	Control & intervention	Yes	Yes	Patient	N/A
Perceived peer support	Control & intervention	Yes	Yes	Patient	.90
Adherence to posttreatment oncologist and primary-care physician visits	Control & intervention	No	Yes	Patient	N/A
Secondary Outcome: Treatment-related morbidity					
Fatigue (Brief Fatigue Inventory)	Control & intervention	Yes	Yes	Patient	.96
Depression (CES-D 10[c])	Control & intervention	Yes	Yes	Patient	.86
Anxiety (GAD-7[d])	Control & intervention	Yes	Yes	Patient	.79-.91
Sexual function (Female Sexual Function Index)	Control & intervention	Yes	Yes	Patient	>.90
Distress (NCCN[e] Distress Thermometer)	Control & intervention	Yes	Yes	Patient	.81
Sleep quality (Pittsburgh Sleep Quality Index)	Control & intervention	Yes	Yes	Patient	.83
Body weight (participant-owned weighing scale)	Control & intervention	Yes	Yes	Patient	N/A
Control Variables					
Age, race/ethnicity, education, income, etc.	Control & intervention	Yes	No	Patient	N/A
Breast cancer diagnosis (staging and hormone receptor status)	Control & intervention	Yes	No	Patient	N/A
Type of breast cancer treatment	Control & intervention	Yes	No	Patient	N/A

[a]N/A: not applicable.

[b]WiSDOM-B: Wisconsin Survey of Cancer Diagnosis and Management in Breast Cancer.

[c]CES-D-10: 10-item Center for Epidemiological Studies Depression Scale.

[d]GAD-7: 7-item Generalized Anxiety Disorder scale.

[e]NCCN: National Comprehensive Cancer Network.

All participants will be informed at enrollment that the tool is to support survivor education and for self-management, and that it is not intended to replace the advice of a clinician. The content and presentation of the educational alert messages have been curated by a team of experts, comprising a breast cancer oncologist, a breast cancer nurse practitioner, and 3 breast cancer survivors. All alert messages will include text to consult the primary-care physician if symptoms do not improve or worsen. The online discussion forum will be moderated by a nurse to prevent the sharing of inaccurate and potentially harmful health

information, unauthorized use (such as spamming or advertising), hateful conduct, or harassment. However, no research staff will actively participate in conversations on the discussion forum to let conversations among survivors develop organically, and to mitigate the potential of the Hawthorne effect [39]. Participants will be exposed to the intervention for 6 months for the measurement of postintervention outcomes; however, they may continue to use the resource even beyond the study period if they find it beneficial and wish to continue using it.

Outcome Measures

For the first aim, we will employ a mixed-methods approach [40] to evaluate ACESO's feasibility based on the survivors' online user experience and short-term adoption (25/50). Quantitative data on the participants' online user experience based on their use and perception of ACESO will be collected using a structured survey [41,42]. We will measure online user experience after 6 months of use to measure user perception of ACESO based on 4 dimensions: pragmatic (or utilitarian experience), hedonic (or affective experience), sociability, and usability experience [41,42]. It has been shown that sustained use and adoption for any technological environment depend on whether participants rate these experiences satisfactory or above [41-43]. To measure adoption, we will use automated tracking of logins to ACESO. In addition, we will also track the average time spent for each login session, the number of days of login, the visits for each page of the web application, and discussion group participation (number of original posts and replies to other posts). Qualitative data will be collected by inviting all ACESO users to share their experiences and perceptions of the intervention via a postintervention, in-depth interview conducted on the phone. We will use open-ended questions in combination with probing to gather participant experiences (Multimedia Appendix 3). To ensure participant confidentiality, the research assistants will conduct all interviews in a private, closed room. All interviews will be audiotaped and subsequently transcribed for data analysis by the research assistants.

To measure the primary outcome of self-efficacy for self-management, we will survey all participants at baseline and at 6 months using a structured web-administered questionnaire [27]. To evaluate the survivor's knowledge of their diagnosis, treatment, and related after-effects, survivor responses to a structured knowledge test [28] will be scored for accuracy by cross-tabulating with the SCP data obtained in the baseline survey. To measure the intervention's impact on the secondary outcome of treatment-related morbidity, we will utilize a structured web-administered survey using the REDCap survey tool [17] at baseline and at 6 months to evaluate the extent of the intervention's impact. We will utilize previously developed instruments that have demonstrated high internal consistency and validity in prior studies with cancer patients. Participants will self-report on weight (using participant-owned scales), fatigue [30], depression [32], anxiety [34], sexual function [36], distress [37], and sleep quality [38].

Finally, we will utilize mixed methods to assess perceived peer support among breast cancer survivors. A modification of a structured scale [29] will be used to measure perceived peer support at baseline and postintervention to collect quantitative data. Content analysis [44] will be performed on the online discussion postings made by the participants on ACESO to examine survivor conversations for sources of informational, emotional, and instrumental support by peers. To measure adherence to posttreatment follow-up, we will ask participants to self-report the number of any posttreatment clinical visits made by them at 6 months. We will use their SCP-recommended follow-up schedule data obtained in the baseline survey to compute any missed recommended visits and any additional non-SCP recommended visits made over the last 6 months. We will collect data on both oncology and primary care visits. The structure, timing, and sources for each study outcome are described in Table 1.

Data Analyses

For the first aim, descriptive statistics (means, percentages, and standard deviations) will be reported for participant demographics and online user experience (for all 4 subscales: pragmatic, hedonic, sociability, and usability). To assess adoption, we will compute the percentage of repeated logins to ACESO (not including the first-time login during the initial set-up); we consider ACESO to be adopted among breast cancer survivors if at least 75% of the users log in at least once after the first-time login. Participants will be classified as adopters or nonadopters, and exact logistic regression will be performed against participant demographics, types of diagnosis, and treatment types. To analyze qualitative data, audio-recordings of participant interviews will be transcribed to text and subsequently coded in NVivo (version 10; QSR International) for thematic analysis [45]. Thematic analysis will allow for the identification of patterns or themes within respondents' accounts of their experiences with ACESO. Inductive coding [46] of the transcribed recordings will be conducted to allow for the emergence of dominant and frequent themes highlighting any barriers and motivators in using ACESO within the respondents' narratives. We will use multiple coders to strengthen the validity of the qualitative analysis, who will meet periodically to resolve any coding disagreements.

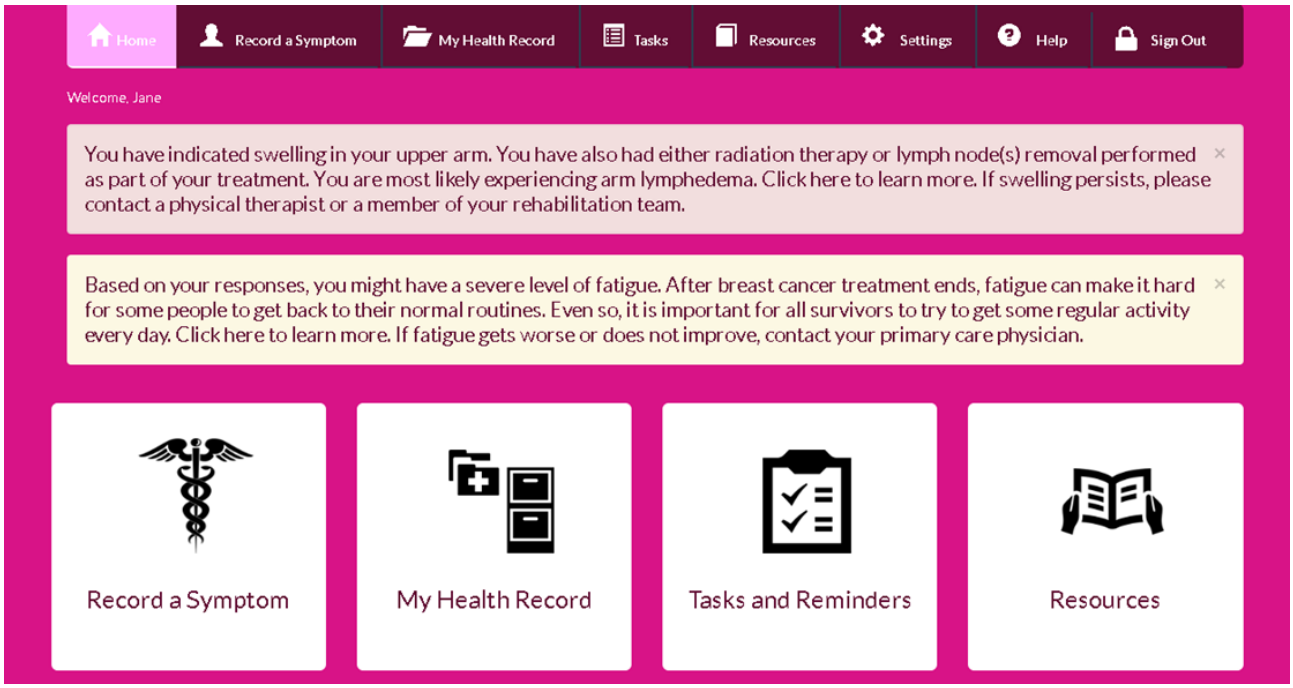
For the second aim, we will follow the intention-to-treat principle and conduct analysis on data obtained from all enrolled participants, irrespective of the extent of exposure to the intervention. We will report descriptive statistics and confidence intervals for each treatment-related morbidity, patient knowledge, self-efficacy, perceived peer support, and adherence to follow-up visits. Pre-post changes in our primary and secondary outcomes will be compared between the intervention group and the control group using 2-sample *t* tests, chi-square tests, and ANCOVA models, controlled by patients' breast cancer diagnosis, type of breast cancer treatment, and demographics. To assess follow-up adherence, posttreatment-oncologist and primary-care visits will also be compared between the intervention and the control group using similar models to compare overuse and underuse of follow-up visits between the 2 groups. In addition, time series of observations tracked using ACESO over 6 months (intervention group only) will be plotted and analyzed using repeated measure models for specific change patterns over time.

Results

The study will be conducted over a period of 2 years. Approval for the study protocol has been obtained from the Institutional Review Boards of East Carolina University and the University of Wisconsin-Milwaukee. Upon consultation with breast cancer oncologists, survivors, and a nurse, we have developed and refined the online survivorship care plan, ACESO (Figure 1), and subsequently completed an initial usability assessment to identify any issues. In prior usability and acceptance evaluations, survivors indicated high levels of acceptance and interest in the online survivorship plan [14].

We have also established the ACESO Community Advisory Board (ACAB), consisting of breast cancer survivors and health care professionals who will meet biannually and provide community oversight of the proposed research study. The ACAB will make recommendations to the research team to ensure that the study meets its goals in serving the needs of breast cancer survivors and that our recruitment efforts are inclusive and representative of the community. In addition, we have created a National Advisory Committee (NAC) consisting of nationally recognized scientists and advocates in cancer survivorship who will monitor the progress of the study and provide guidance and recommendations to the principal investigators. The NAC will be updated via progress reports before the commencement and achievement of all study milestones. The NAC will convene annually and will be updated on research progress and activities.

Figure 1. ACESO homepage.



Discussion

ACESO is a one-of-a-kind educational and behavioral intervention that challenges the standard discharge procedure for survivors and seeks to address several inadequacies found in conventional SCPs. The standard discharge process entails a single visit by the survivor after the completion of their initial breast cancer treatment, where they receive the SCP document and an explanation of its contents. This approach is flawed in its assumption of the appropriate timing of the information delivery by the SCPs. The proposed educational intervention delivers time-relevant information and reminders to the survivors at the point of need rather than the point of care; this is especially pertinent given that not all of the information within the SCP is relevant or applicable to individual survivors at the time of discharge, and several treatment-related side effects occur several weeks or more after completing treatment. Moreover, the intervention is radical in the presentation of the content in SCPs. Conventional SCPs include an exhaustive list of common treatment-related side effects experienced by breast cancer survivors as well as corresponding recommendations, which can be overwhelming [47] and may cause a diminished recall over time [48].

The proposed intervention also transforms the static, paper-based SCP into a dynamic SCP, allowing continuous access to the most recent guidelines. As we witness steadily lengthening lifespans of breast cancer survivors, the SCP must shift from being an extant guide of recommendations to a living, organic document that adapts in response to survivors' changing needs over time [49]. The proposed intervention's dynamic framework makes this possible by providing tailored content in response to survivors' most current health statuses and care needs. It also ensures that this content is always consistent with the latest guidelines, thus providing constant access to an up-to-date SCP.

ACESO also innovates the format of SCPs by transforming the passive, paper-based SCP into an online, interactive SCP that allows two-way interaction between the survivor and their SCP. In contrast to the paper-based SCP, which employs passive learning based on the reading and retaining of SCP content by

survivors, the proposed educational intervention employs active learning to enhance cognition and learning [50].

ACESO incorporates self-regulatory tools and real-time feedback absent in conventional SCPs, such as self-tracking, logging and charting of symptoms and quality of life observations, and tailored alerts (Figure 1). ACESO uses these alerts to provide survivors with real-time feedback based on their observations and to identify specific areas of concern. This combination of self-tracking and real-time feedback has been shown to improve self-efficacy and reactivity for behavior change [51]. Similar patient-centered approaches have previously been shown to improve survivors' knowledge [52]. Increased levels of self-efficacy and knowledge among survivors should further result in improved physical and psychosocial morbidity [53,54]. ACESO also improves upon the generic, conventional SCP by facilitating personalization and tailoring.

Finally, even though social support, including peer counseling [55], has been shown to be greatly beneficial in improving psychosocial distress, conventional SCPs are devoid of any elements that provide this support to survivors during discharge. ACESO features a discussion group for survivors to interact with peers, develop an online community, and offer informational, emotional, and instrumental peer support, which should prove to be highly beneficial for survivors as they attempt to transition into routine life after treatment.

It is also important to note some of the limitations to the study protocol. Lack of time or interest on the part of prospective participants will be a potential barrier to recruitment. To ensure robust recruitment, we will adopt recruitment procedures previously shown to be successful in our pilot [14] and in other studies [56,57]. In addition, the recruitment window will last a full year to allow for adequate recruitment time. Successful retention of participants for the entire study duration of 6 months is another concern. In addition to offering all participants an incentive (eg, a $50 Amazon gift card) to compensate for their time and effort, we will further split this incentive into 2 installments over the study period (at baseline and 6 months) to promote continued participation. We also acknowledge the likelihood of certain eligible participants not having access to a web-enabled device or the internet. For these participants, we will provide electronic touchscreen tablets with cellular internet connectivity to facilitate participation during the entire course of the study. Certain participants may have limited web literacy skills to meaningfully utilize the online intervention. All participants in the intervention group will receive basic training on how to use ACESO and will be familiarized with its features and functions. We will also provide all participants with clear, structured instructions on operating the website. In addition, the patient navigator will be available for any technical assistance for all participants via the ACESO website, email, or phone (during business hours). We also acknowledge that certain participants will not have access to a weighing scale or will have varying kinds of weighing scales. To improve the internal validity of the data and ensure consistency, we will provide all enrolled and eligible participants with a standard weighing scale to use when self-reporting weight.

By innovatively combining self-monitoring, personalized knowledge delivery, and peer support elements into one comprehensive intervention, the proposed study significantly improves upon standard discharge procedure by equipping survivors with tools that provide the long-term support currently lacking in standard SCPs. Future work should explore the feasibility of directly incorporating patient-generated health data using ACESO into health care providers' electronic medical record.

The study will help toward significantly advancing current practices in the format, timing, and delivery of SCP content. We expect that this study will reveal variation in posttreatment breast cancer survivorship outcomes among the 2 study groups. Value-laden features within the SCP that allow survivors to track survivor symptoms and quality of life, as well as risk-adapted educational alerts, will have a positive impact on knowledge and self-efficacy for self-management in breast cancer survivors. The results of this pilot trial will inform the feasibility and design of a larger-scale pragmatic trial.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Inclusion enrollment report.
[DOCX File , 67 KB - resprot_v9i12e23414_app1.docx]

Multimedia Appendix 2
Study timeline.
[DOCX File , 13 KB - resprot_v9i12e23414_app2.docx]

Multimedia Appendix 3
Postintervention interview questions.
[DOCX File , 14 KB - resprot_v9i12e23414_app3.docx]

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Abbreviations

ACAB: ACESO Community Advisory Board
ACESO: After-Cancer Education and Support Operations
ACS: American Cancer Society
IOM: Institute of Medicine
NAC: National Advisory Committee
NCI: National Cancer Institute
REDCap: Research Electronic Data Capture
SCP: survivorship care plan

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Protocol

App-Controlled Treatment Monitoring and Support for Head and Neck Cancer Patients (APCOT): Protocol for a Prospective Randomized Controlled Trial

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Abstract

Background: Head and neck cancers (HNCs) are among the most common malignancies, which often require multimodal treatment that includes radiation therapy and chemotherapy. Patients with HNC have a high burden of symptoms due to both the damaging effects of the tumor and the aggressive multimodal treatment. Close symptom monitoring over the course of the disease may help to identify patients in need of medical interventions.

Objective: This APCOT (App-Controlled Treatment Monitoring and Support for Head and Neck Cancer Patients) trial is designed to assess the feasibility of monitoring HNC patients during the course of (chemo)radiation therapy daily using a mobile app. Additionally, symptom patterns, patient satisfaction, and quality of life will be measured in app-monitored patients in comparison to a patient cohort receiving standard-of-care physician appointments, and health economy aspects of app monitoring will be analyzed.

Methods: This prospective randomized single-center trial will evaluate the feasibility of integrating electronic patient-reported outcome measures (ePROMs) into the treatment workflow of HNC patients. Patients undergoing definitive or adjuvant (chemo)radiation therapy as part of their HNC treatment at the Department of Radiation Oncology, University Medical Center Freiburg (Freiburg, Germany) will receive weekly physician appointments and additional appointments as requested to monitor and potentially treat symptoms during the course of treatment. Patients in the experimental arm will additionally be monitored daily using a dedicated app regarding their disease- and treatment-related symptoms, quality of life, and need for personal physician appointments. The feasibility of ePROM monitoring will be tested as the primary endpoint and will be defined if ≥80% of enrolled patients have answered ≥80% of their daily app-based questions. Quality of life will be assessed using the validated European Organisation for Research and Treatment of Cancer questionnaires, and patient satisfaction will be measured by the validated Patient Satisfaction Questionnaire Short Form at the initiation, in the middle, and at completion of radiation therapy, as well as at follow-up examinations. Additionally, the number and duration of physician appointments during the course of radiation therapy will be quantified for both ePROM-monitored and standard-of-care patients.

Results: This trial will enroll 100 patients who will be randomized (1:1) between the experimental arm with ePROM monitoring and the control arm with standard patient care. Recruitment will take 18 months, and trial completion is planned at 24 months after enrollment of the last patient.

Conclusions: This trial will establish the feasibility of close ePROM monitoring of HNC patients undergoing (chemo)radiation therapy. The results can form the basis for further trials investigating potential clinical benefits of detailed symptom monitoring and patient-centered care in HNC patients regarding oncologic outcomes and quality of life.

Trial Registration: German Clinical Trials Register DRKS00020491; https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00020491

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KEYWORDS

mHealth; head and neck cancer; HNSCC; radiotherapy; mobile app; quality of life; patient-reported outcome measures

Introduction

Head and neck carcinomas (HNCs) are among the most common malignancies worldwide with more than 600,000 new diagnoses and 400,000 deaths annually [1]. Disease-associated morbidities are widespread in HNC patients and can affect the ability to breathe or swallow, often requiring life-saving placements of tracheostomy or gastrostomy tubes [2-4]. For nonmetastatic HNCs, multimodal treatment comprises surgery and radiation therapy, and locally advanced cancers often require a combination of radiation therapy and concomitant chemotherapy [5,6]. The treatment itself can result in severe acute and long-lasting toxicities that may significantly impact patients' quality of life and require medical interventions [7].

Usually, treatment-related acute toxicities are assessed several times during the course of (chemo)radiation therapy and in increasing intervals during the follow-up period by medical professionals. However, there are several downsides to physician-assessed outcome measures for HNC patients. There are increasing gaps between appointments, during which no assessment is possible and patients may get lost to follow up; additionally, patients may not report the entirety of their symptoms during timed interactions with their health care provider [8,9]. In this respect, mobile apps may help to bridge the gap between appointments, and may provide a low-threshold tool to regularly and frequently report disease-related and treatment-related symptoms and outcomes. Previous surveys have demonstrated high acceptance levels for the usage of patient monitoring apps both for health care providers and cancer patients [10,11]. Additionally, two randomized controlled trials have been published that demonstrated a survival benefit of telemonitoring for patients with nonsmall cell lung cancers and metastatic cancers compared to the standard of care, likely due to an earlier initiation of salvage treatments in cases of recurrence symptoms [12,13].

HNC patients may especially benefit from app-based electronic patient-reported outcome measures (ePROM) monitoring, as frequent symptom control may not only help to detect recurrences earlier but could also help to assess the dynamics of treatment-related toxicities, thereby enabling faster medical interventions. In this respect, both patient outcomes and quality of life may potentially be improved. However, the compliance and acceptance levels of HNC patients toward an app-based ePROM monitoring system remain to be demonstrated. The aim of this trial, APCOT (App-Controlled Treatment Monitoring and Support for Head and Neck Cancer Patients), is to assess the feasibility of ePROM monitoring and support for HNC patients, as well as to measure global and disease-related quality of life, patient satisfaction, and economic aspects.

Methods

Study Design

This trial is designed as a single-center prospective randomized controlled trial and will be carried out at the Department of Radiation Oncology, University of Freiburg Medical Center in Freiburg, Germany. Patients with histologically proven HNCs scheduled for (chemo)radiation therapy will receive weekly physician appointments and additional appointments if medically indicated in both trial arms to monitor and potentially treat symptoms occurring during the course of treatment (standard of care). Patients in the experimental arm will additionally receive daily ePROM monitoring during (chemo)radiation. Patient-reported outcomes regarding symptom control as well as general and disease-specific quality of life will be monitored daily by a mobile app in the experimental arm that is provided to the patients on a tablet computer. All patients in the experimental arm will have the ability to request a physician appointment if necessary on a daily basis via the app. The frequency and total duration of consultations will be quantified, and the necessity and duration of inpatient care will be assessed if necessary during the course of treatment. Routine blood test results and clinical data from the patient files, including physician-reported outcomes, will be analyzed to find potential correlations with the ePROMs and to assess potential predictive factors necessitating intensified medical care.

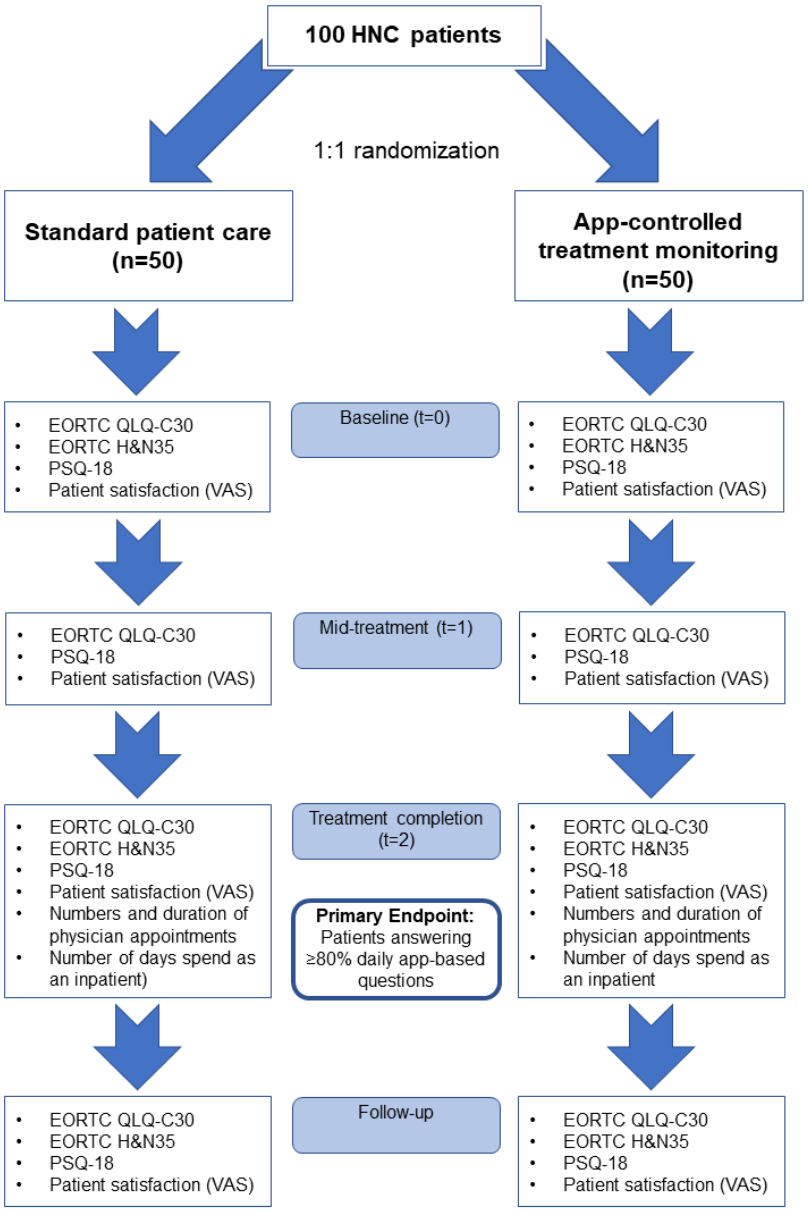
Patient Recruitment

All patients with HNCs are screened for their eligibility to participate in this trial by a study nurse prior to the initiation of (chemo)radiation therapy; the treating physician then informs potential patients about the details of the trial and answers potential questions. If (chemo)radiation therapy is medically warranted and patients provide written informed consent to participate, they are randomized between the standard-of-care monitoring and ePROM monitoring arms during the course of treatment. Block randomization with a variable block length will be used to allocate patients to the study arms.

According to institutional patient statistics, approximately 300 eligible patients are treated annually in our department. The recruitment period is set at 18 months to recruit 50 patients to

each study arm, assuming a participation rate of 20%. The study duration for each patient varies according to the treatment concept, and the average time from enrollment in the trial to the first follow up ranges from 12 to 14 weeks. Figure 1 provides a detailed timeline for the individual trial steps and assessments. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) flowchart is presented in Multimedia Appendix 1.

Figure 1. Flow chart outlining the study design and the timeline for the individual trial endpoints. HNC: head and neck cancer; VAS: visual analog scale; EORTC: European Organisation for Research and Treatment of Cancer; PSQ-18: Patient Satisfaction Questionnaire Short Form.



Inclusion and Exclusion Criteria

To participate in this trial, patients must fulfill the following inclusion criteria: (1) histologically confirmed tumor in the head and neck region, (2) indication for chemoradiation or radiation therapy, (3) aged ≥18 years, (4) Karnofsky performance score ≥50%, and (5) provision of written informed consent.

The following criteria will exclude patients from participating in this trial: (1) significant neurological or psychiatric diseases and (2) inability to give informed consent.

ePROM Monitoring During Treatment and Support

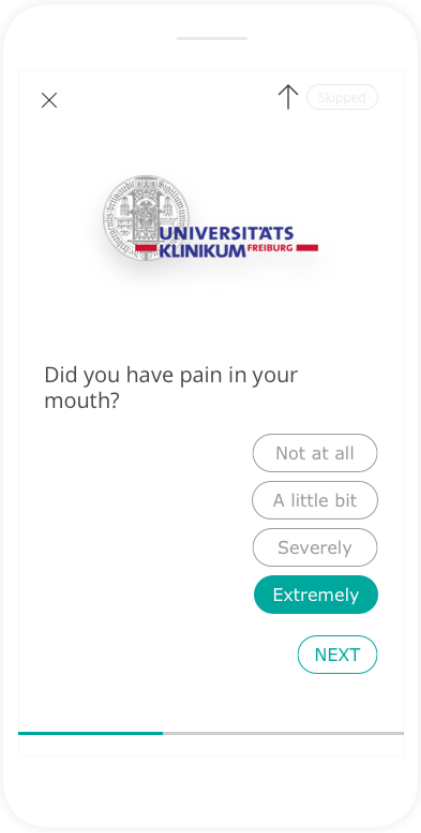
Patients that are randomized to the experimental arm will be provided with a mobile app on a tablet computer prior to each radiation treatment fraction and will be asked to answer 7-8 questions. The app will be provided by ONCARE GmbH (Munich, Germany) and will be run on an Android system. An introductory session with a study nurse will be scheduled for each patient in the experimental arm to familiarize them with the tablet and the app. If requested, this introductory session can be repeated once. The answers will be collected and documented as patient-reported outcomes. Questions will be

taken from the validated H&N35 quality of life questionnaire developed by the European Organisation for Research and Treatment of Cancer (EORTC). The questions cover overall and treatment-related well-being as well as specific symptoms, and the 35 questions of the EORTC module will be rotated so that each patient is presented with each question once weekly. As the respective questionnaires have been validated in multiple languages, the monitoring app will be multilingual. After completing the daily EORTC questions, patients will be asked about their need to consult a physician on each treatment day. If they require a physician appointment, the radiation technologist is informed by an automatic notification system prior to applying the daily treatment and will schedule a consultation with the treating physician on that day. Each patient in the experimental study arm will be seen by the treating physician for routine checkups weekly in addition to the visits requested through the app. The total number and duration of all physician appointments will be measured and documented.

Patients in the standard-of-care arm will receive routine weekly physician appointments during the course of treatment and can request additional consultations through the treating radiation technologist as per institutional standards. Patients in both study arms will also receive weekly blood tests. As the standard-of-care physician appointments are also part of the experimental arm, the mobile therapy monitoring provides an additional individualized method of care during (chemo)radiation therapy.

A sample screenshot of the mobile app is shown in Figure 2.

Figure 2. Sample screenshot of the mobile app used for patient monitoring during radiation therapy.



Primary and Secondary Endpoints

This trial aims to test the feasibility of an ePROM-based treatment monitoring and support system for HNC patients as the primary endpoint. The trial will measure the percentage of patients answering ≥80% of ePROM questionnaires during the course of (chemo)radiation therapy, and the number of answered questions for each treatment day will be documented for every patient to assess feasibility. Feasibility in this trial is defined based on clinical and logistical considerations. We assume that due to logistic constraints unrelated to this trial, patients will not receive ePROM questionnaires for a certain percentage of treatment fractions (eg, due to personnel changes, technical outages, postponement of treatment fractions). Based on clinical experience from preliminary tests, we assume that the proportion of irregularities during routine patient treatment will amount to approximately 20%.

The following secondary endpoints will also be measured: patient satisfaction, health-related quality of life, number and duration of physician appointments, number of days spent as an inpatient for treatment-related toxicities, and cost aspects. Patient satisfaction will be measured by a 10-step visual analog scale and the validated Patient Satisfaction Questionnaire Short Form (PSQ-18) questionnaire that tests 18 items in 7 subscales using a Likert scale ranging from 1 to 5. A total sum score will be calculated from the PSQ-18 questionnaire and will be transformed to a 5-point scale. Health-related quality of life for patients in both study arms will be measured using the validated EORTC QLQ-C30 questionnaire.

Patients will be asked to answer questionnaires before the initiation of (chemo)radiation therapy, in the middle (usually week 4), and upon completion of treatment (Figure 1). Additionally, patients will be presented with the questionnaires at follow-up visits.

The number of all physician appointments will be documented, and the duration of individual appointments will be measured to estimate cost factors for ePROM monitoring during treatment. The beginning and completion of physician appointments are routinely marked by status flags by the physician within the hospital's radiation oncology information system (MOSAIQ, Elekta, Stockholm, Sweden), and the duration of each individual consultation can therefore be extracted from the system. A randomized design was chosen for this trial to assess the completeness of acquired data between both arms and to compare the two groups regarding the secondary endpoints.

Statistical Analysis

The sample size was calculated based on the primary endpoint using the exact binomial test. For this trial, we defined feasibility as the ability of ≥80% of trial patients to answer ≥80% of mobile ePROM questions during the course of (chemo)radiation therapy. With an assumed percentage of 89% for the primary endpoint, a sample size of 50 patients in the experimental arm provides a power of 80% ($1 - \beta$) to a one-sided significance level of 5% (α). Power calculations were carried out using G*Power software version 3.1.9.2 (University of Düsseldorf, Germany).

Descriptive statistics will be used to analyze the secondary endpoints, including mean (SD) as well as median (IQR) for continuous variables, and absolute and relative numbers for categorical variables. Multivariate regression models will be employed to assess potential correlations between clinical parameters and data collected for the primary and secondary endpoints. The control group will be included in the analysis, and the randomization of each patient will be considered as a variable. Sum scores will be derived from the quality of life and patient satisfaction questionnaires, and will be compared between study arms using Mann-Whitney *U* tests.

To investigate the association between patient-reported outcomes and the necessity for inpatient treatment, a chi-square test will be employed.

Informed Consent and Ethics Approval

Participation in this trial is voluntary, and all patients qualifying for enrollment will be informed by the treating physician about the aims, risks, and benefits of the trial, and will be provided with written information and the consent form. Both documents conform to the standards of the International Conference on Harmonization-Good Clinical Practice. All patients will be given appropriate time to consider participation before providing informed consent in writing, including the date and time of signature. Consent forms will be countersigned by the physician. In cases of incapability to sign the consent form, oral informed consent will be confirmed by a witness signature. All patients can decline to participate in this trial and can withdraw consent at any time during the trial without penalty. Patient treatment will not be affected by the participation or withdrawal from this trial. All trial data will be saved on a dedicated trial server, and only the staff directly involved in the trial will have access to the files. All trial data will be saved for 10 years as per national guidelines and regulations. Data will not be shared with third parties.

The trial was approved by the Independent Ethics Committee of the University of Freiburg on November 26, 2019 (reference number 87/19).

Results

Recruitment for this trial started in September 2020, and patient enrollment is planned to be completed in February 2022. The results obtained from this trial will be published in a peer-reviewed journal within 12 months of completion of the trial; publication of the data will be independent of the trial outcome. The principal investigator will be responsible for the preparation of any publications resulting from this trial and will assign the first and last authorships.

Discussion

Study Rationale

The widespread availability of mobile electronic devices, and resulting possibilities to interact with and support cancer patients via electronic means enable health care providers to collect disease-related data and notify patients about necessary appointments or test results via dedicated apps. Patients with locally advanced HNCs may benefit from ePROM monitoring during their treatment both regarding the control and recurrence of disease symptoms, and for longitudinal assessment of the often significant treatment-related toxicities. In this respect, HNC patients may be scheduled for earlier medical interventions if necessary, thus improving both oncological outcomes and quality of life. This prospective randomized trial conducted at University of Freiburg Medical Center will investigate the feasibility of monitoring ePROMs of HNC patients via a mobile app during the course of (chemo)radiation therapy, and will measure resulting general and disease-related quality of life, patient satisfaction, and implications regarding health economics.

Limitations and Future Perspectives

This trial involves a mobile app used by patients via an investigator-provided tablet computer, and the acquired data will be integrated into the institutional clinical trial databases according to the required data protection and data security regulations. It is conceivable that a dedicated app on patients' private devices would have logistic advantages and enable patients to report outcome parameters independently from the treatment time and from outside as well. However, we felt that utilizing patient-owned devices for reporting may introduce a selection bias, as this approach would exclude patients who do not own a mobile device, especially elderly patients [14]. By using investigator-provided tablet computers, all HNC patients, irrespective of age or technical abilities, can be included in this trial. Additionally, avoidance of data transmission outside the hospital network complies with current national data protection standards.

As each cycle of ePROM collection is carried out over 5 days, it is possible that symptom reporting may be delayed for up to 4 days before items are repeated. However, in case of new symptoms, all patients in the experimental arm have the ability to request physician appointments daily via the app if deemed necessary. The frequency of ePROM assessment corresponds well with current national and international standards of weekly physician appointments during radiotherapy.

Once feasibility has been demonstrated for HNC patients using institutional devices, the range of the app will be expanded in a future trial to patients' personal devices so as to uncouple reporting from the hospital visits.

To date, there is no consensus on how feasibility for app-based treatment monitoring is defined and can be tested. We therefore chose a feasibility endpoint for this trial based on clinical experience. Two previously published large surveys suggest that more than 75% of patients would be willing to report ePROMs as part of treatment monitoring during radiation therapy [10,15]. Therefore, patient adherence of ≥80% is within the estimations of these surveys and seems to be a realistic assumption to prove feasibility.

Beyond demonstrating that ePROM monitoring of HNC patients during radiotherapy is feasible, this trial will provide systematic and specific patient-reported outcomes for a distinct patient population. These data may serve as a template to develop thresholds and patterns for high-risk constellations that require medical interventions and will therefore form the basis for further trials testing clinical benefits for app-surveyed HNC patients.

Conclusions

The present trial aims to demonstrate the feasibility of ePROM monitoring of HNC patients during (chemo)radiation therapy. The planned secondary endpoints of this study will provide useful data regarding patterns of symptoms during therapy that may predict inferior outcomes or the occurrence of higher-grade treatment-related toxicities. In this respect, this trial will form the basis of future, larger investigations that will assess the potential clinical benefits of app-based monitoring for HNC patients.

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Authors' Contributions

TS and NN developed this trial and wrote the trial protocol. DZ and HB are responsible for the statistical aspects of this trial. RS, AR, TK, EH, and AG helped with the trial design. HF and FH will maintain the app and the required information technology infrastructure necessary for this trial, and will manage the electronic data. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT chart for the trial.
[PDF File (Adobe PDF File), 171 KB - resprot_v9i12e21693_app1.pdf]

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Abbreviations

EORTC: European Organisation for Research and Treatment of Cancer
ePROM: electronic patient-reported outcome measure
HNC: head and neck cancer
PSQ-18: Patient Satisfaction Questionnaire Short Form
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Online and Recovery-Oriented Support Groups Facilitated by Peer Support Workers in Times of COVID-19: Protocol for a Feasibility Pre-Post Study

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Abstract

Background: In times of pandemics, social distancing, isolation, and quarantine have precipitated depression, anxiety, and substance misuse. Scientific literature suggests that patients living with mental health problems or illnesses (MHPIs) who interact with peer support workers (PSWs) experience not only the empathy and connectedness that comes from similar life experiences but also feel hope in the possibility of recovery. So far, it is the effect of mental health teams or programs with PSWs that has been evaluated.

Objective: This paper presents the protocol for a web-based intervention facilitated by PSWs. The five principal research questions are whether this intervention will have an impact in terms of (Q1) personal-civic recovery and (Q2) clinical recovery, (Q3) how these recovery potentials can be impacted by the COVID-19 pandemic, (Q4) how the lived experience of persons in recovery can be mobilized to cope with such a situation, and (Q5) how sex and gender considerations can be taken into account for the pairing of PSWs with service users beyond considerations based solely on psychiatric diagnoses or specific MHPIs. This will help us assess the impact of PSWs in this setting.

Methods: PSWs will lead a typical informal peer support group within the larger context of online peer support groups, focusing on personal-civic recovery. They will be scripted with a fixed, predetermined duration (a series of 10 weekly 90-minute online workshops). There will be 2 experimental subgroups—patients diagnosed with (1) psychotic disorders (n=10) and (2) anxiety or mood disorders (n=10)—compared to a control group (n=10). Random assignment to the intervention and control arms will be conducted using a 2:1 ratio. Several instruments will be used to assess clinical recovery (eg, the Recovery Assessment Scale, the Citizenship Measure questionnaire). The COVID-19 Stress Scales will be used to assess effects in terms of clinical recovery and stress- or anxiety-related responses to COVID-19. Changes will be compared between groups from baseline to endpoint in the intervention and control groups using the Student paired sample t test.

Results: This pilot study was funded in March 2020. The protocol was approved on June 16, 2020, by the Research Ethics Committees of the Montreal Mental Health University Institute. Recruitment took place during the months of July and August, and results are expected in December 2020.

Conclusions: Study results will provide reliable evidence on the effectiveness of a web-based intervention provided by PSWs. The investigators, alongside key decision makers and patient partners, will ensure knowledge translation throughout, and our massive open online course (MOOC), *The Fundamentals of Recovery*, will be updated with the evidence and new knowledge generated by this feasibility study.

Trial Registration: ClinicalTrials.gov NCT04445324; https://clinicaltrials.gov/ct2/show/NCT04445324

International Registered Report Identifier (IRRID): PRR1-10.2196/22500

(JMIR Res Protoc 2020;9(12):e22500) doi:10.2196/22500

KEYWORDS

peer support workers; internet-based peer support groups; personal-civic recovery; clinical recovery; COVID-19 Stress Scales; peer support; feasibility; mental health; COVID-19; intervention; recovery

Introduction

Need for a Feasibility Trial

In recent pandemics, social distancing, isolation, and quarantine have precipitated depression and anxiety [1,2]. It is expected that isolation and physical (social) distancing due to the COVID-19 pandemic will lead to similar consequences as confined people are detached from their loved ones, deprived of personal liberties, and devoid of purpose owing to altered routine and livelihood. These consequences will probably be amplified by the economic recession and the ensuing increase in unemployment and poverty. Moreover, those with pre-existing mental illness might suffer from limiting interpersonal interactions that are central to their management, as well as reduced access to helpful but "nonessential" (and thus often canceled) psychiatric services [3]. Successful use of quarantine and distancing as a public health measure requires us to reduce, as much as possible, the negative effects associated with it [4].

In response to this situation, this feasibility study of a trial offers a transitional measure of online social support for people suffering from (1) psychotic disorders or (2) anxiety or mood disorders, and to assess its effects in terms of both personal-civic recovery and clinical recovery. Transitional peer support groups will be organized and led by trained peer support workers (PSWs). PSWs are persons with first-hand lived experience of mental health problems or illnesses and who are further along in their own recovery journey. Upon training, they can provide supportive services when hired to fill such a paid specialty position, as now recommended by recovery-oriented best practices guidelines [5,6]. Indeed, recovery focuses on how individuals can have more active control over their lives (agency) [7]. It is characterized by a search for the person's strengths and capacities, satisfying and meaningful social roles, and mobilizing formal and informal support systems. Peer support has thus become one predominant feature of the recovery paradigm and, as per their title and function, PSWs specialize in peer support.

A Problem to Be Addressed: Measuring the Effects of PSWs on Recovery

In Canada, the incremental economic burden of mental health problems or illnesses (MHPIs), which incorporates the use of medical resources and productivity losses due to long-term and short-term disability, as well as reductions in health-related quality of life, is estimated to be more than $50 billion per year. By calculating all health services utilization, long-term and short-term work loss, and health-related quality of life and their dollar valuations, Lim et al [8] have concluded that over one-half was due to reductions in health-related quality of life. Decreasing pain and suffering, overcoming disability due to MHPIs, and helping Canadians affected by MHPIs to recover, instead of solely treating them for their MHPIs, is a major public health issue, even more so in times of isolation and quarantine in the midst of a pandemic since social support is known to be an important factor that can affect mental health [9]. This is why, along with other sociopolitical or historical considerations, recovery is now the official leading paradigm in the transformation of mental health systems and policies in Canada [10], as is also the case in the United States [11], the United Kingdom [12], and elsewhere in the world, and as promoted by the World Health Organization (WHO) [13].

As a social movement echoing the historical claims of other social movements since the 1960s and 1970s, including the antipsychiatry movement, the origins of recovery in mental health are now fairly well documented [14,15]. Yet, tensions persist about the meaning and ownership of recovery [16,17]. Generally speaking, there are two major portrayals of recovery [18,19]. One is akin to the notion of cure in the field of physical health; *clinical* recovery refers primarily to the reduction of psychiatric symptoms through a curative approach to the disease using psychopharmacology and psychotherapy. With this first axiom of recovery, the role of the ill person is mainly to follow the instructions of professionals and comply with prescribed treatments. On the other hand, a more *personal-civic* axiom of recovery promotes the empowerment of the persons, their ownership and authorship of their own history, their autonomy, and their independence in living free from any labeling diagnosis [20]. Recovery is not the disappearance or the eradication of symptoms but a redefinition of oneself in light of lived

experience as a person who managed to live with an MHPI, and who found a new balance in life toward well-being and quality of life, with or without enduring psychiatric symptoms or treatment.

The experience of living in recovery is particularly useful for sharing among peers who are coping, and/or have coped, with similar issues. The commonality is the struggle and emotional pain that can accompany the feeling of loss and/or hopelessness due to the consequences of MHPIs, rather than in relation to a specific symptom or psychiatric diagnosis. This commonality might also be in relation to sex and gender considerations [21,22], more than in relation to specific conditions. Peer-to-peer communication is a widespread phenomenon (eg, in groups like Alcoholics Anonymous [23] or Al-Anon for families [24]). Access to PSWs has been widely advocated internationally by service user researchers [25,26] and by professional organizations [27,28]. Provision of peer support has been identified as a fidelity requirement for recovery-orientated services [11,29] where the PSWs bring a focus on health, recovery, and quality of life, rather than on illness and disability [30]. They provide the mental health service users a validation of their lived experience and unique experiential knowledge for facilitating the reclaiming of their lives as full members of the community and for remaining so [31]. The Mental Health Commission of Canada emphasizes that patients living with MHPIs who interact with PSWs "will not only feel the empathy and connectedness that comes from similar life experiences, but that this interaction also fosters hope in the possibility of a recovery that includes health, wellbeing, quality of life, and resilience" [32]. Since 2005, recovery and PSWs have also been at the core of Mental Health Action Plans in the province of Quebec [33,34]. Yet, we still do not know how a recovery-oriented mental health organization that would include PSWs as staff members would improve recovery from the perspective of persons living with MHPIs.

Principal Research Questions

The principal research questions are whether our novel PSWs-facilitated online intervention will have an impact in terms of (Q1) clinical recovery potential and (Q2) personal-civic recovery potential. We also question (Q3) how these potentials can be impacted by the COVID-19 pandemic and (Q4) how the lived experience of people in recovery can be mobilized to cope with the situation. Finally, we also explore (Q5) how sex and gender considerations can be taken into account for the pairing of PSWs with service users beyond considerations based solely on psychiatric diagnoses or specific MHPIs [35]. We aim to collect data for a future randomized controlled trial (RCT) [36] by clarifying a certain number of remaining uncertainties and by detecting an effect that would be specifically attributable to transitional peer support as facilitated by trained PSWs. We will thus consider scientific reasons, processes, resources, and management in preparation for a more definitive trial. Indicators of feasibility will include recruitment rates practices, participants and facilitators, as well as feasibility and retention rates in the study protocol [37].

Why a Feasibility Study of a Trial Is Needed Now

The main problem that this feasibility study of a trial addresses is that the scientific literature on the attribution of a specific effect of paid PSWs, in terms of clinical and personal-civic recovery potentials among persons living with psychotic disorders and/or anxiety and mood disorders, is sparse. Indeed, although we already know that patients served by case management teams with PSWs have shown greater treatment engagement, more satisfaction with their life situation and finances, and fewer life problems than compared to case management alone [38], it is the effect of teams with PSWs that has been mostly evaluated. It is thus possible that such effects could be attributable to mental health professionals, other than PSWs, and who would have endorsed recovery as a guiding principle for their own professional practice. We may know who PSWs are, but we do not know much about what PSWs do that would be complementarily different to these professionals. This has the adverse potential of hindering the harmonious integration of PSWs into professional teams when their role is not well accepted or understood, which was sometimes the case, for instance, in France, and as suggested by Demailly (and Garnoussi), who observed a possible rejection phenomenon of PSWs [39-41].

Evidence From the Literature

In 2014, Lloyd-Evans et al [42] published a systematic review and meta-analysis of RCTs of peer support programs, defining peer support "as a way to promote recovery for anyone who has experienced mental ill health, irrespective of diagnosis." Their systematic review and meta-analysis included trials intended for people with psychotic disorders. They found that programs varied in content, group, or individual delivery; face-to-face or internet-based delivery; degree of support from local mental health services; and extent of provider training. Such limitations make it difficult to recommend the practice on a scientific basis rather than as a response to the otherwise very legitimate social and political demands of the mental health service users' movement. Several programs focused on individual self-management, as shown by Johnson et al [43], and Milton et al [44], who reported that 64 (29%) of 218 participants in the intervention versus 83 (38%) of 216 in the control group were readmitted to acute care within 1 year (odds ratio 0.66, 95% CI 0.43-0.99; P=.044). This "individualistic" approach to recovery and focus on readmission to acute care as a primary outcome has been criticized by some advocates of service users' involvement in mental health research [45] and who see this as a practice of silencing and of masking the epistemic injustice [46] that people living with MHPIs have collectively and historically suffered in traditional psychiatry [47].

A quasi-experimental group design was used by Felton at al [48] to compare outcomes of patients with psychotic disorders (n=104). They reported that among these patients, those served by teams *with* PSWs demonstrated greater gains in several areas of quality of life, and overall reduction in the number of major life problems experienced. This might be due to team dynamics and culture, not necessarily to the supportive presence of PSWs toward these patients. Then, with regards to anxiety and mood disorders, Pfeifer and colleagues [49] also conducted a

meta-analysis, examining the effect of peer support on clinical recovery (symptoms), but not on personal-civic recovery. They included professionally led peer support groups and found that voluntary peer support complementary interventions from nonprofessionals were superior to usual care in reducing depressive clinical symptoms. They also conclude that despite potential economic advantages and the multiple mechanisms through which these could help patients with anxiety and mood disorders, such programs have been limited in their availability and integration with formal mental health treatment. This is currently the case in the province of Quebec, where it is planned that there would be PSWs in teams dedicated to the treatment of psychotic disorders (but not in teams dedicated to treatment of anxiety or mood disorders). Psychotic disorders affect about 1% of the population. Studying the potential impact of PSW-led online group interventions for much more common disorders like anxiety and mood disorders, in conjunction with formal mental health treatment, could benefit 10 times more people. Indeed, Statistics Canada reports that 10.1% of Canadians ≥15 years of age declared symptoms that met the criteria for anxiety (4.7%) and depression (5.4%) [50].

Search for Existing Trials

As part of the development of a new training program for PSWs, a joint undergraduate program of the Department of Psychiatry and the Vice-Deanery for Health Sciences at the Faculty of Medicine of the University of Montreal, we systematically searched the literature for examples of evidence-based PSWs interventions we could replicate and train our students to conduct. A recovery-oriented group intervention by PSWs that we became familiar with over the years is the Citizenship Enhancement Project [51]. Derived initially from research on mental health outreach to persons who are homeless [52], this intervention was designed to address the specific community and social inclusion needs of persons with MHPIs and comorbid criminal justice histories, as well as to respond to the high rates of criminal recidivism for this population. Indeed, drawing from social science theories that propose social and civic participation as a measure of one's involvement in society [53], our engagement framework [54] emphasizes the importance of opening up opportunities for participation to persons at risk of marginalization. An RCT was conducted in the United States in 2012 to compare outcomes for participants receiving this intervention, along with the usual public mental health services, to those receiving public mental health services alone. Analysis of baseline, 6-month, and 12-month interviews showed significantly reduced alcohol and drug use and significantly increased quality of life for the intervention group compared to the control group [55]. In close collaboration with the Yale Program for Recovery & Community Health that initiated the Citizenship Enhancement Project, with patient research partners we have successfully translated and transposed this model into the Projet Citoyen at the Institut universitaire en santé mentale de Montréal (IUSMM) [56]. In both places, the role of PSWs consisted of facilitating discussion groups on issues of social and civic participation. Three key differences make it necessary to further evaluate the effect of the PSWs' group intervention specifically. Firstly, involvement in the Criminal Justice System within the past 2 years is an inclusion criterion for the former, not for the latter. Secondly, another inclusion criterion for the former is that it was intended for people living with psychotic disorders and concurrent substance abuse disorders, therefore not including people living with anxiety or mood disorders, as was the case with the Projet Citoyen. Thirdly, the Citizenship Enhancement Project and Projet Citoyen have been evaluated, but not in terms of personal-civic recovery with a pre-post research design. In brief, searches for existing meta-analysis of clinical trials for PSWs' group intervention confirm that no previous randomized trial has compared the outcomes of a group intervention led by PSWs combined to formal mental health treatment in terms of clinical and personal-civic recovery for people living with psychotic disorders, and/or anxiety and mood disorders.

How Results Will Be Used

A result of PSWs' online group intervention efficacy in terms of both clinical and personal-civic recovery potentials for people living with psychotic disorders, and/or anxiety and mood disorders, would privilege the role of PSWs in recovery-oriented peer-to-peer support groups. The study will impact the conceptualization of recovery- and citizenship-oriented mental health care, clinical training, and in mental health treatment resource allocation and for informing nonspecialized clinicians as well as the public. Indeed, an embedded observational and qualitative study performed with postgraduate students and patient research partners will improve the understanding of the experiential knowledge translation and knowledge sharing dynamics among participating patients living with MHPIs and among PSWs. Decision making will also be informed for the definition of a university mission for all psychiatric facilities of the University of Montreal's Integrated University Health and Social Services Network (IUHSSC). This network advances the integration of the university mission of care, teaching, and research, by facilitating knowledge translation and technology assessment in order to improve access to evidence-based care. This is a vast integrated network of health and social services organizations and public establishments with a university vocation, including those psychiatric facilities where PSWs do their final internship before being eventually hired. The territory of this network represents 46% of the population of the province of Quebec and the three Integrated University Health and Social Services Centers affiliated with the University of Montreal are partners of this study. Since 2015, the IUHSSC organization is the gateway to the public service system where the Quebec population can turn in case of health problems and/or psychosocial problems, including MHPIs. Due to their university affiliation, their mission is to contribute to academic training as well as to the development and dissemination of scientific knowledge. The study will inform the PSWs' training program by generating a better understanding of the specific effects attributable to the PSW group intervention.

Previous Works

In 1994, Daniel Fisher, a person with lived experience of several psychiatric hospitalizations prior to becoming a psychiatrist and renowned author and speaker, released an empowerment model of recovery based on the principles that emerged from the lived experience of persons living with MHPIs. Among those

principles is *personhood*: "we are full human beings and deserve respect and full citizenship" [57]. More recently, Davidson and colleagues suggested that, as a sense of empowerment and control over one's life emerges, people in recovery may start to demand the same rights and duties as other citizens [58,59]. Supporting people living with MHPIs in exercising their citizenship (which refers to personal confidence/hope, willingness to ask for help, goal/success orientation, reliance on others, and no domination by symptoms) might be a precondition for their recovery, not an eventual reward contingent on the person overcoming his/her disability first. Rowe and Davidson [60] have thus suggested that research on clinical recovery, often invoked to illustrate personal recovery's different meaning and mission, also inspired the mental health community with its findings that people with chronic MHPIs often do "get better" in the traditional clinical sense. Personal recovery transferred the hope these findings gave to the conviction that people could recover a full and meaningful life even without achieving a clinical cure or remission. Rowe and Davidson [60] state:

> *Finally, recovering citizenship means that while recovery is replenishing its social roots, it also reminds citizenship, with its emphasis on the person's rightful place in society, of the person's unique journey to citizenship and life as a citizen.*

Social interaction, which is essential to community membership, involves the development and maintenance of reciprocal relationships between members of a community, each of whom are, in principle, equal cocitizens to each other [52,61]. Thus the notion of collective citizenship, as suggested by Quinn et al [62] when applying this model to the domain of mental health, where people are often treated in individualistic ways, kept apart separately, and experience marginalization. The collectivistic dimension is imperative in promoting participation, empowerment, and social change for people living with MHPIs.

Indeed, the Mental Health Commission of Canada considers that "involvement within community" is an integral component of a definition of personal recovery. We thus combined the Recovery Assessment Scale [63] and the Citizenship Measure [64], because the former does not include any item on this civic participation dimension, as does the latter. We first translated these tools in French using a translation-back-translation method [65], then found statistically high convergent validity between them [66]. Patient research staff have administered these tools to 845 French-speaking IUSMM patients living with various MHPIs. We found statistically significant male-female differences, suggesting that males felt more independent and self-confident but also more isolated than females, especially in relation to the intention to seek and receive help. Such results in terms of sex differences [67,68] were discussed in class among PSW apprentices to inform and guide their future practice. The current proposal will allow us to further explore the influence of sex and gender in the pairing between PSWs and peer-supported service users. We questioned if this pairing could be favored by taking into account such sex-gender considerations, rather than solely on a diagnostic basis (eg, should a patient living with psychotic disorders only be paired to PSWs living with the exact same condition?).

A criterion for being recruited as a PSW will be to have successfully completed at least 180 hours of training within the microprogram (eg, undergraduate courses PST1000-Recovery & Global Health + PST1001-Ethics of Recovery for PSWs). We have published on the "reversed flipped class" approach in use in this 1-year-long microprogram where senior PSWs take turns as recovery experts and teaching partners, and by which patients/students learn from each other in a peer support–like atmosphere by reflecting on their lived experience of recovery [69-71]. This system, including the evaluation of the final internship in clinical environments affiliated with the University of Montreal, was adapted from the Canadian Medical Educational Directives for Specialists (CanMEDS). The CanMEDS are commonly used by medical boards in Canada and elsewhere to create competency-based medical training programs [72]. With permission from the Royal College of Physicians and Surgeons of Canada, we have adapted the CanMEDS for the training and supervision of our PSWs [73,74]. PSWs will be recruited and hired in the form of service contracts through the Association des pairs aidants du Québec because the job title of PSW is not yet recognized in the nomenclature of job titles, labels, rates, and salary scales of the health and social services network. Since they cannot hire them directly under this job title, several Quebec institutions like the IUHSSC organization use this mechanism to have PSWs in their mental health teams, as recommended in the governmental Mental Health Action Plan. The Association des pairs aidants du Québec is a company legally constituted under Part III of the Loi des companies du Québec. It is a social enterprise self-managed by and for PSWs and consumers (peer-run agency), grouped within a professional association in order to improve, promote, and trade their specific expertise and knowledge. Peer-run agencies are staffed and operated completely by self-described mental health consumers who provide services such as self-help, activity groups, and drop-in groups. Yanos et al [75], as well as Miyamoto and Sono [76], have shown that involvement in such services was associated with better community adjustment, the use of more coping strategies, and a greater proportion of problem-centered coping strategies. PSWs recruited by job posting to facilitate transitional peer support groups will not themselves be participants in this study. However, they will have a specific mandate because they will generate certain data analyzed in the context of this study, in particular with regard to the recognition, valorization, and use of the experiential knowledge of persons in recovery, particularly, but not limited to, to their response and coping strategies under the COVID-19 pandemic.

Methods

Proposed Feasibility Trial

Design

The "signatures" of MHPIs is a term formulated by the American National Institute of Mental Health to designate the broad range of genetic, biological, psychological, and social factors that may "sign" a specific mental disorder, depending on an individual's sex, history, lifestyle habits, etc [77]. In 2010, based on the recommendations of an international advisory

committee composed of some of the best scientists in the world in the field of psychiatric research, the Research Centre of IUSMM implemented the "Signature Bank" project for the collection of biological and psychosocial dimensional signatures from all psychiatric emergency patients of the IUSMM (catchment area of about 600,000 inhabitants). More than 4000 patients are treated annually at the IUSMM, while an additional 2000 patients per year are treated by means of outpatient or ambulatory services. Our activities provide us with one of the largest populations of patients with MHPIs in Canada. What is unique about this ambitious longitudinal research project is the extensive involvement of the IUSMM hospital site in the attempt to establish an exclusive niche for discoveries in the signatures of MHPIs. By collaborating with the Research Centre, IUSMM hospital managers have contributed to the implementation of this large-scale project that aims to measure the (epi)genetic, biological, psychological, and social signatures of people living with MHPIs who receive the IUSMM's clinical services. Typically, these measures are obtained at four different points in the clinical visit of patients at the IUSMM: when patients are admitted to the psychiatric emergency services (T1), when they are discharged from the hospital (T2), when they are admitted to an outpatient clinic (T3), and 12 months after T3 (T4) [78]. With this proposal we go even further in understanding not only the signatures of MHPIs but also the dimensions of personal-civic recovery, as reported by our patients who will additionally complete the Recovery Assessment Scale and Citizenship Measure components.

Planned Trial Interventions

Control Intervention

When a person shows up at the Emergency Department of IUSMM for the first time, he or she is systematically approached by a research nurse after a first medical authorization is granted for that person to be approached (sometimes this authorization is not granted for medical or security reasons). The research nurse then explains the objectives of the Signature Bank project and invites the person to participate. Those who agree to participate sign the Information and Consent Form (T1), fill out a series of questionnaires, including ones on sociodemographics; consent to the taking of biological samples; and asked if they are willing to be contacted for other research purposes (like our own study). Then, as with any other IUSMM patients, they are evaluated by the Evaluation and Liaison Module during their hospital stay. A diagnostic is established or confirmed by ward psychiatrists and coded according to the WHO International Classification of Disease–10th Revision (ICD-10) [79]. Based on the diagnosis (or diagnoses), after discharge (T2), they are referred to a specialized outpatient clinic (T3). Whether for psychotic disorders or for anxiety and mood disorders, pharmacotherapy, psychotherapy, or a combination of both are then offered in accordance with the guidelines of the Royal College of Physicians and Surgeons of Canada. Of the Signature Bank participants diagnosed with psychotic disorders, or anxiety or mood disorders, and who consent to participate in our study, half will receive only the control intervention, while the other half will also receive our experimental PSW-led online group intervention (random allocation control/experimental intervention ratio=2:1).

Inclusion criteria include patients recruited from the Signature Bank data collection project diagnosed with (1) schizophrenia and psychotic disorders (ICD F20-F29), or with (2) anxiety or mood disorders (ICD F30-F49), (3) aged 18 years old or more, and (4) who have already consented to be contacted by telephone to be invited by our team to participate in this pilot study. Exclusion criteria include (1) active suicidal intentions, (2) marked cognitive impairment, and (3) no access to an electronic device with a webcam and microphone to participate in the online transitional peer support group.

Experimental Intervention

Trained PSWs will learn with participants via a series of 10 colearning workshops that they will organize and facilitate as focus group panels in a manner to simulate a typical peer support group [80]. The difference between our experimental and transitional online peer support groups and real community-based peer support groups is that (1) they will be facilitated by trained PSWs; (2) they will have a personal-civic recovery focus; and (3) they will have a fixed, predetermined duration (a series of 10 weekly 90-minute online workshops). Indeed, as defined by the WHO [81]:

> *Peer support groups bring together people who have similar concerns so they can explore solutions to overcome shared challenges and feel supported by others who have had similar experiences and who may better understand each other's situation. Peer support groups may be considered by group members as alternatives to, or complementary to, traditional mental health services. They are run by members for members so the priorities are directly based on their needs and preferences. Peer support groups should ideally be independent from mental health and social services, although some services may facilitate and encourage the creation of peer support groups.*

The objective is to prevent the deterioration, in times of pandemic, of the participants' recovery potential. It is also a question of stimulating this potential by encouraging them to share their worries and their coping strategies in relation to the current acute situation. More generally, they will be asked to project themselves beyond this situation and to discuss future challenges of inclusion and social participation (eg, by attending already existing peer support groups) in the short or long term, and of which they will have become aware of during the intervention. This is why this intervention is considered to be transitional. Their own goals during the pandemic may be different from those post pandemic, and the effects of the response may also be different. However, similar to Taylor et al [82] who developed the COVID-19 Stress Scales, which we will use (see the *Outcome Measures at Follow-up* section), the whole intervention is intentionally designed to be readily adaptable to other (pandemic) situations.

To generate a collective narrative [83-85], the output of each workshop will have a brief written account of the group discussion, upon which the next workshop will open, and so on. To trigger discussion, PSWs will use animation cards and techniques inspired and adapted from the Malette COMETE toolkit, which was developed in France to help health care teams

develop the psychosocial skills of patients in therapeutic education. These cards are available for free [86]. Each workshop will be filmed via the Zoom secured video communication system for subsequent qualitative observational and content analyses. In accordance with our model of patient engagement [87,88], PSWs will start every time by disclosing being themselves persons in recovery, and feed with content drawn from their lived experience while asking participants to share their own lived experience and coping strategies. This is in line with experiential learning [89]. After each workshop, the PSWs will meet for a 30-minute debriefing session, asking themselves what they learned, personally and professionally (also recorded). Christens [90] has conceptualized the relational process of recovery mentorship as an expression of psychological empowerment, as embodied in and practiced by the PSWs as mentors, and as an egalitarian relationship that helps facilitate the empowerment of the mentees. There are no reports of PSW-led online group intervention–related adverse reactions, but participants will be monitored for any contraindications and adverse events.

Allocation

Upon reception of the signed Information and Consent forms by email, consecutive referrals will be randomly allocated by computer algorithm to one of the two modalities at point of entry into the study on acceptation into the protocol using a computerized program (eg, randomization.com). At this entry point, the participant will have been evaluated, diagnosed, met inclusion criteria, and given formal consent for the randomization procedure. To ensure a balance in the allocation for the strata and thus control the risk of a secular trend in the composition of groups, random block sizes in a random order will be used (3, 6, 9, etc). Participants will thus be randomly allocated to the trial arm (n=20, 2 groups of 10) or control arm (n=10), and will be identified by a randomly assigned identification number. Among those allocated to the experimental groups, 10 patients with psychotic disorders will be randomly selected to be part of the transitional support group for patients with psychotic disorders, and 10 patients with anxiety or mood disorders will be randomly selected to be part of the transitional self-help group for patients with anxiety or mood disorders. It will be the same for the control group; 5 patients with psychotic disorders will be randomly selected to be part of the control group for patients with psychotic disorders, and 5 patients with anxiety or mood disorders will be randomly selected to be part of the control group for patients with anxiety or mood disorders. In both cases, those who have not been selected will be placed on a substitute list in the event of withdrawal of a selected patient, who will be replaced at random by one of the corresponding substitutes.

The groups will be studied together and separately: the experimental group for patients with psychotic disorders (n=10) will be compared to the control group for patients with psychotic disorders (n=5); the experimental group for patients with anxiety or mood disorders (n=10) will be compared to the control group for patients with anxiety or mood disorders (n=5); and the combined experimental group for patients with psychotic disorders and for patients with anxiety or mood disorders (n=20; 2×10) will be compared to the combined control group for patients with psychotic disorders and anxiety or mood disorders (n=10).

This study will be reported following the CONSORT (Consolidated Standards of Reporting Trials) guidelines [91] and registered before the enrollment of the first participant (eg, ClinicalTrials.gov).

Protecting Against Sources of Bias

IUSMM clinical staff will receive no information on how participants scored on the Recovery Assessment Scale and Citizenship Measure questionnaires. PSWs will receive no information on participants' results related to clinical recovery measures routinely taken for the Signature Bank. The PSWs will be separated from the outpatient clinic therapists and will sign agreements not to discuss cases.

Primary and Secondary Outcome Measures

Several instruments have been developed by clinicians and academics to assess clinical recovery. Based on their life narratives and to assess personal-civic recovery, measurement tools have also been developed through community-based participatory research and validated by persons living with MHPIs (eg, the Recovery Assessment Scale and the Citizenship Measure questionnaires). As users of mental health services typically tend to prefer interventions to help them recover, reintegrate with society, and achieve their personal goals [92], we propose this pre-post research feasibility trial design to evaluate the outcomes on personal-civic recovery (primary outcome), on clinical recovery and stress- or anxiety-related responses to the COVID-19 pandemic (secondary outcome).

Outcome Measures at Follow-up

The COVID-19 Stress Scales (36 items) and the measures of personal-civic recovery (47 items) will be repeated, along with the following measures of clinical recovery, which are routinely collected among all Signature Bank participants:

1. Anxiety: Anxiety State-Trait Anxiety Inventory Form Y6, 6 items (STAI-Y6) [93];
2. Depression: Depression Patient Health Questionnaire, 9 items (PHQ-9) [94];
3. Alcohol dependence: Alcohol Use Disorders Identification Test, 10 items (AUDIT-10) [95];
4. Drug dependence: Drug Abuse Screening Test, 10 items (DAST-10) [96];
5. Psychosis: Psychosis Screening Questionnaire, 12 items (PSQ) [97]; and
6. Social functioning: WHO Disability Assessment Schedule, 12 items (WHODAS 2.0) [98].

The COVID-19 Stress Scales

Research and clinical observations suggest that during times of pandemic many people exhibit stress- or anxiety-related responses that include fear of becoming infected, fear of coming into contact with possibly contaminated objects or surfaces, fear of foreigners who might be carrying infection (ie, disease-related xenophobia), fear of the socioeconomic consequences of the pandemic, compulsive checking of and reassurance seeking related to possible pandemic-related threats, and traumatic stress symptoms about the pandemic (eg,

nightmares, intrusive thoughts). Taylor et al developed the 36-item COVID-19 Stress Scales to measure these features, as they pertain to COVID-19. The COVID-19 Stress Scales were developed to better understand and assess COVID-19–related distress. A stable 5-factor solution was identified, corresponding to scales assessing COVID-19–related stress and anxiety symptoms: (1) concerns related to danger and contamination (12 items, Cronbach α=0.94); (2) concerns about economic consequences (6 items, Cronbach α=0.90); (3) xenophobia (6 items, Cronbach α=0.92); (4) traumatic stress symptoms (6 items, Cronbach α=0.93), and (5) compulsive checking and reassurance seeking (6 items, Cronbach α=0.83). In collaboration with the original authors (ie, Steven Taylor), we have translated the COVID-19 Stress Scales into French, and it can be completed using a 5-point Likert scale.

The Recovery Assessment Scale

Salzer and Brusilovskiy [99] have published an in-depth review of the quantitative properties of the Recovery Assessment Scale, based on 77 articles that included psychometric data. They concluded that these studies indicate very good results for internal consistency, test-retest reliability, and internal reliability. Among the tools available to empirically assess recovery, this scale has been the most published. Its items cover the following five dimension scales: (1) personal confidence (9 items, Cronbach α=0.86), (2) willingness to ask for help (3 items, Cronbach α=0.83), (3) goal and success orientation (5 items, Cronbach α=0.68), (4) reliance on others (4 items, Cronbach α=0.65), and (5) no domination by symptoms (3 items, Cronbach α=0.73).

The Citizenship Measure

The Citizenship Measure was developed through a community-based participatory research design in response to a prompt (*For me, being a citizen means…*) suggested by persons living with MHPIs who were involved as research partners and research staff. The Citizenship Measure items cover the following five dimensions: (1) self-determination (6 items, Cronbach α=0.67), (2) respect by others (4 items, Cronbach α=0.74), (3) involvement in the community (4 items, Cronbach α=0.65), (4) basic needs (5 items, Cronbach α=0.60), and (5) access to services (4 items, Cronbach α=0.60).

When completing the Recovery Assessment Scale and Citizenship Measure questionnaires, participants will be asked to rate on a 5-point Likert scale (1=strongly disagree, 5=strongly agree) the extent to which the respective statements apply to them since the COVID-19 pandemic (in French: *situation depuis le début de la période COVID-19*). To simplify the instructions, COVID-19 will be referred to as "the virus." Although COVID-19 actually refers to the disease and SARS-CoV-2 is the virus, in line with the developers of the COVID-19 Stress Scales, we expect that many respondents will not be aware of this distinction. Based on feedback from the pilot testing, respondents readily understood what the developers of these scales were referring to.

Recruitment

As of February 2020, 2136 IUSMM patients have been enrolled in the Signature Bank since the year 2012, including 822 individuals with psychotic disorders, and 853 with anxiety and/or mood disorders. The study was approved by the local ethics committee in accordance with the Declaration of Helsinki, and the Signature Bank's management framework provides further details on recruitment and consent forms. Between August 26, 2019, and February 26, 2020 (6 months), a preliminary validation study [100] allowed us to recruit 93 of the Signature Bank participants diagnosed with either psychotic disorders, or with anxiety and mood disorders. In total, 36 were female (39%) and 57 were male (61%). They further completed the Recovery Assessment Scale and Citizenship Measure, both of which a 5-point Likert scale was used to rate items. For the former, the mean was 3.77 (out of 5; SD 0.78). For the latter, the mean was 3.91 (out of 5; SD 0.63). The type of participants we need can thus easily complete our questionnaires in parallel to those of the Signature Bank. A research assistant with lived experience of an MHPI will contact by phone all the above-mentioned 93 Signature Bank participants who have already been in touch for the previous validation study and who have already accepted to be contacted again by our team for such purposes. If needed, other Signature Bank participants who meet the inclusion criteria will also be contacted until 30 Information and Consent forms are returned. The Information and Consent form will be sent by email to those who provide an email address. They will be offered CA$20 as compensation indemnity for the baseline and follow-up completions of the Recovery Assessment Scale, the Citizenship Measure, and the Bem Sex Role Inventory (see the *Sex and Gender* section).

Quantitative Analyzes

Baseline characteristics will be summarized, including for the measures of clinical recovery (see the *Outcome Measures at Follow-up* section), the Recovery Assessment Scale, the Citizenship Measure (personal-civic recovery), the COVID-19 Stress Scales, and the Bem Sex Role Inventory. All participants with data at baseline (T1) and follow-up will be included in the analyses. We will compare within-patient change from baseline to intervention versus control group in the study outcome measures using the Student paired sample *t* test. The analysis will run on intervention and control practices separately so as to explore practice level impact on the differences in outcomes. Comparison of confidence interval and effect size between groups will be assessed.

Qualitative Analyses

Each workshop and the corresponding debriefing session among PSWs will be transcribed verbatim. The data analysis team will employ thematic analysis [101-103], and a combined deductive and inductive approach to coding [104]. We are particularly interested in understanding life trajectories and transitions in relation to the five domains of the Recovery Assessment Scale and the five clusters of the Citizenship Measure. The chosen approach combines the perspective of the life course and the relational perspective of social networks. This approach makes it possible to understand the different trajectories that make up the life course of individuals in the light of the dynamic relationships that place them (or not) in support networks while taking into account their subjectivity and ability to act (agency). From the life course perspective, the development of the person

is posited as a process that does not necessarily stop at predetermined stages [105]. The structured and unstructured material will also be analyzed through natural language processing [106], which is one area of artificial intelligence using computational linguistics that provides parsing and semantic interpretation of text, which allows systems to learn, analyze, and understand human language.

Sex and Gender

Biological sex is a categorical construct comprised of genes, anatomy, gonads, and hormones that make up male and female differences [107]. Beyond one's birth-assigned sex, sociocultural gender refers to diverse roles, orientations, and identities that influence health across lifespan development. Sex and gender have rarely been considered together in recovery research. To address this gap, we will conduct secondary analyses stratified by sex following recent recommendations in promoting rigor and reproducibility in health research [108]. In qualitative analyses, verbatims will also be coded with considerations of participants' sex in order to identify themes unique to men and women. For example, social support is a health-promoting factor that is experienced differently by men and women, as we have seen in a previous study with the results of the personal-civic recovery measures. In addition to sex, we will explore sociocultural gender roles using a validated questionnaire (Bem Sex Role Inventory) that will allow us to assess dimensions of masculinity, femininity, and androgyny along continuums [109,110]. Previous work by Juster et al [111] has shown how measuring gender-roles provides unique within-sex understanding of mental and physical health. In quantitative analyses, we will explore correlations among gender roles (masculine and feminine subscales) in association with study outcomes representing recovery. Taken together, our sex- and gender-based analyses will provide insights into sex-specific and gender-specific recovery.

Ethical Considerations

Declaration of Helsinki protocols are being followed, and patients will give written informed consent. The study was approved on June 16, 2020, by the Research Ethics Committees of the Montreal Mental Health University Institute (#2020-1948). For all participants of the Signature Bank, including those participating in the research presented in this manuscript, an overseeing mental health expert have ruled that all adult patients were deemed ethically and medically capable of consenting for their participation.

Results

This pilot study was funded in March 2020. Recruitment took place during the months of July and August 2020. Table 1 presents the distribution of recruited participants. We anticipate the publication of two key papers in accordance with the Canadian Institutes of Health Research open access policy: (1) the registered research protocol and (2) description of the main conclusions of our case-control study. Table 2 presents the calendar of activities.

Table 1. Distributions of participants in the pilot study.

Characteristic	Participants, n (%)
Total eligible participants (N=92)	
Participants with AMD[a]	31 (33.7)
Participants with PD[b]	61 (66.3)
Total eligible participants who agreed to receive the ICF[c] by email (N=92)	54 (58.7)
Participants with AMD (n=31)	23 (74.2)
Participants with PD (n=61)	31 (50.8)
Total eligible participants who returned the signed ICF (n=54)	36 (66.7)
Participants with AMD (n=23)	17 (73.9)
Participants with PD (n=31)	19 (61.3)
Total eligible participants who completed the questionnaires at T1 (n=36)	32 (88.8)
Participants with AMD (n=17)	16 (94.1)
Participants with PD (n=19)	19 (100.0)
Total eligible participants who completed the questionnaires at T2 (n=30)	24 (80.0)
Participants with AMD in the experimental group (n=10)	7 (70.0)
Participants with PD in the experimental group (n=10)	10 (100.0)
Participants with AMD or PD in the control group (n=10)	7 (70.0)

[a]AMD: anxiety and mood disorders

[b]PD: psychotic disorders.

[c]ICF: Information and Consent Form.

Table 2. Calendar of activities.

Date	Activity	
	Convergent and Concurrent Validity Between Clinical Recovery and Personal-Civic Recovery	Effects of Online and Recovery-Oriented Peer Support Groups Facilitated by Peer Support Workers
	ClinicalTrials.gov ID NCT04125030	ClinicalTrials.gov ID NCT04445324
September 2019 to March 2020	• Study suspended due to the COVID-19 pandemic • 92 eligible participants completed the study	—[a]
April-May 2020	—	• Writing and submission of the research protocol to the institutional review board
June 2020	—	• Institutional review board approval of research protocol
July 2020	• Submission of the study protocol for publication in a peer-reviewed journal	• Submission of the study protocol for publication in a peer-reviewed journal
August 2020	—	• Recruitment of study participants among those 92 from the previous validation study • Precompletion of measures (T1)
September to October 2020	• Publication of the research protocol [100]	• 10 weekly peer support groups for patients with psychotic disorders • 10 weekly peer support groups for patients with anxiety or mood disorders
November 2020	• Data analyses	• Postcompletion of measures (T2) • Addenda to study protocol • Submission of the revised study protocol for publication
December 2020	• Submission of the study's main conclusions for publication in an open access peer-reviewed journal	• Data analyses • Submission of the study's main conclusions for publication in an open access peer-reviewed journal

[a]Not applicable.

Discussion

Qualitative and quantitative results will be provided to all stakeholders and knowledge users, and posted on our massive open online course (MOOC) platform. Several PSWs and engaged service users take turns as teaching partners in *The Fundamentals of Recovery* MOOC [112], for which there are 1553 registrants from 51 different countries (Multimedia Appendix 1).

MOOCs are free interactive step-by-step courses developed by universities with the aim of reaching an unlimited number of participants and to create a community of lifelong e-learners (electronic learners). PSWs will be involved in the presentation and discussion of the findings, and acknowledged as coauthors in the publications, whenever appropriate, including within the MOOC (second edition). Indeed, the MOOC will be used as a knowledge translation platform for ongoing discussion among registrants, and updated with the findings of this pilot study in particular. Undoubtedly, the COVID-19 pandemic has disrupted many aspects of academic medical missions [113]. When the pandemic has subsided, although there will likely be some "return to normal," some of the innovations developed in response to the COVID-19 pandemic will most likely remain a part of academic psychiatry's everyday clinical and educational operations. The MOOC was not originally conceived as an innovative response to any particular pandemic. It has been nevertheless particularly appreciated in times of lockdown due to the COVID-19 pandemic. For the first 20 weeks of 2020, Figure 1 shows the cumulative total of registrants, whereas Figure 2 shows the weekly variations of new registrants to the MOOC; both figures show accelerated counts since WHO officials announced on March 11, 2020, that the COVID-19 contagion should henceforth be considered a pandemic.

Figure 1. Cumulative total of MOOC (massive open online course) registrants during the first 20 weeks of 2020. WHO: World Health Organization.

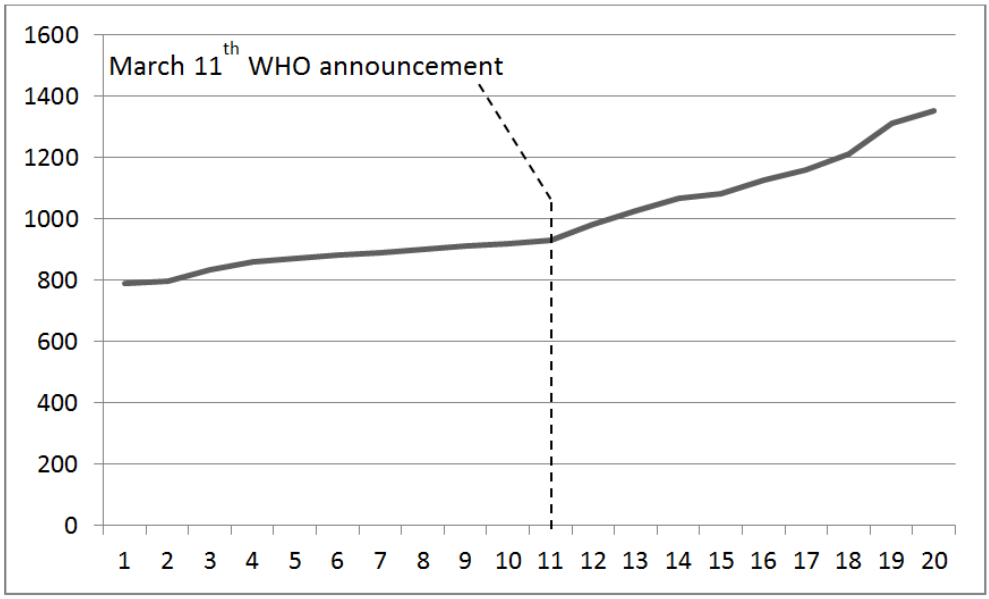
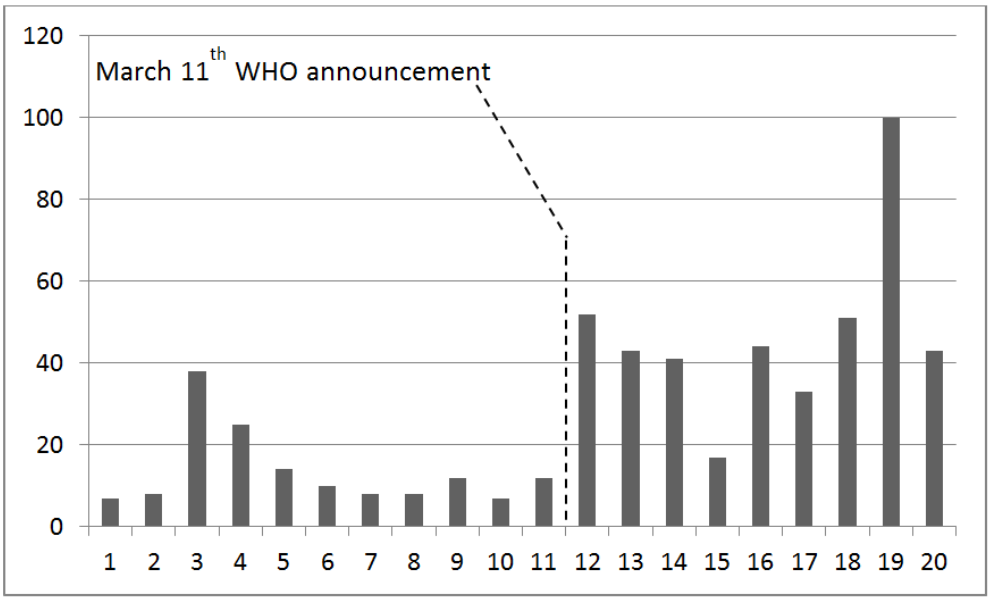


Figure 2. Weekly variations in new registrants to the MOOC (massive open online course) during the first 20 weeks of 2020. WHO: World Health Organization.



In 2017, before the current COVID-19 crisis, Bendezu-Quispe and colleagues [114] suggested that the emergence and re-emergence of communicable infectious diseases like Ebola or Zika were already increasing the necessity of knowledgeable and skilled health professionals, specifically with MOOCs arising as opportunities that allow people around the world to participate in higher-education courses. They argued that MOOCs can be used to learn about health issues of global relevance, and with the necessity of fast divulgation of knowledge and skills. Given the scope of mental health problems and the constraints of resources in training psychiatrists and other mental health professionals in most parts of the world, continuing education for medical and health or social services professionals and students, including in primary care, is vital [115]. In this MOOC, PSWs are included as training partners, as well as a subgroup of colearners.

Moreover, millions of people worldwide experienced moderate to severe levels of stress- or anxiety-related symptoms in response to COVID-19. This is true for the general population [116] as well as for people already diagnosed with psychotic disorders [117] or anxiety and mood disorders [118]. Yet, if general conditions remain the same for the participants of the experimental groups and for those of the control groups, and significantly different benefits are still observed among these groups, these differences will, in principle, be attributable to the intervention and not to the pandemic context.

Some psychiatrists even warn of a “tsunami” of mental illness due to problems arising during lockdown. They are particularly concerned that children and older adults are not receiving the support they need because of school closures, self-isolation, and fear of hospitals [119]. It could take years for some people to recover from these problems and find their own recovery

pathway if they do not get support. During the pandemic, our new online intervention, combined with the MOOC, will add to already existing services. Several studies report on such experiments, such as online peer support for patients [120] but also for health professionals on the frontline of the COVID-19 outbreak [121] and whose mental health and well-being are at stake. This pandemic context indeed has major impacts on stress, anxiety, and possible depression in people who are already in treatment [122] as well as the general population and current health care workers, including PSWs. Supporting the mental health of medical staff and affiliated health care workers is a critical part of the public health response [123]. Given that three Integrated University Health and Social Services Centres affiliated with the University of Montreal—with a total of more than 40,000 employees—are supporting this pilot project, they may wish to come together and widen access to this relatively low-cost intervention for other current patients as well as their employees in need of support and information to prevent deterioration of their own mental health and recovery potential. The arrival of PSWs in the workforce as a new type of additional provider will no doubt be welcome.

Beyond the current acute context, this feasibility study of a trial and corresponding future RCT, plus the MOOC as an innovative knowledge translation strategy, have the potential to demonstrate the relevance of this online group intervention of PSWs for many more current and future patients. Indeed, the Quebec Ministerial Mental Health Action Plan currently in force mentions the Assertive Community Treatment teams as potential models for the inclusion PSWs. Several reviews concluded that Assertive Community Treatment is more effective than standard services in reducing hospital use and increasing community tenure, and numerous practice guidelines endorsed this model as an evidence-based practice for the treatment of psychotic disorders like schizophrenia [124]. Psychotic disorders affect about 1% of the population, while anxiety and mood disorders are much more common disorders from which 10% of the population experiences during normal times, a figure that will inevitably rise with the current COVID-19 pandemic and its aftermaths. There are already existing (online) self-help groups for these people, with or without PSWs, but which are not necessarily complementary to treatment offered by formal public mental health services, as is the case for people treated by Assertive Community Treatments teams where there are PSWs. Conversely, as the potential of digital mental health has become urgently apparent, the surge in interest and use of digital health to meet the demands of patients in quarantine, with social and physical distancing restrictions, and a lack of in-person care has centered on anxiety and mood disorders—and largely ignored those with psychotic disorders [120]. As uses of telehealth during the COVID-19 crisis increase, the potential of digital mental health to increase access is becoming clearer [125,126]. Access to a transitional and intermediary online self-help groups between the institutional environment and the community environment, for both people living with psychotic disorders or anxiety and mood disorders alike, could become a good practice to recommend beyond the current context of the COVID-19 pandemic.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Profile of MOOC registrants after the first year (N=1553).
[DOCX File , 15 KB - resprot_v9i12e22500_app1.docx]

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Abbreviations

AUDIT-10: Alcohol Use Disorders Identification Test, 10 items
CanMEDS: Canadian Medical Educational Directives for Specialists
CONSORT: Consolidated Standards of Reporting Trials
DAST-10: Drug Abuse Screening Test, 10 items
e-learner: electronic learner
ICD-10: International Classification of Disease–10th Revision
IUSMM: Institut universitaire en santé mentale de Montréal
MHPI: mental health problems or illness
MOOC: massive open online course
PHQ-9: Patient Health Questionnaire, 9 items
PSQ: Psychosis Screening Questionnaire, 12 items
PSW: peer support worker
RCT: randomized controlled trial
STAI-Y6: Anxiety State-Trait Anxiety Inventory Form Y6, 6 items
WHO: World Health Organization
WHODAS 2.0: WHO Disability Assessment Schedule, 12 items

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Protocol

Identifying Targets for Substance Use Prevention in Young People Exposed to Childhood Adversity: Protocol for a Systematic Review

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Abstract

Background: Adverse childhood experiences are prevalent robust risk factors for the development of substance use problems. However, less is known about the causal mechanisms that explain these relationships. While directly preventing adverse childhood experiences is ideal, it is not always possible. In such cases, the mechanisms themselves may be amenable to intervention, allowing for the effective prevention of problematic substance use among children exposed to adversity. Identifying such mechanisms is therefore a critical step for efforts aiming to reduce the high individual and societal burdens associated with substance use globally.

Objective: This study aims to systematically identify and synthesize evidence on the modifiable mediators and moderators of the relationship between adverse childhood experiences and substance use outcomes in young people (age 10-24 years).

Methods: A systematic review will be conducted using PubMed, MEDLINE, PsycINFO, Web of Science, and CINAHL databases to determine the modifiable mediators and moderators of the relationship between adverse childhood experiences and substance use in young people. Data from the review will be qualitatively synthesized, unless we identify a sufficient number of studies (at least five) that examine the same type of adversity (eg, physical or sexual abuse) and the same mediator/moderator, in which case a quantitative synthesis (meta-analysis) will be conducted. If a quantitative synthesis is warranted, standardized effect estimates of the indirect (mediated) effect between adverse childhood experiences and substance use outcomes will be combined using a random-effects meta-analysis. Mediators/moderators will be grouped according to a socioecological perspective, using the four levels of individual, interpersonal, community, and public policy/culture.

Results: Electronic searches were completed in August 2019. A total of 4004 studies were included for screening after removing duplicates. After evaluating titles and abstracts against eligibility criteria, a further 3590 studies were excluded, leaving 415 studies for full-text screening. The results of the review are expected to be available by December 2020.

Conclusions: The mechanisms linking adverse childhood experiences and substance use outcomes in young people are vital targets for substance use prevention efforts. This review will provide evidence to inform the development of prevention strategies in order to interrupt the negative life trajectory that can begin with childhood adversity.

Trial Registration: PROSPERO International Prospective Register of Systematic Reviews CRD42020148773; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020148773

International Registered Report Identifier (IRRID): DERR1-10.2196/22368

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KEYWORDS

adverse childhood experiences; substance use; adolescence; mediation; moderation

Introduction

Children exposed to adversity are at greater risk of developing substance use problems later in life compared with children not exposed to such adversity [1,2]. Adverse childhood experiences, defined as abuse, neglect, household violence, parental psychopathology, and separation [3], increase the risk of harmful alcohol use by 47% and psychoactive drug use by 64% [1]. The risk is even greater for those exposed to abuse in particular, with meta-analytic estimates demonstrating that these children are twice as likely to develop harmful drinking [4] and have up to two times the odds for any substance abuse [5] compared with those not exposed. Moreover, meta-analytic estimates for individuals exposed to at least four adverse childhood experiences indicate an almost six-fold increase in the odds for illicit drug use and problematic alcohol use and a 10-fold increase in the odds for problematic drug use compared with individuals having no adverse childhood experience exposure [6]. It is therefore no surprise that population attributable risk proportions indicate that elimination of adverse childhood experiences would prevent more than one-quarter of all cases of substance use disorder [7]. Unfortunately, prevalence rates for adverse childhood experiences are alarmingly high, with around 39% of children having experienced an adverse childhood experience globally [7] and high likelihood of experiencing multiple categories of adverse childhood experiences [8,9]. The eradication of adverse childhood experience exposure, while an ultimate goal, may not be readily achievable. Therefore, understanding how best to prevent the negative sequelae resulting from adverse childhood experience exposure is vital in order to lessen the individual, economic [10,11], and global disease burdens [12] attributable to substance use.

Adolescence and emerging adulthood are critical periods for intervention and prevention of substance use problems, given the relatively young age of onset of substance use and development of substance use disorder symptoms [13]. Initiation of substances typically occurs during this period [14] and escalates sharply from early to late adolescence. While trends in adolescent substance use show continuing declines [14,15], there remains a substantial proportion of adolescents who are engaging in harmful substance use. For example, 14% of American 12th graders binge drink fortnightly [15]. This suggests that current prevention approaches may be inadequate for those most at risk for substance use problems. In this respect, young people exposed to adverse childhood experiences represent an important population to target. Adverse childhood experiences substantially increase the odds of early experimentation with substances and early onset of regular use [16,17], which in turn is associated with an increased risk of substance dependence and use disorder [18,19], a more chronic course of dependence [13], and comorbid mental and physical health problems [20]. An estimated 75% of lifetime cases of substance use disorder have their onset before age 24 years [21], highlighting the need to intervene early, prior to the onset of maladaptive patterns of substance use. Given the increased odds of early initiation in those with histories of childhood adversity, intervention prior to young adulthood is especially important.

However, effective prevention of substance use problems in young people with a history of adverse childhood experiences is lacking. This may be in part due to a lack of clarity around specific targets for prevention in this population. Mechanisms that mediate or moderate the relationship between adverse childhood experiences and substance use outcomes and are amenable to change reflect key targets for prevention. Existing research points to such mechanisms at the individual, interpersonal, and community levels of behavior. Specifically, early adversity has been linked to changes in inhibitory control and reward processing, which in turn predict vulnerability to substance use disorder [22]. Differences in executive control were indeed found to mediate the relationship between adverse childhood experiences and substance use in adolescents [23]. Internalizing and externalizing symptoms appear to also be involved in the risk for substance use problems associated with child adversity [24]. Additionally, there is some evidence that emotion regulation processes mediate the link between emotional abuse and substance use in adults [25]. Interpersonal factors, such as social support [26] and relationships with parents/caregivers [27,28] and peers [28], have also been implicated as mechanisms in the relationship between childhood adversity and substance use. At the community level, preliminary evidence indicates that a sense of school belonging may moderate the effect of adverse childhood experiences on adolescent cigarette smoking, with a higher sense of school belonging protecting against substance use [29].

The literature reviewed above provides some candidates for intervention in the pathway from childhood adversity to substance use outcomes. However, the existing literature on mechanisms involved in the relationship between adverse childhood experiences and substance use outcomes is limited in three important ways. First, studies often examine a single mediator or moderator, or a single type of adversity, despite evidence of multiple mechanisms that contribute to the relationship [26,30] and evidence that children experiencing one type of adverse childhood experience are often exposed to multiple categories [9]. To our knowledge, no systematic effort to identify the range of mediators/moderators in the relationship between adverse childhood experiences and substance use outcomes has been undertaken, hindering our ability to understand the potentially broad range of factors involved in this pathway. Second, longitudinal studies delineating the mechanisms linking adverse childhood experiences and substance use problems are rare. Reliance on cross-sectional data requires substantial and often untenable assumptions to establish a developmental relationship between exposure and substance use outcomes. Longitudinal data upholds the assumptions of mediation analysis, namely, that the temporal relationship between variables is correct [31]. Third, many studies examining the mechanisms that operate between adverse childhood experiences and outcomes focus on static factors that are not amenable to change via traditional strategies, such as genes [32], race/ethnicity [33,34], sex [35], neurobiological mechanisms [36], and brain structure/function [37]. While such research aids our understanding, identifying targets amenable to intervention is a critical next step in preventing the negative sequelae associated with adverse childhood experiences.

This study aims to address these gaps by systematically identifying and synthesizing evidence on the modifiable mediators and moderators of the relationship between adverse childhood experiences and substance use outcomes in young people. Specifically, through a systematic review of the literature, this study aims to determine what modifiable factors mediate or moderate the relationship between childhood adversity and substance use outcomes in young people (age 10-24 years).

Methods

Registration

This protocol adheres to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement [38]. The protocol has been registered in the PROSPERO registry (University of York, registration number: CRD42020148773).

Eligibility Criteria

For this review, eligibility criteria are defined using population, intervention/exposure, comparator, outcome, and study characteristics (PICOS) [39]. The inclusion criteria are defined in Textbox 1 [40-45].

Textbox 1. Eligibility criteria for studies to be included in the systematic review and synthesis.

Population

Included studies must include human participants (no animal studies). Participants must have experienced childhood adversity between the ages of 0 and 18 years, and must have a measured substance use outcome between the ages of 10 and 24 years, corresponding to an inclusive definition of adolescence [40] and aligning with the World Health Organization's definition of "young person" [41].

Intervention/Exposure

Studies must include a measure of childhood adversity, occurring between the ages of 0 and 18 years. Childhood adversity is defined here as experiences measured by the CDC-Kaiser Permanente Adverse Childhood Experiences Study [3] as follows: from age 0 to 18 years, emotional, physical, or sexual abuse; emotional or physical neglect; mother treated violently; a member of the household engaged in substance abuse, experienced mental illness, or went to prison; and parents separated or divorced. Moreover, it involves three items proposed by Finkelhor et al as follows: being a victim of bullying, experiencing social isolation/rejection, and prolonged loneliness [42]. These additional items have been included owing to evidence suggesting that they increase the prediction of mental health outcomes when added to the adverse childhood experience survey items [42]. For the purposes of this study, parental psychopathology (substance abuse and mental illness) must have occurred during the child's lifetime between the ages of 0 and 18 years.

Comparator

No comparator/control group required for inclusion.

Outcomes

Studies must include a substance use outcome between the ages of 10 and 24 years. This includes alcohol, tobacco, psychoactive drugs, and nonmedical use of prescription drugs and any of the following:

- Initiation and age of initiation of substance use.
- Frequency of substance use.
- Problem substance use or abuse, defined as the presence of any of the following: failure to fulfil major obligations at work, school, or home; recurrent use in situations in which it is physically hazardous; recurrent substance-related legal problems; and continued use despite persistent social or interpersonal problems.
- Quantity of substance use, including single occasion risky drinking (binge drinking/heavy episodic drinking, defined here as at least four standard drinks on any one occasion).
- Substance use disorder/dependence. The definition for this outcome will be according to the diagnostic criteria set out in the Diagnostic and Statistical Manual of Mental Disorders (DSM) version that was in use at the time the study outcome data were collected (either DSM-IV [43] or DSM V [44]).

Study Characteristics

Studies must include a mediation/moderation analysis of at least one factor that is modifiable after birth. We consider a mediation analysis to be present if the authors test the indirect effect from the adverse childhood experience to the substance use outcome via a hypothesized mediator. In mediation analyses, we do not require studies to first demonstrate a significant direct effect from the adverse childhood experience to the substance use outcome. This is in recognition of consensus among mediation researchers that if the direct effect is presumed small or temporally distant to the outcome, it need not be significant for mediation to be established [45]. This is plausible in the case of childhood adversity and substance use, whereby the risk conferred from distal factors, such as adverse childhood experiences, may operate through more proximal risk factors that occur in adolescence, thus decreasing the magnitude of the association between childhood adversity and substance use outcomes. We consider a moderation analysis to be present if authors test the interaction between the adverse childhood experience and the proposed moderator.

In addition, studies must be published in English, must be peer-reviewed, must employ a longitudinal study design, and must be original research. Full-text studies must be published from January 1, 1998, to August 14, 2019. The year 1998 was chosen as the historical cut-off point to include only studies published following the CDC Kaiser Permanente Adverse Childhood Experiences study [3].

Specific exclusion criteria were identified. Studies will be excluded if they meet any of the following conditions: evaluation of intervention or treatment outcomes only; assessment of scale formation only; reporting of the incidence of substance use only; and review of the literature. In addition, studies that presume physical neglect owing to poverty status or another income-related measure will be excluded if they do not examine another adverse childhood experience. This was due to the understanding that a family's income does not necessarily reflect whether a child's basic physical needs of food, shelter, adequate medical care, and clothing are met.

Information Sources

Electronic searches will be conducted in PubMed, MEDLINE, PsycINFO, Web of Science, and CINAHL from 1998 to August 2019. Two databases (MEDLINE and PubMed) will be searched without English language restriction to determine whether relevant studies published in other languages are being excluded. Searches will be rerun in 2020 prior to data analysis to identify any relevant studies published since the initial searches were conducted. Table 1 provides the search terms used for MEDLINE, which will be replicated for other databases. Database-specific Medical Subject Heading (MeSH) searches will be generated where exact matches are unavailable. Full search terms for each database are presented in Multimedia Appendix 1.

Table 1. MEDLINE search strategy.

Number	Term
1	life change events/
2	adverse childhood experiences/ or domestic violence/ or exp child abuse/ or physical abuse/
3	((childhood or adolescent) adj3 advers*).tw.
4	(child* or life or early) adj2 stress.tw.
5	bullying/ or cyberbullying/
6	social isolation/
7	((family or parent*) adj3 (substance or alcohol* or drug or smok* or depression or illness or suicid* or jail or prison)).tw.
8	divorce/ or family conflict/ or family separation/
9	(trauma* or maltreat* or assault* or violen* or molest* or neglect* or victim* or isolat* or reject* or mistreat* or poverty or depriv* or abus* or lonel*).tw.
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	resilience, psychological/
12	adaptation, psychological/
13	(adapt* or protect* or resilien* or mediat* or moderat*).tw.
14	protective factors/
15	11 or 12 or 13 or 14
16	substance-related disorders/ or exp alcohol-related disorders/ or alcoholic intoxication/ or alcoholism/ or binge drinking/ or amphetamine-related disorders/ or cocaine-related disorders/ or drug overdose/ or inhalant abuse/ or marijuana abuse/ or exp opioid-related disorders/ or phencyclidine abuse/ or substance abuse, intravenous/ or substance abuse, oral/ or "tobacco use disorder"/
17	((substance or alcohol* or tobacco or drug or smok*) adj3 (misuse* or initiat* or abus* or problem or heavy or binge or disorder* or dependen* or frequen*)).ti,ab.
18	16 or 17
19	cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/ or cohort.ti,ab. or longitudinal.ti,ab. or prospective.ti,ab. or retrospective.ti,ab.
20	10 and 15 and 18 and 19
21	child* or adolescen* or teen* or youth* or pediatr* or paediatr* or young or emerging or youth).tw
22	20 and 21
23	limit 22 to (("all child (0 to 18 years)" or "young adult (19 to 24 years)") and English)
24	limit 23 to yr="1998 -current"

If additional information is required from authors of studies identified by the review, the corresponding author of that study will be contacted by email to provide this information. After 3 weeks from the date of the first contact and one follow-up email, if no response has been received from the authors, we will deem them unreachable and proceed with our analysis. If any of the inclusion criteria cannot be confirmed, the study will be excluded.

Study Records

Data Management

Studies identified in the databases will be exported to Covidence [46] and duplicates will be removed by the software.

Selection Process

Researcher 1 will screen 100% of the titles and abstracts for inclusion in the review. A second and third researcher will screen 5% of the titles and abstracts, and proportionate agreement will be calculated through the systematic review software [46]. This represents the number of votes in agreement divided by the total number of votes. If discrepancies exist between scores, they will be resolved through consultation between the three researchers. If proportionate agreement is less than 90%, the three reviewers will review the screening process and resolve any ambiguities that may be causing the discrepancies. A second researcher will screen additional studies until agreement is above 90%.

Full-text studies will be obtained for studies deemed eligible for inclusion. Two researchers will read all full-text studies. Discrepancies in the scores of the two researchers will be resolved through consultation, and if required, a third researcher will be included.

Data Collection Process and Data Items

From the studies included in the final selection, researcher 1 will independently extract author information, publication year, study characteristics (sample size, age of participants, gender, length of follow-up, and location), substance use outcomes (age of initiation, any use, frequency of use, problem use, heavy use or binge drinking, abuse, and disorder/dependence), characteristics of child adversity (type, age of exposure, and duration of exposure where available), mediators examined, and moderators examined. A summary of the findings for each mediator/moderator will be extracted, including statistical significance and the effect size of the mediated and/or moderated effect.

Risk of Bias in Individual Studies

Study quality will be assessed using the Joanna Briggs Institute Critical Appraisal Checklist for Studies Reporting Prevalence Data [47]. The checklist has nine questions that assess six domains. One point is allocated per question, and points are combined as a measure of overall study quality, allowing comparison across studies. This critical appraisal tool was chosen as it is well suited to the type of studies that will be extracted from the review, that is, as the review is focused on the presence of mediating factors between an exposure and outcome and not involved in evaluating treatments or interventions, this tool is useful because it does not include questions assessing the appropriateness of randomization procedures, blinding, and intervention integrity that are found in other tools assessing quantitative study quality. Two reviewers will complete the critical appraisal for all studies. Inconsistencies will be resolved through consultation between the two reviewers. The risk of bias of studies will be reported in a narrative synthesis.

Data Synthesis

We will synthesize mediators and moderators. These will be grouped according to the socioecological model [48], at the individual, interpersonal, organizational/community, and public policy levels. If there is a sufficient number of studies (at least five) that examine the same category of adversity and the same mediator/moderator, a quantitative synthesis will be conducted. If a quantitative review is warranted, standardized effect estimates of the indirect (mediated) effect between the adverse childhood experience and the substance use outcome will be combined using a random-effects meta-analysis. A random-effects approach was chosen as given the likely heterogeneity in samples based on the broad inclusion criteria of the review, it is likely there will be a range of different effect sizes across studies that are not simply due to sampling error. If conditions are not met for a quantitative review, a narrative synthesis will be conducted.

Confidence in Cumulative Evidence

The GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) approach will be used to assess the strength of the evidence overall [49].

Ethical Approval

This study does not include human or animal participants and thus does not require approval from ethical review boards.

Results

Electronic searches were conducted in August 2019. After removing duplicates, 4005 studies were included for screening. On evaluating titles and abstracts against eligibility criteria, a further 3590 studies were excluded, leaving 415 studies for full-text screening. The results of the review are expected to be available by December 2020 (Table 2).

Table 2. Progress and timeline (adapted from the PROSPERO International Prospective Register of Systematic Reviews).

Month, Year	Aug-Dec, 2019	Jan-Mar, 2020	Apr-Jun, 2020	Jul-Sep, 2020	Oct-Dec, 2020
Preliminary searches	✓				
Piloting of the study selection process	✓				
Formal screening of search results against eligibility criteria		✓	✓	✓	
Data extraction				✓	
Risk of bias assessment					✓
Data analysis					✓

Discussion

Substance use and mental disorders are the leading causes of disease burden in young people and are associated with 3.4 million years of health lost [50]. In order to reduce this high burden, prevention must be tailored toward those most at risk for problematic substance use. In this respect, young people with histories of adverse childhood experiences are an important population to target, given the prevalence of adverse childhood experiences and the strong relationship these experiences have with increased risk for substance use. By examining and synthesizing evidence regarding the mechanisms that underlie this relationship, this review will provide valuable knowledge to inform the development of prevention programs to be delivered to this population. Beyond prevention, knowledge of mechanisms in the relationship between adverse childhood experiences and substance use outcomes in young people has important implications for clinical assessment, case formulation, and treatment approaches. Early intervention and treatment may benefit from addressing the mechanisms identified in this review. Moreover, these mediators/moderators may impact treatment success, potentially shedding light on variability in treatment outcomes and offering new opportunities to increase effectiveness. This is especially important as there are minimal evidence-based integrated treatment options for young people with co-occurring traumatic stress and substance use. This review thus seeks to improve outcomes for young people exposed to adverse childhood experiences and interrupt the negative life trajectory that can start with childhood adversity.

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Authors' Contributions

LRG conceived the idea of this study, with input from EVK and NCN. ELB and KMK provided advice on technical aspects of the planned review. All authors contributed to the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Database search terms.
[PDF File (Adobe PDF File), 92 KB - resprot_v9i12e22368_app1.pdf]

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Protocol

Prevalence of Postoperative Pain Following Hospital Discharge: Protocol for a Systematic Review

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Abstract

Background: Pain is one of the most common, feared, and unpleasant symptoms associated with surgery. However, there is a clear gap in patient care after surgical patients are discharged from hospital, resulting in poorly controlled postoperative pain. Inadequate pain management after discharge can have detrimental effects on quality of life and lead to the development of chronic postsurgical pain. The severity of postoperative pain before discharge is well described, but less emphasis has been placed on assessing pain at home after hospital discharge.

Objective: The objective of this review is to summarize the prevalence of moderate-to-severe postoperative pain within the first 1 to 14 days after hospital discharge.

Methods: A detailed search of epidemiological studies investigating postoperative pain will be conducted on MEDLINE and EMBASE from their inception until the date the searches are run. The primary outcome will be the proportion of patients reporting moderate-to-severe postoperative pain at rest and with movement within the first 1 to 14 days after hospital discharge. The secondary outcomes will include a comparison of postoperative pain after discharge between patients who underwent ambulatory and inpatient surgery, and adverse outcomes attributable to poor pain control after hospital discharge (eg, readmission to hospital, emergency room or other unplanned medical visits, or a decrease in quality of life).

Results: The protocol has been registered in PROSPERO (registration number CRD42020194346). The search strategies for MEDLINE and EMBASE have been completed. The final results are expected to be published in May 2021.

Conclusions: This systematic review is expected to synthesize evidence describing the prevalence of postoperative pain after hospital discharge. Available epidemiological evidence may help inform the magnitude of the problem of postoperative pain at home after hospital discharge.

Trial Registration: PROSPERO International Prospective Register of Systematic Reviews CRD42020194346; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=194346

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KEYWORDS

pain; postoperative; prevalence; ambulatory; postdischarge; systematic review; epidemiology

Introduction

Background

The global volume of surgery is large and growing, with approximately 312.9 million operations performed in 2012 [1]. Based mostly on in-hospital evidence, data suggest that up to 80% of patients experience pain after surgery, with over 70% of these patients describing their pain as moderate to severe [2,3]. With advances in surgical and anesthetic techniques and attempts to reduce costs and hospital-acquired morbidity, the duration of hospital stays after surgery continues to decrease [4,5]. In fact, it is estimated that ambulatory surgeries constitute over 60% of all surgeries in the United States, as well as in other countries [6-8]. Shorter hospital stays after surgery shift the onus of adequate pain management from the hospital staff to the patient and their family caregivers. However, discharge instructions provided to patients regarding pain management self-care may be inadequate, unclear, or forgotten by the patient, potentially explaining previous reports of higher pain levels (moderate to severe) following hospital discharge compared with time spent in hospital [4,9].

Adequate pain control after surgery is imperative for successful recovery, and poorly controlled pain can have devastating impacts on patients' physical functioning, mental health, relationships, and productivity [10,11]. In addition to causing unnecessary suffering, the pain-induced release of catecholamines can cause cardiac complications such as myocardial ischemia and cardiac failure [12]. Pain can also result in chest and abdominal wall splinting, resulting in hypoxemia and alveolar collapse [12]. These complications are associated with an increased economic burden resulting from increases in readmissions, emergency room visits, and the workload of community staff [7,13]. Furthermore, undertreated acute postoperative pain increases the risk of developing chronic postsurgical pain (CPSP) [14,15]. CPSP is estimated to affect 10% to 40% of surgical patients, and given the growing burden of surgical diseases and global volume of surgery, the negative impacts of CPSP are large [16,17]. CPSP is similar to other chronic pain conditions and thus is associated with a severe symptom burden and large economic impact and requires a comprehensive multidisciplinary approach to treatment [18-20].

The goal of relieving acute postoperative pain after hospital discharge must be carefully balanced with the competing goals of managing the adverse effects of analgesic treatments and minimizing other risks, such as the development of persistent opioid use [17]. In addition to acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), opioids are the mainstay of postoperative pain management [21]. As has been long recognized, adverse effects of commonly used nonopioid analgesics (eg, hepatoxicity with acetaminophen; bleeding, impaired bowel anastomosis healing, and renal toxicity with NSAIDs) necessitate careful prescribing and follow-up, and may limit their use and consequently their opioid-sparing effect [21]. With respect to postoperative opioids after hospital discharge, reports suggest that they are frequently prescribed in excess, with potentially inadequate instructions and prescriber follow-up [18,22]. This is particularly concerning given reports of high rates of persistent opioid use after surgery, even in opioid-naïve individuals [23-25]. In addition to these clinical concerns surrounding acute pain management, postsurgical patients may also experience surgical complications (eg, bleeding, and wound infection or dehiscence) and other postoperative cardiorespiratory problems. Since perioperative clinicians (eg, surgeons and anesthesiologists) are generally more focused on higher acuity in-hospital patient care and general practitioners may be uncomfortable managing complex postsurgical patients while they're recovering at home, the early postdischarge postoperative period may be a vulnerable period, leaving patients' pain inadequately managed.

Appropriate pain management for surgical patients after hospital discharge is of great importance. The majority of studies focusing on postoperative pain have been conducted on inpatients or ambulatory surgery patients before discharge, whereas the period after discharge appears to be much less investigated. Thus, we aim to perform a systematic review to investigate this period for patients in regard to postoperative pain to quantify the extent of this problem and identify future research needs.

Objectives

The objective of this review is to synthesize the available evidence on the prevalence of moderate-to-severe postoperative pain within the first 1 to 14 days after hospital discharge and compare the findings in patients who underwent ambulatory surgery (same day) with those who underwent inpatient surgery (at least 1-night hospital stay). We will also describe the adverse outcomes that participants experienced that are attributable to poor pain control after hospital discharge, including readmission to hospital, emergency room or other unplanned medical visits, and decreased quality of life.

Methods

Guidelines

This protocol was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) checklist [26] (Multimedia Appendix 1) and has been registered in the PROSPERO database (registration number CRD42020194346). The systematic review will be carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [27] and the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) checklist [28].

Sources of Evidence

We will conduct a detailed search on MEDLINE and EMBASE from their inception until the date the searches are run. The search will include terms relating to postoperative pain, the time frame following hospital discharge, and search filters for epidemiological studies. The search strategies for MEDLINE (Multimedia Appendix 2) and EMBASE (Multimedia Appendix 3) were developed in consultation with a librarian with expertise in literature searches. We will also review the bibliographies of any studies identified for relevance. We will not be contacting experts or searching the grey literature to identify additional studies.

Types of Studies

The review will include postoperative pain epidemiological observational studies with postsurgical patients that assessed postoperative pain at home (ie, after hospital discharge). Studies with fewer than 100 participants will be excluded.

Types of Participants

We will include studies with adults aged 18 years and over that underwent a surgical procedure.

Data Collection, Extraction, and Management

Two trained reviewers (RP and MM) will independently evaluate studies for eligibility. Screening will be performed on titles and abstracts using Covidence software [29]. Citations will be stored in EndNote software (Clarivate Analytics). Full-text screening will be performed on citations felt to be potentially eligible. Disagreements between reviewers will be resolved by discussion and consensus, and if necessary, a third reviewer will be consulted (IG). The screening and selection process will be presented using a PRISMA flowchart, and reasons for exclusion will be reported.

Data from included studies will be extracted using standardized extraction forms specifically designed for this review. These forms will capture information about the surgical procedure (eg, total knee arthroplasty), total number of participants before and after dropouts, patient inclusion and exclusion criteria, patient characteristics (eg, age, medical diagnoses), time points for pain intensity measurements, primary and secondary outcome measures, and other study characteristics (eg, date of publication).

Primary Outcome

Our primary outcome will be the proportion of patients reporting moderate-to-severe postoperative pain at rest or with movement, or both, within the first 1 to 14 days after hospital discharge. We chose this time frame because the first couple of weeks after surgery are most commonly associated with pain of the highest severity and most functional consequences [30,31]. We will preferentially use 4/10 (numerical rating scale), 40/100 (visual analog scale), or ≥moderate pain (category scale) as the bottom threshold for moderate pain. However, if those specific data are not available and if a study provides pain prevalence estimates using their own definition of moderate pain, we will use those data as provided.

Secondary Outcomes

Our secondary outcomes will include the following: (1) a comparison of the proportion of participants reporting moderate-to-severe postoperative pain within the first 1 to 14 days after discharge between those who underwent ambulatory surgery (same day) and those who underwent inpatient surgery (at least 1-night hospital stay); and (2) adverse outcomes experienced by participants within the first 1 to 14 days after discharge that are attributable to poor pain control, including readmission to hospital, emergency room or other unplanned medical visits, and decreased quality of life.

Analysis of Outcomes

Only similar studies (eg, similar surgical procedures, similar postoperative days, and outcomes measured) will be combined for analysis in order to avoid clinical heterogeneity. Extracted data will be compiled in Microsoft Excel for analysis. Analysis will be performed using Review Manager (RevMan) software (version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration). We plan to use a random-effects model for meta-analysis for primary and secondary outcomes if it is deemed appropriate to combine heterogenous studies.

If inappropriate to combine studies, a descriptive approach will be used to report the primary and secondary outcomes. The findings will be organized and presented by type of surgical procedure.

Assessment of Risk of Bias in Included Studies

Risk of bias for each study will be independently assessed by 2 reviewers (RP and MM). We will use the risk-of-bias tool for prevalence studies developed by Hoy et al [32], which includes 10 items plus a summary assessment (Multimedia Appendix 4). Items 1 to 4 assess the external validity of the study, and items 5 to 10 assess the internal validity. Disagreements between reviewers will be resolved with discussion and consensus. If necessary, a third reviewer (IG) will be consulted.

Assessment of Heterogeneity

Heterogeneity will be evaluated using the I^2 statistic. When the I^2 value is higher than 50%, we will consider possible explanations for it.

Sensitivity Analysis

We plan to conduct a sensitivity analysis where we combine data from all studies that focused on any degree of postoperative pain after discharge rather than only the studies that focused on moderate-to-severe pain.

Results

The protocol has been registered in PROSPERO (registration number CRD42020194346). The search strategies for MEDLINE and EMBASE have been completed. The final results are expected to be published in May 2021.

Discussion

The postoperative period after hospital discharge is a particularly vulnerable time in patients' clinical trajectory. Patients continue to experience unacceptable levels of pain after discharge [2,3]. Given the dynamic nature of postoperative pain, provision of optimal pain management requires ongoing assessments and adjustments of pain management plans [30]. However, after hospital discharge, this is difficult for surgeons, general practitioners, and other community health care workers because of time constraints. There may also be limited transitional pain services available and, as a result, patients are required to take on a large responsibility for their own pain management. Patients may also be overprescribed opioids with insufficient instructions, increasing their risk of opioid misuse, abuse, and addiction [22,33]. To complicate matters, some general

practitioners lack the comfort in weaning their patients off opioids, which may partly be due to the limited research available on safe and effective postoperative opioid weaning strategies [23,34]. On the contrary, physicians responding to the opioid crisis by minimizing opioid prescriptions or tapering their patients off opioids without other nonopioid strategies to help control their pain may put postsurgical patients at risk of pain undertreatment and the development of CPSP. Additionally, patients may not have assistance at home, where mobility obstacles are plentiful and when pain intensity may be at its greatest as hospital-administered multimodal analgesics, including regional analgesia, are wearing off [2].

Poor postoperative pain control after discharge may cause unnecessary discomfort, the development of CPSP, and various pathophysiological complications of pain. In addition to improving clinical outcomes, prevention and effective management of pain after discharge may reduce hospital readmissions, unsafe analgesic use, and the burden on community-based health care providers [35]. However, research evaluating the magnitude of this problem or the adequacy of pain assessment of postsurgical patients who are recovering at home is limited. This is especially true when compared with the evidence of inpatient postoperative pain. Various and diverse sources of evidence about this topic are accumulating and vigilant evaluation and synthesis are needed. Thus, this review aims to summarize the prevalence of moderate-to-severe postsurgical pain after hospital discharge. The findings of this review may guide further research evaluating this large gap in patient care after hospital discharge, highlight services in need of more resources and consideration, and improve patient outcomes at home.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) checklist.
[DOC File , 84 KB - resprot_v9i12e22437_app1.doc]

Multimedia Appendix 2
Search strategy developed for MEDLINE.
[DOC File , 25 KB - resprot_v9i12e22437_app2.doc]

Multimedia Appendix 3
Search strategy developed for EMBASE.
[DOCX File , 14 KB - resprot_v9i12e22437_app3.docx]

Multimedia Appendix 4
Risk-of-bias tool for prevalence studies.
[PDF File (Adobe PDF File), 222 KB - resprot_v9i12e22437_app4.pdf]

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Abbreviations

CPSP: chronic postsurgical pain
MOOSE: Meta-analyses Of Observational Studies in Epidemiology
NSAIDs: nonsteroidal anti-inflammatory drugs
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols

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Protocol

Digital Interventions for Depression and Anxiety in Older Adults: Protocol for a Systematic Review

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Abstract

Background: There is a high prevalence of older adults experiencing depression and anxiety. In response to heightened demands for mental health interventions that are accessible and affordable, there has been a recent rise in the number of digital mental health interventions (DMHIs) that have been developed and incorporated into mental health treatments. Digital interventions are promising in their ability to provide researchers, medical practitioners, and patients with personalized tools for assessing behavior, consultation, treatment, and care that can be used remotely. Reviews and meta-analyses have shown the benefits of DMHIs for the treatment and prevention of depression, anxiety, and other mental illnesses, but there is still a lack of studies that focus on the benefits and use of DMHIs in the older population.

Objective: The aim of this systematic review is to investigate the current evidence for the effect of technology-delivered interventions, such as smartphone/tablet applications, remote monitoring and tracking devices, and wearable technology, for the treatment and prevention of depression and anxiety in adults older than 50 years.

Methods: The academic databases SCOPUS, PsycINFO, AgeLine (EBSCO), and Medline (PubMed) will be searched from January 1, 2010, to the date of search commencement to provide a review of existing randomized controlled trial studies. The search will include 3 key concepts: “older adults,” “digital intervention,” and “depression/anxiety.” A set of inclusion criteria will be followed during screening by two reviewers. Data will be extracted to address aims and objectives of the review. The risk of bias for each study will be determined using appropriate tools. If possible, a random-effects meta-analysis will be performed, and the heterogeneity of effect sizes will be calculated.

Results: Preliminary searches were conducted in September 2020. The review is anticipated to be completed by April 2021.

Conclusions: The data accumulated in this systematic review will demonstrate the potential benefits of technology-delivered interventions for the treatment of depression and anxiety disorders in older adults. This review will also identify any gaps in current studies of aging and mental health interventions, thereby navigating a way to move forward and paving the path to more accessible and user-friendly digital health interventions for the diverse population of older adults.

Trial Registration: PROSPERO International Prospective Register of Systematic Reviews CRD42020192532; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020192532

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KEYWORDS

systematic review; digital intervention; mental health; depression; anxiety; older adults

Introduction

Among older adults, 1 in 5 suffer from one or more mental disorders, with the numbers climbing as the world's population gets older [1]. Recent literature has shown that older adults are highly vulnerable to mental disorders such as depression and anxiety [2,3]. The scarcity of access to mental health treatments and care for older adults in North America further diminishes help-seeking behaviors and increases the mental health stigma of the population [4], thereby deteriorating the already-low mental health literacy of many individuals [5]. Many seniors do not recognize a need for treatment but rather believe that these depressive and anxious feelings are normal, a side effect of growing old [6]. Additionally, older adults who do recognize a need for mental health services often face multiple barriers to accessing care, such as having limited knowledge regarding available services, few monetary resources, lack of access to transportation, and an overall negative view of mental illness [7,8].

Over the last several years, there has been an increase in popularity and availability of mobile digital technologies, which has triggered and pushed the development of mobile digital mental health interventions (DMHIs) including smartphone applications, remote monitoring and tracking devices, and wearable computers such as smartwatches and virtual/augmented reality headsets [9]. The World Health Organization, the United Kingdom's National Health Service, and the US National Institute of Mental Health have recently identified smartphone, desktop, and tablet apps as efficient, cost-effective, and valuable methods to provide accessible treatments for mental disorders such as depression and anxiety [10].

Emerging research has found that DMHIs can be utilized for early identification, diagnosis, management, and analysis of adult mental health patients [11,12]. However, there are significantly fewer studies that focus on older adults, who have unique needs and preferences when it comes to technology-based health interventions [13]. The management of daily activities within the lives of older adults are extremely complex, as the majority of the older population must also deal with a multitude of late-onset chronic diseases [14]. Moreover, vulnerable older adult populations, such as those who live in rural areas, are suffering from a shortage of mental health care delivery due to the lack of care facilities, mental health professionals, and services in nonurban areas [15]. It is therefore important to acknowledge that the use of DMHIs is not confined within primary mental health care and facilities, but may also be used by individuals, in communities, and in senior centers. For example, technology can provide seniors, individually or in a group, access to participate in physical activities using motion sensors or other exergaming technologies, which can alleviate symptoms of depression and anxiety [16] and improve their general perceived wellness and quality of life [17]. Furthermore, improvement of mental health and quality of life can be a secondary outcome of using tech-based services that are based on individual needs, including various service deliveries [18], access to transportation [19], and the ability to participate in teleconferencing, distance education, and socialization [20].

DMHI research has the potential to spearhead a breakthrough in disease/illness intervention research as it has the ability to reach populations who otherwise might not engage in standard mental health interventions, expand the boundaries of the types of services available, and overcome geographic barriers through delivery of services to remote areas [21]. Despite the promises that DMHIs offer, there is the danger that comes from the digital divide. Older adults may feel unfamiliar with and excluded by new technologies, which may in turn exacerbate their feelings of inequitable healthcare, aggravate help avoidance behaviors, or even trigger self-deprecating feelings [22,23].

This systematic review aims to investigate the evidence for the effect of DMHI for the treatment and prevention of depression and anxiety in adults older than 50 years. We hope to not only understand the effectiveness of the most current DMHIs on older adults, but also gain insight into the various designs of interventions to understand what digital methods are accessible and more accepted by the older population.

Methods

Study Design

This systematic review protocol has been prepared following the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols) 2015 checklist [24] (Multimedia Appendix 1). This review will gather recent studies to explore the effect of DMHIs in the prevention and treatment of depression and anxiety in adults older than 50 years.

Search Methods

The academic databases SCOPUS, PsycINFO, AgeLine (EBSCO), and Medline (PubMed) will be searched for publications between January 2010 and the date of commencement. DMHIs for the treatment of depression and anxiety in older adults do exist prior to 2010 [25]. The reason behind this cutoff is that this review is focused on a modern and fast-paced topic. With the current production rate of new technologies, older studies using decade-old technologies are unlikely to still be relevant. A systematic search of each database will be conducted using a combination of search terms relating to the mental health problems targeted (depression and anxiety disorders), the means of intervention delivery (via the internet, using smartphones, using tablets, etc), population age (older adults), and the study design (RCT). Table 1 contains the full list of search strings to be input into each database search. Reference lists of included articles will also be screened for potentially relevant studies.

Table 1. Complete list of terms to be input into each database, separated into clusters of main key terms.

Cluster	Search items
A (older adults)	"older adult$" OR "senior$" OR "elderly" OR "elder$" OR "aged 50" OR "50+"
B (intervention)	"intervention$" OR "treatment$" OR "therapy"
C (mental health)	"mental health" OR "mental illness" OR "mental disorder$" OR "psychiatric illness*" OR "depress*" OR "anxiety"
D (technology)	"technol*" OR "digital" OR "online" OR "internet" OR "mobile" OR "electronic*" OR "social media" OR "smartphone$" OR "web*" OR "mobile app*" OR "smartphone app*" OR "VR" OR "AR" OR "virtual reality" OR "augmented reality" OR "wearable tech*" OR "wearable$" OR "computer*" OR "personal digital assistant$" OR "PDA$" OR "laptop$" OR "e-reader$" OR "Enterprise digital assistant$" OR "EDA$"

Screening and Selection Process

All search results from the aforementioned databases will be downloaded into a reference management software in order to identify duplicates and allow for an easier screening procedure. First, all article titles and abstracts will be screened by two reviewers independently based on the inclusion and exclusion criteria. The results will then be discussed, and any disagreement will be resolved through consensus-based discussion or by a third reviewer. Next, full texts will be examined. Any disagreement between two reviewers will be resolved by discussion with a third reviewer.

Eligibility Criteria

This review will include RCTs of digitally delivered mental health interventions for use by adults older than 50 years for their depressive or anxiety disorders. We will also include DMHIs that were used by caregivers, family members, and close relationships to aid or provide support for older adults with depressive or anxiety disorders. For the purposes of this review, DMHIs will be defined as interventions that are delivered using devices that have wireless cellular communication capability or are able to run software applications. We will therefore include interventions using smartphones, enterprise digital assistants, personal digital assistants, portable media players, video game consoles (including virtual/augmented reality headsets), desktop computers, laptops, tablets, and e-readers. Studies will be included if the sample population was assessed pre-intervention and post-intervention for anxiety or depressive symptoms by a clinician or assessed by the research team through the use of an anxiety or depression questionnaire. Studies that used self-administered depression/anxiety questionnaires that were completed online or by paper without the presence of a physician, psychologist, or a member of the research team will also be included. Only RCT studies will be included. There will be no restrictions placed on the theoretical basis of the interventions. We will include peer-reviewed papers in all languages and from all countries. Non–peer-reviewed articles, conference proceedings, case reports, editorials, opinion papers, and letters, as well as studies that focus on children or young adults, will be excluded.

Data Extraction Process

We will extract the following data from each eligible study, prior to full-text extraction, into a bespoke Microsoft Excel (Microsoft Corporation) template: author or authors, aims, study design, participant information, sampling/recruitment methods, number of participants, the intervention (including the length of the interventions; the number of interventions, if multiple interventions were used; and the form or forms of delivery), and the author's results or conclusion for the interventions. Participant information will include sample age and mental health status prior to the intervention (assessed using a depression/anxiety questionnaire).

Risk of Bias Assessment

The risk of bias (ROB) will be assessed using the revised Cochrane risk-of-bias tool for randomized trials, version 2 (RoB 2) [26]. ROB will be evaluated for each bias domain listed in the RoB 2 assessment tool, which covers (1) bias arising from the randomization process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in measurement of the outcome, and (5) bias in selection of the reported result. The ROB will be conducted by the primary author and then checked by two reviewers independently. Disagreements will be discussed and resolved by a third reviewer. Studies will be assigned either "low risk," "unclear risk," or "high risk" status for each of the aforementioned 5 domains of bias.

Data Analysis

A narrative synthesis of the findings from the included studies will be provided. This will describe the studies according to the following characteristics: (1) the components and method of delivery of interventions (eg, what type of device was used, was it delivered remotely or in person, what was the length of the study); (2) the characteristics of the sample population (mean age, gender, ethnicity, and socioeconomic status) and, if available, their views on mental health and mental health interventions; (3) the aim of the intervention (prevention or treatment of depression/anxiety, or both); (4) the types of outcome (eg, change in overall quality of life, change in depression/anxiety questionnaire answers, or structural changes in the brain observed using neuroimaging techniques); and (5) the longevity of outcome or the outcome of a follow-up study (were the subjects able to use these interventions beyond the observation period?).

If sufficient data is available, a random-effects meta-analysis will be conducted using the standardized mean differences to calculate effect size (Hedges *g*). Heterogeneity of effect sizes will then be calculated using the Q statistic and I^2 statistic. Significant heterogeneity can be deciphered from a significant Q statistic, indicating more variation in effect sizes (which can solely be attributed to chance). I^2 statistics will show

heterogeneity as a percentage, with values of 25%, 50%, and 75%, which are associated with low, moderate, and high heterogeneity, respectively [27,28]. If possible, subgroup analyses will be conducted to examine the influence of the control conditions and the severity of mental health problems. We will assess for the presence of publication bias by displaying and examining the symmetry/asymmetry of a funnel plot of all studies included [29]. Furthermore, we will be using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework to evaluate the quality of evidence for individual outcomes [30]. Sensitivity analysis will be performed following the Cochrane handbook recommendation by taking the poorest-quality evidence to determine its effects on the meta-analysis.

Results

As of October 21, 2020, we have conducted preliminary searches on the aforementioned academic databases. Title and abstract screening will commence in December 2020, and full text screening will follow shortly after. We expect to begin data analysis in February 2021. The review is anticipated to be completed by April 2021.

Discussion

DMHIs have the potential to offer unique and innovative opportunities for the treatment of mental health in older adults. Developers and medical practitioners in the mental health field can use the advantages of digital innovations to provide older adults with helpful instruments that are not limited by the patient/user's geographical location. This systematic review will offer insight into the potential benefit of technology-delivered programs and provide up-to-date information on existing DMHIs for older adults through the exploration of current digital interventions for the treatment of depression and anxiety. This systematic review also hopes to identify any gaps in current studies of mental health interventions and the aging population, thereby navigating a path for DMHI research to move forward.

The fundamental advantage of DMHI is the opportunity it brings to blur the lines of inequality when it comes to the accessibility of mental health resources. However, currently, there are very few studies looking at the effects of DMHIs in populations that specifically face significant social and physical challenges. Within the (already vulnerable) older adult population, there exists a subpopulation of more vulnerable older adults such as, but not limited to, those living in abusive families, the homeless, the poor, racial minorities, refugees, gender/sexual minorities, and people with physical disabilities and chronic diseases. Schueller et al [31] have written extensively about how digital interventions can provide opportunities to alleviate mental health disparities among marginalized populations, stating that technology can be tailored to be culturally sensitive and low cost, and can also overcome barriers of time, place, and language. Despite this progress, it has been understood that each subpopulation of marginalized older adults has differing strengths and needs when it comes to using DMHIs. Extensive work still needs to be done in order to translate the potential of technology to address mental health needs among diverse, marginalized older populations into reality.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P Checklist.
[PDF File (Adobe PDF File), 159 KB - resprot_v9i12e22738_app1.pdf]

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Abbreviations

DMHI: digital mental health intervention
GRADE: Grading of Recommendations Assessment, Development and Evaluation
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols
RCT: randomized controlled trial
ROB: risk of bias
RoB 2: risk-of-bias tool for randomized trials, version 2

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Protocol

Perspectives and Experiences of Policy Makers, Researchers, Health Information Technology Professionals, and the Public on Evidence-Based Health Policies: Protocol for a Qualitative Study

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Abstract

Background: Evidence-based health policy (EBHP) development is critical to the judicious use of public funds. EBHPs increase transparency, accountability, effectiveness, and efficiency of policies. Encouraging collaboration between researchers or knowledge producers and policy makers is important because both communities have distinct professional cultures, resulting in them working separately without understanding each other. Knowledge sharing is a complex process that requires understanding of cultural aspects that may reduce cultural differences and increase the use of common language. Health information technology (HIT) is a useful tool to increase knowledge translation, which may result in the transparent use of evidence and networking in developing EBHPs. Our vision is to leverage HIT tools for a better health system that includes digitalized, open source, evidence-based, and transparent ways for collaboration and development of robust mechanisms and for sharing of synthesized evidence with knowledge user–friendly forms.

Objective: The aim of this study is to develop a conceptual framework on Knowledge translation and health Information Technology for Transparency (KhITT) in policy making and EBHPs (ie, the KhITT framework). The framework will be informed by the views of four key stakeholder groups (ie, policy makers, knowledge producers, HIT professionals, and the public) toward EBHP. The informants may also describe practices that demonstrate the EBHP development process and suggest technology platforms to enable this process.

Methods: We propose an exploratory, descriptive qualitative study to take place in British Columbia, Canada, using in-depth semistructured interviews. To ensure data saturation and trustworthiness, we will use a nonprobability, purposive snowball sample of up to 15 eligible participants in each of the four stakeholder groups. We will analyze the data using content analysis.

Results: The KhITT framework focuses on various stakeholders' perspectives to better understand their perceived needs and priorities in identifying issues with EBHP, in order to make informed recommendations. Ethics approval has been obtained by the harmonized Behavioural Research Ethics Board at the University of British Columbia. We anticipate that we will complete data collection and analysis by December 2020. Preliminary results will be published in summer 2021.

Conclusions: Our ultimate goal of this study is to develop a conceptual framework and describe the technology platforms that would enable the EBHP process. We anticipate that our rigorous content analysis will be able to produce insights and themes

that are able to address our objectives, contribute to an in-depth understanding of the EBHP process within British Columbia, highlight all influential factors, explicitly disseminate and communicate the study results, identify issues with EBHP and provide informed recommendations to address them, and enhance efforts toward transparent EBHPs.

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KEYWORDS

evidence-based health policy; knowledge translation; transparency; policy makers; researchers; knowledge producers; health information technology

Introduction

Background

The movement for evidence-based health policy (EBHP) has made progress at all levels of government: local, provincial or state, and federal. Developing EBHPs is a critical way to ensure effective and efficient use of public funds and other scarce resources. In addition, using evidence-based methods in health policy development can increase transparency and accountability of these policies. Focus and efforts must align with innovative and effective products and services that will lead to stronger collaborations. Encouraging collaboration and innovative ways of policy making is important, especially when evidence is thin, research is limited, or when some public agencies lack the capacity, skills, knowledge, funding, commitment, and/or support of political leaders to integrate evidence into policy. A movement toward policy-based evidence, noted as found in Young [1], was depicted in *The New Yorker* magazine as a cartoon: a policy maker handed a paper to an advisor saying, "Here is my policy; go find some evidence based on it." Health policy makers have their own priorities and processes that influence and have implications on health outcomes.

Culture of Collaboration

In the literature, there is an ongoing debate between researchers and policy makers about EBHP, mainly because of a misunderstanding or a lack of a common definition of *evidence* [2,3] as well as a lack of agreement on what constitutes evidence across disciplines [4]. The communities of researchers have perspectives in the development of health policies that are distinct from those of policy makers, which result in these professional cultures working in separate "silos." For example, Glazer and Karpati [5] described several cross-cultural differences in decision-making styles; however, it is unclear whether those different decision-making approaches are focused on scientific evidence. Evidence matters to policy making, which is political due to the trade-offs involved between multiple competing interests [6], but choosing the right evidence may politicize science (eg, misuse and cherry picking). On the other hand, knowledge producers suggest that synthesized scientific knowledge is the foundation of health policy. Other cultural differences and discrepancies between knowledge producers and policy makers include the definition of, and perceptions about, evidence and its validity and reliability, adequacy and interpretation of research findings, and the understanding of using evidence as part of the decision process. While discussions about these topics are frequent and inherent to policy debates that develop distrust and conflict between knowledge producers and policy makers [7], "collaboration between these groups, regardless of its complex and time-intensive process, requires trust and partnership" [8]. Both knowledge producers and policy makers need to resolve these differences, connect, communicate, understand each other, and collaborate in order to improve the process of policy making and to develop robust policy, since study designs, assessments of quality, and the ability of research to inform policy making varies by discipline. There is also a need to develop technology platforms that allow for the exchange of knowledge and information. Communication among knowledge producers and policy makers could promote shared and mutual understanding of evidence in each discipline and ways that evidence can be applied to other disciplines (eg, application of health informatics research findings to evidence-based policy-making activities) [4,9]. For example, more effective, efficient, and humane responses to disasters can be provided when key stakeholders' perspectives are taken into account, community is engaged in the required discussions and collaborations, and strong evidence is available [10].

In Australia, evidence-generation partnerships and levels of collaboration between researchers and policy makers vary widely from minimal to coproduction, which all partners considered as a worthy goal with many benefits [11]. Furthermore, the main themes underpinning the challenges faced in health communication and participation among researchers and other stakeholders were culture and organizational structures, health professional attitudes and assumptions, lack of shared or overlapping knowledge of a domain area, and lack of shared understanding in the health sector. Therefore, setting priorities for knowledge-synthesis research, including evidence-based policy making, embraces interventions to enhance health professional education, to change health service and health professional cultures and attitudes, and to improve health service policies and standards [12].

Data Visualization

Researchers also need to make their studies transparent and available to the public, including to policy makers; help people make sense of the data; and develop and share their study results using visual means (eg, data visualizations) for better understanding and uptake of key messages [13]. Data visualization, when aligned with the principles of trustworthiness and accessibility, supports decision making and *facilitates understanding* through three main ways. First, it effectively communicates data. Second, it provides people with the opportunity to explore, examine, analyze, and identify patterns within the data and to better understand large data sets. Finally,

it encourages and affects user engagement via "consumption and production processes" [13] of visual data. Production of data visualization and its consumption have the power to change people's minds and maybe change the world. Understanding data production, visualization, and consumption processes within certain contexts may unveil the entanglement of, and the power within, the data and may contribute to the political impact for doing good, guidelines for good practice, and the limits of data visualization within complex situations [14].

Evidence-Based Health Policy

Despite important advances, rigorous evaluation requirements, and other evidence-based approaches in policy making, the majority of policies are rarely based on rigorous evidence [15]. Evidence-based policy frameworks are usually not intended to be prescriptive but are intended to emphasize the multidimensionality of the policy-making process, the causal relationships between the different dimensions, the indicators to measure selected dimensions, the determinants of poor outcomes, the assessment of the policy environment, the interplay among policies and social norms, the evaluation of the impact and cost-effectiveness of interventions and programs, the approaches to support people's voices, and the inclusion of relevant evidence in policy-making processes [16]. The political and institutional context is one of the most important issues around evidence-based policy [17,18]. Within this context, the process of policy making and the nature of information and evidence used varies according to key personnel approaches, since individuals negotiate the concept of socially constructed evidence (eg, common sense, expert opinion, and filters to transferred evidence) [18]. Therefore, study and interpretation of locally tailoring contextual complexities of policy-making practices and processes may be more useful than a one-size-fits-all evidence-based policy framework. These frameworks may provide a better understanding of processes to influence and develop meaningful collaborations between knowledge producers and policy makers [19]. In addition, capacity building, one of the identified barriers for collaboration between knowledge producers and policy makers, may be overcome by involving policy makers in conducting research and by involving knowledge producers in developing policies within a certain context [18].

The Preliminary Conceptual Framework

In this environment, we developed a vision for an ideal health system where everything will be digitalized, open source, evidence based, and transparent. That health system may lead to fewer adverse events; better patient, provider, and system outcomes; greater innovation; and less ineffective use of resources (eg, monetary and human). To achieve this ideal health system, we need to focus on three main principles:

1. Collaboration between knowledge producers and policy makers for sharing the understanding of an issue and accepting each other's knowledge, evidence base, and cultural manifestations.
2. Development of robust mechanisms at an organizational level for synthesizing existing knowledge on a policy maker's interesting topic.
3. Communication and sharing of synthesized evidence in forms that are friendly to policy makers [20].

To actualize this vision, we propose a conceptual framework called the Knowledge translation and health Information Technology for Transparency (KhITT) in policy making and EBHPs (ie, the KhITT framework). A preliminary conceptual framework was recently developed and published [21]. Our idea for a conceptual framework to connect researchers and policy makers originated during the development of a course for graduate students at the University of Victoria School of Nursing: *Evidence-Based Health Policy*. We argue that health care professionals need to be aware and contribute to the health policy–making process. We anticipate further development of the KhITT conceptual framework to provide insights and ways for improving collaboration between researchers and policy makers for the development of health policies that are transparent and evidence based. The KhITT framework builds upon the strong commitment of knowledge producers and policy makers to finding effective solutions and encourages the use of technology that supports the development of innovative health policies. For example, Tran and colleagues' [22,23] work is an example of the successful use of technology to predict consequences of future scenarios and to inform policy making that has resulted in the development of innovative health policies to bring computerized order entry and electronic medical records into health settings. This area of research on the impact of information technology interventions in health and the decision-making process is underexplored, especially for outcomes commonly required by policy makers and government [24]. Collaboration between policy makers and knowledge producers would enhance efforts to set and realize high-reaching goals.

The KhITT framework aims to *support* strong relationships between knowledge producers and policy makers and to *inspire* individuals and the public to commit to excellence in engaging communities and stakeholders toward transparent, system-based knowledge dissemination and EBHPs. The KhITT framework is comprised of recommendations that are organized within three domains: structure, reference and guide, and capacity building. Specifically, the goals of these domains are as follows:

1. To provide a structure for understanding each other's perspective, improving communication, and strengthening coordination efforts for effective solutions.
2. To serve as a reference and guide for strategic choices and for setting priorities and strategies in incorporating evidence into health policy innovation.
3. To nurture existing and emerging knowledge producers and policy makers who are interested in promoting EBHPs by exploring ways to use health information technology (HIT) (ie, capacity building).

This framework emphasizes the important contribution of HIT as a useful tool to increase knowledge translation and transfer via communication among knowledge producers and policy makers that may result in the transparent use of evidence and networks in developing EBHPs [25]. Sharing knowledge is a complex process that also incorporates sharing of cultural aspects, which in turn may reduce the cultural differences

between knowledge producers and policy makers and may increase the use of common language [25]. The development of information and communications technologies has dramatically changed the context and the way we accumulate evidence and make policies. Access to evidence, including academic and grey literature, used to depend on consultants or other persons who had access to libraries and who knew how to navigate scholarly journals. The development of searchable online databases changed the way policy makers access evidence. However, we need more efforts to enhance collaboration between researchers; knowledge users, including policy makers; and HIT professionals and researchers to develop EBHPs. There is a need to develop technology platforms that allow for the exchange of knowledge and the development of shared and mutual understanding across disciplines regarding what is good-quality evidence and how that evidence could be interpreted and effectively applied to policy-making tasks and activities in another discipline [26,27]. HIT is most commonly used in hospitals and nonhospital-based clinics to support clinical decision making [24]. We need to evaluate the impact of HIT interventions in the health sector beyond this area.

Purpose

The purpose of this study is to develop a conceptual framework on KhITT in policy making and EBHPs (ie, the KhITT framework). The specific objectives to achieve this aim are as follows:

1. Explore and better understand key stakeholders' (ie, policy makers, knowledge producers, HIT professionals, and the public) different approaches on EBHPs.
2. Capture those different approaches within three main categories—perceptions, perspectives, and experiences—to better understand participant expectations and insights from each stakeholder group and to incorporate them into the KhITT conceptual framework.
3. Describe practices used for demonstrating the EBHP development.
4. Describe the technology platforms that would enable the EBHP development process.

Definitions

For the purposes of this study, we define the relevant specific terms as follows:

1. Knowledge translation, as defined by the Canadian Institutes of Health Research, is "a dynamic and iterative process that includes synthesis, dissemination, exchange and ethically sound application of knowledge to improve the health of Canadians, provide effective health services and products and strengthen the health care system" [28]. This process takes place within a complex system of interactions between knowledge producers and knowledge users, including policy makers, which may vary in intensity, complexity, and level of engagement depending on the nature of knowledge [29].
2. HIT is defined as the technology applied to the health sector that supports information management across computerized systems and improves all aspects of health care (eg, safety, effectiveness, timeliness, equity, and efficiency). Open access sources of information embody radical change, make HIT broadly available, and provide a forum for sharing information and knowledge toward software development and democratic action. This open communication model could start political discourse among knowledge producers and policy makers.
3. Transparency is defined as openness, accountability, obligation, and honesty to share information and knowledge with the public.
4. Policy making is defined as a messy iterative process with various opportunities to incorporate evidence and strengthen decisions [30].
5. EBHP is defined as the integration of individual (ie, policy makers) professional expertise, experience, and practice with the best available research findings in the context of specific preferences and values. We adopted this description of EBHP by paraphrasing Sackett and associates' [31] definition of evidence-based practice, including policy making.
6. Perception is defined as a way of understanding, interpreting, or thinking about something through the fundamental senses. Perception depends on complex effortless functions of the nervous system and is influenced by experiences, feelings, and thoughts [32,33].
7. Perspective is defined as a point of view, a particular way of viewing things that depends on one's attitude, experience, and personality.

Methods

Design, Settings, and Sample

To achieve the aim and objectives of this study, we propose an exploratory, descriptive, qualitative study design to take place in British Columbia, Canada. We will collect data from policy-making centers (eg, the Ministry of Health), universities (eg, the University of Victoria and University of British Columbia), public areas (eg, malls, cafeterias, and personal contacts), and HIT workplaces (eg, health authorities and the Ministry of Health) using a nonprobability, purposive snowball sample of four stakeholder groups: knowledge producers, policy makers, HIT professionals, and the public. Specifically, in Victoria and Vancouver, we will carefully target, invite for participation, recruit, and interview up to 15 participants from each of the following stakeholder groups:

1. Researchers in academic institutions, whose work is relevant to health policies, including HIT researchers, to ensure that evidence from HIT research is introduced, due to the differences in how evidence is generated through research and how it is used in practice.
2. Policy makers at all levels of governance (ie, local, provincial, and federal) whose work focuses on health policies.
3. HIT professionals, such as electronic health record managers, developers, or analysts. We hypothesize that there will be a disconnection between HIT researchers and HIT practitioners in terms of perspectives and the definition and use of evidence to drive policy and decision making.
4. Citizens (ie, the public), regardless of gender, age, ethnicity, class, education, socioeconomic status, position, or other

demographic characteristics. We will invite individuals older than 18 years of age who are interested in EBHP to participate in the research project.

We will start recruiting study participants at the University of Victoria (ie, researchers), the Vancouver Island Health Authority (ie, HIT professionals), and the provincial government located in Victoria (ie, policy makers and the public). We are focusing on those stakeholder groups because we expect each group of participants to provide different perceptions, perspectives, and experiences relevant to EBHP and the EBHP development process, which we want to capture and incorporate into the KhITT conceptual framework for a better understanding of their expectations and insights.

We estimate that the number of participants we plan to recruit will provide the needed data saturation [34,35]. Data saturation is reached when (1) there is adequate information to replicate the study [36,37], (2) the ability to obtain additional new information or new themes has been attained [38], and (3) further coding is no longer feasible [38].

To ensure that data saturation has been reached in our study (ie, no new themes), we will construct a saturation grid, where major topics will be listed on the vertical axis and conducted interviews on the horizontal axis; at least two research team members will conduct coding of transcripts independently [39]. In addition, we may apply the mathematical model developed by Tran and colleagues [40] to compute the theme accumulation curve and the local slope of the curve at the point of data analysis and our chosen stopping criterion.

Instrument

We will collect the data using in-depth face-to-face or telephone-based semistructured interviews [41]; the interview format will depend on participant availability and preference, and interviews will last about 60 minutes for each participant. All interviews will be recorded on a digital tape (ie, face-to-face interviews) or electronically (ie, interviews via telephone) with participants' informed consent.

For the interviews, we will develop and use our own semistructured instrument and guide (see example questions in Multimedia Appendix 1). The interview guide will cover the general and main study topics, provide the setting to encourage participants to share their perceptions and experiences, and focus on the following key areas:

1. Participant background information.
2. Definitions (eg, policy process and EBHPs).
3. Main themes that explore participants' knowledge, perceptions, perspectives, and experiences on methods and/or practices used to identify EBHPs.
4. Follow-up questions, including prompts and stimuli aimed at following respondents' answers and in-depth investigation of any issues raised.

Prior to data collection, we will test and pilot the interview instrument and guide with several eligible participants, and we will revise and adapt it accordingly to ensure that the interview questions are meaningful to the respondents' backgrounds [42]. In addition, we will adjust the instrument based on formative or ongoing data analysis [43].

Data Collection Process

We will recruit study participants through professional lists, email address listservs, personal contacts, and advertisements in social media accounts (ie, study Twitter and Facebook accounts), local newspapers (eg, the *Times Colonist*), and public places (eg, restaurants and malls). Upon ethics approval, a recruitment posting will be sent to the social media accounts of all known British Columbia policy makers, knowledge producers, and HIT professionals, including links to the study materials. We will ask eligible participants (ie, policy makers, knowledge producers, HIT professionals, and the public) to pass our study information (ie, invitation to participate and information letter) to any other interested participants. Research assistants will approach potential eligible participants in all stakeholder groups, inform them about the study, and answer questions for clarification in person, via email, or via phone. Research assistants will also provide hard copies of the study materials to interested individuals and request their signed informed consent to participate in the study. Then, research assistants will arrange a face-to-face or telephone-based interview at a time and place that is convenient to each participant. At the beginning of the interview, research assistants will again request verbal consent and explain the interview process. During the audio-recorded interviews, pseudonyms or numerical identifiers will be used to protect the anonymity and confidentiality of the participants. In addition, research assistants will make *field notes* during and immediately after each interview about observations, thoughts, and ideas about the interview to help the data analysis process.

Data Analysis

We will analyze the collected data following the steps of a content analysis and describe the emerged themes and patterns about the EBHP process. First, we will deidentify (ie, anonymize) the data for study participant anonymity and confidentiality. Then, we will transcribe verbatim the collected data (ie, recorded interviews). The lead researcher will transcribe two to three interviews to inform the analytic process; a professional transcription agency, or the research assistants themselves, will transcribe the remaining audio files. Finally, we will manage, process, and store the deidentified data files in a secure, digital, password-protected form in the principal investigator's locked office using the University of Victoria's technology and servers (eg, lockable computer systems with encryption protection).

According to Braun and Clarke's [41] approach, to generate a good thematic analysis we will include the following steps:

1. Transcription and review of transcripts for accuracy.
2. Open coding by at least two researchers independently; themes to be checked against each other and against the original data for internal coherence, consistency, and distinctiveness.
3. Development of an initial codebook in agreement with the research team.

4. Analysis of the remaining interviews based on the initial codebook may follow, such as creating new codes or refining of existing ones, developing themes and subthemes to identify similarities and differences in the interviews, developing categories of meanings in order to group themes into broader (ie, more abstract) concepts, and establishing a good balance between analytic narrative and illustrative extracts.
5. Thematic map to be developed based on the identified themes, subthemes, and categories as well as their relationships.

During our thematic data analysis, which is guided by Lincoln and Guba [44], we will ensure trustworthiness of our study by addressing the following tenets:

1. Credibility, which refers to the establishment of "confidence in the truth of the findings."
2. Transferability, which refers to the extent to which the study findings are applicable in other contexts (ie, generalizability).
3. Dependability, which refers to whether the research question is clear and logically associated with the study purpose and design, as well as to the consistency of findings in a replicated study.
4. Confirmability, which refers to objectivity or neutrality; that is, the degree to which the study findings are determined by the participants and clearly derived from the data and not by the researcher's "biases, motivations, interests, or perspectives."
5. Reflexivity, which refers to the researcher's own conceptual lens, explicit and implicit assumptions, preconceptions, and values that may affect research decisions during all phases of a study [45].

Throughout data collection and analysis, we will ensure traceability and verification as part of the study quality using the following strategies to establish trustworthiness [46-48]:

1. Researcher triangulation, for credibility, transferability, and dependability. That is, engagement of multiple researchers, as well as graduate and undergraduate students, to incorporate their unique insights into the interpretation of findings; planned debriefing sessions among the research team members to provide a sound space on elaborating different study ideas and interpretations; and reporting the background and context descriptions of our study findings from the study participants.
2. Participant validation, for credibility and confirmability, by seeking respondents' reflections on the transcripts and interpretation of results.
3. Reflexive journal to document researchers' thoughts and reflections throughout the research process and for discussing any emerging issues.
4. Other general strategies, such as storing raw data systematically, recording the rationale and justification of methodological and analytical choices, transparently describing all the study steps, documenting detailed notes about the development and hierarchies of themes, and establishing consensus on themes.

Additionally, we may provide the opportunity to all interested stakeholders to have free access to the research process by developing the KhITT study website and data visualizations to better understand, and make better use of, our study findings.

Patient and Public Involvement

Our research team includes policy makers, researchers, HIT experts, and members of the public as key informants for better understanding their perceived needs and priorities in identifying issues with EBHP, in order to make informed recommendations. Together, we designed the proposed study and we will collaborate closely in the data collection and in the interpretation, dissemination, and diffusion of study findings. In addition, we will establish an advisory group of policy makers, HIT professionals and researchers, and citizens, who will support the research process, provide input and insights into the data analysis and interpretation of the findings, and contribute to the dissemination plan. The advisory group will meet on a regular basis during the study.

Ethics

We have already obtained ethics approval by the harmonized Behavioural Research Ethics Board at the University of British Columbia using their online research administration tool. For the duration of the study, we incorporated procedures that intended to protect participant anonymity and confidentiality.

Data Sharing Statement

Supplementary and raw data will be placed online, made publicly available, and linked to the University of Victoria repository.

Dissemination Plan

At the completion of the study, we will present the findings at local, national, and international scientific conferences; professional events for stakeholder groups, including interviewees if they are interested in and willing to share their contact information, for better stakeholder engagement; and our professional websites, where we will provide data visualizations. Findings will be presented in a summarized form with no identifying information. We will also publish the results in peer-reviewed journals, professional and lay magazines, and the study website.

Results

The KhITT framework focuses on various stakeholders' perspectives to better understand their perceived needs and priorities in identifying issues with EBHP, in order to make informed recommendations. Ethics approval has been obtained by the harmonized Behavioural Research Ethics Board at the University of British Columbia. Currently, we are recruiting study participants and collecting their consent forms. We anticipate that we will complete data collection and analysis by December 2020. Preliminary results will be published in summer 2021.

Discussion

Principal Findings

The KhITT conceptual framework focuses on the routine enhancement of engagement, flexible accessibility, and strong relationships among knowledge producers and policy makers as key factors influencing transparent policy making [49]; the framework also focuses on addressing and teasing out disciplinary differences and their impact on policy makers' decisions due to lack of experience in a particular domain area. We are also interested in determining research quality between clinical research, policy research, health services research, and health informatics research. For example, health informatics researchers value mixed methods studies more than randomized clinical controlled trials. Evidence from mixed methods studies better informs the practice of health informatics than evidence from clinical controlled trials. We believe that health services research and policy research suffer from the same issue: study quality varies based on prior disciplinary work. What works for one discipline is not necessarily transferable to another, in terms of research quality. This phenomenon may influence cross-disciplinary education. In addition, we will examine and take into consideration context as a factor that might influence evidence use in policy making [50], and we will illuminate barriers and facilitators in making EBHPs based on the various participant perspectives. Finally, the potential development of an electronic tool, emphasizing the important contribution of HIT, can support and increase the exchange of evidence among knowledge producers and policy makers.

Impact of the KhITT Framework

The KhITT framework fills a gap in the literature, since there are not a lot of technology policy frameworks. There is a need to delineate policy to help guide implementations, as there have been issues with the success of health care information technology implementations worldwide. We hope that the developing conceptual framework, which includes an electronic platform, will be a useful tool for researchers and policy makers to practice closer collaboration and to influence each other's world and work. In addition, we anticipate that the KhITT study findings will have an impact on changing behaviors and enhancing use of evidence in health policy. Specifically, we expect that the use of our research findings will serve as a tool that may help with the following [51,52]:

1. Inform and enlighten policy making and change knowledge, awareness, attitudes, or opinions about the process of making decisions and health policies, but not necessarily action (ie, indirect or conceptual use).
2. Make specific decisions and policies or interventions by directly applying research in a useable form, such as a brief or a protocol (ie, direct or instrumental use).
3. Legitimate a position, win an argument, make a case, or persuade those in decision-making positions, in order to change.

Conclusions

The ultimate goal of the proposed KhITT framework is to develop a conceptual framework and describe the technology platforms that would enable the EBHP development process. We anticipate that our rigorous content analysis will be able to produce insights and themes that are able to address our objectives, contribute to an in-depth understanding of the EBHP process within British Columbia, highlight all influential factors, explicitly disseminate and communicate the study results, identify issues with EBHP and provide informed recommendations to address them, and enhance efforts toward transparent EBHPs.

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Authors' Contributions

All authors read and approved the final manuscript. AM contributed to the conceptualization of the study, funding acquisition, development of the methodology, and supervision; wrote the original draft of the manuscript; and wrote, reviewed, and edited subsequent drafts. DD contributed to funding acquisition, development of the methodology, and writing, reviewing, and editing the manuscript. EB contributed to the conceptualization of the study, funding acquisition, development of the methodology, and writing, reviewing, and editing the manuscript. AK contributed to the conceptualization of the study, funding acquisition, development of the methodology, and writing, reviewing, and editing the manuscript. KSY contributed to the development of the methodology and to writing, reviewing, and editing the manuscript. JF contributed to the development of the methodology and to writing, reviewing, and editing the manuscript. SA contributed to the development of the methodology and to writing, reviewing, and editing the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview questions.

[DOCX File , 39 KB - resprot_v9i12e16268_app1.docx]

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Abbreviations

EBHP: evidence-based health policy
HIT: health information technology
KhITT: Knowledge translation and health Information Technology for Transparency

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Protocol

Predictors and Consequences of Veterans Affairs Mental Health Provider Burnout: Protocol for a Mixed Methods Study

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Abstract

Background: In the Veterans Health Administration (VHA), mental health providers (MHPs) report the second highest level of burnout after primary care physicians. Burnout is defined as increased emotional exhaustion and depersonalization and decreased sense of personal accomplishment at work.

Objective: This study aims to characterize variation in MHP burnout by VHA facility over time, identifying workplace characteristics and practices of high-performing facilities.

Methods: Using both qualitative and quantitative methods, we will evaluate factors that influence MHP burnout and their effects on patient outcomes. We will compile annual survey data on workplace conditions and annual staffing as well as productivity data to assess same and subsequent year provider and patient outcomes reflecting provider and patient experiences. We will conduct interviews with mental health leadership at the facility level and with frontline MHPs sampled based on our quantitative findings. We will present our findings to an expert panel of operational partners, Veterans Affairs clinicians, administrators, policy leaders, and experts in burnout. We will reengage with facilities that participated in the earlier qualitative interviews and will hold focus groups that share results based on our quantitative and qualitative work combined with input from our expert panel. We will broadly disseminate these findings to support the development of actionable policies and approaches to addressing MHP burnout.

Results: This study will assist in developing and testing interventions to improve MHP burnout and employee engagement. Our work will contribute to improvements within VHA and will generate insights for health care delivery, informing efforts to address burnout.

Conclusions: This is the first comprehensive, longitudinal, national, mixed methods study that incorporates different types of MHPs. It will engage MHP leadership and frontline providers in understanding facilitators and barriers to effectively address burnout.

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KEYWORDS

burnout; mental health providers; patient outcomes; provider experience; mental health; veterans

Introduction

Background

Clinical provider burnout is a key indicator of how well a health care system functions. Health care providers face a large and increasing number of demands to do more work in less time (work compression) to try to achieve the triple aim of improving the patient experience of care, improving the health of populations, and reducing per capita costs of care [1]. Physicians have higher levels of burnout compared to other professionals with advanced degrees and the general US populations of workers [2].

Provider burnout remains a systemic problem associated with reductions in work effort within 24 months [3,4]. Burnout contributes to missed workdays, decreased job satisfaction and engagement, accelerated turnover, premature retirement, and at its most extreme, increased risk of suicide [5-9]. It is estimated that the cost of burnout in a health care system is 3.4%-5.8% of a medical center's annual operating budget [10]. A meta-analysis found that greater provider burnout was associated with poorer quality health care and reduced patient safety [11].

In the Veterans Health Administration (VHA), mental health providers (MHPs), which include psychiatrists, psychologists, and social workers, report the second highest levels of burnout after primary care physicians [12]. MHPs in the VHA may experience burnout due to factors such as patient violence and suicide, limited resources, changing resources in mental health services, high work demands, inability to effect systemic change, and isolation [13].

MHP burnout gained national attention at the 2017 American Psychiatric Association conference, which featured a crowded town hall session of MHPs sharing their stories of burnout [14]. The VHA recognized this growing area of concern with a number of recent studies focused on burnout at the system and individual levels for physicians and MHPs [15-19]. One study focused on the system level found that the amount of time that VHA psychiatrists spend providing pharmacological intervention increased emotional exhaustion and cynicism scores [16]. At the individual level, VHA tenure appeared strongly associated with burnout, highest for providers with 10-15 years of VHA experience and lowest for those with less than 6 months of Veterans Affairs (VA) service [15].

VHA MHPs face unique challenges compared to other MHPs, increasing their risk of burnout and associated consequences. An external audit found that VHA employees, including MHPs, experience a complex operating environment, including silos, inadequate and often one-way communications, limited access to resources, Congressional inquiries, and ongoing "thrashings" from the press, leading to a lack of empowerment in resolving issues [20]. In addition, the VHA patient population, particularly those with mental disorders, poses more treatment challenges than the private sector patient population, including greater socioeconomic disadvantage; more comorbid medical, psychiatric, and substance use disorders; and poorer self-reported health [21,22].

In light of ample and increasing evidence of negative internal and external pressures leading to MHP burnout, burnout may not soon abate. The VHA recognizes the problem of MHP burnout but could use additional and more nuanced data and guidance regarding potential interventions applicable at both the system and facility levels. Candidate interventions may include implementing team-based care at the system level to reduce MHP isolation [23] and prioritizing hiring clinical and support staff to address resource shortages at individual facilities. VHA MHPs provide care across a wide variation of contexts (eg, telemental health, rural veterans, veterans with complex comorbidities); therefore, our study will examine the range of resources needed both within and across contexts. This study proposes to obtain such information and disseminate findings regarding health system level responses within and outside the VHA.

Purpose

This article describes a VHA Health Services Research and Development–funded project that will characterize variation in MHP burnout by facility over time and identify workplace characteristics and practices of facilities with low levels of burnout that can be translated for potential implementation at facilities with high levels of burnout. We describe the study objectives and methods and discuss its potential for assisting developing and testing interventions with VHA partners to improve MHP burnout and employee engagement.

Methods

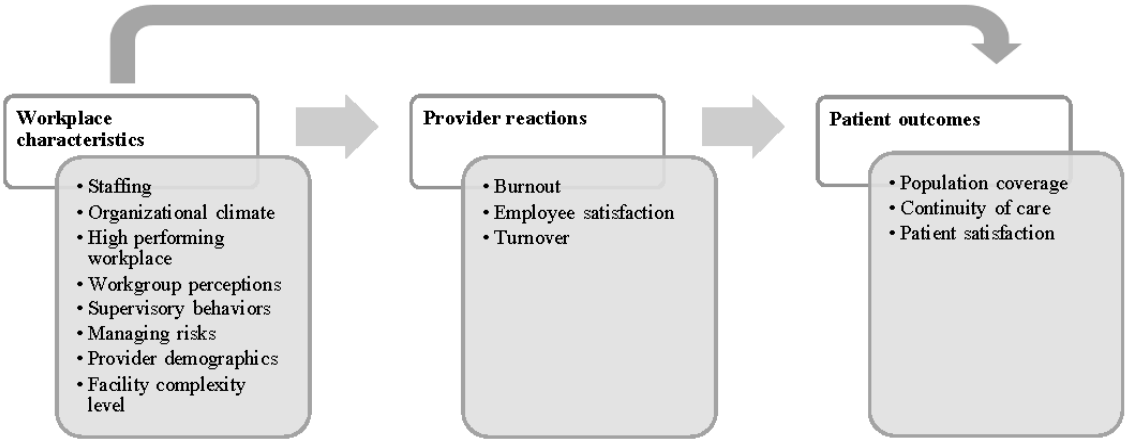
This study will investigate predictors and consequences of MHP burnout and use these insights for quality improvement within the VHA and elsewhere. We will accomplish 3 aims that focus on assessing both provider and Veteran outcomes to identify existing or new approaches for improving provider working conditions and patient care. Our sequential explanatory mixed methods study aims to understand the factors that contribute to MHP burnout and associated patient outcomes (quantitative), as well as opportunities and challenges that individual facilities experience with trying to address burnout (qualitative) [24].

This will allow us to develop options and recommendations for context-sensitive approaches and interventions for burnout that are acceptable to MHPs and health care system leadership.

Conceptual Model

The Minimizing Error, Maximizing Outcome (MEMO) Study (Figure 1) guides our project [25]. The MEMO Study examined working conditions in 119 non-VHA primary care clinics across 5 regions and how these conditions affected physician reactions and patient outcomes. The MEMO Study tested 3 hypotheses: (1) unfavorable working conditions would be associated with negative physician reactions such as burnout and (2) poorer patient outcomes, and (3) adverse physician reactions such as burnout to workplace characteristics would be associated with poorer patient outcomes. We will adapt this model to be relevant for mental health care and link VHA survey and administrative data.

Figure 1. Conceptual model.



Aim 1: Identifying Predictors of VHA MHP Burnout

We will conduct a quantitative analysis using linked VHA facility-level survey and administrative data to examine predictors and consequences of MHP burnout at VHA facilities (N=141). We will compile annual survey and other data (2014-2018) from 4 VHA sources: All Employee Survey (AES), Mental Health Provider Survey (MHPS), staffing and productivity identified using the Mental Health Outpatient Clinic Method (MHOC), and the SAIL Mental Health Domain (MH-SAIL).

The AES is an annual census of workplace perceptions and satisfaction open to all VHA employees [26]. The annual response rate is 55%-60%. There are no personal identifiers below the workgroup level to ensure anonymity as the survey is focused on organizational improvement needs. There are 3 questions on the AES that are designed to address burnout: (1) I feel burned out from my work (emotional exhaustion), (2) I worry that this job is hardening me emotionally (depersonalization), and (3) I have accomplished many worthwhile things in this job (personal accomplishment). Burnout measures are scored as 0 (never) to 6 (every day).

The MHPS is an annual survey for MHPs designed to assess perceptions about access to and quality of mental health care and overall job satisfaction [27]. The survey is open to all licensed and nonlicensed independent MHPs at the VHA. The annual response rate is ~25%. There is 1 question regarding burnout that is scored from 1 (I enjoy my work. I have no symptoms of burnout) to 5 (I feel completely burned out and often wonder if I can go on).

The MHOC identifies and tracks mental health staffing and productivity in inpatient and outpatient settings across all VHA clinics. We will calculate total mental health annual adjusted productivity (ie, by time spent delivering care) for each provider type (psychiatrists, psychologists, social workers) for each facility. We will primarily use annual staffing and productivity measures but will also conduct sensitivity analyses using quarterly measures.

The MH-SAIL is the mental health domain of the VHA's quality monitoring system, which is a composite of 3 measures including population coverage, which represents access to care; continuity of care, to assess whether services were provided in a coordinated manner and in the appropriate amount; and experience of care, representing patient-rated treatment experiences and provider-rated assessment of access, quality, coordination of care, and job satisfaction [28]. We will include the provider job satisfaction metrics as part of the provider reactions component of our analyses and the patient experience metrics as part of our patient outcomes analyses. In addition to the 3 composite measures, we will use components of each to create a comprehensive picture of how burnout may be affecting subgroups of patients based on their diagnoses or treatments. These components include percentage of patients with posttraumatic stress disorder receiving psychotherapy for posttraumatic stress disorder and percentage of patients on new antidepressants with 84 days of continuous treatment in order.

Our multilevel analyses clustered at the facility level will incorporate 3 sub-aims: (1) to identify predictors of VA MHP burnout, (2) to examine access and quality of patient care associated with VHA MHP burnout, and (3) to test mediators of the relationship between workplace characteristics and patient outcomes. We present our analytic models in Table 1.

Table 1. Sub-aims, models, and data sources for quantitative analyses.

Quantitative aim	Analytical model[a,b]
1a. To identify predictors of VHA[c] MHP[d] burnout	$ProviderReactions_{ik} = WorkplaceCharacteristics_{ik} + e_{ik}$
1b. To examine access and quality of patient care associated with VHA MHP burnout	$PatientOutcomes_{ik} = ProviderReactions_{ik} + e_{ik}$
1c. To test mediators of the relationship between workplace characteristics and patient outcomes	
Model 1[e]	$PatientOutcomes_{ik} = WorkplaceCharacteristics_{ik} + e_{ik}$
Model 2[f]	$PatientOutcomes_{ik} = ProviderReactions_{ik} + WorkplaceCharacteristics_{ik} + e_{ik}$

[a]We will conduct separate models for each outcome of interest, using both individual predictors and groups of predictors; we will also include (1) year as an additional indicator in the model to account for potential year-to-year variation in findings and (2) facility response rates for All Employee Survey (AES) and Mental Health Provider Survey (MHPS) data.

[b]ProviderReactions is a series of provider reaction measures, including burnout, employee satisfaction, and turnover measures for the $_i$ year in the $_k$ facility (AES, MHPS). WorkplaceCharacteristics includes staffing-related covariates for the $_i$ year in the $_k$ facility (MHOC); culture-related covariates, including organizational climate, workgroup perceptions, and supervisory behaviors, for the $_i$ year in the $_k$ facility (AES, MHPS); and facility-level demographic characteristics for the $_i$ year in the $_k$ facility (AES). PatientOutcomes is a series of patient access, continuity of care, and experience measures for the $_i$ year in the $_k$ facility (Strategic Analytics for Improvement and Learning [SAIL], MHPS). Finally, e is the error term.

[c]VHA: Veterans Health Administration.

[d]MHP: mental health provider.

[e]Represents the total effect.

[f]Represents the direct effect.

We will use Aim 1 findings to select facilities (N=8), including 4 with high burnout scores and 4 with low burnout scores, for the qualitative phase for our Aim 2 work. We will select sites with varying levels of burnout; if we find several sites with similar levels of burnout, we will include facilities with different sizes, geographic locations, the presence of an academic affiliation, and facility-level patient complexity to increase representativeness of our findings.

For each facility, we will first compute their burnout score using AES survey responses to single items from the Maslach Burnout Inventory including emotional exhaustion (“I feel burned out from my work”) and depersonalization (“I worry that this job is hardening me emotionally”). We will define facility scores by the proportion of providers reporting that either of these 2 statements were true once a week or more frequently. To standardize, we will convert facility burnout scores to a corresponding Z-score by subtracting the overall mean score and dividing by the standard deviation of facility-level burnout scores. Then we will rank facilities into 3 categories based on the magnitude of their Z-score: 0 to 1 for low burnout sites and ≥2 for high burnout sites.

We will select sites primarily based on rankings related to burnout scores; we will not focus on patient outcomes in our site selection. However, if we need to choose between multiple sites with similar burnout scores but differing patient outcomes, we will select sites that allow for more variation in patient outcomes.

Aim 2: Understanding VHA MHP Leadership and Provider Perspectives Regarding Burnout

Using qualitative methods, we will explore VHA MHP leadership and frontline provider perspectives regarding factors that protect against or exacerbate burnout in facilities with differing levels of burnout. We will conduct semistructured telephone interviews (up to 48) with mental health leadership and frontline MHPs from the 8 facilities identified from Aim 1 findings. Our sample size was chosen based on prior research studies and literature that suggest that, to reach data saturation, between 12 and 50 interviews should be conducted [29,30]. We will work with our operational partners from VA Central Office of Mental Health and Suicide Prevention and the National Center for Organizational Development to identify VHA MHP leadership within the selected facilities to participate in our interviews. We will conduct interviews with mental health leadership and then move to frontline providers. We will ask leadership for a list of frontline MHPs and will randomly select and recruit providers until we identify 5 participants per facility.

Our semistructured interview guides were developed using our conceptual model, MEMO. We will ask leadership questions such as, “How would you describe burnout?” “How do you address provider burnout within your facility?” “What role do you think burnout has in providers’ abilities to care for their patients?” “In the last year, please describe any strategies your hospital has used to address MHP burnout.” We will conclude with, “What do you think your facility needs in order to successfully address burnout among MHPs?” For frontline providers, we will ask them such questions as, “Please describe your experiences with burnout.” “What do you think contributes to provider burnout?” “Has your organization ever provided resources to cope with burnout?” “What suggestions do you have to address burnout among MHPs?”

Our qualitative research team will use a mix of deductive and inductive coding for our analyses. Deductive coding uses previous theories or studies to generate variables or concepts, and our deductive coding will be based on the MEMO model [31]. We will also use inductive coding in which we will

carefully examine the data to identify any nuanced themes and categories that are not explained using MEMO. We will create a data codebook that will include definitions and examples of text. We will conduct the qualitative analysis concurrently with the interviews. This will ensure that we can further investigate any themes that are emerging from multiple interviews. We will then use a matrix analysis to organize the data by site and compare sites to determine how each facility experiences burnout, contributing factors, past or existing strategies used to address burnout, and additional beneficial resources identified by the site.

Aim 3: Identify Strategies to Reduce VHA MHP Burnout

We will identify context-sensitive strategies for facilities to successfully reduce VHA MHP burnout. We will create joint displays (Table 2) by integrating our quantitative (Aim 1) and qualitative (Aim 2) findings to develop an inventory of local strategies to combat burnout as well as identify the facilitators and barriers of MHP burnout. Based on the joint display, the research team will identify potential strategies for both managing burnout and meeting patient needs.

Table 2. Sample joint display.

Workplace characteristics (MEMO[a] model)	Facility	Burnout level[b]	Context (eg, barriers, facilitators)[c]	Strategies tested or considered[c]
Staffing[d]	A	High burnout	Not enough providers to meet patient needs	None
	C	High burnout	Providers feel overworked but get job done	Hire additional support staff
	F	Low burnout	Have right mix of staffing and coordination among providers	Flexible work schedules
	H	Low burnout	Staff do not report being burdened but facility struggles to address required metrics	Request OMHSP[e] support to meet benchmarks

[a]MEMO: Minimizing Error, Maximizing Outcome.

[b]Based on Aim 1 analyses.

[c]Based on Aim 2 analyses.

[d]Repeat display for all components of MEMO model, including organizational climate, high performing workplace, workgroup perceptions, supervisory behaviors, managing risks, Veterans Affairs initiatives.

[e]OMHSP: Office of Mental Health and Suicide Prevention.

Our exemplar joint displays will be stratified by high and low burnout scores. Using the MEMO model, we will identify barriers and facilitators to addressing burnout in each facility. We will also include any specific strategies that the facility has tested or considered for addressing MHP burnout. Our research team will review the joint display to identify mechanisms that appear most linked with outcomes of interest. For example, our sample joint display suggests that flexible work hours could be a successful strategy for both managing burnout and meeting patient needs.

We will present our findings and understanding of mechanisms associated with MHP burnout to an expert panel including our operational partners, VHA clinicians, administrators, policy leaders, and burnout experts in an online web-based meeting. We will use the Delphi panel protocol, which does not require consensus as each panel member will have a confidential vote [32]. In Round 1, we will send the expert panel a list of potential strategies. Panel members will be asked to rate strategies based on (1) potential impact, (2) acceptability to leadership and providers, and (3) feasibility of implementation and relevance outside of VHA. In Round 2, we will provide an analysis of Round 1 votes and will ask the expert panel members to discuss their rationale. We will then ask the panel members to re-rate the strategies by confidential ballot in terms of the feasibility of implementation based on their experience with or knowledge of the resources available in an average VHA facility.

Our research team will then tabulate the ratings from Round 2 and develop a final set of recommended strategies. The strategies will be chosen based on the panel's median ratings of impact, acceptability, feasibility, and levels of agreement among panel members. We will not include any strategies that were rated as no or low impact or those that had significant disagreement by the expert panel.

Once the context-sensitive best practices have been identified, we will reengage facilities that participated in Aim 2 and conduct focus groups (up to 16). Prior to the focus groups, we will distribute site-specific integrated findings from the quantitative data, interviews, and expert panel recommendations to participants. The purpose of the focus groups will be to solicit feedback on study findings, which we will then disseminate broadly within and outside VHA.

Results

This project received notice of intent to fund in October 2018 and received funding to begin the work in December 2019. Institutional review board approval was obtained in July 2019 by the Ann Arbor VA Human Studies Committee. Primary analysis for Aim 1 began in June 2020, recruitment for Aim 2 will begin in March 2021, and Aim 3 work will begin in December 2021.

Discussion

This study represents the first comprehensive, longitudinal, national, mixed methods analysis to focus on a variety of MHPs. By directly engaging with MHP leadership and frontline providers in the largest integrated health care system in the United States, we will be in a unique position to identify and understand the barriers and facilitators to addressing burnout.

Our work will identify a broad set of recommendations to assist facilities and supervisors address MHP burnout. VHA will be able to use our findings to facilitate future planning and interventions to improve MHP burnout, employee engagement, and patient outcomes. Our work will contribute to broad health care improvements within VHA and beyond and will generate new insights for health care delivery, informing efforts to address burnout in MHPs and other clinical providers. Based on previous research showing the effects of burnout on individual providers and the entire health care system, we believe that our work could improve quality of care and access and reduce costs associated with staff turnover and lost productivity.

We anticipate that we will select, develop, and test the effectiveness of one or more of the selected recommendations and/or study how the recommendations can be successfully implemented. This study will lay important groundwork for a future intervention study or a service directed project, including a randomized program evaluation to study a new practice or policy.

Conflicts of Interest

None declared.

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Abbreviations

AES: All Employee Survey
MEMO: Minimizing Error, Maximizing Outcome
MHOC: Mental Health Outpatient Clinic Method,
MHP: mental health provider
MHPS: Mental Health Provider Survey
MH-SAIL: Mental Health Strategic Analytics for Improvement and Learning
OMHSP: Office of Mental Health and Suicide Prevention
VA: Veterans Affairs
VHA: Veterans Health Administration

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Proposal

Monitoring the Spatial Spread of COVID-19 and Effectiveness of Control Measures Through Human Movement Data: Proposal for a Predictive Model Using Big Data Analytics

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Abstract

Background: Human movement is one of the forces that drive the spatial spread of infectious diseases. To date, reducing and tracking human movement during the COVID-19 pandemic has proven effective in limiting the spread of the virus. Existing methods for monitoring and modeling the spatial spread of infectious diseases rely on various data sources as proxies of human movement, such as airline travel data, mobile phone data, and banknote tracking. However, intrinsic limitations of these data sources prevent us from systematic monitoring and analyses of human movement on different spatial scales (from local to global).

Objective: Big data from social media such as geotagged tweets have been widely used in human mobility studies, yet more research is needed to validate the capabilities and limitations of using such data for studying human movement at different geographic scales (eg, from local to global) in the context of global infectious disease transmission. This study aims to develop a novel data-driven public health approach using big data from Twitter coupled with other human mobility data sources and artificial intelligence to monitor and analyze human movement at different spatial scales (from global to regional to local).

Methods: We will first develop a database with optimized spatiotemporal indexing to store and manage the multisource data sets collected in this project. This database will be connected to our in-house Hadoop computing cluster for efficient big data computing and analytics. We will then develop innovative data models, predictive models, and computing algorithms to effectively extract and analyze human movement patterns using geotagged big data from Twitter and other human mobility data sources, with the goal of enhancing situational awareness and risk prediction in public health emergency response and disease surveillance systems.

Results: This project was funded as of May 2020. We have started the data collection, processing, and analysis for the project.

Conclusions: Research findings can help government officials, public health managers, emergency responders, and researchers answer critical questions during the pandemic regarding the current and future infectious risk of a state, county, or community and the effectiveness of social/physical distancing practices in curtailing the spread of the virus.

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KEYWORDS

big data; human movement; spatial computing; COVID-19; artificial intelligence

Introduction

COVID-19, which is caused by SARS-CoV-2, was originally detected in Wuhan, China, in December 2019. On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic due to its rapid spread to several geographic regions [1]. To limit the spread of COVID-19, unprecedented measures, such as mass quarantines of cities (eg, Wuhan, China) and lockdowns of entire countries (eg, Italy), have been taken. Due to the rapid human-to-human transmission of COVID-19, models or measurements that contribute to increased knowledge about potential infectious risk at different geographic levels can play an essential role for residents, medical workers, and governments. Such models can help local authorities and communities better allocate resources and efforts at a community level. Meanwhile, it is equally important for policy makers and emergency responders to understand how people practice social/physical distancing and how effective these control measures are at curbing the spatial propagation of the virus.

Human movement is an important driver of the geographic spread of infectious diseases [2]. For example, studies on severe acute respiratory syndrome (SARS) [3], Middle East respiratory syndrome (MERS) [4], and influenza H1N1 [5,6] all confirmed that airline travel was a major contributor to virus transmission on a large spatial scale. From a public health perspective, prediction and control of the spread of infectious diseases benefits greatly from our growing capacity to quantify human movement [7]. COVID-19 has a high human-to-human transmission rate and can be transmitted during the preclinical incubation period. So far, limiting and tracking human movement during the outbreak has proven effective at reducing the spread of COVID-19 in different countries [8-10]. In this sense, monitoring and analyzing human movement patterns or population flows at different spatial scales (global, country, state, county, and community) is critical for us to gain a better understanding of the current and future infectious risk at a population level during the pandemic. Such situational awareness can help governments at all levels (local, state, federal, and international) proactively reallocate medical supplies and medical workforces to more vulnerable areas, enabling better preparation and readiness for disease outbreaks.

Existing studies have used various data sources to quantify human movement and model the spread of infectious diseases. On a large scale, airline data are important sources in understanding global transmission of infectious diseases. For example, global spread of SARS simulation models have been generated with airline data [11]. Although airline data deepened our understanding of the transmission mechanism of infectious diseases at large geographical scales, the data have shown a limited usefulness for understanding transmission across short distances [12,13]. On a local or regional scale, mobile phone data have been used as a measurement of human mobility; such data improved our understanding of spatial transmission patterns of malaria [14], cholera [15], and influenza [16]. Due to privacy issues, mobile phone data are generally limited in terms of accessibility and are often limited to a local region or one country; therefore, this data cannot provide systematic global coverage [17]. Besides mobile phone data, commuting patterns derived from census data also play an important role in understanding virus spread patterns on a local scale [13,18].

With the increasing prevalence of location-enabled social media, geotagged Twitter data have been widely used in human mobility studies (eg, [19-21]), yet limited research has been conducted to validate the potential and limitations of these data for studying human movement at different geographic scales (eg, from global to local) in the context of global infectious disease transmission. Meanwhile, the recent development of artificial intelligence (AI) has proven useful for diagnosis, drug analysis, data collection, and outbreak prediction [22]. Various types of neural network algorithms have demonstrated capacity in predicting HIV epidemics [23], influenza-like illness [24], and SARS [25]. However, the majority of these AI-based prediction algorithms have focused on mathematical models of trend development and outbreak identification, in which limited geospatial information (especially at different geographic scales) is considered. The recent COVID-19 pandemic provides us with a unique opportunity to explore innovative approaches to effectively use big data from Twitter and AI-based algorithms, and examine their efficiency in enhancing situational awareness and risk prediction in public health emergency response and disease surveillance systems.

By leveraging the interdisciplinary team's collective expertise in spatiotemporal modeling, big data analytics, infectious disease, spatial epidemiology, and health promotion and behavior modification, we propose to develop a novel data-driven public health approach using big data from Twitter coupled with other human mobility data sources and AI to monitor and analyze human movement at different spatial scales (from global to regional to local). With the proposed approach, we aim to answer the following critical questions relating to the COVID-19 pandemic:

1. Where are people coming from and going to during the pandemic? We will answer this question by developing an Origin-Destination-Time data cube (ODT cube) to efficiently extract historical and near real-time population flows from worldwide geotagged tweets.
2. What is the current and future infectious risk of a country, state, or county? This will be estimated using a spatial-temporal fused neural network considering historical human movement patterns and real-time population flows.
3. How well are people following the social/physical distancing orders? This question will be examined by performing spatial-temporal aggregation of the ODT cube at different spatial scales and temporal resolutions to quantify human movement at different spatial scales.

4. How effective is social/physical distancing for curtailing the spread of the virus? We will answer this question by conducting spatiotemporal and geostatistical analysis (eg, regression and correlation) for the aggregated population flows, the daily confirmed cases, and other factors such as face mask policies.

The answers to these questions will be compiled as maps, diagrams, news releases, technique reports, and peer-reviewed journal articles.

Methods

Data Collection and Database

This project will collect the following 4 types of data worldwide (where data are available): (1) geotagged Twitter data, (2) daily confirmed COVID-19 cases at the available highest spatial resolution for all countries, (3) the most recent socioeconomic and demographic information (at the county level in the United States and a similar level of administrative unit for other countries), and (4) human movement information from other mobility data sources, such as mobile phone–based mobility data (eg, SafeGraph [26] and Descartes Labs [27]), the Google Mobility report [28], and the Apple Mobility report [29]. We have developed a computer program to stream geotagged tweets using Twitter's Standard (free) streaming application programming interface (API). In addition, we will subscribe to Twitter's Decahose API for a limited time period, which delivers a 10% random sample of real-time full Twitter streams [30]. Worldwide historical geotagged Twitter data collected by the team over the past 5 years will be used to construct past population flows and identify spatiotemporal patterns of human movement. Building upon our previous work on indexing and processing geospatial big data [31,32], we will develop a scalable database to store and manage the aforementioned multisource data sets. The database will be indexed with multilevel spatial scales (eg, country, state, and county) and temporal resolutions (eg, year, month, day, and hour) and will be connected to our in-house Hadoop computing cluster for efficient big data computing, analytics, and visualizations.

Analytic Approach

Develop an ODT Data Cube for Efficient Analysis of Human Movement From Geotagged Tweets With Varying Spatiotemporal Scales

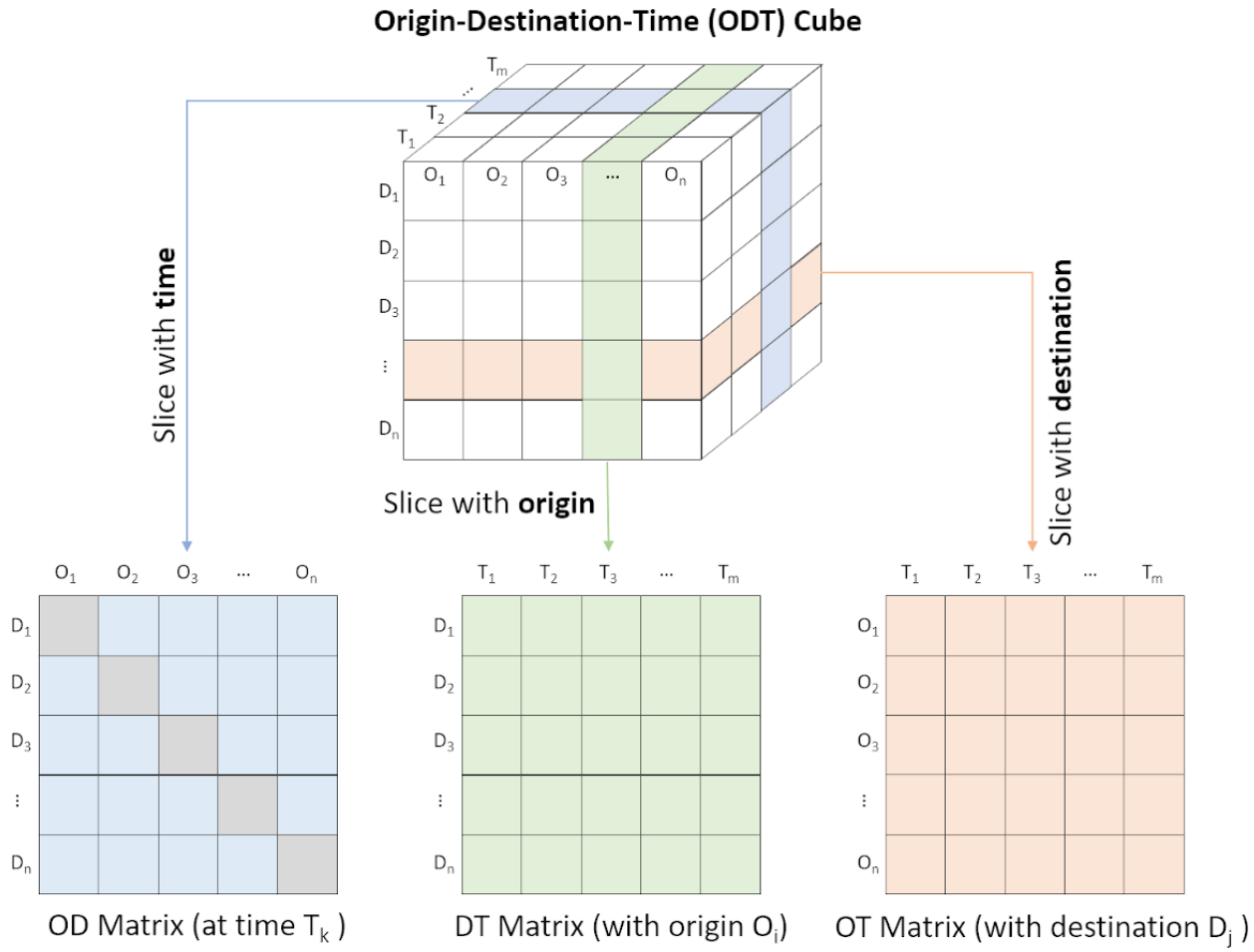
Data cube has been widely used to model high-dimensional spatiotemporal data (eg, [33,34]). We will develop an ODT data cube as a high-level conceptual model for quantifying human movement across different places or locations over time (Figure 1) from billions of geotagged tweets. The ODT cube will serve as a foundation data model for efficiently conducting human movement analysis at different spatial and temporal scales. In the ODT cube, origin (O) and destination (D) are a set of places or locations (eg, administrative boundaries such as county, state, and country, or latitude/longitude grids) that can be displayed on a map. Each cell in the data cube has a value that indicates the number of people that moved from the origin location to the destination location during a specific time period (eg, an hour, day, or month). In other words, each cell value indicates the connection (measured by population movement) between two locations. Using the ODT cube, we can efficiently retrieve the number of people that moved from O_i to D_j at time T_k.

In total, 3 types of matrices will be derived from the data cube: the origin-destination (OD) matrix quantifies the population flows between all the origin and destination locations during a time period. The destination-time (DT) matrix captures the number of incoming people to all destination locations from a specific origin location over a series of times, while the origin-time (OT) matrix captures the number of outgoing people from all origins to a specific destination over a series of times. In addition, the number of unique Twitter users can be calculated for a specific location over time. This enables us to efficiently conduct spatial-temporal aggregations of human movement at varying spatial and temporal resolutions.

The OD matrix is an $n \times n$ matrix, where n is the number of geographic entities included in the study. Column O_x and row D_x are the same location (x). An entry v_{ij} in this matrix represents the number of people moving from origin i to destination j. It should be noted that human movements are directional. Therefore, v_{ij} and v_{ji} stand for two different spatiotemporal movements that are likely to have different values. We define the values in the diagonal cells (grey cells in the OD matrix), v_{ii},as the number of unique Twitter users in location i.

The process of constructing the ODT cube is extremely data- and computationally intensive because we need to perform a large number of point-in-polygon spatial operations, and the output will contain billions of connections. We will leverage our expertise in geospatial big data computing to perform the computation using an in-house Hadoop-based computing cluster. Based on the generated ODT cube, we will further derive a number of indices to quantify human mobility at varying spatiotemporal scales including, for example, the daily number of Twitter visitors, daily number of movements (inflow, outflow, intraflow), average travel distance, and place connectedness index between two counties.

Figure 1. Illustration of Origin-Destination-Time data cube for modeling human movement.



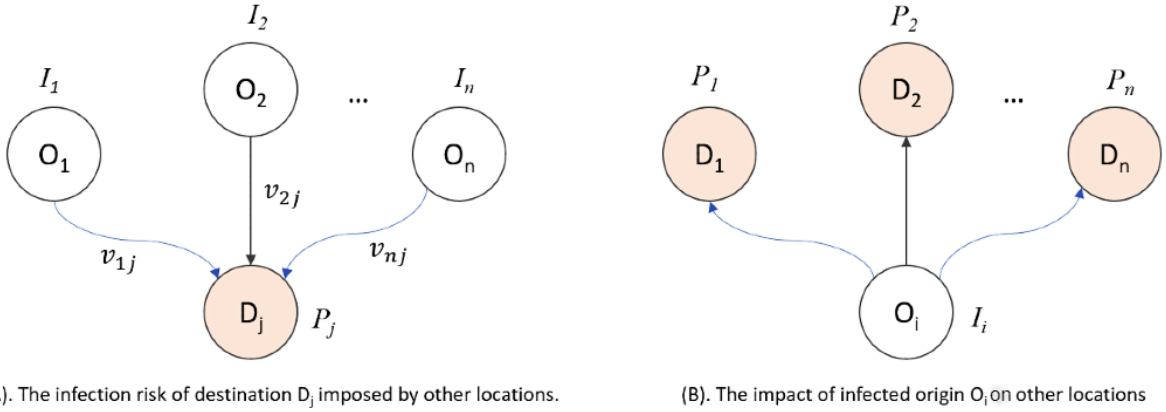
Develop Population-Level Infectious Risk Maps at Different Spatial Scales Based on Population Flows to Enhance Situational Awareness

The ODT cube quantifies human movement among different places (eg, US counties or census tracts) during a given time period. Knowing such movement information is essential for assessing infectious risk at the population level in a given place. We propose to model the current infection risk of a given place (eg, county) by integrating the following information: (1) population flows derived from the ODT cube during the recent time period among all places (eg, past 14 days), (2) the number of total COVID-19 cases for each place, and (3) socioeconomic and demographic variables that relate to the infection risk of that location (eg, a county's population density and age and race distributions).

We will create an infection risk index for each place by combining the abovementioned factors. For example, suppose that, based on the ODT cube, we observe a significant population flow from county *A* to county *B* during the past week and county *A* already has a number of COVID-19 cases, then the infectious risk for county *B* is high (people from a highly infected area are likely to carry the virus). Note that the real scenario is more complex due to the fact that the risk of county *B* is also affected by other counties with confirmed cases that have connections with county *A* and that population movement is not the only factor for infectious risk. In other words, the infection risk of destination D_j can be considered a function of local factors (P_j), combined with population flow from each origin (v_{1j}, v_{2j}, …v_{nj}) weighted by the number of cases at each origin (I_1, I_2, ..., I_n; Figure 2A). A risk index will be calculated for each location to produce an infectious risk map. Based on the ODT data cube, risk map generation can be efficiently implemented using matrix computation. Such risk maps would be useful for targeting surveillance and outbreak control activities for a region.

Besides modeling the infection risk of a location using the incoming populations, we will also estimate the risk impact of a location with confirmed cases on other locations. For example, since Italy was severely infected at the early stage of the pandemic, it would be helpful to understand where the outgoing population from Italy traveled to. As illustrated in Figure 2B, we will build a model that combines the population movement information between the targeted location (O_i) and other locations (D_1, D_2, ..., D_n), as well as other factors associated with each location (P_1, P_2, ..., P_n). The output of the model will be a map showing the potential impact of the incoming populations from the targeted location (eg, Italy).

Figure 2. Illustration of (A) infection risk modeling based on the incoming population to a location and (B) the impact modeling of an infected location on other locations.



(A). The infection risk of destination D_j imposed by other locations.

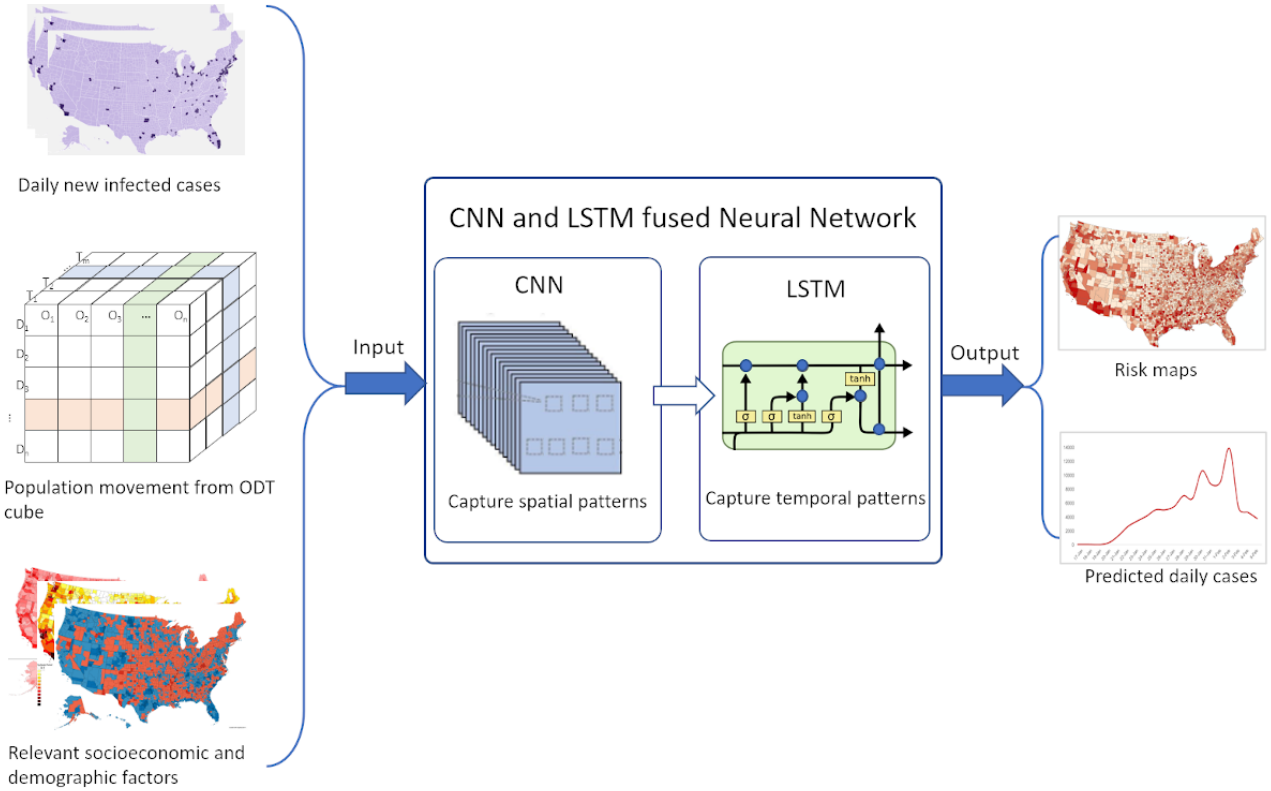
(B). The impact of infected origin O_i on other locations

Develop a Predictive Model to Estimate Future Infectious Risk Using a Fused Neural Network by Considering Both Spatial Patterns and Temporal Trends of the Population Movement

In this research task, we aim to explore the feasibility and performance of a predictive model for future infectious disease potential at the US county level based on the following information: (1) near real-time human movement information (from real-time Twitter data streams), (2) the daily case count of each county (will be collected/compiled each day), and (3) other factors such as socioeconomic and demographic information.

Given the complex epidemiological and geographic processes of different infectious factors, we propose to use deep learning to explore complex infectious processes using the large volumes and high dimensions of the input data. Deep learning is one type of machine learning in AI. Unlike traditional machine learning, in which the parameters of an algorithm (eg, support vector machine) are configured by experts, deep learning determines these parameters by learning the patterns in a large amount of data based on artificial neural networks. Specifically, we will develop a fused neural network that integrates two types of neural networks, convolutional neural network (CNN) and long short-term memory recurrent neural network (LSTM), to consider spatial patterns and temporal trends simultaneously in the predictive model (Figure 3). The fused neural network will include a series of CNN layers in the front end followed by LSTM layers with a Dense layer on the output. The locations in the ODT cube (eg, counties) would be treated as pixels (neurons) in the CNN network to capture spatial relationships and local patterns, and the temporal trend will be predicted with the LSTM network. Different combinations of socioeconomic and demographic factors will be tested during the model building, training, and validation process, and the combination yielding the highest accuracy will be used in the final model.

Figure 3. Conceptual architecture of the CNN-LSTM fused neural network for infectious risk prediction. CNN: convolutional neural network; LSTM: long short-term memory recurrent neural network; ODT: Origin-Destination-Time.



Ethics and Dissemination

This research does not involve human subjects and received an exempt review from the Institutional Review Board (IRB). All data collected in this project are in the public domain. Twitter data are collected using the official Twitter API. We are fully aware of the potential privacy concerns related to handling geotagged tweets, which contain location information and may include some personal information provided by the users directly. We have been following and will continue to follow Twitter developer policies strictly when collecting and sharing Twitter data. The raw individual tweets with exact latitude and longitude will not be published in any format, including maps, technical reports, or journal publications. All data collected in this study will be stored in an in-house Hadoop computing cluster hosted in a secure server room at the University of South Carolina with firewall protection, two-factor authentication, and endpoint security. The results of this project will be disseminated as maps, summary graphics, news reports, research articles, and interactive web portals.

Results

This project was funded as of May 2020. We have started the data collection, processing, and analysis, and have built a spatial web portal for sharing the human mobility data extracted from geotagged tweets and SafeGraph data [35].

Discussion

Overview

In this paper, we report a research protocol that will use big data from social media to derive information on human movement or population flows to monitor the spatial spread of COVID-19, quantify the effectiveness of control measures, and predict the current and future infectious risk at various geospatial scales. We believe geotagged Twitter data are sufficient for studying population flows on a large spatial scale with low or medium spatial resolutions, such as the movement between countries and between states in the United States. For the county level, our previous studies indicate that these data perform well for examining human movement between different US counties [36-38]. For finer resolutions than county, we have successfully conducted human mobility studies at the census tract level [21] and street/community level within a city [39]. However, we are aware that studies at a spatial resolution higher than city or county only work in highly populated areas since at this resolution we can only use tweets with exact coordinates. Considering this issue, we will only perform community-level analysis for highly populated cities (eg, New York City) when using Twitter-derived population flows.

Another limitation we would like to point out is that Twitter data has intrinsic demographic and socioeconomic biases as suggested in a few studies [40-42]. Despite this limitation, Hawelka et al [19] confirmed that geotagged tweets are exceptionally useful for quantifying country-to-country population movement. Our recent study also suggests that the county-level population movement derived from Twitter data

can accurately reflect regular (eg, holidays) and nonregular (eg, hurricanes) events [36]. The third issue is that Twitter users' tweeting behavior and Twitter's APIs and platform change over time and may continue to change in the future, which affects the volume of streamed geotagged tweets. For example, Twitter removed support for precise geotagging in June 2019 [43] and Twitter users may stop geotagging their posts due to privacy concerns. To tackle the aforementioned limitations of geotagged tweets, we will integrate human mobility data derived from other aforementioned data sources including SafeGraph (which provides US Census Block Group–level human movement information) to better capture and quantify human movement during the pandemic [44].

Conclusions

Human movement is among the essential forces that drive the spatial spread of COVID-19. During a global pandemic, monitoring and analyzing human movement patterns or population flows is critical for us to gain a better understanding of current and future infectious risk at the population level. This research aims to use big data from a social media site (Twitter), AI, and spatiotemporal analysis to monitor and model the spatial spread of COVID-19 at different spatial scales (from local to regional to global) through the lens of human movement. The results of this study will not only provide enhanced situation awareness for the government at all levels, but also offer valuable contributions for building collective public awareness of the role people play in the evolution of the COVID-19 crisis. The findings of this research may also have implications for policy by assisting the policy makers and general public to evaluate the effectiveness of various control measures that aim to reduce human movement during the pandemic. For example, the debate about the true effectiveness of social distancing as a public health tool for limiting COVID-19 transmission requires mobility research to generate evidence-based guidance [45]. This is especially important in the context of mixed research findings about COVID-19 aerosolization [40,46,47] and the true effectiveness and costs of social distancing [48,49]. As universities and schools reopen, and traditional socialization activities like sporting and musical events resume, measuring and tracking the impact of human mobility will take on greater significance.

We hope that the results can help government officials, public health managers, emergency responders, and researchers to answer critical questions during the pandemic as elaborated above. Although this research is a response to the current COVID-19 pandemic, the proposed research will make significant contributions to data sources, applications, models, and methodology for a variety of human mobility studies. This research is expected to have a broad impact on diverse fields that can benefit from a better understanding of human movement at varying spatial scales, such as infectious disease spread in public health, transportation, tourism, and economics.

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Authors' Contributions

ZL, XL, and DP conceptualized and designed the study protocol. ZL, YJ, and JZ contributed to the methodology for the study. ZL, XL, and BO are responsible for the study coordination. ZL, YJ, and JZ are responsible for data quality control, management, and analysis. SW, XL, and YJ made substantial contributions to manuscript editing. All authors read and contributed to the writing of the study protocol and approved the final draft of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
API: application programming interface
CNN: convolutional neural network
DT: Destination-Time
MERS: Middle East respiratory syndrome
LSTM: long short-term memory recurrent neural network
ODT: Origin-Destination-Time
OD: Origin-Destination
OT: Origin-Time
SARS: severe acute respiratory syndrome
WHO: World Health Organization

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Protocol

Helping Optimize Language Acquisition (HOLA) Online Parent Training Modules for Latinx Parents of Toddlers at Risk for ASD: Protocol for a Pilot Funded by the Organization for Autism Research

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Abstract

Background: Culturally competent parent training in evidence-based intervention for autism spectrum disorder (ASD) can provide young Latinx children from underserved communities with early interventional support while they wait for professional services, thus reducing the impact of intervention delays. Providing parents with brief bilingual training in Pivotal Response Treatment (PRT) is a strategy that can overcome these barriers and is inexpensive to disseminate. Brief PRT training has been shown to significantly improve joint attention, expressive language, responsivity, and adaptive skills in young children with ASD. However, it is unknown whether an interactive, culturally competent online parent training in PRT is effective in a Latinx population.

Objective: To this end, we will recruit 24 children (16-36 months old) at risk for ASD and their parent(s) from East and South Los Angeles and provide them with a series of 6 online learning modules in their choice of Spanish or English.

Methods: This pilot study will utilize a single-group, pilot, pre-post design with follow-up assessments 6 weeks later. Linear mixed-effects model analysis will be used to explore most parent-reported and coded outcomes.

Results: Brief online parent training in evidence-based treatments has the capacity to increase access to culturally competent early communication interventions for young children at risk for ASD.

Conclusions: The results of this trial may have particular salience in additional underresourced communities where children have limited access to interventions prior to entering school.

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KEYWORDS

autism spectrum disorders; cultural diversity; parent training; pivotal response treatment; health disparities; online training; autism; intervention delay; online learning; pediatrics

Introduction

Background

Early access to evidence-based intervention leads to best-case, long-term outcomes for children with autism spectrum disorder (ASD) [1], with the greatest developmental gains experienced by children who begin intervention before their third birthday [2,3]. A recently published meta-analysis revealed that intervention benefits to social communication begin to diminish before a child turns 4 years, highlighting the importance of ASD-focused early intervention services in the developmental period [4]. Delay in the receipt of ASD-focused intervention has been associated with later autism severity, placement in segregated learning environments, and lower scores on tests of student achievement [5].

Parents from underserved communities often have less knowledge about ASD and are less likely to recognize ASD symptoms [6,7]. Therefore, their children are less likely to receive an early diagnosis of ASD. This marks a missed opportunity for intervention during the critical developmental period. Additionally, underserved families may find interventions that require a significant time commitment or cause their child to react emotionally untenable due to cultural mismatch [8].

Targeted outreach to early childhood centers and coordination with early intervention systems and health care providers, paired with dissemination of culturally competent, parent-mediated intervention models are crucial to reduce this service-need discrepancy for underserved families [9]. White, middle to upper class participants represent a significant majority in quality research studies of evidence-based practice for young children with ASD, so it is yet unclear whether established treatments are effective in nonprivileged or racially or ethnically diverse samples [10]. Virtual parent training interventions for ASD that have shown merit utilize telehealth models [11,12] that are limited by inflexible scheduling, as parents must be available to attend at predetermined times, require hard-copy hand-outs, and are limited to English-proficient participants. To make parent-mediated interventions more accessible to diverse samples of families, it has been suggested that clinicians make training materials less complicated, allow for flexibility in how the program is delivered, and teach families how to practice the intervention within their preexisting routines [13,14].

Research With Latinx Families of Children With ASD

According to recent qualitative research on the implementation of evidence-based interventions for ASD in Latinx families, parents frequently have limited knowledge regarding ASD and require additional information. However, they are ultimately eager to participate in teaching their child and focused on helping them improve their functioning [15]. Latinx mothers of young children with ASD may also have a heightened sense of guilt regarding their child's diagnosis, possibly believing it a punishment for something they have done in the past [16], making the delivery of accurate, culturally informed Spanish language information and intervention even more crucial [17]. In addition to these barriers, the climate of anti-immigrant sentiment and media coverage of the Immigration and Customs Enforcement detention centers and family separations may keep Latinx families who need services for their young children from seeking help.

Providing Latinx parents with brief online training in Pivotal Response Treatment (PRT) strategies in their language of preference can help overcome barriers and reduce disparities. Brief PRT training has been shown to significantly improve joint attention, expressive language, responsivity, and adaptive skills in young children with ASD [18,19]. And a recently published report on a pilot study of an online PRT parent training reported significant improvements in parent fidelity of implementation and social communication in a diverse sample of young children [20]. However, brief online PRT training has not been tested for effectiveness in a bilingual Latinx sample.

Latinx families have rapidly grown to be among the highest users of smartphone technology [21], and recent eHealth studies have shown preliminary success in using mobile technology to increase knowledge regarding diagnosis and improve health-related behaviors [22]. To this end, we are in the process of developing a smartphone-optimized, interactive, bilingual, culturally competent brief online PRT training curriculum titled "Helping Optimize Language Acquisition" (HOLA) with feedback from an advisory committee comprised of a bilingual parent of a young child with ASD, a PRT expert with over 20 years of experience in parent-mediated PRT coaching, and a bilingual Early Intervention (EI) program administrator. The HOLA curriculum is based on the information, lessons, and examples included in "Using Pivotal Response Treatment to Teach First Words to Children with Autism" [23] and "Pivotal Response Treatment: Using Motivation as a Pivotal Response" [24] by Koegel, as well as information from "Parents Taking Action," a culturally informed bilingual training program for parents of children with ASD or developmental disabilities [25]. HOLA will be delivered to parents in 6 brief (20-40 minute) weekly modules in English or Spanish (Textbox 1).

Textbox 1. Topics addressed in each of the 6 modules in the Helping Optimize Language Acquisition (HOLA) program.

Module 1

- Child Development
- Autism Spectrum Disorder

Module 2

- Child Choice
  - Getting Started
  - Natural Environments
  - Favorite Things!
  - What is HOLA?

Module 3

- Providing Natural Rewards
  - What are Natural Rewards?
  - Rewarding Good Trying
  - Easy Tasks

Module 4

- Providing Clear Opportunities
  - Getting Your Child's Attention
  - Providing a Clear Opportunity
  - Responding Right Away

Module 5

- Putting it All Together
  - Reviewing the Strategies
  - Teaching in Daily Routines
  - Celebrating Your Child

Module 6

- Planning for the Future
  - Troubleshooting
  - Task Variety
  - Family Balance
  - Taking Care of Yourself

The HOLA modules will differ from other virtual parent trainings in that they will be accessible online at any time of day, they can be viewed multiple times, and all needed materials will be integrated into the training modules. The HOLA training will make use of adult learning principles and use multiple modalities including presentations, visual representations, gamification, and video examples to teach the content, and text will be simplified and supported by visuals to allow for participants of varying levels of literacy (Figures 1 and 2). These training strategies have been shown to improve learning outcomes when compared to traditional presentation methods such as narrative slideshows for a variety of learners [26].

Figure 1. Example video enhanced page from an HOLA module.

Figure 2. Example interactive page from an HOLA module.

Methods

Objectives and Study Design

This pilot study will utilize a single-group, pilot, pre-post design with follow-up assessments 6 weeks later. All assessments described in the subsequent paragraphs are available in English and Spanish. It is hypothesized that the HOLA parent training will improve parent knowledge of ASD and child development, increase fidelity of implementation of the strategies taught, and improve child social communication. Additionally, we predict that the parent will experience gains in empowerment and reductions in parenting stress, and the children will have reductions in challenging behavior and display improved social skills. Finally, we predict that there will be no difference in participant outcomes between Spanish and English language trainings.

To test the HOLA intervention, we will recruit 24 Latinx toddler-parent dyads (16-36 months old) with elevated risk for ASD from the East and South Los Angeles regions to measure the effects of the HOLA intervention on parent knowledge of child development, parent PRT fidelity of implementation, and child social communication. We will also measure parent satisfaction with the intervention and explore the impact of HOLA on parent stress, family empowerment, and child behavior. Additionally, because participants will choose whether they would prefer to receive the intervention in Spanish or English, we will assess whether language has an impact on effectiveness of and satisfaction with HOLA.

All screening and assessment activities as well as data entry and monitoring for this study will take place in the Parent Education and Support (PEAS) Lab of author RD in the Charter College of Education at California State University, Los Angeles (Cal State LA). The PEAS Lab is located in the same building as the Robert L. Douglass Speech and Language Clinic, Center for Multicultural Education, C. Lamar Mayer Learning Center, and Center for Excellence in Early Intervention and Low Incidence Disabilities. This dedicated research space includes an assessment room; a waiting area for families; access to family-friendly, American Disabilities Act–compliant bathroom facilities; and 3 additional computers/workstations for data entry, transcription, coding, statistical analysis, and data storage. Specifically, the subject testing room consists of a dedicated 8-foot by 8-foot room containing a chair for caregivers, toddler-sized furniture, child-friendly furnishings, and keyed storage for toys and assessment materials.

Centro de Niños y Padres (located next door to the PEAS Lab) is a family-focused program providing early intervention services to children from birth to age 3 years, who have or are at risk for a developmental disability. The Centro de Niños y Padres program serves families in the neighboring culturally diverse communities through developmentally appropriate practices. The program serves children who have been identified as having developmental disabilities and children who are at risk, including those with complex and intensive medical needs. Infants and toddlers without disabilities whose parents are interested in a family-centered early learning environment dedicated to diversity and celebration of the family role in development and learning are also welcome to participate in the program. Although many of the children served by Centro de Niños y Padres have a range of abilities, many of the children they serve exhibit delays in social communication, making it an appropriate agency for recruitment of families who may qualify for participation in the proposed study.

Recruitment and Consent Procedures

The Cal State LA Institutional Review Board (IRB) will approve all recruitment and consent procedures prior to enrollment begins. All study staff will complete IRB research training through Cal State LA. Recruitment will take place in 2 ways: through referrals from entities that serve young children and through targeted outreach. The primary recruitment site for this project will be Centro de Niños y Padres early intervention program. Additional sites identified for referrals include Federally Qualified Community Health Centers, Family Resource Centers, and the Diagnostic Clinics, all programs that serve children with disabilities from low-resource communities in the Los Angeles area. Presentations on ASD and free screening events will be scheduled for parents and staff at childcare and Early Head Start locations in proximity to the university as well as pediatric practices to facilitate recruitment. Parents of children identified as having elevated concern for ASD will be informed about potential participation in our research study. The referring organization will proceed, as appropriate, with standard referrals (EI, Child Find), regardless of interest in participating in our research study. The partnering organization will provide referral contact information (study flyer) to the project staff for all families that indicate interest and consent to be contacted by the project staff.

Once a telephone or email inquiry or referral from a partnering organization is received, project staff will call the family to explain the purpose and procedures of the study. If the participant indicates interest in participation, project staff schedule an assessment appointment with the family. The potential participant will complete a screening assessment consent form, which will allow the assessor (principal investigator [PI] for English, bilingual research assistant for Spanish) to administer the Modified Checklist for Autism in Toddlers, Revised, with Follow-Up (MCHAT), which is a parent-report screening tool to assess autism risk [27]. If the child scores below 3 on the MCHAT or does not meet all eligibility requirements, the parent will be compensated for the visit (US $25) and receive an assessment report, and all study materials will be destroyed. The assessor will continue with baseline assessments if the child and family meet all eligibility criteria: child is between 16 and 36 months of age, is minimally verbal or pre-verbal, scores 3 or above on the MCHAT, and has no other physical or sensory disabilities.

Before starting baseline assessments, the assessor will review the informed consent form in the appropriate language with the participant, and any questions will be answered. The participant will be told that this is a research study, that his or her participation will not positively or negatively affect the provision of services to the family, and that he or she is free to decline to answer any questions or to cease participation at any point. The confidentiality of the information will be assured. The participant will be told that no identifying information will be retained on any of the data collection forms and that a unique and nonidentifying ID code number will be assigned in lieu of his or her name. The participant will be asked to sign 2 copies of the informed consent (1 for the participant to keep, 1 for the project files), after which baseline assessment will begin. Participants will then receive 6 weekly links to the online

modules in their language of preference as outlined in the following sections.

Considerations for Families From Low Income and Diverse Communities

Some families, especially from communities of color, may have had negative experiences that result in a lack of trust in the research community. Further, they may perceive research participation as lacking benefit to them and their child. Bonevski and associates [28] outlined strategies to improve trust and participation in low-resource and culturally diverse communities in a systematic review. They highlight a need for increased flexibility in scheduling, the provision of monetary or tangible incentives, reduced travel to the research site, and capitalizing on connections within the community of interest [28]. These recommendations have been incorporated in the development of this study, so that the assessor will schedule appointments with the parent to accommodate their schedule and preferences, participants will receive compensation for their time after each assessment visit, and community-based EI providers and medical practices that accept Medicaid reimbursement will be the main referral points for the study.

Baseline assessments will be conducted with all children and parents prior to participation in the study. The purpose of the screening and baseline assessments is to confirm ASD risk and assess parent, child, and family characteristics prior to their receipt of intervention. In addition, posttest (6 weeks after the start of intervention) and follow-up (6 weeks postintervention) assessments will be conducted to assess changes in parent and child characteristics over time. Parents will receive US $25 for their time for completing screening or baseline, posttest, and follow-up assessments (US $75 total). All time point assessments will involve travel to Cal State LA.

Enrollment and Participation

Over 1 year, 24 parent/child dyads will participate in the study. The parents will receive 6 weekly emails or text messages, each with an active link to access an online training module. All electronic data will be stored in a password-protected university

server, and only IRB-authorized personnel will be granted password access.

Screening Measures

For autism risk, the MCHAT [27] is a parent-report autism screening tool for children 16 to 30 months of age. It will be collected pre-intervention. Children who score above 3 will qualify to participate in the study and will be referred for a diagnostic evaluation.

Control Measures

Demographic Questionnaire

The demographic questionnaire will be created by investigators. The questionnaire will include questions regarding parent age, education, income, employment, English language proficiency, health status, child age, and gender. It will be collected pre-intervention.

Service Use Questionnaire

The service use questionnaire will be created by the PI. Parents will be asked to indicate which services the child is currently receiving, including the number of hours received weekly for each service. Services may include applied behavior analysis therapy, occupational therapy, physiotherapy, speech therapy, recreational or social activities, or education-based services (EI, preschool). Services used and hours of services will be counted for a total score and will be examined individually. This will be collected pre-intervention, postintervention, and at follow-up.

Recruitment Site

I will control for recruitment site, as participants recruited from different sites may have had very different experiences related to their child's development and represent distinct demographic groups. This will be collected pre-intervention.

Primary Outcome Measures

Social Communication

Social communication will be coded from a recorded play session between the parent and child with a standard set of toys using frequency counts to identify the presence of the communicative behavior (vocalizations, eye contact, or positive affect) over a 5-minute video-recorded play session. The overall percentage of intervals in which the children used any type of social communication will be calculated. This will be collected pre-intervention, postintervention, and at follow-up.

Parent Fidelity of Implementation

Parent Fidelity of Implementation will be scored using a continuous 1-minute interval recording system over a 10-minute video segment of a recorded play session between the parent and child with a standard set of toys. Parents will be scored for the correct use of each of 5 PRT principles (presenting clear opportunities, child choice, immediate contingent responses, natural reinforcers and reinforcing verbal attempts, and correct verbal responses), and an overall percentage will be calculated. This will be collected pre-intervention, postintervention, and at follow-up.

Satisfaction

Parents will complete a survey rating their satisfaction with their training on a 5-point Likert scale. Items will include, but are not limited to, accessibility, helpfulness, convenience, and thoroughness of training program and materials. Space for parent suggestions will also be provided. This will be collected postintervention.

Child Development Knowledge

To assess child development knowledge, a researcher-created measure will be used that was developed to assess parent knowledge of typical and atypical development. This will be collected pre-intervention, postintervention, and at follow-up.

Secondary Outcome Measures

Overall Language

The Preschool Language Scales Fifth Edition [29] is a norm-referenced, play-based, comprehensive developmental language assessment for children from birth to age 7 years. This will be collected pre-intervention, postintervention, and at follow-up.

Expressive Language

The MacArthur Bates Communicative Development Inventories Words and Gestures Form [30] is a standardized, parent-report form that tracks young children's language and communication skills including words the child understands, words the child uses, and gestures tried or completed. This will be collected pre-intervention, postintervention, and at follow-up.

Parent Stress

The Parenting Stress Index-Short Form [31] is a self-report screening tool that helps providers and families identify the sources and different types of stress that come with parenting. The 36 items are divided into 3 domains that combine to form a Total Stress scale: Parental Distress, Parent-Child Dysfunctional Interaction, and Difficult Child. This will be collected pre-intervention, postintervention, and at follow-up.

Empowerment

The Family Empowerment Scale [32] is a 24-item self-report measure that evaluates levels of empowerment experienced by parents or other caregivers of children with emotional or behavioral challenges. This will be collected pre-intervention, postintervention, and at follow-up.

Challenging Behavior

The Child Behavior Checklist 1.5-5 [33] obtains caregivers' self-report ratings of 99 problem items. Items are scored on the following scales: Emotionally Reactive, Anxious/Depressed, Somatic Complaints, Withdrawn, Attention Problems, Aggressive Behavior, and Sleep Problems. The assessment also includes open-ended questions to obtain additional qualitative information about child problems and strengths. This will be collected pre-intervention, postintervention, and at follow-up.

Social Skills

The Ages & Stages Questionnaire-Social Emotional is a parent-report measure focused on social and emotional

development in young children. The Ages & Stages Questionnaire-Social Emotional provides insight into important developmental areas, such as self-regulation, communication, autonomy, compliance, adaptive functioning, affect, and interaction with people. This will be collected pre-intervention, postintervention, and at follow-up.

Sample Size Determination

A recently published report on a monolingual, brief, online, PRT pilot reported significant improvement in parent fidelity of implementation of PRT strategies and measures of child social communication (vocalizations, eye contact, and positive affect) after 5 weeks, with large effect sizes of 1.80 and 1.12, respectively [20], similar to findings from earlier studies. Therefore, given a conservative estimated effect size of 0.8 for our primary outcomes between baseline and postintervention timepoints, a sample size of 13 is needed to have 80% power to detect a significant difference in primary outcomes between these timepoints given an α of .05. Given our goal of enrolling 24 participant dyads and assuming normal distributions, we can estimate 97% power to detect a significant difference in primary outcomes between baseline and postintervention.

Quantitative Analysis

Linear mixed-effects model analysis will be used to explore most parent-reported and coded outcomes because (1) it allows for individual differences in parent responses over time to be included in the model as a random effect so that the variance in responses is partitioned into a time-within-parent component and a between-parent component, (2) using maximum likelihood estimation in a linear mixed-effects model allows for the use of all available data to evaluate the parameter values and is currently considered the state-of-the-art method for handling missing data, and (3) linear mixed-effects models perform well with small samples. The linear mixed-effects models will evaluate time as the main fixed effect using discrete time variables (ie, 2 dummy variables with baseline as the “referent”). Separate regression models will be run for each outcome. Additional variables to be included in each regression model will include total score of other services used, recruitment site, and only demographic variables significantly related to the outcome (given the small sample size).

Cohen d effect sizes will be calculated between time periods and reported for all analyses of interest as a measure of the magnitude of any changes in outcome measures. Mixed models will also be utilized to test if changes from baseline on outcome variables differ by parent language preference for training (Spanish or English) over time. HOLA acceptability will be determined by the average parent rating on the Parent Satisfaction measure. If the average ratings for parent satisfaction items are 3.5 or higher, the training may remain as written. Items with parent satisfaction ratings lower than 3.5 will be explored during Spanish and English focus groups, and individual items will be refined according to feedback. Focus group transcripts will be coded and analyzed thematically to inform continued program improvement.

Qualitative Analysis

Focus groups comprised of a subsample of Spanish-speaking and English-speaking parents who have completed the HOLA intervention and follow-up activities will be gathered either on campus or by Zoom. The focus groups will last between 1 and 2 hours, and topics related to intervention satisfaction, alignment with cultural beliefs, and socially valid outcomes will be discussed using a flexible protocol that includes open-ended questions and follow-up probes. The facilitator (bilingual graduate research assistant/PI) will engage all participants and allow additional topics to emerge as necessary, while being sure to discuss all protocol questions. The focus groups will be audio-recorded and transcribed verbatim. Analysis will proceed in 3 stages following a modified grounded theory procedure [34]. Initial codes will be written in the margins, actively summarizing but remaining close to the original text. Next, focused coding will proceed where the most frequent and significant codes will be used to synthesize and organize the data. Finally, codes will be sorted into theoretical categories, and relationships among codes and theoretical categories will be hypothesized [34]. Data from focus groups will inform HOLA intervention improvements and may identify areas of participant growth not measured by quantitative assessments.

Results

In a recent commentary on the state of current ASD research, Kasari and Smith [35] recommended additional research be conducted with diverse samples of children with ASD who are minimally verbal to determine whether evidence-based interventions in common use are effective in underrepresented populations. As much of the research on evidence-based interventions for ASD has utilized single-subject designs and homogeneous samples, a trial of a brief bilingual PRT intervention in a Latinx sample will provide the field with valuable insights. The HOLA intervention is simple, cost-effective, and scalable because it can be delivered to parents directly by computer modules accessible by wireless technology and can be easily embedded into existing family routines. As wireless access has expanded, nearly 80% of Latinos in the United States own a smartphone, with those under 30 years old using their cellphone for most of their online activities [21], and cell phone–based interventions have been popular and effective in addressing health disparities in this and other underserved groups [36]. While HOLA is not intended to replace more intensive interventions for ASD, it may provide parents of at-risk or newly diagnosed children with important knowledge about child development and autism symptoms and bridge the gap in access to services for underserved Latinx children.

HOLA modules will teach parents to follow their toddler’s lead and respond to and reinforce their child’s communicative attempts in order to increase child motivation and engagement and improve social, cognitive, and language development. Because most children in underserved communities are unlikely to receive early intervention services for ASD, a missed opportunity to develop crucial social communication, the development of culturally informed bilingual parent-mediated brief PRT interventions like HOLA could bring quality, flexible,

evidence-based interventions to toddlers at risk for ASD while awaiting diagnosis. The HOLA intervention will also increase parenting efficacy by improving a parent's ability to engage with their child through play and daily routines such as mealtime and bath time and may have additional benefits related to decreased child challenging behavior.

To my knowledge, there are no published trials of ASD-focused, parent-mediated interventions designed for Latinx families. As Latinx children are consistently underdiagnosed and underserved by the ASD community, it is crucial to provide parents with knowledge and strategies to assist their child in developing language. The HOLA intervention will require large-scale randomized controlled trials to provide robust evidence of effectiveness in Latinx and additional underserved populations, utilizing fewer parent-report and more observational measures.

The results of this pilot study will be used in the preparation of an application to the National Institute of Deafness and Communication Disorders Early Career Award or to the Institute of Education Sciences Research Training Programs in Special Education Early Career Award for a multiyear randomized controlled trial of the HOLA intervention. Future plans for the HOLA bilingual online training include free public access to all training modules and multilingual peer support pages, as well as links to high-quality resources for families and service providers by way of a university website paired with outreach to local and national disability and autism-focused organizations and childcare providers to inform stakeholders of HOLA's availability. Translation of modules into additional languages including Chinese, Tagalog, Korean, Armenian, Vietnamese, Farsi, Japanese, and Russian should be considered in order to provide access to families who speak the top 10 languages in Los Angeles County.

Discussion

HOLA will help Latinx parents create rich learning environments for their children in Spanish or English, by teaching them how to embed language development opportunities into everyday routines and to improve the reciprocity in their relationship with their child. Our program focus will educate parents about child development and the signs of ASD, thereby improving parents' ability to communicate concerns to appropriate service providers and gain access to diagnostic referrals and quality services. HOLA will also empower parents to better support their child's academic progress through culturally informed advocacy and provide them with information on the importance of self-care when raising a child with learning differences in order to maintain emotional balance and improve family quality of life. Taken together, these outcomes may reduce stigma and depression experienced by Latinx mothers of children with disabilities, reduce the age of ASD diagnosis, and reduce service disparities for Latinx children.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report.
[PDF File (Adobe PDF File), 92 KB - resprot_v9i12e18004_app1.pdf]

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Abbreviations

ASD: autism spectrum disorder
Cal State LA: California State University, Los Angeles
EI: Early Intervention
IRB: Institutional Review Board
MCHAT: Modified Checklist for Autism in Toddlers, Revised, with Follow-Up
PEAS: Parent Education and Support
PI: principal investigator
PRT: Pivotal Response Treatment

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Original Paper

A Culturally Adapted SMS Text Messaging Intervention to Promote Antiretroviral Therapy Adherence Among African Americans: Protocol for a Single-Arm Trial

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Abstract

Background: African Americans are disproportionally affected by HIV and have poorer rates of antiretroviral therapy (ART) adherence compared to other racial or ethnic groups in the United States. Factors associated with poor HIV disease outcomes are commonly associated with sociostructural barriers that prevent engagement with and retention in HIV care. SMS text messaging interventions to promote ART adherence among predominantly non-Hispanic White persons with HIV (PWH) have been shown to be efficacious; however, limited research has been devoted to culturally tailoring interventions for underrepresented racial/ethnic groups. Considering African Americans show poorer engagement along the HIV care continuum, we developed an individualized and culturally tailored two-way SMS text messaging intervention to improve ART adherence and associated virologic suppression among African American PWH.

Objective: In this paper we describe the protocol of a culturally tailored individualized Texting for Adherence Building (iTAB) intervention in a 24- to 48-week, single-arm study.

Methods: We developed a culturally tailored iTAB intervention, which we are implementing in a 24- to 48-week, single-arm study. Participants were recruited from the Family Health Centers of San Diego (FHCSD), a federally qualified health center. Patient inclusion criteria were (1) receiving care at the FHCSD, (2) living with HIV, (3) self-identification as Black, African American, or of African ancestry, (4) English speaking, (5) age 18 or older, (6) currently on ART, and (7) able to provide informed consent. Study enrollment began in November 2017 and closed in July 2019. A total of 90 participants from the FHCSD enrolled in the iTAB intervention, and we anticipate completing data collection in July 2020. Participants were assisted in individualizing and customizing their SMS text message preferences at the baseline study visit. Self-assessment measures are collected at baseline, interim, and final study visits. Problems related to sending/receiving SMS text messages and barriers to ART adherence are assessed at each interim study visit. The FHCSD staff monitors and tracks participants' daily SMS text message responses to ART adherence reminders using a clinical dashboard.

Results: We hypothesize that the proportion of individuals achieving HIV virologic suppression (viral load <40 copies/mL) will be greater at the end of the intervention period compared to the proportion prior to study implementation. Additionally, we anticipate that rates of virologic suppression at the end of the intervention among participants receiving iTAB will be comparable to those among the general FHCSD non-African American population who did not receive iTAB. Finally, we anticipate a high

response rate to iTAB SMS text messages as well as positive participant feedback at the end of the intervention with regard to the acceptability of, satisfaction with, and perceived efficacy of iTAB.

Conclusions: The iTAB intervention is a novel individualized two-way SMS text messaging intervention that has been culturally tailored for use among African Americans with HIV. We anticipate that iTAB will demonstrate efficacy in future randomized control trials and will be supportive of medication adherence among other populations facing health disparities.

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KEYWORDS

medication adherence; behavior modification; short message service; mHealth; HIV/AIDS

Introduction

Across the United States, African Americans are disproportionally affected by HIV compared to other racial or ethnic groups, accounting for approximately 42% of persons with HIV (PWH) [1,2]. As national rates of HIV diagnosis are declining, incident rates among African Americans remain the highest among racial/ethnic groups [3]. In 2017, African Americans accounted for 42% of new HIV diagnoses in the United States, nearly 8 times the rate of infection among non-Hispanic Whites [2]. African Americans have poorer outcomes along the HIV care continuum, including decreased retention in care, lower likelihood of having an antiretroviral therapy (ART) prescription, worse ART adherence, and lower likelihood of achieving viral suppression [4-6]. These disparities along the HIV care continuum significantly contribute to worse overall health, risk of early morbidity, and heighted HIV-related burden compared to other racial/ethnic groups. Indeed, African Americans account for approximately 52% of those who have died from HIV [1]. Thus, providing support for sustained engagement in HIV care among African American PWH is a public health priority.

Factors associated with racial and ethnic disparities in rates of ART adherence influence adherence multidimensionally, operating at the structural (eg, political climate), health system (eg, accessibility of resources), community (eg, societal norms), interpersonal (eg, social support), and individual levels (eg, individual beliefs) [7,8]. Poor health literacy, dissatisfaction with health care providers, insufficient access to mental health services, fear or experience of HIV-associated stigma, incarceration, and poverty pose significant barriers to maintaining optimal ART adherence among African Americans living with HIV [8-12]. Despite efforts to provide widespread access and promote engagement in HIV care [13], many socio-structural barriers that disproportionally affect African Americans living with HIV continue to limit their utilization of health care services [14]. Therefore, developing culturally tailored ART adherence interventions are essential to improving HIV-related health outcomes [15], thereby reducing racial/ethnic health disparities among PWH.

Mobile health-related technologies have the potential to improve access to health care and promote health care management among a broad range of patients, including individuals from racial/ethnic minority groups [16]. Mobile phone ownership is now nearly universal, with 96% of adults in the United States owning a cellphone (including 98% of adult African Americans) in 2019 [17]. SMS text messaging is the most common and frequently used function of mobile phones, comprising 92%-100% of mobile phone usage among adults over the course of a typical week in the United States [18]. Given the ubiquity of mobile phones and high usage of SMS text messaging services, interventions delivered via SMS text message have the potential to support engagement in health care and in health behaviors.

In addition to being low-cost scalable alternatives to in-person interventions, SMS text messaging interventions can be efficacious [19-21]. For instance, the individualized Texting for Adherence Building (iTAB) intervention is a bidirectional SMS text messaging system that was designed to deliver automatic and individualized SMS text messages to assess and promote medication adherence among PWH. The efficacy of iTAB to improve adherence and dose timing has been evaluated among various populations at-risk for lower adherence (eg, ART adherence among PWH with co-occurring methamphetamine use disorder and co-occurring bipolar disorder) [22-24]. Despite evidence of efficacy among individuals from these vulnerable populations, previous intervention studies implementing bidirectional SMS text messaging medication reminders, including iterations of iTAB and other SMS text messaging interventions, may lack sensitivity toward the specific factors affecting ART adherence among African Americans living with HIV [25].

Our research team from the University of California, San Diego (UCSD) HIV Neurobehavioral Research Program (HNRP) and Antiviral Research Center (AVRC) has partnered with one of the top 10 largest (based on the number of patients served) federally qualified health centers, the Family Health Centers of San Diego (FHCSD), to meet the unique sociocultural needs of African American PWH in San Diego by adapting the iTAB intervention. FHCSD is the largest comprehensive HIV/AIDS services provider in the San Diego region, and 11.3% of its patient population are African American. When this project was conceived in 2016, only 77% of African Americans receiving care at FHCSD were virologically suppressed as compared to 90% of the non-African American clinic population. Given this significant disparity, we aimed to implement a culturally tailored bidirectional SMS text messaging intervention to improve ART adherence and related HIV disease outcomes among African Americans receiving care at FHCSD.

This study is a longitudinal project (Individual Community Care for HIV/AIDS Now: Getting Engaged—iC-CHANGE) funded by the California HIV Research Program (CHRP: HD15-SD-059). The formative phase of our intervention study assessed supports and barriers to ART adherence and solicited opinions among a sample of African American FHCSD patients and their providers of HIV care on how to best tailor the iTAB intervention. Suggestions for modification of the iTAB SMS text messaging system included: (1) matching the degree to which SMS text messages disclose HIV-related content depending on participants' level of comfort; (2) variability of SMS text messages, incorporating positive, inspirational, entertaining, and culturally tailored content to their health; (3) personalization of SMS text message content and timing of SMS text messages; (4) positively reinforcing SMS text messages to encourage future adherence; and (5) tracking adherence over time using calendars to facilitate conversations between patients and care coordinators [26]. We also included culturally relevant health messages and trivia factoids (ie, messages including facts and quotes from historical African American figures and trivia pertaining to African Americans, Africa, or the African diaspora) to the extant pool of SMS text messages. Altogether, these features were incorporated into the current iTAB intervention to meet the diverse needs of the target population.

In this paper we describe the protocol followed in the implementation of the tailored iTAB intervention in a 24- to 48-week, single-arm study to evaluate changes in ART adherence and associated virologic suppression among African American FHCSD patients. Early formative work for this study with FHCSD revealed that providing participant's the choice of the length of the intervention (ie, either 24 or 48 weeks) would encourage participation. We hypothesize that a greater proportion of participants will be virologically suppressed (viral load <40 copies/mL) at the end of the intervention period (week 24 or week 48) compared to the proportion of individuals suppressed prior to study participation. Additionally, we hypothesize that rates of virologic suppression at the end of the intervention among participants receiving iTAB will be comparable to rates among the general FHCSD non-African American population who did not receive iTAB. Finally, we anticipate a high response rate to iTAB SMS text messages as well as positive participant feedback at the end of the intervention with regard to the acceptability of, satisfaction with, and perceived efficacy of iTAB.

As an exploratory analysis of service utilization, we will examine whether participation in the iTAB intervention increases engagement in health care and utilization of services at the FHCSD, including fewer missed appointments and greater use of mental health and substance use disorder services. If found to be efficacious among our sample of African Americans living with HIV, the modified iTAB intervention could be used in other settings serving PWH to address, in part, the growing disparity in HIV treatment and care across the United States.

Methods

Participants, Interventions, and Outcomes

Study Setting

Participants were recruited from the FHCSD, a community health organization in Southern California dedicated to providing primary and mental health care to underserved diverse populations. FHCSD is the largest provider of HIV services in the San Diego area and receives Ryan White Part C funds. During the study, participants continue receiving health services at FHCSD and will also attend study visits at FHCSD. Participant data are stored and managed at the UCSD HNRP Center and AVRC.

Study visits are facilitated by care coordinators at the FHCSD. Care coordinators at the FHCSD are required to successfully complete trainings in clinical practices related to research with human participants and HIV education. The investigative team at UCSD's HNRP and AVRC is required to successfully complete training according to standards of the Health Insurance Portability and Accountability Act (HIPAA) and National Institutes of Health, including annual training in "Research Aspects of HIPAA" and "Principles of Human Research Subjects Protection," which emphasize the privacy rights of patients and research study participants and confidentiality safeguards for protected health information.

Eligibility Criteria

Patient inclusion criteria were (1) receiving care at the FHCSD, (2) living with HIV, (3) self-identification as Black, African American, or of African ancestry, (4) English-speaking, (5) age 18 or older, (6) currently on antiretroviral treatment, and (7) able to provide informed consent. Exclusion criteria were minimal, including visible intoxication at the time of the first study visit, having a diminished capacity to provide consent (eg, due to severe neurologic disease, active psychosis, or diminished capacity), or receiving hospice care.

Sample Size

Study enrollment began in November 2017 and closed on July 31, 2019. A total of 90 participants from the FHCSD enrolled in the iTAB intervention (ie, 90% of planned enrollment). Given the timing of enrollment of the last study participant, we anticipate to complete data collection in July 2020. Thus far, we have had 2 participants voluntarily withdraw from the study.

Recruitment

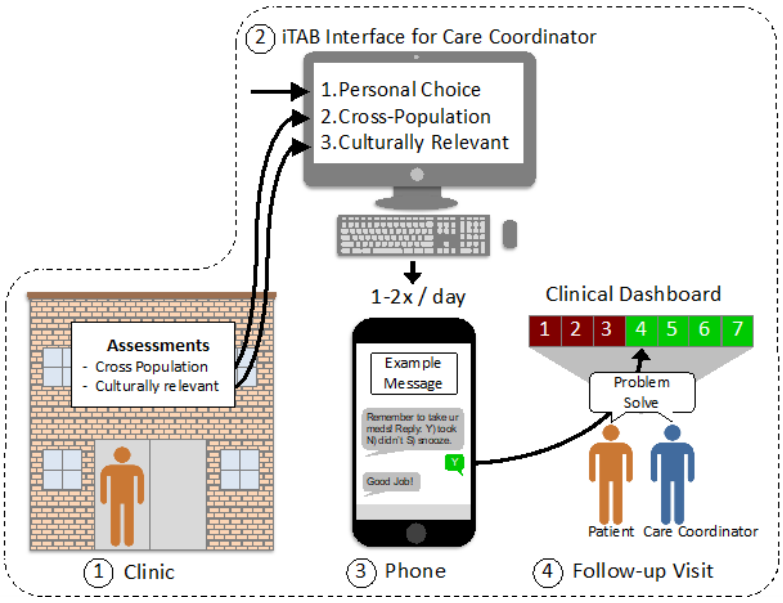
Potential participants were identified by FHCSD staff and invited for study participation through a variety of ways. In particular, the FHCSD care coordinator briefly reviewed the medical records of individuals with upcoming scheduled appointments in order to approach potentially eligible individuals at their in-person clinic visits. Potentially eligible individuals without upcoming appointments were also identified from their medical records and invited by phone to participate. Additionally, potentially eligible individuals were referred to the care coordinator by clinical care providers or self-referred themselves into the study after responding to flyers and recruitment cards. The care coordinator provided a thorough

explanation of the study aims and participant responsibilities (eg, commitment to study visits and SMS text message responding) at the time of recruitment.

Participant Timeline

Participants receive the culturally tailored iTAB intervention, consisting of personalized SMS text messages sent daily to promote ART adherence. Participants have the option to enroll in a 24-week study with 3 visits (baseline, Week 12, and Week 24) or a 48-week study with 5 visits (baseline, Week 12, Week 24, Week 36, and Week 48). The initial visit lasts up to 3 hours and consists of completing a comprehensive battery of psychosocial assessments and setting up the iTAB intervention (eg, customizing SMS text message content and delivery time). Participants return every 12 weeks for interim visits, where they complete psychosocial assessments and discuss any concerns regarding the iTAB system with the FHCSD staff. The final study visit, at either week 24 or 48, lasts approximately 1 hour and includes completing psychosocial assessments and completing an exit interview during which participants are asked to provide feedback on the intervention (see Figure 1 for a schematic depicting the participant timeline).

Figure 1. Schematic depicting study timeline, including iTAB setup. iTAB: individualized Texting for Adherence Building.



iTAB Setup

At the initial study visit, each participant meets with an FHCSD care coordinator to review the informed consent documents for the study, completes psychosocial assessments, and sets up the iTAB system to receive SMS text messages on their mobile phone.

During iTAB set up, the HIV care coordinator first discusses with participants the time of day they want to receive the daily medication reminder SMS text messages. Participants are encouraged to set their SMS text message delivery time to coincide with their regular ART administration time and are able to select different SMS text message delivery times for week days versus weekend days. Participants are also informed that the iTAB system automatically sends their daily SMS text messages at random times within a half-hour window of their selected target time to limit habituation.

With regard to customizing SMS text message content, participants can select between receiving "low-disclosure" SMS text messages (ie, SMS text messages with no mention of HIV or the presence of a health condition) or "moderate-disclosure" SMS text messages (ie, SMS text messages that might allude to the presence of a health condition or contain factoids related to HIV, but do not disclose HIV status). In order to protect against unintentional divulgence of sensitive health information, when participants elect to receive moderate-disclosure SMS text messages, they are asked to also provide a word or brief phrase by which their ART will be referred to within the body of the SMS text messages (eg, "For some, taking all of their medications is part of a healthy and happy life. Please take your [insert word or brief phase]).

Within each disclosure category (ie, low versus moderate), participants are instructed to select at least five and up to 14 health promotion domains (eg, social support, celebrate health, self-esteem) and at least five and up to 18 factoid domains (eg, music, sports, food) for SMS text message content variability. For illustration, a low-disclosure health promotion SMS text message within the social support domain reads, "You are an asset to your community!" Examples of SMS text messages within the health promotion and factoid domains for both low- and moderate-disclosure categories are listed in Tables 1 and 2. As shown in Table 1, domains and SMS text messages within each disclosure level are overlapping and similar. In addition to daily medication reminder SMS text messages, participants are scheduled to receive health promotion SMS text messages during the standard working week and factoid SMS text messages on weekend days.

Table 1. Examples of health promotion SMS text messages by disclosure level (low versus moderate).

Health promotion domains	Low-disclosure sample SMS text message	Moderate-disclosure sample SMS text message[a]
Celebrate health	This is a friendly reminder to help keep you feeling good.	To help keep you feeling good, this is a friendly reminder to take your *iC-CHANGE*
Time/Focus	It only takes a second!	It only takes a second to be adherent!
Social support	You are an asset to your community!	You are an asset to your community! Please take your *iC-CHANGE*
Family support	You have wonderful family and friends.	Your family wants you to be happy and healthy! Please take your *iC-CHANGE*
Prevent disease	Take charge of your health!	Protect your health. Please take your *iC-CHANGE*
Self-esteem	You are special.	You are special. Please take your *iC-CHANGE*
Believing in yourself	You've been doing great!	You've been doing great with your adherence!
Dangers of poor habits/nonadherence	Being healthy won't happen if you don't work for it.	Meds don't work if you don't take them. Please take your *iC-CHANGE*
Religious (Christian)	We need God as much in the calm as in the storm—Jack Hyles	We need God as much in the calm as in the storm—Jack Hyles
Religious (non-Christian)	Nothing is ever lost in following one's own dharma—Bhagavad Gita	Nothing is ever lost in following one's own dharma—Bhagavad Gita
Linking meds to behaviors	For some people, health behaviors are easier done soon after they wake up.	For some, taking meds is made easier when paired with something they do every day.
Other med taking	Remember that it helps you in different ways to stay healthy and happy.	Remember that all of your medications help you in different ways to stay healthy and happy. Please take your *iC-CHANGE*
SMS text messages from your provider	Wellness is key to a healthy life.	Wellness is key to a healthy life.
FHCSD[b] support SMS text messages	FHCSD offers a wide range of health care services, including dental clinics, mental health, and substance abuse treatment.	FHCSD offers a wide range of health care services, including dental clinics, mental health, and substance abuse treatment.

[a]In the moderate-disclosure SMS text messages, participants were asked to provide a word or brief phase by which their medication would be referred to within the body of the text SMS text messages (ie, instances of *iC-CHANGE* in the moderate-disclosure SMS text messages was a space-filler and indicated whether the word or brief phase would be placed in the SMS text message).

[b]FHCSD: Family Health Centers of San Diego.

Table 2. Examples of factoid SMS text messages.

Factoid domains	Sample SMS text message
Health facts[a]	Our eyes never grow, but our nose and ears never stop growing.
HIV facts[b]	About 1/4 of HIV+ people have hepatitis C.
Affirmations	My body is healthy; my mind is brilliant; my soul is tranquil.
Fashion	The skirt is the 2nd oldest piece of clothing, outdated only by the loincloth.
Food	An ounce of chocolate contains about 20 mg of caffeine.
History	Madame Walker invented hair straightening formula and became the first female African American millionaire.
Jokes	What's the best thing about Switzerland? Not sure, but the flag is a big plus.
Lifehack	Can't sleep? Inhale for 4 seconds. Exhale for 8 seconds. Repeat. This will relax your body right to sleep.
Music	Michael Jackson bought the rights to most of the Beatles' music for US$47.5M in 1985. It's now worth US$450M.
Quotes	Seven days without laughter makes one weak. -Mort Walker
Science	The hottest planet in the solar system is Venus, with an estimated surface temperature of 864 F (462 C).
Southern California	The Ruins of Bombay is a town on the Salton Sea, one of the lowest settlements in altitude in North America.
Sports	Pittsburgh is the only city where all the major sports teams (MLB, NHL, NFL) have the same colors: Black/gold.
General trivia	The word malaria means bad air. This derives from when it was thought that diseases were caused by dirty air.
TV/Movies	The 1st movie with sound was The Jazz Singer (1927). 1st words: 'Wait a minute, you ain't heard nothing yet'.
Word of the Day	kalimba: a plucked instrument of African origin.
SMS text messages about health[a]	Take care of your body. It's the only place you have to live.—Jim Rohn.
SMS text messages about HIV[b]	HIV changed my life, but it doesn’t keep me from living.—Magic Johnson

[a]Factoid domain present only in the low-disclosure setting.

[b]Factoid domain present only in the moderate-disclosure setting.

After customizing SMS text message content, participants have the option to personalize their response options to the iTAB SMS text messages. The standard iTAB setup provides participants with 3 response options to the iTAB SMS text messages: Y) Yes, N) No, and S) Snooze. However, participants are able to select alternative response options that maintain the same letter codes: for example, Y) Yeh, N) Nah, and S) Zzzz.... Participants are also asked to select at least ten positive reinforcement SMS text messages from a pool of 26 SMS text messages. Reinforcement SMS text messages are sent to participants after they send an SMS text message response indicating ART adherence. A typical reinforcement SMS text message reads, “Great job!” Participants are also able to customize the reinforcement SMS text messages by composing their own reinforcers.

Once participants make their various SMS text message selections, the care coordinator reviews the settings with the participant before they are saved to the secure iTAB system database (Figure 2 shows a screenshot of the iTAB interface with SMS text message selections). Prior to concluding the baseline visit, a sample SMS text message is sent to ensure the participant can receive SMS text messages and successfully respond to the system. Once the iTAB system is set up for an individual, automatically generated SMS text messages can be sent to the participant following a decision tree algorithm (Figure 3). For example, a personalized reminder SMS text message might read, “Be covered! It’s dose time.” If the participant replies “Y,” a personalized positive reinforcement SMS text message is automatically sent to the participant (eg, “Keep up the good work!”). If a participant replies “N,” an encouraging SMS text message to take their medications is sent (eg, “Please take a moment for your health ASAP. Call us if you need assistance or have a question”). If a participant responds “S,” a follow-up reminder SMS text message is sent after an hour delay (eg, “Hi. You did not take a break for yourself an hour ago, have you been able to do so since then?”). Finally, if a participant sends an unexpected response to an SMS text message (ie, anything other than a “Y”, “N”, or “S”), the iTAB system sends an automatic response to the participant stating that their response was not understood.

Figure 2. iTAB interface with SMS text message selection options. iTAB: individualized Texting for Adherence Building.

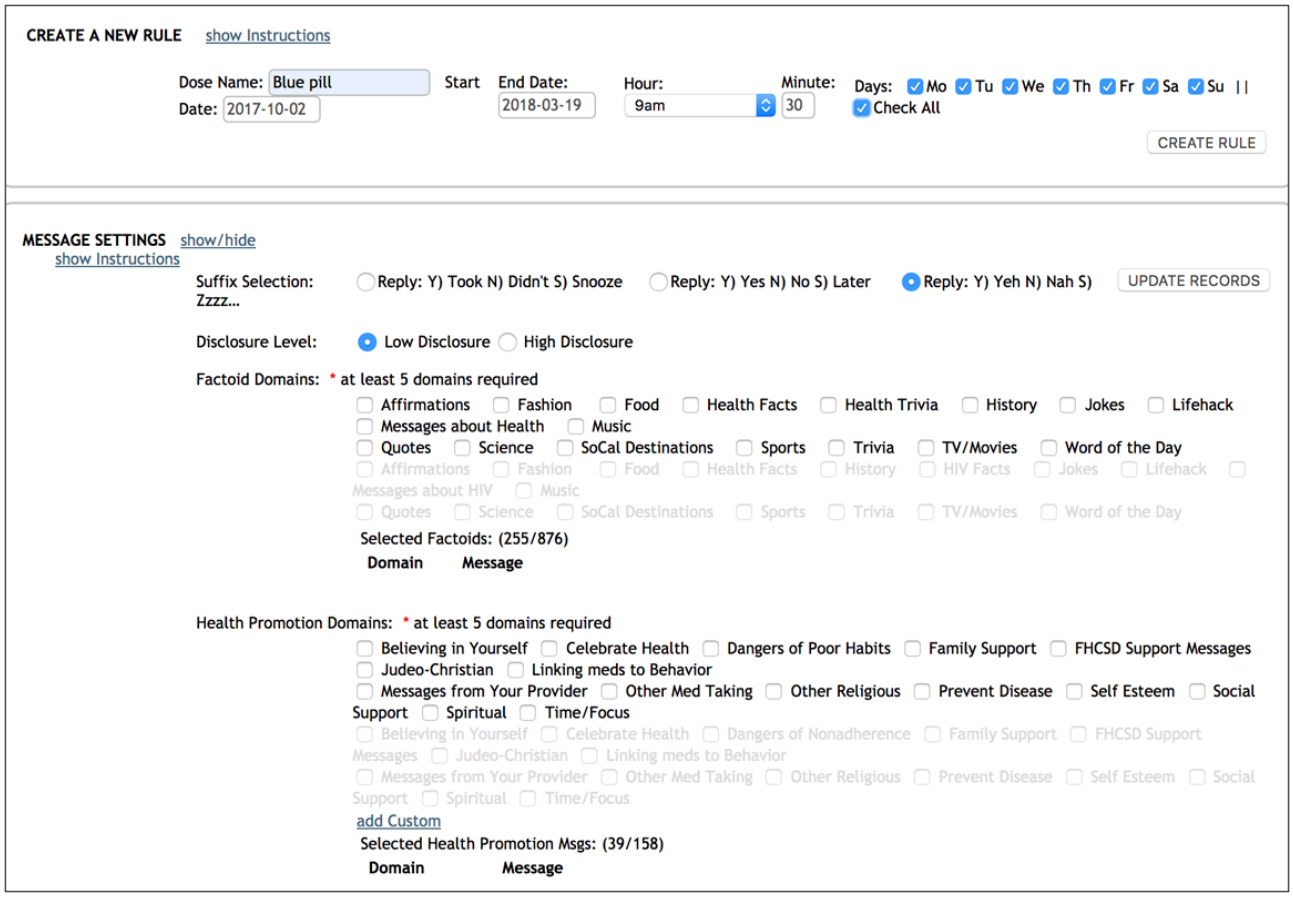
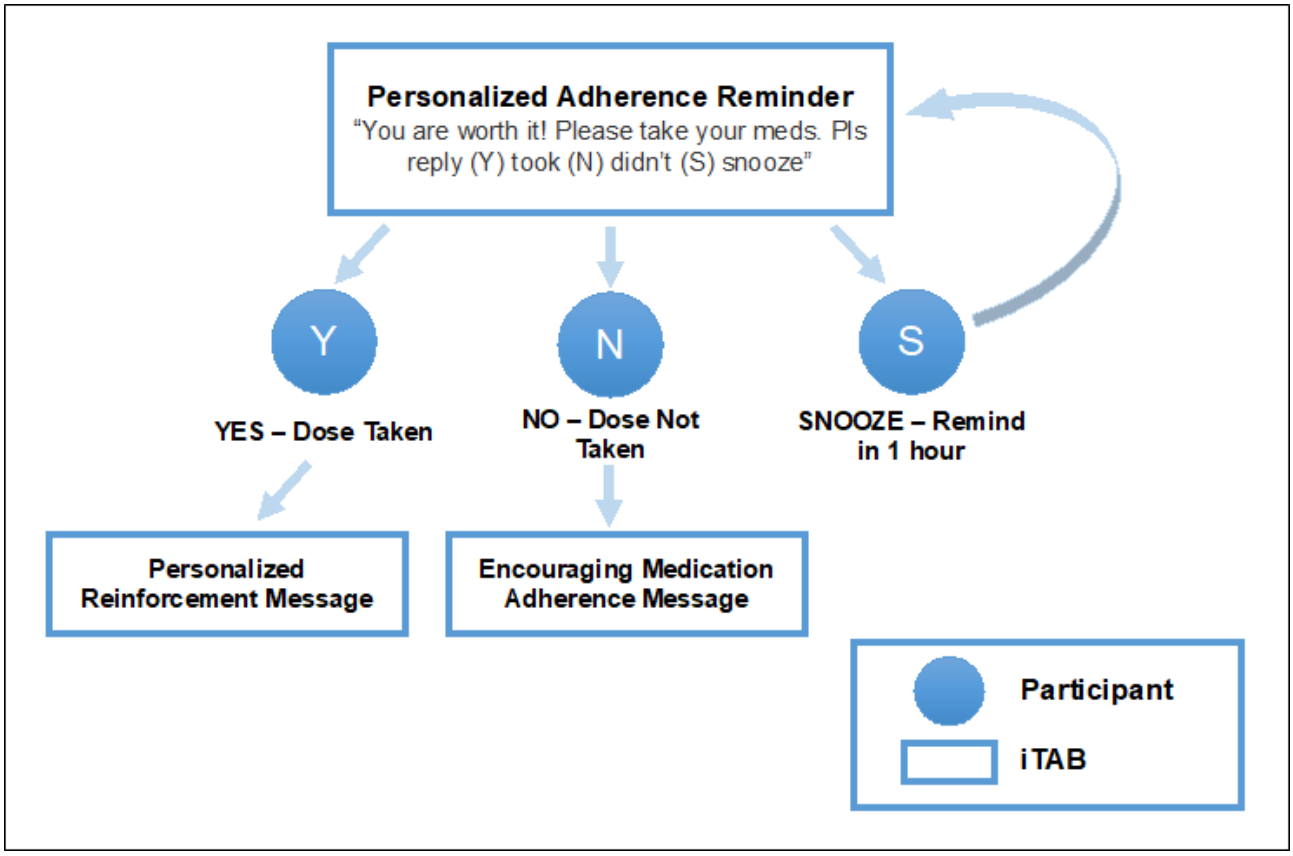


Figure 3. iTAB SMS text message decision system. iTAB: individualized Texting for Adherence Building.



Participant Monitoring

Within 2 weeks of the baseline visit, participants are contacted by an FHCSD care coordinator over the phone to discuss any issues related to receiving and responding to SMS text messages. Participants are also contacted by an FHCSD care coordinator 4 weeks prior to their in-person study visits to schedule their upcoming appointment. At interim study visits (Week 12, 24, and 36, depending on the duration of the intervention), participants are asked to complete a set of psychosocial questionnaires and discuss concerns regarding the iTAB system. Additionally, participants and care coordinators reassess SMS text message customizations at each interim clinic visit to ensure participant satisfaction with the system and to optimize ART adherence.

All SMS text messages sent (eg, reminders, reinforcement SMS text messages) and received (eg, participant responses) by the iTAB system are recorded. After 3 consecutive days of nonresponse to SMS text messages or "N" responses to prompts about medication adherence, an automated SMS text message regarding participant noncompliance to the study and to their medications is triggered. An FHCSD care coordinator attempts to contact the participant to discuss barriers to medication adherence (eg, forgetting dose time) and potential solutions (eg, pairing medication taking with another daily behavior, such as brushing one's teeth).

The care coordinator is also able to monitor and track participants' daily SMS text message responses to medication adherence reminders using the iTAB clinical dashboard. For ease of interpretation, the dashboard utilizes a "Stop-Light" system as a simple summary of the self-reported adherence rate (Figure 4). Adherence rates greater than 90% are displayed with a green circle, those between 70% and 90% with a yellow circle, and those less than or equal to 70% with a red circle. Furthermore, a monthly calendar summarizes past daily adherence and is color coded according to participants' daily self-reported adherence (Figure 4). The iTAB clinical dashboard is used to facilitate conversations between the participant and care coordinators during interim clinic visits about ART adherence and to problem solve instances of nonadherence or nonresponse to SMS text messages. Information from the clinical dashboard is not shared with health care providers.

Figure 4. Example of the iTAB dashboard and summary of medication adherence with the Stop-Light System. Example of iTAB Calendar Report for ART adherence and SMS text message responses. These examples are of an individual on 2 doses of medication a day, receiving 2 iTAB SMS text messages per day. ART: antiretroviral therapy; iTAB: individualized Texting for Adherence Building.

Outcomes

Undetectable plasma viral load and ART adherence (as measured by participants' responses to daily SMS text messages) are the primary outcomes for this single-arm trial. In addition, participants complete an in-person comprehensive battery of psychosocial assessments at the baseline, interim, and end-of-study visits (at either Week 24 or Week 48). Specific assessments administered at each study visit are listed in Table 3. Assessments with strong reliability and validity among HIV populations were chosen, where possible. Measures collected at the baseline study visit include plasma viral load (abstracted from FHCSD electronic medical records), medication adherence behaviors (eg, percentage of adherence in the past 30 days), psychosocial risk factors associated with poor HIV-related outcomes among PWH (eg, sociodemographic characteristics, substance use, and social support), and culturally specific risks for nonadherence among African Americans (eg, subjective experiences of discrimination, HIV-related stigma, and medical mistrust). Measures collected at interim study visits (ie, every 12 weeks) are a subset of the baseline measures (eg, perceived stress, alcohol use, substance use, and depressive symptoms). Upon completion of the intervention (at either week 24 or 48), participants complete a subset of psychosocial assessments, as well as a feedback questionnaire assessing their experience, satisfaction with, and perceived usefulness of the intervention. Laboratory data on HIV-disease characteristics (eg, plasma viral load and CD4 count) and utilization of FHCSD services are collected from electronic medical records by care coordinators at each in-person study visit.

Table 3. Assessments administered[a]

Domain	Assessments	Baseline	Week 12, 36	Week 24, 48
HIV disease variables and antiretroviral therapy adherence				
Primary outcome: Viral load[b]	Data acquired from FHCSD[c] blood draw at clinical visit	X		X
CD4 count[b]	Data acquired from FHCSD blood draw at clinical visit	X		X
Self-report of ART[d] adherence	Ira Wilson Adherence Questionnaire (IWQU) [27]	X	X	X
Factors that may impact antiretroviral therapy adherence				
Sociodemographic characteristics	Self-reported sex, gender, age, race, ethnicity, birth location, relationship status, HIV status disclosure, employment, income, housing stability, education	X		
Depression symptoms	Beck Depression Inventory-II (BDI)	X	X	X
Alcohol and illicit substance use	Alcohol Use Disorders Identification Test (AUDIT) and Drug Abuse Screening Test (DAST-10 Modified)	X	X	X
Subjective social status	MacArthur Scale of Social Status Scale	X		
Beliefs related to HIV medications	Beliefs Related to Medications Questionnaire	X		
Supports and barriers to adherence	Supports and barriers to adherence	X		
Self-efficacy for medications	Self-efficacy for managing medications and treatments	X	X	X
Illicit substance use and sexual behaviors	Risk Questionnaire	X		X
Collective self-esteem	Collective Self Esteem Scale	X		X
Medical mistrust	Trust in the medical system; attitudes toward the health care	X		X
Instrumental and social support	NIH Toolbox Emotional Support, Instrumental Support, and Loneliness scales	X		X
Beliefs about HIV	Beliefs about HIV	X		X
Subjective experiences of discrimination	Everyday Discrimination Scale; Multiple Discrimination Scale	X		X
Quality of life	Medical Outcomes Study: 36-item Short Form Survey (MOS: SF-36)	X	X	X
Personality	Ten-Item Personality Inventory	X		
Perceptions of stress	Perceived Stress Scale	X	X	X
Lifetime exposure to stress/adversity	Negative life events	X		
Health care utilization	Utilization of care	X		X
Health literacy	Short Assessment of Health Literacy-English (SAHL-E)	X		
Stigma and psychosocial aspects of living with HIV	HIV Stigma Scale	X		
Religiousness/Spirituality	Brief Multidimensional Measure of Religiousness and Spirituality	X		
Cellphone Usage	Cellphone Usage Questionnaire	X		
Medication-taking behavior[e]	Medication-Taking and Text-Responding Behavior Questionnaire			X
Intervention feedback[e]	iC-CHANGE Feedback Questionnaire (Likert scales of feasibility, acceptability, and satisfaction)			X

[a]The X denotes those visits where the assessment will be administered.

[b]Data collected from electronic medical records from FHCSD clinical visit during the study period or provided by the participant.

[c]FHCSD: Family Health Centers of San Diego.

[d]ART: antiretroviral therapy.

[e]Administered only at the final visit.

Participant Compensation

In consultation with FHCSD, we determined the amount of funds that would be appropriate for compensation. Participant compensation was consistent with levels used in other studies at FHCSD. The goal was to provide at least US $13 per hour, inclusive of travel time. Participants are compensated US $50 for the baseline visit and each interim visit. Additionally, they receive US $70 for their final visit, at either Week 24 or Week 48. Consequently, participants stand to be compensated up to US $170 for the 24-week study, or US $270 for the 48-week study.

Data Collection, Management, and Analysis

Data Collection Methods

The iTAB system records all SMS text messages that are sent (eg, reminders, reinforcement SMS text messages) and received (eg, participant responses). Indicators of medication adherence as well as adherence to the intervention are collected via the iTAB system.

Measures (data derived from the electronic medical record and psychosocial assessments) are collected at baseline, interim, and the final study visits. Assessments within a given domain were selected based on reliability and validity among African Americans living with HIV. The self-assessments administered at each study visit are listed in Table 3. Participants are allowed to continue study participation at any point, even after multiple missed in-person visits or periods of nonresponsiveness to SMS text messages. If a participant is lost to follow-up, the care coordinator will attempt to contact the participant by phone on a weekly basis for a 1-month period. If contact is not made within the 1-month period, the care coordinator will attempt to contact the participant by phone on a monthly basis. The care coordinator can additionally check if the participant has a primary care appointment scheduled. If successfully contacted, the care coordinator will assess the participant's unique barriers and challenges to committed participation in the study and attempt to collaboratively find appropriate solutions (eg, if the participant no longer has a cell phone, a study phone may be provided [up to 1 replacement phone]). Participants expressing the desire to terminate their study participation are formally withdrawn from the study and their data excluded from analyses.

Data Management

FHCSD has implemented a HIPAA-compliant electronic health record system. This system has built-in access controls, such as passwords and PIN numbers, limited access to protected information, encrypted storage, and an audit trail, which tracks records accessed and by whom. Medical information (eg, HIV status, toxicology results, and medical history) gathered by the FHCSD care coordinators at each in-person visit is deidentified so that investigators at UCSD's HNRP and AVRC cannot link the unique study IDs to identifying information, such as names or medical record numbers. Participants' actual names, medical record numbers, and other identifying information remain with the FHCSD at all times.

Participant self-report psychosocial assessments are completed at the FHCSD. To promote data quality, care coordinators continuously assess for unusual patterns of responding (eg, providing the same response to all questions) and missing questions at each study visit. Physical copies of the self-report psychosocial assessments are regularly transferred to the HNRP in a secured case by at least two study personnel. Prior to data entry, questionnaires are double-scored and flagged for missing responses using the code "999." Assessments are then entered into the secure HNRP database using the participant's deidentified study ID.

Outcomes

The primary outcomes of the intervention are undetectable plasma viral load and self-reported ART adherence, as measured by participants' responses to daily SMS text messages. We hypothesize that a greater proportion of iTAB participants will be virologically suppressed (viral load <40 copies/mL) at the end of the study period (either week 24 or 48) compared to the proportion at study entry. Currently, 77% of African Americans living with HIV receiving services at the FHCSD are virally suppressed. We hypothesize an increase of 11% (ie, from 77% to 88%) in the proportion of participants with undetectable viral loads at study completion. We additionally hypothesize that the rates of viral load suppression after the intervention will be comparable to the general FHCSD non-African American population who did not complete the iTAB intervention. Lastly, we hypothesize high engagement with the iTAB system reflected by high response rates to iTAB SMS text messages and positive feedback regarding the acceptability, satisfaction with, and efficacy of iTAB.

In addition to these primary anticipated results, we hypothesize that participants involved in the iTAB intervention will utilize more comprehensive FHCSD services, have fewer missed appointments, and greater use of substance use and mental health services compared to those not in iTAB.

Statistical Methods

We will characterize HIV disease characteristics (eg, CD4 count) and psychosocial characteristics of the study population using descriptive statistics. Linear regressions will be used to examine psychosocial factors associated with ART adherence. The number and proportion of virologically suppressed participants at baseline and at the final study visit will be compared. We will use McNemar test for paired proportions to compare virologic control within-subjects using data from the baseline and final study visits. Based on a 2-sided, 1-sample test for proportions to compare the viral suppression rate before and

after the 48-week study, we have 74% power to detect an increase of 11% in suppression rate (ie, from the reference 77% to 88%) with N=88 participants and alpha =.05.

In secondary/sensitivity analyses, multivariable conditional logistic regression analysis will be performed to study the association between demographic factors and plasma viral load, adjusting for baseline demographic variables and clinical characteristics. Variables with some association to plasma viral load ($P<.10$) will be included as covariates. Data from participants will also be analyzed using methods appropriate for examining longitudinal data, for instance, linear mixed-effect modeling/multilevel modeling, latent growth curve modeling, and growth mixture modeling. These model types will allow for interpreting fixed effects (average group trajectory), random effects (individual variability), and heterogeneity in shape of longitudinal change. All tests of significance for secondary outcomes will be 2-sided; following standard conventions, a *P*-value of less than .05 will be considered as statistically significant. Appropriate nonparametric alternatives will be considered, if parametric assumptions are not appropriate for the data.

The secondary outcomes of the intervention will be responses from the various Likert-type assessments administered at each study visit (eg, medical mistrust, provider satisfaction, barriers to health care access, and alcohol or illicit substance use) and the iTAB feedback questionnaire. We will use regression-based models to examine the associations between these nonadherence risk factors and other study outcomes (eg, association between perceived efficacy of iTAB and virologic suppression).

Monitoring

Harms

No significant harms associated with participation in the iTAB intervention are anticipated. Significant and severe problems, including those related to mood, substance use, or structural barriers to adherence, are closely monitored and addressed appropriately. At each study visit, care coordinators and study investigators review participants' psychosocial assessments and appropriately consider referral to mental health services. If participants endorse thoughts of harm to self or others, care coordinators triage the participant to the FHCSD clinical team for further evaluation of risk and for appropriate coordination of care.

Auditing

FHCSD and HNRP staff including primary investigators and care coordinators are responsible for data quality assurance and monitoring of study visit completions.

Ethics and Dissemination

Research Ethics Approval

The study protocol was approved by the Institutional Review Board at UCSD and all participants provided written informed consent to participate.

Protocol Amendments

All protocol amendments will be submitted for approval by the UCSD Institutional Review Board. Study funders and key staff will be informed of protocol amendments. Study participants will review and sign a revised consent form in the event that the consent form is changed.

Consent or Assent

At the initial study visit, the care coordinators thoroughly review the consent form with the participant, specifically noting the descriptions of study procedures and potential risks to participating. Any individual who was unable to adequately complete the consent form was not enrolled in the study. If a participant's capacity to consent was in question, the participant was evaluated by a clinical psychologist or FHCSD health care provider who made the final determination of decisional capacity. This decision and a detailed explanation from the clinician/health care provider was documented.

Confidentiality

Efforts to maintain and protect patient privacy are of the utmost importance. Recruitment of participants, informed consent procedures, and study visits are conducted individually in a private medical examination room in order to maintain confidentiality. Additionally, to ensure confidentiality, data linking participant IDs to their nonidentifiable study ID are stored in a secure database at the FHCSD. Only the participant's code number appears on all data collection forms at the HNRP and FHCSD. Identifiable protected health information, including participant study information and signed consents, is stored in locked file cabinets within secured rooms at FHCSD.

Physical files containing deidentified quantitative data (ie, self-report psychosocial assessments) are routinely transported from the FHCSD to the HNRP in a locked briefcase by 2 study personnel (EP and RG). Quantitative data are entered into a database at the HNRP, and all physical records are stored in a locked file room. The only protected health information that is obtained or stored on a multilevel hardware/software firewalled and encrypted UCSD network is a phone number, which is necessary to send the SMS text messages.

The study design minimizes risk associated with using mobile communication. At study enrollment, each participant's mobile phone number is linked to an anonymous ID that is verified through a 2-step authentication process. Furthermore, SMS text messages that arrive on participants' phones are sent from a generic UCSD phone number and do not include any participant identifying information (eg, participant name). All text SMS text message data are secured on a private UCSD network and can only be accessed via a virtual private network and secure password-protected website. These systems comply with HIPAA regulations for protection of person-identifiable health data over the internet. An HNRP Confidentiality Committee performs regular inspections to monitor procedures.

Results

Study Enrollment

Study enrollment began in November 2017 and closed in July 2019. A total of 90 participants from the FHCSD enrolled in the iTAB intervention. Given the timing of enrollment of the last study participant, we anticipate completing data collection in July 2020. As of April 2020, 64 participants have completed the study. Two participants have withdrawn from the study, resulting in the total sample of 88 participants.

Participant Characteristics

Baseline demographic characteristics are presented in Table 4. The mean age of participants was 46.4 (SD 11.9) years. Participants primarily identified as male, Black/African American/African origin, and reported some college education. In terms of employment status, nearly two-thirds of the sample were either currently unemployed or currently on disability. With respect to HIV disclosure, a majority of participants have disclosed their HIV status, with approximately three-fourths confiding in their friends and family.

Table 4. Baseline demographic characteristics (N=88).

Descriptive	Value
Age, mean (SD)	46.4 (11.9)
Education, mean (SD)	14.7 (13.2)
Sex assigned at birth (male), n (%)	76 (86)
Gender identity	
Men, n (%)	73 (83)
Women, n (%)	13 (15)
Transman/Trans Male/Transmasculine, n (%)	0 (0)
Transwoman/Trans Female/Transfeminine, n (%)	1 (1)
Genderqueer/Gender nonconforming, n (%)	1 (1)
Race	
Black/African American/African origin, n (%)	74 (84)
Black mixed-race identity[a], n (%)	14 (16)
Spanish/Hispanic/Latino Origin, n (%)	9 (10)
Born in United States (Yes), n (%)	79 (90)
Born in California (Yes), n (%)	33 (38)
Disclosed HIV status (Yes), n (%)	79 (90)
Disclosed to family, n (%)	64 (81)
Disclosed to friends, n (%)	70 (89)
Employment status	
Full-time employment, n (%)	18 (20)
Part-time employment, n (%)	13 (15)
Currently unemployed, n (%)	27 (31)
Currently on disability, n (%)	24 (27)
Other[b], n (%)	6 (7)

[a]Black mixed race identity refers to identifying as Black as well as other racial identities including American Indian or Alaska Native, Asian American or Asian Origin, Native Hawaiian or Pacific Islander, or White.

[b]Includes looking for a job, applying for supplemental security income (SSI), applying for disability, or retired.

Discussion

Protocol Summary

This longitudinal study, titled “Individual Community Care for HIV/AIDS Now: Getting Engaged (iC-CHANGE),” aims to improve ART adherence among African Americans living with HIV using a culturally adapted bidirectional SMS text messaging intervention. Previous studies have demonstrated the efficacy of 2-way SMS text messaging interventions in supporting ART adherence; however, these studies primarily enrolled non-Hispanic white PWH despite epidemiological evidence of greater HIV-related burden among African American PWH [25]. This protocol details the implementation of an intervention that was adapted using feedback from African American PWH and their providers of care [26]. We anticipate that the tailored iTAB intervention will significantly improve ART adherence

among the targeted population and, consequently, could be implemented among other African American PWH across the state of California.

Challenges

In formative study phases, issues arose related to integrating community-based participatory research with clinical practice. Focus group discussants suggested that the study facilitate interactions between patients and their providers of clinical care [26]. Thus, we aimed to provide study participants with the choice to share their iTAB adherence calendars with their providers to promote conversations around adherence. FHCSD has a proprietary medical record system and integrating our research findings with health care providers in a reliable and secure fashion proved to be a substantial barrier. Future implementation science studies will aim to strategically incorporate iTAB with electronic medical records where health care providers can access study-derived outcomes to enhance clinical care.

Future Directions

Should findings for this study indicate this intervention is useful in improving ART adherence, future research may include conducting a randomized control trial of the iTAB intervention among African Americans living with HIV against a control group. Following evidence of efficacy in a randomized control trial, we may also conduct a larger-scale implementation study across multiple settings. Additionally, future work will examine the possible unidentified moderators of intervention effects including structural, health system, community, interpersonal, and individual facilitators or barriers to adherence that may supersede the beneficial potential of iTAB. Furthermore, there may be other subgroups of PWH at FHCSD (eg, other racial/ethnic minorities, persons with low socioeconomic status, or intravenous drug users) that would similarly benefit from individualized adherence SMS text messages and should be the focus of future efficacy studies. Finally, future work will expand on the identification of key predictors and SMS text message types for improving ART adherence. For instance, some constructs assessed may have good predictive value of future decline in viral load and may be effective tailoring variables for supporting adherence in subsequent interventions.

Conclusions

In summary, given the integration of the feedback from key stakeholders in a previous study, we anticipate that the modified iTAB intervention has great potential for improving HIV disease outcomes, including medication adherence and virologic suppression among African American PWH.

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Conflicts of Interest

MH received research funding from Gilead and Pfizer, outside the submitted work.

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Abbreviations

ART: antiretroviral therapy
AVRC: Antiviral Research Center
FHCSD: Family Health Centers of San Diego
HIPAA: Health Insurance Portability and Accountability Act
HNRP: HIV Neurobehavioral Research Program
iTAB: individualized Texting for Adherence Building
PWH: persons with HIV
UCSD: University of California, San Diego

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Protocol

Remote Assessment of Disease and Relapse in Epilepsy: Protocol for a Multicenter Prospective Cohort Study

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Abstract

Background: In recent years, a growing body of literature has highlighted the role of wearable and mobile remote measurement technology (RMT) applied to seizure detection in hospital settings, whereas more limited evidence has been produced in the community setting. In clinical practice, seizure assessment typically relies on self-report, which is known to be highly unreliable. Moreover, most people with epilepsy self-identify factors that lead to increased seizure likelihood, including mood, behavior, sleep pattern, and cognitive alterations, all of which are amenable to measurement via multiparametric RMT.

Objective: The primary aim of this multicenter prospective cohort study is to assess the usability, feasibility, and acceptability of RMT in the community setting. In addition, this study aims to determine whether multiparametric RMT collected in populations with epilepsy can prospectively estimate variations in seizure occurrence and other outcomes, including seizure frequency, quality of life, and comorbidities.

Methods: People with a diagnosis of pharmacoresistant epilepsy will be recruited in London, United Kingdom, and Freiburg, Germany. Participants will be asked to wear a wrist-worn device and download ad hoc apps developed on their smartphones. The apps will be used to collect data related to sleep, physical activity, stress, mood, social interaction, speech patterns, and cognitive function, both passively from existing smartphone sensors (passive remote measurement technology [pRMT]) and actively via questionnaires, tasks, and assessments (active remote measurement technology [aRMT]). Data will be collected continuously for 6 months and streamed to the Remote Assessment of Disease and Relapse-base (RADAR-base) server.

Results: The RADAR Central Nervous System project received funding in 2015 from the Innovative Medicines Initiative 2 Joint Undertaking under Grant Agreement No. 115902. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation program and European Federation of Pharmaceutical Industries and Associations. Ethical approval was obtained in London from the Bromley Research Ethics Committee (research ethics committee reference: 19/LO/1884) in January 2020. The first participant was enrolled on September 30, 2020. Data will be collected until September 30, 2021. The results are expected to be published at the beginning of 2022.

Conclusions: RADAR Epilepsy aims at developing a framework of continuous data collection intended to identify ictal and preictal states through the use of aRMT and pRMT in the real-life environment. The study was specifically designed to evaluate

the clinical usefulness of the data collected via new technologies and compliance, technology acceptability, and usability for patients. These are key aspects to successful adoption and implementation of RMT as a new way to measure and manage long-term disorders.

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KEYWORDS

epilepsy; seizures; telemedicine; medical device; mobile phone

Introduction

Background

The last decade has seen an explosion in the capability of monitoring individuals via sensors in smartphones or wearable devices, and the range of parameters that can be measured by such technologies will continue to grow [1]. Remote measurement technologies (RMTs) can unobtrusively measure human behavior and physiology and, combined with active measurement of daily experiences via smartphone apps, is an innovation that could be used to provide real-time information about the current clinical state of patients and information potentially predictive of future deterioration [1]. RMT appears to be particularly interesting for those chronic conditions whose course is dynamic and characterized by multiple variations in parameters that can be measured remotely, actively and/or passively [2,3]. Epilepsy is one of the most common neurological disorders, affecting approximately 0.6% of the population worldwide [4]. It is characterized by recurrent seizures that manifest with physiological and behavioral phenomena [5]. Seizures are mostly unprovoked and unpredictable, and about 1 in 3 of all people with epilepsy do not respond to any medication and continue to have uncontrolled seizures [6]. The personal, social, and economic costs of uncontrolled epilepsy are considerable: seizure recurrence and unpredictability worsen the quality of life (QoL) of people with epilepsy and their families [7], people with active epilepsy have 4 to 5 times higher standardized mortality ratios compared with seizure-free individuals [8-12], and the economic burden for the health system is significant across countries [13,14]. Despite new antiepileptic drugs coming to the market, there is limited evidence of a substantial difference to treatment-refractory patients [15], and overall, the mortality associated with epilepsy has not decreased in the last 50 years [16]. One reason for the failure of trials of new treatments is that it is difficult to collect objective data regarding relevant clinical outcomes (eg, number of seizures and response to treatment) and that subjective patient and family recall and reporting is of limited utility and largely unreliable [17]. Similarly, an objective and continuous collection of information on seizure occurrence, frequency, and distribution would guide a more tailored management and inform decisions on treatment optimization in the clinical setting. In the diagnostic setting, the gold standard for seizure detection is electroencephalography (EEG) in combination with video monitoring. This method has, by definition, a high sensitivity and a positive predictive value close to 100%. However, video EEG monitoring is not a practical procedure for long-term seizure tracking for different reasons: it cannot be implemented for more than a few days at a time, wearing EEG electrodes is uncomfortable and potentially stigmatizing for the patient, EEG requires considerable care by technicians to maintain a high signal quality, and analysis of videos and EEG signals are time consuming and costly [18].

The advent of small, wearable sensors embedded in devices and smartphones has progressively attracted attention in the epilepsy research field [19]. Wearable sensors can be worn comfortably for continuous monitoring of biosignals, and no input from the wearer is required to gather data (passive remote measurement technology [pRMT]). Different studies, mostly based on epilepsy monitoring units (EMUs), have demonstrated the possibility of capturing cardinal seizure manifestations using wearable sensors [20-26]. Movements presenting during seizures have been recorded with accelerometry and surface electromyography. Heart rate variations have been captured by wearable electrocardiogram (ECG) and photoplethysmography (PPG), and alteration of the autonomic nervous system has been recorded with ECG, PPG, and electrodermal activity (EDA) sensors, with different levels of signal and seizure detection accuracy [27].

However, although seizures are the hallmark of the condition, most people with epilepy also develop a range of comorbid conditions of variable severity, including mood disturbances and memory impairment, which are strong predictors of QoL [28]. Moreover, the majority of people with epilepsy self-identify seizure precipitants, usually identified as social and behavioral factors, such as stress, sleep deprivation, and fatigue, which lead to increased seizure likelihood [29]. Despite their clinical importance, there is limited evidence regarding the temporal trajectory of cognitive and psychiatric comorbidity of epilepsy, and insufficient studies have prospectively evaluated the correlation between seizure precipitants and seizure occurrence.

RMT provides tools to reliably measure mood states, cognition, thoughts, and behaviors in real time [30-32], with evidence highlighting the increased validity of this methodology in comparison with traditional retrospective reports [33]. Smartphone apps can be used to deliver validated questionnaires, cognitive games, speech tasks, or electronic diaries to provide fine-grained understanding of mood changes and stressors in the context of daily life (active remote measurement technology [aRMT]) [34]. Moreover, information gathered through smartphones, including GPS, communication logs, ambient noise, light levels, and screen interactions, has been successfully used to identify changes in sleep and activity patterns in psychiatric conditions [35,36] and represent an additional pRMT

feature. Despite the growing body of research evidence, there has been limited assessment of the utility of multiparametric RMTs (aRMT and pRMT) in specific clinical populations, and a paucity of studies performed in the context of daily life have used wearables for people with epilepsy [25]. Remote Assessment of Disease and Relapse-Central Nervous System (RADAR-CNS) is an international research program, which has developed an open-source platform to support pRMT and aRMT data collection to assess and monitor 3 different clinical conditions, major depressive disorder [37], epilepsy, and multiple sclerosis, in the ambulatory setting.

This study reports the methods of a clinical study, RADAR Epilepsy, designed to test patients' acceptability and the clinical utility of multiparametric RMT in a clinical population with epilepsy in the real-world environment.

Study Development and Patients' Involvement

Systematic reviews have examined the barriers and facilitators of RMT uptake [38]; surveys and service user focus groups have identified device preferences and the variables of interest to the specific patient group [39,40]. Alongside clinical experts, the RADAR-CNS consortium has a team dedicated to ensuring patient and public involvement at every stage of development. People with epilepsy took part in focus groups to gather their views on the outcomes of importance to patients and potential barriers and facilitators to engagement [40]. We have appointed several people with epilepsy, in collaboration with a national charity (Epilepsy Action), to join a patient advisory board to help steer the project. These members and people with epilepsy in a hospital-based setting were involved in user testing the wearable devices and smartphone apps, contributing to crucial design choices throughout [40]. All information sheets have been reviewed and approved by a local service user advisory board (Feasibility and Acceptability Support Team for Researchers) and patients seen in local epilepsy clinics to ensure their accessibility. We will continue to involve patients throughout this study and include them in the dissemination of research findings.

Study Objectives

The main aims of the RADAR Epilepsy study are (1) to determine the usability and acceptability of RMT to provide real-time objective multidimensional indications of clinical state in individuals with epilepsy; (2) to assess the correspondence of patient-marked seizure events (via aRMT) with the data collected from the pRMT; and (3) To determine whether multiparametric RMT collected in populations with epilepsy can prospectively estimate variations in seizure occurrence and other outcomes, including seizure frequency, QoL, and comorbidities.

Methods

Study Design and Population

This study is a multicenter, prospective, observational, nonrandomized, and noninterventional cohort study in which 32 individuals with a diagnosis of epilepsy will be asked to download several RMT apps and use a wearable device for up to 6 months of follow-up. The inclusion and exclusion criteria are provided in Textboxes 1 and 2, respectively.

Textbox 1. Inclusion criteria.

Inclusion criteria

- Able to give informed consent for participation
- Diagnosis of epilepsy
- Aged between 18 and 70 years
- Minimum average seizure frequency of 2 seizures per month
- Willing and able to complete self-reported assessments via smartphones
- Fluent in English (German in Freiburg) and able to read and write English (German in Freiburg)
- Willing to continuously wear the study wearable device
- Existing ownership of an Android smartphone (or willingness to use an Android smartphone, which will be provided as their only smartphone)
- Existing ownership or the possibility of connecting to a Wi-Fi connection on a daily basis

Textbox 2. Exclusion criteria.

Exclusion criteria

- Established diagnosis of psychogenic nonepileptic attacks (dissociative seizures) as the only seizure type
- Frequent vigorous involuntary movements (eg, chorea and athetosis) or frequent parasomnias with major motor components (eg, sleep walking and night terrors)
- Inability to comply with the trial procedure, such as cognitive or behavioral problems
- Inability to give informed consent
- Unwillingness to use an Android smartphone

Study Technology

The open-source RADAR-base platform [41] developed to support the RMT data collection is described elsewhere [42]. A number of variables will be collected from each patient through the RMT.

pRMT includes the following:

1. Smartphone app: Participants will be assisted in downloading a purpose-built app that will run in the background, requiring no further input. Using sensors commonly present in all modern smartphones, the app will collect data on ambient noise, ambient light, GPS location, bluetooth connectivity, and battery life. GPS location data will be randomized (providing relative location data, not absolute coordinates).
2. Wearable device: Participants will be asked to wear the Empatica E4 device, a Conformitè Europëenne–marked wristband (Figure 1), for the entire duration of the study (6 months). The device will require a few hours of charging once daily, and participants will receive training and accessories to do so on a routine basis and a second E4 device to be worn during the charging procedure. The sensors included in this wearable device and the parameters measured are PPG and series of interbeat intervals derived from it, 3D acceleration, body temperature, and EDA.

A number of variables of interest to this study will be collected through a second purpose-built aRMT app, which will prompt the study participant to complete validated questionnaires and assessments according to the study schedule (Table 1):

1. Psychiatric comorbidities: Anxiety will be measured via the 7-item Generalized Anxiety Disorder Questionnaire [43]; depressive symptoms will be monitored via the 8-item Patient Health Questionnaire [44].
2. Seizure occurrence and precipitants: Each evening, participants will be prompted to complete a daily assessment to provide self-reported information about medication compliance, sleep quality, alcohol use, menstrual cycle, stress, mood, anxiety, and seizure occurrence. If a seizure is reported, the participant will be automatically directed to an ad hoc created seizure diary. Information on clinical symptoms and manifestations, time of the event, and possible precipitants will be collected through the diary.
3. Experience sampling method: Participants will be asked to complete a series of short electronic diary assessments, also known as the experience sampling method (ESM). ESM assesses experiences and behavior in the realm of daily life and will be administered to provide real-time self-reported data on mood, stress, cognition, activity, location, social interactions, physical state, and medication use. An ESM period will be initiated once every 6 weeks, during which participants will receive notifications to complete 9 questionnaires per day over a 6-day period (semirandom interval between 8:30 AM and 10 PM).
4. Speech task: On a random schedule, participants will be asked to hold down a button on their phone to start recording and will then be asked to say aloud, and in a quiet area, some excerpts from *The North Wind and the Sun*, which are shown to be phonetically balanced in different languages. In addition, participants will be asked to respond to the following question: *Can you describe something you are looking forward to this week?* These data will be recorded in a raw audio format, allowing speech recognition to extract content and automatic sentiment detection.
5. Cognitive function: Cognitive assessment will use the THINC-ITapp, which has been validated to screen for cognitive dysfunction [45] and examines executive functions, such as memory, attention, and concentration.

Figure 1. The Empatica E4 device.

Table 1. Schedule of events for Remote Assessment of Disease and Relapse Epilepsy.

Events	Weeks (months)												
	0 (0)	2 (0)	4 (1)	6 (1)	8 (2)	10 (2)	12 (3)	14 (3)	16 (4)	18 (4)	20 (5)	22 (5)	24 (6)
Visit	1 (Baseline)	—[a]	2 (Follow-up)	—	—	—	3 (Follow-up)	—	—	—	—	—	4 (Study end)
Assessment													
Study explanation	✓[b]	—	—	—	—	—	—	—	—	—	—	—	—
Informed consent	✓	—	—	—	—	—	—	—	—	—	—	—	—
Introductory training (60 min)	✓	—	—	—	—	—	—	—	—	—	—	—	—
Sociodemographics	✓	—	—	—	—	—	—	—	—	—	—	—	—
Medical history	✓	—	—	—	—	—	—	—	—	—	—	—	—
Study debrief	—	—	—	—	—	—	—	—	—	—	—	—	✓
Monitoring telephone call	—	✓	—	✓	✓	✓	—	✓	✓	✓	✓	✓	—
Qualitative interview	—	—	✓	—	—	—	✓	—	—	—	—	—	✓
TAM-FF[c]	—	—	✓	—	—	—	✓	—	—	—	—	—	✓
PSSUQ[d]	—	—	✓	—	—	—	✓	—	—	—	—	—	✓
Passive RMT [e]													
Wearable sensors	—	—	—	—	—	—	Continuous	—	—	—	—	—	—
Smartphone sensors	—	—	—	—	—	—	Continuous	—	—	—	—	—	—
Active RMT													
Seizure diary and precipitants	—	—	—	—	—	—	Daily questionnaire	—	—	—	—	—	—
ESM[f] assessment	✓	—	—	✓	—	—	✓	—	—	✓	—	—	✓
Cognition	✓	—	—	✓	—	—	✓	—	—	✓	—	—	✓
Speech task	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Mood PHQ8[g] (A[h])	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Anxiety GAD7[i] (A or W[j])	✓	—	—	—	—	—	✓	—	—	—	—	—	✓
Self-esteem RSES[k] (A)	✓	—	—	—	—	—	✓	—	—	—	—	—	✓
Quality-of-life WSAS[l] (A or W)	✓	—	—	—	—	—	✓	—	—	—	—	—	✓
BIPQ[m] (A or W)	✓	—	—	—	—	—	✓	—	—	—	—	—	✓
Change in medications (T[n] or F2F[o])	—	—	✓	—	—	—	✓	—	—	—	—	—	✓
CSR[p] (T or F2F)	—	—	✓	—	—	—	✓	—	—	—	—	—	✓
LTE-Q[q] (T or F2F)	—	—	✓	—	—	—	✓	—	—	—	—	—	✓

[a]—: Task or assessment not required.

[b]✓: Task or assessment required.

[c]TAM-FF: Technology Assessment Model Fast Form.

[d]PSSUQ: Post-Study System Usability Questionnaire.

[e]RMT: remote measurement technology.

[f]ESM: experience sampling method.

[g]PHQ8: 8-item Patient Health Questionnaire.
[h]A: assessed via app.
[i]GAD7: 7-item Generalized Anxiety Disorder questionnaire.
[j]W: web-based assessment.
[k]RSES: Rosenberg Self-esteem Scale.
[l]WSAS: Work and Social Adjustment Scale.
[m]BIPQ: Brief Illness Perceptions Questionnaire.
[n]T: telephone assessment.
[o]F2F: face to face assessment.
[p]CSRI: Client Service Receipt Inventory.
[q]LTE-Q: List of Threatening Experiences Questionnaire.

Study Procedures

Participants will be recruited over 6 months from the Epilepsy Service and Clinical Neurophysiology Department at King's College Hospital, London, and from the Epilepsy Center, Department of Neurosurgery, University of Freiburg, Germany.

Potentially eligible individuals will be identified among those attending a routine outpatient appointment or hospital video–EEG EMU admission or home video–EEG monitoring appointment at the participating sites. These individuals will be approached by a member of the on-site research team and given the study information sheet and consent form.

Study Overview

The study schedule of events and assessments is detailed in Table 1.

After a minimum of 24 hours from the time they receive the study information sheet and consent form, the research team will contact the potential participant to assess their interest in taking part in the study. Following a positive response, a first visit will be scheduled for them at the research center to confirm eligibility, discuss the study, explain study procedures, answer any questions, and obtain written informed consent. Sociodemographic information, medical history, and baseline data will be collected (Table 1).

Participants will also receive a 60-min introductory training session on the use of the wearable device and will be assisted in downloading the apps. A leaflet summarizing key information will be provided. At the end of the training session, study participants will be asked to start wearing the device, and active and passive recording of data will begin. Participants will receive a follow-up call 2 weeks after the start of data recording to provide any additional support as required (Table 1).

After this, participants will attend a follow-up visit after 1 and 3 months (visits 2 and 3), where primary outcomes (as given in the *Study Outcomes* section) will be assessed. At visit 4 (study endpoint), participants will be invited to have a last face-to-face meeting to assess outcomes. A debrief session of 60 min will take place at visit 4, and acceptability and usability of the technology will be assessed with a qualitative interview and questionnaires (as given in the *Study Outcomes* section).

Study Outcomes

The primary outcome of interest was participants' acceptability and usability of the RADAR technology, including the wearable, the apps, and the assessment scheme. Acceptability and usability will be evaluated using the Post-Study System Usability Questionnaire (PSSUQ) [46]; the Technology Assessment Model Fast Form (TAM-FF) [47]; and ad hoc created qualitative interviews undertaken at 1, 3, and 6 months postenrollment. Participants who dropped out before the study endpoint will be contacted to complete an interview.

Secondary outcomes include (1) sensitivity and false alarm rate of the device, as compared with patient seizure diary, for different seizure types: generalized tonic-clonic seizures, focal seizures (FS) with motor features, FS with autonomic features, and FS with dyscognitive features and (2) identification of variables influencing the long-term trajectory of seizure frequency: pRMT features (measured through the wearable sensors and smartphone sensors), and aRMT assessments, including comorbidities, seizure precipitants, ESM, speech, and cognitive functions.

Contextual Variables

Variation in self-esteem will be measured using the Rosenberg Self-Esteem Scale [48], a 10-item self-reported questionnaire. QoL or disability will be measured using the Work and Social Adjustment Scale [49], a 5-item assessment of perceived social and work-related functional impairment used widely across a range of mental and physical disorders. Illness perceptions will be assessed using the Brief Illness Perceptions Questionnaire [50], which provides an insight into participants' views about their underlying conditions, including a measure of how well they see themselves coping with its symptoms and treatments.

We will seek to identify major changes in participants' circumstances that may materially affect participants' outcomes and may also impact the use of RMT. In particular, we will collect information about change in medications for epilepsy, health service utilization (the modified Client Service Receipt Inventory [CSRI]) [51], and change in life circumstances (List of Threatening Experiences Questionnaire [LTE-Q]) [52].

Study Monitoring

In addition to evidence of the acceptability and usability of the RADAR technology, data obtained throughout the course of the study will be used to make iterative developments to the platform software and to the questionnaire schedule and to optimize the usability of the system. During the scheduled monitoring telephone calls, the correct use of device and apps will be assessed to identify whether a loss of data is because of potential technical or practical issues that can be resolved.

Participants' problems, concerns, and questions will also be discussed to facilitate engagement and to support adherence to the protocol. These contacts will be recorded as evidence of feasibility and acceptability outcomes. The research team will systematically review upcoming data and may decide to schedule additional monitoring telephone calls if some discrepancies were found during the data collection and streaming.

Study Withdrawal

There may be several reasons for withdrawal from the study. Participants were free to withdraw from the study at any point without providing reasons. The research team may withdraw the participant in the event of intercurrent illness, adverse events, protocol violations, and administrative or other reasons. In the case of participant self-withdrawal, all attempts will be made to have a face-to-face appointment with the participant to establish the cause of withdrawal and to collect qualitative data regarding the experience of participation. All data, including those from study withdrawals (unless participants request for deletion of their data), will be included in the final analysis.

Data Handling and Confidentiality

All digital and nondigital information related to study participants will be nonidentifiable, in accordance with the General Data Protection Regulation. Each participant will be assigned a sequential identification number, used to collect, store, and report participant information. Data acquired from the wearable devices and from the apps will be encrypted, anonymized, and uploaded automatically via Wi-Fi to secure servers and infrastructures (RADAR platform) managed by the research team.

Statistical Analysis Plan

Descriptive statistics for demographics, attrition rate, and number of participants using remote assessment measurements will be estimated. The primary outcome measurement (PSSUQ and TAM-FF) will be analyzed using a mixed-effect model for repeated measures based on observed case data. The model will include the duration in the study and contextual variables (CSRI, LTE-Q, etc) as covariates. Using classification approaches, we will investigate whether any demographics and/or other numerical information might serve as a predictor for subjects dropout. Using mixed-effect models with participants as a random factor, we will estimate whether there is a univariate relationship between the amount of RMT usable data during the weeks before the outcome assessment and obtained scale measurements (PSSUQ and TAM-FF). Acoustic features such as pitch, jitter, shimmer, formants, and intensity of the voice will be extracted from the speech task and will be analyzed.

To assess seizure detection performance of a multiparametric wearable system, we will relate seizures detected by the wearable system to the information from the seizure diary, kept by each participant. We will estimate the sensitivity of seizure detection by the wearable system (ie, whether all seizures reported in the diary were detected by wearable system) and false alarm rate (ie, number of seizures detected by the wearable system but not reported in the diary per unit of time, eg, day).

We will develop an analysis strategy for managing multi-sensor data. To this end, we will investigate what type of features derived from the pRMT and aRMT correlate with seizure occurrence and frequency per unit of time (eg, day and week). Seizure occurrence and frequency will be derived from the multiparametric wearable system and from seizure diaries and analyzed separately. Data obtained from wearable biosensors will be used to derive information about participants' activity during the day and information about sleep and mood. Aggregated features obtained from biosensors, smartphones, and cognitive tests and from ESM and their changes from baseline or previous time points (delta features) will be used for statistical analysis. First, we will use a univariate approach, where the number of seizures per unit of time will be modeled with each variable or feature as a fixed effect and participant as a random effect. Demographics and other baseline characteristics will be added to the model when necessary. Correction for multiple comparisons will be taken into account. Second, using aggregated data obtained through some time duration to predict the number of seizures per the same time duration, we will construct predictive models. Under the assumption that data are missing at random, multiple imputation will be applied for covariates, where missingness is not drastically high. Multivariate prediction models will be constructed, and variable selection, based on, for example, least absolute shrinkage and selection operator L1-regularization for linear models, or different feature selection algorithms will be applied. Model performance will be characterized through cross-validation, putting stress on the sensitivity and specificity of the predictive model.

Qualitative Data Analysis

A thematic analysis will be performed on the interviews. Once transcribed, the topics of interest will be identified. A framework will be developed to guide indexing of the major themes and subthemes. All data extracts will be reviewed for coherence and further refinement of the framework. Once the themes and subthemes have been identified, a framework matrix will be constructed to create summaries of the data. There will be a further step of performing a secondary analysis to categorize and classify the extracted dimensions. A final written summary of explanations for these dimensions will be presented.

Ethics Approval

RADAR Epilepsy will be conducted per the Declaration of Helsinki and Good Clinical Practice, adhering to the principles outlined in the National Health Service (NHS) *Research Governance Framework for Health and Social Care* (2nd edition). Ethical approval was obtained in London from the Bromley Research Ethics Committee (REC reference: 19/LO/1884) and in Freiburg from the Ethics Committee at the University of Freiburg. All staff working on the study have received training in study conduct, informed consent, and risk assessment. RMT data will be pseudonymized and stored in a research database in accordance with the General Data Protection Regulation. The informed consent process will ensure that participants understand the nature of the study and the data being collected. Interested individuals will be provided with the study materials, including information sheets and consent

forms for review. If, after reading, they wish to participate, they will be invited to an enrollment session that will involve the collection of written consent before the administration of any study procedures. They will understand that their privacy is protected and that they can withdraw at any time without giving a reason and request to have all data collected from them deleted.

Results

The RADAR-CNS project has received funding in 2015 from the Innovative Medicines Initiative 2 Joint Undertaking under Grant Agreement No. 115902. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation program and European Federation of Pharmaceutical Industries and Associations (EFPIA). Ethical approval was obtained in London from the Bromley Research Ethics Committee (REC reference: 19/LO/1884) in January 2020. The first study participant was enrolled on September 30, 2020. Data will be collected until September 30, 2021. The results of the study are expected to be published at the beginning of 2022.

Discussion

Principal Findings

Epilepsy is a complex neurological condition characterized by seizures and by multiple factors that have been demonstrated to affect seizure control. The development of automated seizure detection systems is important for many reasons. In clinical practice, a more objective and continuous collection of information on seizure occurrence, frequency, and distribution during the day and night would more consistently guide patient management and decision-making processes, including treatment. Moreover, objective measures are required to improve outcome assessments in clinical trials. Finally, and most importantly, people with epilepsy have largely expressed their interest in digital tools for seizure detection and a desire to use multimodal devices to supplement major unmet needs, such as improving safety and self-management and providing reassurance to self and others [39,40]. Acquiring objective evidence of accuracy and timing of seizure detection is very important in this context, as false alarms can increase distress and have a detrimental impact on technology acceptance and long-term use [39,40].

Although a growing body of literature has focused on mobile biosensors for seizure detection, the majority of these studies are performed in hospital environments; hence, data from ambulatory studies are required. Moreover, to meet the needs of people living with epilepsy and ensure tools that can significantly improve their QoL, it appears necessary to think beyond seizures.

In the general epilepsy population, psychiatric comorbidities are frequent, up to 90% identify the presence of at least one seizure precipitant and many report feelings preceding their seizures, including mood, behavior, and cognitive alterations (premonitory features) [53-55]. The presence of complex interactions between seizure precipitants and premonitory features [56,57] makes the assessment of their real impact on seizure risk variation difficult. In addition, studies performed so far are lacking methodological tools that allow an objective and adequate assessment of precipitants, including a measurement of their sudden variation. In fact, irrespective of their retrospective or prospective design, research studies have surveyed patients with the use of cross-sectional questionnaires and diaries, which are subject to recall bias and lack of time stamps. Another major methodological issue of the current literature data is related to the choice of arbitrary time windows between the assessment of a specific factor and the consequent occurrence of a seizure, usually using the data collected the day before to speculate about their influence on seizures occurring the following day. Prediction might be more robust over short time frames for some precipitants and premonitory features and over long time periods for others. Moreover, it is not clear whether a single report of a status (eg, stress or anxiety) reflects the average over the course of a day [58], and multiple collection points per day might be necessary to take into account symptom fluctuations and variations from day to day or moment to moment.

A complete assessment of seizure occurrence, precipitants, premonitory features, and their interactions cannot leave aside all the aforementioned considerations. RADAR Epilepsy aims to overcome the current methodological issues and to develop an ideal framework of continuous data collection intended to identify ictal and preictal states through the use of aRMT and pRMT. Context-sensitive fine-grained assessments with an excellent temporal resolution in the context of daily life are the hallmarks of RADAR Epilepsy.

Conclusions

Currently, it is paramount to find innovative, safe, and reliable ways to monitor and manage patients with epilepsy at home. RMT may soon represent a new way to measure and manage long-term disorders in a real-life environment, and RADAR Epilepsy is a step forward to achieve this goal. Our future work will have the objective of specifically evaluating the clinical usefulness of the data collected via RMT and compliance, technology acceptability, and usability for patients. RADAR Epilepsy has been specifically designed to primarily evaluate these aspects and the potential challenges to the successful adoption and implementation of RMT in conventional health care systems.

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Authors' Contributions

EB has contributed to the design of the study and coordination of the study in London and writing the protocol for ethical approval and for publication. AB has contributed to the design of the study, coordination of the study in Freiburg, and review of the protocol for publication. SB has contributed to the design of the study and in reviewing the protocol for publication. GV has contributed to the design of the study and in reviewing the protocol for publication. RD, AF, YR, and ZR have contributed to the development of the RADAR-base system used for data collection and management across all sites, data protection, security and storage systems, and the development of the protocol. NM has contributed to the design of the study, review of the protocol for publication, and development of an analytic method for handling data collected via the RADAR-base system. AR and IMG contributed to the design of the study and reviewed the protocol for publication and contributed to the design and implementation of the ESM. SS and TK have contributed to the design of the study, including the integration of service user research and patient and public involvement activities, and review of the protocol for publication. AN and MR have contributed to the design of the study and review the protocol for publication. AS, AL, ST, and SL were involved in user testing the wearable devices and smartphone apps and reviewing the protocol for publication. All authors have been involved in reviewing the manuscript and have given approval for it to be published.

Conflicts of Interest

NM is an employee of Janssen Research & Development, Limited Liability Company (LLC), and holds company stocks or stock options. GV is an employee of Neurology UCB Pharma.

Multimedia Appendix 1
Peer Review Report.
[PDF File (Adobe PDF File), 133 KB - resprot_v9i12e21840_app1.pdf]

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Abbreviations

aRMT: active remote measurement technology
CSRI: Client Service Receipt Inventory
ECG: electrocardiogram
EDA: electrodermal activity
EEG: electroencephalography
EFPIA: European Federation of Pharmaceutical Industries and Associations
EMU: epilepsy monitoring units
ESM: experience sampling method
FS: focal seizures
LTE-Q: List of Threatening Experiences Questionnaire
NHS: National Health Service
NIHR: National Institute for Health Research
PPG: photoplethysmography
pRMT: passive remote measurement technology
PSSUQ: Post-Study System Usability Questionnaire
QoL: quality of life
RADAR Epilepsy: Remote Assessment of Disease and Relapse Epilepsy
RADAR-CNS: Remote Assessment of Disease and Relapse-Central Nervous System
RMT: remote measurement technology
TAM-FF: Technology Assessment Model Fast Form

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Protocol

Mobile App (UPrEPU) to Monitor Adherence to Pre-exposure Prophylaxis in Men Who Have Sex With Men: Protocol for a User-Centered Approach to Mobile App Design and Development

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Abstract

Background: Daily and on-demand pre-exposure prophylaxis (PrEP) has been well demonstrated to effectively prevent HIV acquisition for men who have sex with men (MSM). More than half of the MSM PrEP users in Taiwan prefer on-demand PrEP; however, on-demand PrEP involves a complicated dosing regimen because it requires precoital and postcoital dosing and sex events are hard to anticipate. Although there are a growing number of mobile apps designed to improve access to HIV prevention services and HIV medication adherence, few mobile apps focus on adherence to PrEP or are designed to accommodate a complicated, on-demand PrEP dosing schedule.

Objective: The aim of this project is to evaluate the usability of a newly developed mobile app (UPrEPU) to assist MSM PrEP users to self-monitor their adherence to either daily or on-demand PrEP using a user-centered scheme.

Methods: This research will be conducted in 2 phases: app development and usability study. In the app development phase, we will first conduct formative research with end users and stakeholders through in-depth interviews; the results will provide PrEP users' and PrEP navigators' personas as material used in the app conceptualization stage. PrEP navigators are individuals in the health care system that help HIV-negative individuals who need assistance in accessing PrEP care. A low-fidelity prototype of the app feature will be formatted by applying a participatory design approach to engage PrEP users, designers, and app developers in the design process of the app. Then, a high-fidelity prototype of the app will be developed for the usability study and refined iteratively by the multidisciplinary team and new internal testers. Internal testers include the research team consisting of experts in public health, infectious disease, and industrial design and a close network of the research team that is taking PrEP. In the

usability study phase, we will enroll 70 MSM PrEP users and follow them up for 4 months. Usability, feasibility, and effectiveness of adherence monitoring will be evaluated.

Results: Refinement of the UPrEPU app is currently ongoing. The usability study commenced in May 2020.

Conclusions: The UPrEPU app is one of the first apps designed to help MSM PrEP users to self-manage their PrEP schedule better regardless of dosing modes. With a design-thinking approach and adapting to the cultural context in Taiwan's MSM population, this novel app will have substantial potential to be acceptable and feasible and contribute to the reduction of new HIV infections.

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KEYWORDS

mobile apps; pre-exposure prophylaxis; event-driven; sexual behavior; men who have sex with men; user-centered design approach

Introduction

Men who have sex with men (MSM) in Taiwan have been disproportionally affected by the HIV epidemic since 2006 [1]. Since 2015, approximately 2000 MSM per year have been newly diagnosed with HIV infections in Taiwan [1]. HIV biomedical prevention interventions, such as treatment as prevention and pre-exposure prophylaxis (PrEP), have been increasingly used in the past decade. PrEP has been well demonstrated in several clinical trials, and open-label studies have been conducted to provide high-level protection for both heterosexual and MSM against acquiring HIV [2-7]. PrEP has thus been included globally as one of the major components of the HIV prevention toolbox, including in World Health Organization guidelines [8,9], in the United States [10], and in the United Kingdom [11].

Daily PrEP — taking tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) at the same time every day — has been recommended across genders and at-risk populations. For MSM, there is an alternative PrEP-dosing regimen: on-demand PrEP, referring to a double dose of TDF/FTC taken 2-24 hours before each sexual intercourse, followed by 2 single doses of TDF/FTC taken 24 and 48 hours after the first drug intake [12]. The IPERGAY study showed that on-demand PrEP in MSM was more efficacious than placebo administered to controls [7].

In France and the Netherlands, 23%-55% of PrEP users reported using on-demand PrEP [13,14]. Taiwan has a higher acceptance and willingness to use on-demand PrEP than daily PrEP [15]. Since PrEP was introduced in Taiwan in 2016, MSM have enjoyed the flexibility of choosing between daily and an on-demand PrEP schedule based on the recommendations from Taiwan's National PrEP Guidelines [16]. A high proportion of Taiwanese MSM choose on-demand PrEP [17]. Based on real-world data, 56.7% of MSM report the use of on-demand PrEP at baseline and in 49.7% of follow-up visits [18]. PrEP users in Taiwan have various ways to access PrEP, including partially or fully subsidized by government-led demonstration projects, pay out of pocket for Truvada, or pay out of pocket for a generic brand of PrEP. Users are recommended to visit the clinics at least every 3 months for clinical measurements, laboratory measurements, and prescription refills based on Taiwan's PrEP guidelines [16]. MSM in Taiwan have also been uncertain about communicating with sexual partners on social apps regarding their use of PrEP, thereby indicating their struggles with the social stigma related to PrEP [19].

The efficacy of PrEP relies heavily on adherence. The on-demand dosing regimen, however, can be complicated for most users because it requires that individuals anticipate sex in the next 2-24 hours and remember to take the pills before and after sex; therefore, adherence to on-demand PrEP can be hard to achieve.

Using mobile phone apps to seek sex partners has become common among MSM [20-23]. Adopting mobile phone apps to improve access to HIV prevention services and adherence to antiretroviral therapy among people living with HIV has grown increasingly popular [24-27]; however, only a few studies have focused on self-monitoring of PrEP adherence among MSM or were designed for daily dosing PrEP only [28,29], without meeting the growing need of on-demand PrEP and the possibility of switching between the 2 dosing regimens.

In response to the complexity of different dosing regimens and potential switching between the 2 dosing regimens, we developed a self-monitoring tool (UPrEPU app) to improve PrEP adherence regardless of the MSM user's choice of dosing regimen and lifestyle. The aim of this study is to use a user-centered approach to evaluate the usability of this app. Users were involved at the beginning stage and throughout the development of this app to facilitate identifying users' needs, enhancing participants' engagement, and improving the app's usability [30].

Methods

Study Design

This research protocol will be conducted in 2 phases: (1) app development phase, during which the app design and development process will be led by a multidisciplinary team with a user-centered design approach to ensure that the app will be acceptable and designed in line with PrEP users' needs and context of use, and (2) usability study phase, during which we will evaluate the feasibility and usability of this app with a pilot sample.

Phase 1: App Development

The understanding stage will involve in-depth interviews with PrEP users and navigators as well as development of PrEP users' personas and a journey map.

To identify PrEP users' needs and the requirements of the mobile app–based PrEP adherence self-monitoring intervention, MSM who have experience using PrEP will be invited to participate in individual interviews. We will recruit a maximum of 30 participants from various routes, including the online LGBTQ community, PrEP clinics, and PrEP users' online groups. Participants will undergo an in-depth online audio interview using a camera such as that available through Skype, Google Hangouts, or Line. The interview will explore the following: (1) PrEP users' experience such as motivation, choices of PrEP-dosing regimens, and potential barriers to PrEP; (2) technologies used to self-manage adherence to PrEP, find sexual partners, and access PrEP-related information; (3) interactions between PrEP users and PrEP navigators.

PrEP navigators will also be invited to participate in individual interviews to understand their needs, usability requirements, and ideas related to this app. We will ask infectious disease physicians to refer PrEP navigators who are interested in participating in our study to contact us. The interviews will be online audio interviews conducted via Skype, Google Hangouts, or Line. During the interview, the following information will be obtained: (1) information related to the PrEP navigators' routine work, (2) how they follow up with PrEP users and their dosing regimens, (3) tools they use to communicate with PrEP users at follow-ups, (4) challenges they encounter at follow-ups. All interviews will be audio-recorded for transcription and analysis.

Personas and users' journey maps, a visualization of the process of an individual going through to reach a goal, are well-established user-centered approaches in user interface design to contribute to the creation of usable products, are able to provide an understanding of users for designers, and focus on users' needs and pain points [31-33]. Several PrEP users' personas and journey maps will be developed by the research team based on results from the previous stage. It can help developers and users visualize typical days in the PrEP users' lives and PrEP managers' daily routines. Personas will include demographics; goals, needs, and motivations; frustrations; and technologies they have applied to the PrEP-related issue. The journey maps will depict the PrEP service from the perspectives of PrEP users and PrEP navigators. In journey maps, the goals, actions, touch points, thoughts, emotions, and opportunities for stages — before, during, and after providing or receiving PrEP services — will be described. Personas and journey maps will be used in the upcoming participatory design workshop as an illustrative scenario for participants to generate shared understandings and design ideas [30].

During the app conceptualization stage, we will conduct a participatory design workshop (idea generation and prototyping) and develop a high-fidelity prototype.

The workshop aims to generate ideas for features of the UPrEPU app. We will apply a participatory design approach in the workshop to engage PrEP users, designers, and app developers in the app design process [34]. Designers include researchers with expertise in either human-computer interactions or public health. The participatory design approach between users and developers can help facilitate engagement and communication that focus on the users' needs and search for technological solutions by brainstorming, exploring, and iteratively and cooperatively evaluating design ideas [35,36]. The workshop will be held in 1 day for 6 hours and will be held only once. The workshop will be led by a facilitator. In order to better generate ideas for app features, personas and journey maps developed from Phase 1 will be used in the workshop as an illustrative scenario to facilitate discussion and understanding for what PrEP users and navigators may encounter in daily life. A low-fidelity paper prototype of this app will be developed through the evolution and agreement of participants in the workshop.

A high-fidelity prototype of the UPrEPU app will be developed for both iOS and Android operation systems. During the development, the multidisciplinary team will work cooperatively to refine the prototype. After a full prototype is completed, new internal testers will access all features of the UPrEPU app to identify any remaining glitches, bugs, or usability concerns. Afterwards, a polished version of a final app prototype will be developed based on the feedback from the internal testers for an external usability study. We expect that the functions of the app may include sex and medication diary, medication adherence reminders based on users' expected sexual behaviors and dosing regimens, education, and resources, although the final prototype will be developed based on the participatory design workshop.

Phase 2: Usability Study

After the internal test for the UPrEPU app is completed and optimized through feedback from the internal testers, we will evaluate the feasibility and usability of the app through a pilot study. This pilot study will also examine the preliminary effectiveness of the app in monitoring adherence to PrEP. We will enroll 70 MSM in 2 urban cities in Taiwan. Participants will be followed for 4 months and will complete an assessment at the beginning and every month. If they decide to join the study, participants will be asked to wear a wearable device that collects physiological sensor data.

Eligible participants will be HIV-negative men who meet the following criteria: (1) 20 years of age or older; (2) reside in Taiwan and able to understand, read, and speak Mandarin Chinese; (3) tested negative for HIV 3 months prior to enrollment for current PrEP users; (4) have laboratory results eligible to initiate PrEP based on Taiwan's PrEP guidelines [16]; (5) currently taking PrEP or willing to initiate PrEP after enrollment; (6) report having ≥4 episodes of anal intercourse with men in the previous 1 month; (7) own an Android or Apple operating system (iOS) smartphone and are willing to download the study app; and (8) willing to wear the device the research team provides during the study period. Participants with the following characteristics will be excluded from the study: (1) have abnormal kidney function (creatinine clearance rate ≤60 mL/minute) or (2) currently on medications that might interact with PrEP, such as drugs containing lamivudine, at the baseline

assessment. Participants who experience HIV seroconversion during the study period will be terminated from participation and referred to HIV care services. Their data will be still included in the analysis.

We will enroll participants from 2 medical centers in 2 major cities of Taiwan. Both medical centers have provided PrEP since 2016. Potential study participants will be referred by physicians and case navigators from the clinics. Their eligibility will be assessed by a screening tool available online. Afterwards, trained research assistants will inform those who are eligible about the purpose of the study and the information that will be collected in the study. Individuals who express interest in this study will be required to provide signed informed consent. For those who do not consent to participate, the reasons for declining participation will be documented. Eligible participants will download the UPrEPU app on their phone and answer a baseline questionnaire in the app regarding sociodemographics, mental health scales, sexual behaviors, and PrEP use at the baseline visit at the study site. Participants will also receive a wearable device that collects physiological sensor data. Participants will be encouraged to use all app components over the next 4 months and wear the wearable devices at all times.

Participants will be followed up monthly for the 4 months at the 2 medical centers where they were recruited. Each monthly visit will include rapid testing for HIV antigen and antibodies, measuring TDF/FTC concentration, and completing a follow-up questionnaire on their mental health scales, sexual behaviors, and PrEP use. Depression and anxiety will be assessed using the Patient Health Questionnaire-9 and General Anxiety Disorder-7, respectively. We collect these 2 mental health indicators since studies have shown that mental health status may be associated with adherence to medications [37].

Kidney function and sexually transmitted infections will be assessed at the end of the follow-up. The system usability scale for the UPrEPU app will be assessed during the first follow-up visit and at the end of the study. A face-to-face, semistructured qualitative interview will be conducted at each visit to assess the feasibility of the app. It will focus on any technical challenges participants may have encountered, recommendations for app improvement, and their satisfaction and comfort in using this app. All interviews will take around 30 minutes and will be audio-recorded for transcription and analysis.

Users can report bugs in the system and provide feedback in the app and to the customer service portal at any time. The bugs will be reported directly to our technology partners, whereas the issues reported and feedback will be documented, reviewed by the investigator team, and used in the next iterative stages of the app adaptation.

The primary outcomes include usability, feasibility, and effectiveness of adherence monitoring. Usability of the app will be measured using the system usability scale, a 10-item, 5-point Likert scale, which gives a global view of subjective assessment of usability [38]. A score above 50 out of 100 indicates acceptable [39].

The primary feasibility outcomes include frequency of app logins, use of app components such as PrEP-taking and sexual behavior reports, and the length of time the app is used based on the app analytics. Descriptive statistics will be used, and confidence intervals will be calculated to evaluate the primary feasibility outcomes. Secondary feasibility outcomes of this app will be analyzing data using thematic analysis methods from qualitative interviews focusing on technical challenges and satisfaction of the app during the follow-up [40].

We will examine the app users' effectiveness of adherence monitoring with this app by comparing the pill-taking reports in the PrEP-taking diary component of the app with the tenofovir and emtricitabine drug concentrations in dried blood spot samples in the previous 7 days before the follow-up day. We will use correlation analysis to examine the consistency between the drug concentration in the dried blood spot samples and self-reported PrEP diary in the app. Higher correlation reflects higher effectiveness of adherence monitoring.

Participants will receive incentives for completing each follow-up visit and in-depth interview. This includes US $20 cash for each follow-up visit and US $33 cash for twice completing the in-depth interviews. Participants whose cumulative frequency of logins and use of features reach 90% will receive an additional US $33 at the end of the study.

Trial Registration, Ethics, Consent, and Institutional Board Approval

The research and ethics presented in this study have been reviewed and approved by the Institutional Reviewer Board of National Cheng-Kung University in Tainan City, Taiwan (A-ER-107-337).

Results

The usability study began enrollment in May 2020, and participants were followed up for 4 months. Study results will be available in 2021.

Discussion

This paper provides an outline of a protocol for a research study that aims to evaluate the usability of a newly developed mobile app intervention using a user-centered scheme for self-monitoring adherence to either daily or on-demand PrEP.

The UPrEPU app is a novel smartphone app that accommodates the flexibility of switching dosing regimens and assists PrEP users adapt their dynamic lifestyles to better self-manage their PrEP taking, with the overarching goal of improving their adherence to PrEP. The UPrEPU app aims to be an acceptable, feasible, and capable tool for self-monitoring PrEP adherence in MSM populations.

Self-management of PrEP use and adherence to PrEP are particularly important during and after the COVID-19 pandemic. The COVID-19 pandemic may have had an impact on individuals' ability to access HIV prevention medicine or treatment or may have limited access to health care services due to reduced hours [41]; in turn, MSM may be more likely to switch to an on-demand dosing regimen to cope with the possible shortage of pills.

A few mobile health interventions, with some of the most common features such as gamification, notifications, medication log, and education, target HIV prevention or PrEP adherence [28,42-45]. Our study is different from the rest of the mobile apps for PrEP adherence in its emphasis on incorporating sex behavior and medication logs to facilitate a more precise and personal reminder for whether the user has enough protection based on the correct dosage of PrEP. UPrEPU is the first app designed for both on-demand and daily dosing regimens for PrEP users, adopting a user-centered design. As the first app developed and operating in traditional Chinese focusing on PrEP adherence, we emphasized a participatory design throughout the development process to adapt to the cultural context in Taiwan's MSM populations and that is likely in other Chinese-speaking communities around the world.

We anticipate a few limitations in the study protocol. First, we will only recruit individuals ≥20 years of age who are able to be consented legally. Therefore, our study results may not apply to younger MSM or adolescents since the usability or feasibility in such populations might be different. Also, the study might be more likely to recruit participants who have higher incomes and socioeconomic status based on the characteristics of the smartphone ownership eligibility criteria, which also affect the generalizability of the results. Second, the study requests that participants in phase 2 use the app and wear a portable device collecting physiological sensor data. Specifically, higher incentives will be received if participants use the app more frequently. We are likely to recruit highly motivated participants. The feasibility might be biased toward the higher end compared to when the app is released for download to the public in the future. Last, it is possible that providing a financial incentive for app use may impact participants' behavior [46]; however, other factors such as social norms and intrinsic motivations may also influence participants' behavior [47,48]. Our results from this pilot study will not completely reflect how people may use the app in real-world settings. Given that the effectiveness of PrEP depends on adherence and that switching between 2 PrEP dosing regimens is common and complex in real-world settings [18], the importance of obtaining related information and knowledge from this research is significant. The user-centered design approach can help us address the concerns regarding sensitive, private issues raised by marginalized populations. Findings from this study can be further used to design adaptive interventions to address different needs in various contexts and behavioral patterns. This study protocol describes the details of conceptualization of mobile apps and usability evaluation. Future studies could benefit from this study protocol by using a user-centered design approach in complex behaviors such as different drug-dosing regimens contingent on lifestyle behaviors to other mobile health interventions.

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Conflicts of Interest

None declared.

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Abbreviations

MSM: men who have sex with men
PrEP: pre-exposure prophylaxis
SUS: system usability scale
TDF/FTC: tenofovir disoproxil fumarate/emtricitabine

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Protocol

The Swiss Prison Study (SWIPS): Protocol for Establishing a Public Health Registry of Prisoners in Switzerland

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Abstract

Background: The health aspects, disease frequencies, and specific health interests of prisoners and refugees are poorly understood. Importantly, access to the health care system is limited for this vulnerable population. There has been no systematic investigation to understand the health issues of inmates in Switzerland. Furthermore, little is known on how recent migration flows in Europe may have affected the health conditions of inmates.

Objective: The Swiss Prison Study (SWIPS) is a large-scale observational study with the aim of establishing a public health registry in northern-central Switzerland. The primary objective is to establish a central database to assess disease prevalence (ie, International Classification of Diseases-10 codes [German modification]) among prisoners. The secondary objectives include the following: (1) to compare the 2015 versus 2020 disease prevalence among inmates against a representative sample from the local resident population, (2) to assess longitudinal changes in disease prevalence from 2015 to 2020 by using cross-sectional medical records from all inmates at the Police Prison Zurich, Switzerland, and (3) to identify unrecognized health problems to prepare successful public health strategies.

Methods: Demographic and health-related data such as age, sex, country of origin, duration of imprisonment, medication (including the drug name, brand, dosage, and release), and medical history (including the International Classification of Diseases-10 codes [German modification] for all diagnoses and external results that are part of the medical history in the prison) have been deposited in a central register over a span of 5 years (January 2015 to August 2020). The final cohort is expected to comprise approximately 50,000 to 60,000 prisoners from the Police Prison Zurich, Switzerland.

Results: This study was approved on August 5, 2019 by the ethical committee of the Canton of Zurich with the registration code KEK-ZH No. 2019-01055 and funded in August 2020 by the “Walter and Gertrud Siegenthaler” foundation and the “Theodor and Ida Herzog-Egli” foundation. This study is registered with the International Standard Randomized Controlled Trial Number registry. Data collection started in August 2019 and results are expected to be published in 2021. Findings will be disseminated through scientific papers as well as presentations and public events.

Conclusions: This study will construct a valuable database of information regarding the health of inmates and refugees in Swiss prisons and will act as groundwork for future interventions in this vulnerable population.

Trial Registration: ISRCTN registry ISRCTN11714665; http://www.isrctn.com/ISRCTN11714665

International Registered Report Identifier (IRRID): DERR1-10.2196/23973

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KEYWORDS

public health; prison medicine; epidemiology; health register

Introduction

Background

In institutions such as prisons and correctional facilities, health risks are disproportionately widespread. The World Health Organization in the European Region has estimated that approximately 6 million people are incarcerated every year in this region [1]. The health profile of the people in prison is complex and the risk factors for poor health often overlap with the risk factors for incarceration [2]. Cooccurring physical and mental health conditions are often found in close association to entrenched and intergenerational social disadvantage [3]. Data indicate that, in general, prisoners are sicker when compared with counterparts of the same age, race, and sex in a free society [4]. Additionally, prisons and detention centers are known to reduce the resources for inmates substantially, and disease frequencies and the health of individual prisoners are poorly understood owing to the lack of original data [1]. Further, many inmates lack opportunities to articulate themselves (eg, language barriers in Europe), and access to the health care system is extremely limited. Prison physicians often speak of a "blind spot in society" [5]. In contrast to the investigations of the judicial branch, which is obliged to publish numbers on the origin, age, sex, and penalties of convicts, systematic investigations on the health issues of inmates are extremely rare.

Current Situation

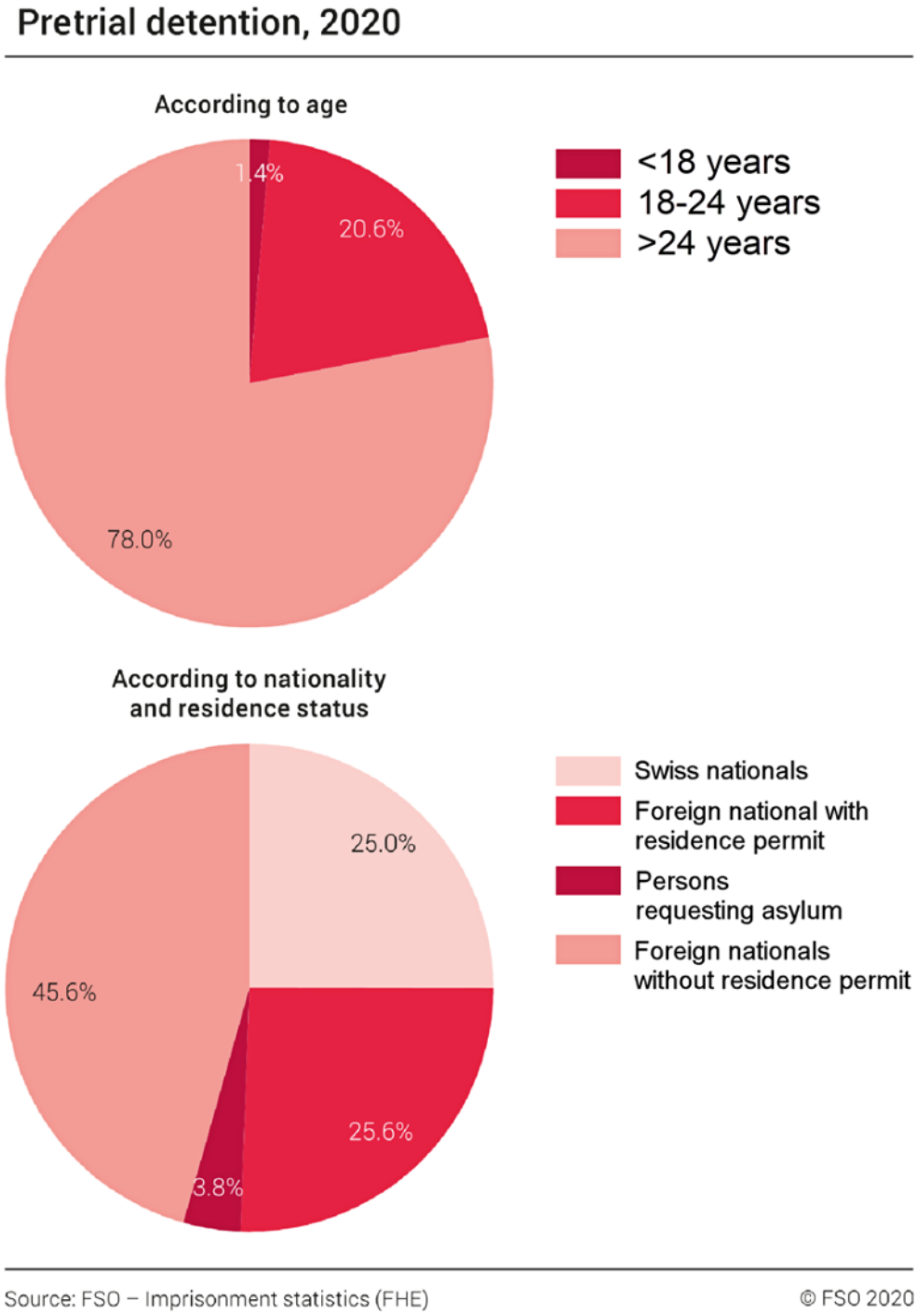
Only a few prevalence studies conducted in the United States and Europe indicate that the disease profile of prison inmates is significantly different from that of the general population. In line with what is generally known about the health of the people in prison, data from the Health in Prisons European Database paint a picture of an extremely vulnerable population that experiences poor health and engages in risky health behaviors, leading to noncommunicable and communicable diseases and mental health conditions [1,6]. In this setting, drugs and nonmedical use of conventional medications seem to play a crucial role in the health of the people in prison [6]. In 2014, a report from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) suggested that besides health-related problems, illicit drug use is highly prevalent among people in prison [7]. More recently, the EMCDDA has warned about the rapidly developing phenomenon of the use of new psychoactive substances (NPS) among prisoners [8]. Monitoring data indicate that prisons are the epicenter of this phenomenon and there is growing concern that NPS may be responsible for a large share of drug-related problems in prison [8]. Approximately 4%-56% of all inmates use psychoactive substances, but the exact percentage requires further investigation [4,9]. For comparison, there is ample evidence that the "opioid crisis" in the United States affects inmates in particular [10]. Currently, only limited data from European institutions are available [8]. Studies conducted in the United States estimate that the "off-label" usage of drugs in prisons is about 36.2% [11]. However, no comparable data from Switzerland are available and there seems to be a lack of systematically collected and comparable data on the health of incarcerated people.

In 2017, approximately 71% of prison inmates in Switzerland were foreigners and most were imprisoned in the Canton of Zurich [12]. One way of systematically recording specific aspects of the disease burden in this population is to analyze medical files and histories. From studies performed in the early 2000s, it has been established that analysis of medical records in prisons is an extremely reliable source. In fact, in some areas of disease burden (eg, infectious disease, assessment of cardiovascular risk), this can be considered superior to information gained from questionnaires or personal interviews [9,13]. Most importantly, a systematic collection and analysis of medical records has not yet been conducted for inmates in Switzerland.

Police Prison Zurich

Prison facilities are required to ensure adequate health care in both the somatic and psychiatric fields. The University Hospital Zurich has taken over the responsibility for providing somatic and psychiatric care to the Police Prison Zurich (PPZ) inmates. The PPZ is the largest inmate correctional facility in Switzerland, and approximately 10,000 to 12,000 prisoners are admitted per year. Data from the Federal Statistical Office in Switzerland indicate that inmates held for pretrial detention are predominantly young and male, and approximately 75% are non-Swiss nationals (Figure 1) [12]. Anecdotal evidence suggests that a large proportion of inmates (eg, refugees) have reported previously using drugs that were prescribed for off-label purposes. One example is the prevalent purchase of the substance *pregabalin* via web-based pharmacies [14]. Other examples include the underestimated usage of recreational drugs (eg, clonazepam) and other NPS [15]. Most of these drugs have potentially substantive health consequences, mainly attributed to their high potential for addiction and adverse effects. Furthermore, little information has been established on how recent refugee patterns may have affected the health conditions of the inmates in recent years.

Figure 1. Imprisonment statistics for pretrial detention in Switzerland for year 2020 from the Federal Statistical Office.



Hypothesis

In summary, the prison population is very vulnerable; yet, hardly any reliable data are available on the health of inmates [1,3]. The current geopolitical situation appears to exacerbate the problem as patients with a disproportionately poor health status have contact with the Swiss health care system. Data from the PPZ offer a unique opportunity globally for a representative analysis of the disease profile of inmates. The aim of this study is to collect health-related data in order to give insight into an unexplored area and underserved patient population. First, we hypothesize that the disease profile of inmates substantially differs from that of the general population. Specifically, certain chronic and psychiatric diseases are disproportionately prevalent among inmates and refugees. Second, a large number of drugs (eg, NPS) may be used "off-label," and the origin of the inmates and the refugee route may have an impact on the disease profile of the affected. Third, recent geopolitical changes have significantly affected the overall disease profile of inmates.

Methods

Study Design

This is an observational study with a population-based cross-sectional baseline measurement and no prospective follow-up.

Study Objectives

The primary objective is to establish a central database to assess the prevalence of diseases (ie, International Classification of Diseases [ICD]-10 codes [German modification]) among prisoners. The secondary objectives are (1) to compare the 2015 versus 2020 disease prevalence among inmates against a representative sample from the local resident population, (2) to assess longitudinal changes in disease prevalence from 2015 to 2020 by using cross-sectional medical records from all inmates at the PPZ, and (3) to identify unrecognized health problems to formulate models for successful public health strategies. Achieving these objectives can result in new insights into public health and in the construction of a valuable database of information regarding the health of inmates and refugees in Swiss prisons, thereby enabling future interventions in this vulnerable population.

Study Questions

The main questions under investigation are as follows.

1. What is the health status of the inmate population and which conditions are overrepresented and underrepresented in the prison setting? In particular, how do psychiatric diseases affect inmates and what is the estimated prevalence of substance abuse in the prison population? Which infectious diseases (eg, tuberculosis, pneumonia, scabies) are highly prevalent among inmates and what are the comorbidities of this population?
2. What are the dynamics in the health profile of inmates (and thus refugees) during the European migrant crisis from 2015 onwards and how does the epidemiology of the prison population affect the balance between acute and chronic conditions?
3. Are there underrecognized health problems among vulnerable populations (eg, children, pregnant mothers, patients with suicidal ideation) or overrepresented populations (eg, body-packers, patients with traumatic injuries).

Study Site

The health registry is based at the PPZ (Kasernenstrasse 29, 8021 Zurich, Switzerland). In this prison, all inmates of the Canton of Zurich are detained for up to a maximum of 7 days. Thereafter, prisoners are transferred to any of the following systems: (1) pretrial detention, (2) serving a particular prison sentence in a long-term facility, (3) anticipatory execution of sentence, or (4) subjection to coercive measures based on Aliens Act. The PPZ is the only central police prison in the Canton of Zurich serving a population of 1,520,968 (as of December 31, 2018), which is the most populous canton in the country. This prison has approximately 10,000 to 12,000 inmates yearly, of which about a third require medical attention (based on historical data from the PPZ/not published). The entire spectrum of medical attention needed to meet inmates' medical needs is covered within the PPZ, such as general internal medicine (eg, asthma), traumatic injuries, psychiatric emergencies, and infectious diseases (eg, HIV).

Participants

This study consists of prisoners within the PPZ from April 1, 2015 until August 31, 2020. The final sample will be exhaustive. All inmates within this timeframe will be included in this study and there will be no random selection. Only in documented cases wherein a prisoner allegedly refuses to participate in health-related activities, he or she will be excluded from the study and his or her data will not be analyzed. Otherwise, there are no exclusion criteria. Extrapolating from current numbers (approximately 850 prisoners per month × 64 months), it is expected that the final database will contain data from approximately 50,000 to 60,000 prisoners.

Cooperation

The study will be conducted in cooperation with the Cantonal Police Zurich (contact person, Ms. Iris Suter), the University Hospital Zurich, which is the designated medical authority for the PPZ, and the Helsana AG (contact person, Dr. Eva Blozik). The Helsana AG is a major Swiss health insurance company with 2.1 million customers insured and will provide data on a matched Swiss cohort. Data will be extracted from the *Helsana Drug Report* [16], which is created in cooperation with the University Hospital Basel and the Institute for Pharmaceutical Medicine at the University of Basel. Another study site includes the University Hospital Zurich, Switzerland, which contractually provides all outpatient and inpatient medical care for the PPZ, including psychiatric consultations. No other parties are involved in the medical care of the PPZ prisoners.

Data Collection and Management

Data entry into the health registry will be performed synchronously or asynchronously by a study team of physicians (TG, NM, PB, and MM) after carefully reviewing the source documents. A unique electronic case report form based on the variables in Table 1 and Table 2 was developed at the inception of this study. All source documents must be placed within the medical history of the prisoner. Table 1 and Table 2 summarize both the parameters and domains used in the study, which includes all variables, and other data extracted from the health registry. Unclear documentation will be discussed among the study team and incomplete data will be made apparent in the registry. After data entry, data will be checked for completeness and plausibility by the data manager. The database will be encrypted and only study personnel will have access to the source documents, which will not leave the prison. Encrypted backups of the database will be periodically conducted using external hard drives.

Table 1. Summary table of the general domains and parameters, which will be part of the registry.

Domain, subcategories	Parameter	Comment
General characteristics		
Age	Years	At baseline
Sex	Male/Female	Self-reported
Date of imprisonment	Date	Data obtained from police
Length of imprisonment	Days (n)	Data obtained from police
Country of origin	Sovereign state according to the United Nations	Data obtained from police
Diagnosis		
Principal diagnosis	ICD[a]-10 code	German modification of the ICD
Secondary diagnosis (up to 20)	ICD-10 code	German modification of the ICD
Medication		
Medication according to external documents	Active agent, dosage, administration	With external verification of drugs with dispensing category "A+"[b]
Daily medication	Active agent, dosage, administration	With external verification of drugs with dispensing category "A+"
On-demand medication	Active agent, dosage, administration	With external verification of drugs with dispensing category "A+"

[a]ICD: International Classification of Diseases.

[b]Category A+ according to the Federal Act on Medicinal Products and Medical Devices (Therapeutic Products Act) Article 24 (eg, opioids, benzodiazepines, methylphenidate).

Table 2. Summary of the systematic characteristics that will be assessed in the registry.

Characteristics, tests	Response	Explanation
Particular characteristics at admission		
Reason for consulting a physician during the imprisonment	Text	Self-reported
Evidence of a traumatic injury at admission	Yes/No	If applicable, then nature of the injury
Need for a "Hafterstehungsfähigkeit"[a]	Yes/No	Data obtained from police
History of illicit drug abuse	Yes/No	Data obtained from police
Participant in the opioid replacement therapy program	Yes/No	Data obtained from police
History of benzodiazepine dependence	Yes/No	Data obtained from police
History of alcohol dependence	Yes/No	According to the DSM-IV[b] criteria
Result of the alcohol breath test at admission	mg/L	Optional
Evidence of body packing (according to computed tomography scan results)	Yes/No	Data obtained from hospital
Particular characteristics during the imprisonment		
Need to consult a psychiatrist during imprisonment	Yes/No	Data obtained from police
Admission to a hospital during imprisonment	Yes/No	Data obtained from police
Special reports		
Blood pressure chart	Source document	Optional
Blood sugar chart	Source document	Optional
Medical history		
External documents	Source document	Optional
Laboratory results (including pregnancy test)	Source document	Optional

[a]Hafterstehungsfähigkeit: initial 24/7 medical assessment by a physician, after which it is decided whether the convict can be admitted to the prison in the first place.

[b]DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.

Quality Control

For this health registry, the following 4 quality control measurements will be implemented, and the results will be provided in the final manuscript:

1. Interobserver variability: The source documentation of 150 random patients will be processed by 2 physicians (ie, 450 degrees of freedom for every variable will be assessed) and disparities observed with regard to all domains will be summarized.
2. Matching with a local database from the jurisdiction: Data from the health registry will be compared with data from the jurisdiction, and discrepancies (eg, country of origin) will be further investigated by the study team.
3. Internal validity: The consumption of medications will be summarized for each month from 2015 to 2020, and these data will be compared with the prescription data collected from the PPZ's local pharmacy, which collects monthly data for all dispensed medications. This step ensures that the actually dispensed medication is equal to the prescribed medication.
4. Verification of the source documents: Foreign health-related documents must be checked and, if necessary, translated to German by a recognized body (eg, translation services). In case of an already established course of pharmaceutical drug treatment with the dispensing category "A+," according to the Federal Act on Medicinal Products and Medical Devices (Therapeutic Products Act) Article 24 (eg, opioids, benzodiazepines, methylphenidate), they require an external verification of the original prescription and a statement from the physician. Written verifications by the federal authorities or nongovernmental organizations involved in the opioid replacement therapy program will also be accepted. Other verifications by nongovernmental organizations (eg, refugee organizations) will not be accepted.

Data Protection

In this registry, anonymized health data will be analyzed and stored. Other sensitive data, particularly, religious, political, social security, or administrative data will not be included as part of this study. The anonymized data sets generated or analyzed during this study will be available upon request from TG. Data are handled according to the Schengen Data Protection Act.

Statistical Considerations

Statistical analyses will be conducted by the study team in consultation with senior statisticians. For baseline analyses, means or medians will be reported according to the distribution of the continuous variable. Proportions will be reported for categorical variables. For hypothesis testing, a two-sided *t* test for normally distributed continuous variables and nonparametric

tests for nonnormally distributed continuous variables will be conducted; chi-square testing will be used for categorical variables. Linear or logistic regression models with or without adjustment for potential confounders (ie, age, sex, nationality) will be used when appropriate. Regression analysis estimates will be reported using 95% confidence intervals, and a two-sided *P* value of <.05 will be considered statistically significant for all reported tests. For the longitudinal data, a generalized linear mixed model with random effects (accounting for the nationality of the prisoner during the refugee crisis) will be used when appropriate. Statistical analyses will be performed using STATA Version 16 (StataCorp LP).

Outcomes

The primary outcome measure will be disease prevalence by using cross-sectional data from prisoner's medical records (ie, using the ICD-10 codes [German modification]) from 2015 to 2020. Secondary outcome measures include the following: (1) A comparison of disease prevalence (ICD-10 codes [German modification]) of the inmates at the PPZ to that of a representative sample from the local resident population by using cross-sectional medical records from all inmates at the PPZ from 2015 to 2020 and (2) longitudinal changes in disease prevalence (ICD-10 codes [German modification]) from 2015 to 2020 by using cross-sectional medical records from all inmates at the PPZ.

Ethical Aspects

This study was approved by the ethical committee of the Canton of Zurich. The committee will be informed about major changes to the protocol in agreement with local requirements. This study will be conducted in accordance with the protocol and the principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice issued by the International Conference on Harmonization, and the requirements from the Swiss Law and Swiss regulatory authorities. This study protocol is reported according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines and results will be reported according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement from the University of Basel, Switzerland.

Results

This study was approved on August 5, 2019 by the ethical committee of the Canton of Zurich with the registration code KEK-ZH No. 2019-01055 and funded in August 2020 by the "Walter and Gertrud Siegenthaler" foundation and the "Theodor and Ida Herzog-Egli" foundation. This study is registered with the International Standard Randomized Controlled Trial Number registry. Data collection started in August 2019 and results are expected to be published in 2021. Findings will be disseminated through scientific papers as well as presentations and public events.

Discussion

This health registry is designed to provide new public health insights into a group of vulnerable patients. The implementation of the study protocol promises to allow for the identification of specific health problems to help prepare successful public health strategies to meet these challenges. To gain a representative sample from the Canton of Zurich inmate population, this study required a high enrollment. Inmates at the PPZ usually spend a minimum of 1 day to a maximum of 7 days in the facility; they are internationally mobile, often unable to speak German, and have no contact details provided. Gaining informed consent from each prisoner is a disproportionately large expenditure. In this observational study, we assume that the expected increase in knowledge will benefit future inmates and thus, outweigh the disadvantages associated with privacy concerns. Moreover, given these operational challenges, any large-scale study on the prisoner population will likely need to be conducted without receiving individualized informed written consent. Thus, in accordance with the Swiss Human Research Act Article 34, the need to obtain informed consent is waived for this study, and data collected from all prisoners will be gathered. Only in case of documented alleged refusal to participate in health-related activities, data from the prisoner will not be included in this study.

Currently, no similar observational studies on Swiss inmates are available. Data from the United States and European registries indicate that prisoners are sicker when compared with their counterparts in a free society [2-4]. However, these data are limited to a certain location and time and they do not investigate changes over time within a certain cohort. Preliminary studies suggest that illicit drugs and especially NPS are a growing problem in European prisons, but only limited data from European prisons are available [7,8]. This study will be able to draw conclusions on these issues based on a 5-year representative sample of approximately 50,000 to 60,000 prisoners from the PPZ. Thus, this study will add valid evidence to the current health status of prisoners, and findings can be used to promote healthy behaviors (eg, future intervention studies) or policy change for this population.

The findings of this study will be disseminated through peer-reviewed journals as well as national and international conference presentations. Collaborations with other researchers in the field will be promoted. The data that support the findings of this study are available from the corresponding author upon reasonable request. Furthermore, data will be presented to Swiss policymakers and health care workers to improve the public health of prisoners in Switzerland. In conclusion, this study will construct a valuable database of information regarding the health of inmates and refugees and will act as groundwork for future interventions in this vulnerable population.

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Authors' Contributions

TG, MK, and SS conceived the concept of the study and its design. TG drafted the protocol. All authors critically reviewed the manuscript for important intellectual content and provided all the administrative, technical, or material support. TG, MK, and SS supervised the study and received the funding. All authors have read and approved the manuscript.

Conflicts of Interest

TG and MK serve as consultants for Bayer AG for the conduction of several phase-II/III trials (e.g. BAY2253651) in pharmacotherapy for obstructive sleep apnea, outside the submitted work. All other authors report no conflicts of interest.

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Abbreviations

EMCDDA: European Monitoring Centre for Drugs and Drug Addiction
ICD: International Classification of Diseases
NPS: new psychoactive substances
PPZ: Police Prison Zurich

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Protocol

Developing a Blockchain-Based Supply Chain System for Advanced Therapies: Protocol for a Feasibility Study

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Abstract

Background: Advanced therapies, including cell and gene therapies, have shown therapeutic promise in curing life-threatening diseases, such as leukemia and lymphoma. However, these therapies can be complicated and expensive to deliver due to their sensitivity to environment; troublesome tissue, cell, or genetic material sourcing; and complicated regulatory requirements.

Objective: This study aims to create a novel connected supply chain logistics and manufacturing management platform based on blockchain, with cell and gene therapy as a use case. Objectives are to define the requirements and perform feasibility evaluations on the use of blockchain for standardized manufacturing and establishment of a chain of custody for the needle-to-needle delivery of autologous cell and gene therapies. A way of lowering overall regulatory compliance costs for running a network of facilities operating similar or parallel processes will be evaluated by lowering the monitoring costs through publishing zero-knowledge proofs and product release by exception.

Methods: The study will use blockchain technologies to digitally connect and integrate supply chain with manufacturing to address the security, scheduling, and communication issues between advanced therapy treatment centers and manufacturing facilities in order to realize a transparent, secure, automated, and cost-effective solution to the delivery of these life-saving therapies. An agile software development methodology will be used to develop, implement, and evaluate the system. The system will adhere to the EU and US good manufacturing practices and regulatory requirements.

Results: This is a proposed study protocol, and upon acceptance, grant funding will be pursued for its execution in 2021.

Conclusions: The successful implementation of the integrated blockchain solution to supply chain and manufacturing of advanced therapies can push the industry standards toward a safer and more secure therapy delivery process.

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KEYWORDS

blockchain; digital health; IOT; internet of things; regenerative medicine

Introduction

Advanced therapy medicinal products (ATMPs) industries, including cell therapy and gene therapy, are forecasted to grow at a compound annual growth rate of 22% from 2018 to 2022 [1]. ATMPs are estimated to be a billion-dollar industry and potentially the fourth therapeutic pillar of health care [2,3]. Commercially available ATMPs make up a very small percentage of total patient interventions as compared to the mainstream first- and second-line therapies in the developed markets. However, for cell and gene therapy, they are expected to grow from a few 1000 patients in 2018-2019 globally to

possibly 100 million by 2025, as the number of commercially available ATMPs matures [1].

To facilitate the growth of the ATMP sector, the supply chain infrastructure is critical in supporting the industry from clinical trials to commercial distribution of life-saving treatments to more patients in a safer and more secure manner. In addition, compliance with data protection laws (Health Insurance Portability and Accountability Act [HIPAA] in the United States and General Data Protection Regulation [GDPR] in the European Union) comes at a very high cost [4-6]. Without proper encryption and selective data disclosure, everyone in the supply chain will have to be GDPR-compliant. Key to the success of these new treatments will be the safe, secure, and timely delivery of advanced therapies in a highly regulated environment (eg, temperature, tilt, time duration, and location) to ensure transparency and accuracy [7,8].

Current logistics tracking solutions are reliant on paper audit trails and legacy cloud infrastructure and are at significant risk of causing treatment failures. Specific to autologous therapies, the starting material collected from the patients can vary greatly. This can cause the final manufactured product to be of different quality, which may cause it to fall out of specification [9]. For example, Novartis had to write off multiple batches of Kymriah (Novartis) due to out-of-specification products since its launch in August 2017 in the United States [10]. Similarly, during the clinical studies, 7%-9% of patients did not receive the CAR-T treatment due to manufacturing failures [11].

Current solutions based on paper and dated legacy standalone information technology (IT) infrastructure that are being used by bioscience companies during precommercialization may be sufficient during research stages. However, these solutions are likely to fail as their operations scale up and out. They are not designed to be scalable, interoperable, or capable of dealing with the complexity of regulation and process that these ATMPs will incur in the real world of patient care. Batch identification through patient initials and date of birth is considered insufficient due to possible mix-ups, which can be catastrophic for patients. Intuitive labeling methods must be simple enough for use across sites while providing sufficient information about the patient to avoid mix-ups [12]. Companies, including Trakcel, Vineti, Danaher (previously, GE), are using cloud-based solutions for manufacturing ATMPs [13-15]. Although cloud-based solution systems are useful in tracking and tracing products in traditional linear logistic supply chains, data in these centralized systems are highly vulnerable to being tampered with, potentially allowing fraudulent or damaged products to enter the supply chain or data falsification. These systems focus only on the logistics part of the delivery process and fail to address the coordination issues between stakeholders (hospitals, patients, manufacturers, logistics providers, and regulatory authorities) in the advanced therapy delivery process.

As new license indications are achieved, the systems will need to be designed to change and adapt across the whole logistics supply chain. From the collection of source material to manufacturing and final delivery of therapies, there are many handoff points, creating the probabilities of mix-ups and supply chain failure. As most advanced therapies are provided as the last line of treatment for patients with critical illnesses, the failure or delay may cost them their chance of survival.

Blockchain technology is a digital ledger of transactions, agreements, and controls that are stored in a distributed network, removing the need for a centralized database. Due to its distributed and transparent nature, the data stored cannot be tampered with and is transparent, traceable, and secure [16,17]. The benefits of the blockchain technology have been explored in various sectors, including finance, health care, and agriculture [18-20]. One of the most highly discussed use cases of blockchain technology is in supply chain management. Integration of blockchain into supply chain architecture can lead to a more reliable, transparent, and resilient system [21-24]. Specific to ATMP supply chain management, a layered blockchain solution with a smart contracts business logic layer can enable a holistic way of managing various stakeholders, ensure needle-to-needle supply chain integrity, and secure data management. The decentralized nature of blockchain can allow this to happen almost instantaneously across the full ecosystem, including the ability to keep regulators updated by publishing on a public chain with zero-knowledge proofs. Cloud environments cannot provide these facilitations; and thus, require frequent on-site monitoring and auditing by regulators. The protocol of this study will focus on developing a patient-to-patient blockchain-based supply chain system for advanced therapies.

Methods

Description of the Blockchain-Based Supply Chain System

This study aims to create a smart and connected supply chain logistics and manufacturing management platform based on blockchain, with cell and gene therapy as a use case. The data collected from sensors can be better connected using an interactive platform to improve coordination between stakeholders. To ensure the security of this platform, which contains sensitive information such as patient data and manufacturing protocols, blockchain allows a transparent, incorruptible, yet encrypted way of tracking and tracing the environmental conditions of advanced therapies from their origins to final administrations. This is particularly important for advanced therapies due to their requirements of cold chain delivery and the sensitivity of live cell products to fluctuations in the environment. The platform technology will allow real-time and centralized monitoring of the needle-to-needle process without compromising patient data security through selective disclosure of information.

Publishing zero-knowledge proofs, when all steps are completed as per the standard protocol, can allow regulatory authorities and manufacturers with multiple collection centers and manufacturing facilities to manage compliance by exception instead of looking through all data points and paper batch records to find regulatory breaches, allowing a reduction in regulatory monitoring costs. This can help improve consistency in all steps of collection, manufacturing, and delivery across centers and allow issues to be identified and the process to be improved through learning from data. The system will adhere

to the EU and US good manufacturing practices and industry bodies for health care distribution requirements.

Development and Evaluation

Based on the agile framework [25], this study will involve the following components for the development and evaluation of the system.

1. Stakeholder analysis
2. Customize and implement track-and-trace software platform
3. Migration and integration of software to blockchain platform
4. Case study for evaluation of the system

Stakeholder Analysis

A detailed stakeholder map shall be derived, including the manufacturer of therapies, health care professionals who engage with the therapy delivery pathway, payers of the treatment (for visibility of the chain of custody of the ATMP), the advanced therapy treatment center, hospital IT system implementation partner, supply chain track-and-trace provider, logistics provider, manufacturing facilities (including contract manufacturers), and regulatory authorities. Focus group meetings will be held to understand the points where regulatory/monitoring costs arise; how a network of facilities is currently managed; the data that need to be collected at different points of the supply chain to enable cheaper monitoring and product release by exception. Outcomes will be user requirement specification for decentralized manufacturing, standardized workflow for target therapy, and the understanding of the capability and gaps in and across the current systems.

Customize Track-and-Trace Software Platform

The design of minimum viable ecosystem and definition of scope of work for each party will be produced. A working prototype of the track-and-trace software platform for autologous advanced therapies has been developed and will be customized to cell and gene therapy. For regulatory activities, we will extend the existing regulatory approval to complete preliminary pathways for support of our new product. The platform will be designed so that it can be easily integrated into existing commercial applications, or it can be a standalone solution if required. A customized prototype will be developed to demonstrate the platform.

Migration and Integration of Software to Blockchain Platform

The prototype track-and-trace software platform will be adapted to combine the characteristics of linear and circular supply chains for advanced therapies. Key outcomes to monitor will be communication time reduction, capacity utilization, resource sharing and utilization, ease of establishing a process comparability across manufacturing facilities, delivery accuracy and reduced number of mix-ups/failures, user satisfaction (eg, ease of use and interoperability).

The core codes of blockchain technology platform for solutions currently developed are patented in the United States and the European Union [26]. Compared to the existing local electronic batch record systems and cloud-based solutions, a blockchain-based platform will allow for more secure ways of recording and storing supply chain data on a distributed ledger and encrypting those data to make the system tamper-proof. Any divergence or discrepancy to the ledger of information captured will be flagged to all, including the authorities.

Participating parties can manage the system so that only the relevant information is made available to each party. A blockchain solution facilitates partnerships between parties with divergent commercial self-interests, leveraging automated smart contracts. Each party is kept honest as the collective objectives of all consortium members using the blockchain solution will not be beneficial to any of the members if members were to collude. Real-time and up-to-date manufacturing process updates are transparent for patients and hospital staff in order to allow more efficient scheduling and resource allocation for treatment preparation. This means that the hospital can provide patient status updates to manufacturing. Information on the blockchain can be encrypted and made selectively available to the approved parties, hence reducing the number of GDPR-trained staff, thus lowering the cost of compliance.

Through integrating the track-and-trace and manufacturing execution system, a greater coordination between stakeholders can be fostered, allowing the delivery process to be more efficient and releasing valuable time of skilled workers for value-added work. Good track-and-trace documentation will allow the manufacturers and hospitals to review their process outcomes to improve the quality and consistency of raw material collection and manufacturing processes.

Use of blockchain will ensure data integrity between the various systems, scanners, and data input devices without mandating substantial integration changes. Moreover, blockchain creates efficiencies through automating payment processes, regulatory reporting, and compliance and audit. This technology can lower the cost of regulatory compliance through publishing zero-knowledge proofs where all standard protocols are followed properly, removing the need for going through all records (on paper or in a cloud). Furthermore, it reduces the cost of GDPR compliance training through encryption of patient data and implementation of multiple levels of access rights.

Case Study

This investigation will be structured via a 6-stage process for case study investigations [27] to evaluate the system's feasibility and economic impact (Table 1). A case study will provide a structured means to generate evidence to subsequently evaluate such claims by collecting baseline data for further evaluation. It will provide an understanding of the feasibility and economic impacts of blockchain for cell therapy in a decentralized fashion at different levels of automation and at different demand levels and scales of the system. The project outcomes and appraisals will help simulate the impacts of widespread use of this methodology for larger systems through modeling. The results will be disseminated through publications and conference presentations.

Table 1. Case study framework.

Stage	Outcome
Plan	Case description and linking of case approach to investigation outcomes.
Design	Construction of research design and linkage of research questions, data, and criteria for evaluation and synthesis.
Prepare	Drafting, execution, and approval of study protocols.
Collect	Data collection strategy.
Analyze	Extraction of data into categories for review and analysis.
Share	Publication of the findings in a peer-reviewed journal.

Results

This proposed study protocol will lay the foundation for future grant applications, and its execution will be completed in 2021.

Discussion

The successful implementation of the integrated blockchain solution to the supply chain and manufacturing of advanced therapies can push the industry standards toward a safer and more secure therapy delivery process and encourage rapid adoption of the innovative technology. Adoption of the innovation in a wider context can reduce the costs of monitoring good manufacturing practices through increased transparency and security of the manufacturing and delivery process. A more transparent process can reduce communication errors and overall time spent, hence reducing health care costs. The integrated platform solution will enable more accurate and transparent tracking at all stages of the needle-to-needle delivery pipeline, allowing treatment-centric care pathways to be truly personalized through a digital evolution in supply chain and manufacturing management.

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Authors' Contributions

CL, MHV, and EM wrote different parts of the protocol.

Conflicts of Interest

None declared.

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Abbreviations

ATMP: advanced therapy medicinal products
GDPR: General Data Protection Regulation
HIPAA: Health Insurance Portability and Accountability Act
IT: information technology

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Protocol

Feasibility, Acceptability, and Effectiveness of Enhanced Cognitive Behavioral Therapy (eCBT) for Children and Adolescents With Obsessive-Compulsive Disorder: Protocol for an Open Trial and Therapeutic Intervention

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Abstract

Background: Although the evidence base of cognitive behavioral therapy (CBT) for pediatric obsessive-compulsive disorder (OCD) has been broadly established, the treatment is hampered by limited access, poor compliance, and nonresponse. New technologies offer the opportunity to improve the accessibility, user friendliness, and effectiveness of traditional office-based CBT. By employing an integrated and age-appropriate technologically enhanced treatment package, we aim to execute a more focused and attractive application of CBT principles to increase the treatment effect for pediatric OCD.

Objective: The aim of this open study is to explore the acceptability, feasibility, and effectiveness of a newly developed enhanced CBT (eCBT) package for pediatric OCD.

Methods: This study is an open trial using a historical control design conducted at the outpatient clinic of the Department of Child and Adolescent Psychiatry at St. Olavs University Hospital (Trondheim) or at BUP Klinikk (Aalesund). Participants are 30 children (age 7-17 years) with a primary Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 diagnosis of OCD, and their parents. All participants receive eCBT. eCBT consists of the usual evidence-based CBT for pediatric OCD in an "enhanced" format. Enhancements include videoconferencing sessions (supervision and guided exposure exercises at home) in addition to face-to-face sessions; an app system of interconnected apps for the child, the parents, and the therapist; psychoeducative videos; and frequent online self-assessments with direct feedback to patients and the therapist. Primary outcome measures are the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) (effectiveness), the Client Satisfaction Questionnaire-8 (acceptability), and treatment drop out (feasibility). Assessments are conducted pretreatment, posttreatment, and at 3- and 6-month follow-ups. A 12-month follow-up assessment is envisioned. The treatment outcome (CY-BOCS) will be compared to traditional face-to-face CBT (data collected in the Nordic Long-term OCD Treatment Study).

Results: Ethical approval has been obtained (2016/716/REK nord). Inclusion started on September 04, 2017. Data collection is ongoing.

Conclusions: This study is the first step in testing the acceptability, feasibility, and preliminary effectiveness of eCBT. In case of positive results, future steps include improving the eCBT treatment package based on feedback from service users, examining cost-effectiveness in a randomized controlled trial, and making the package available to clinicians and other service providers treating OCD in children and adolescents.

Trial Registration: ISRCTN, ISRCTN37530113; registered on January 31, 2020 (retrospectively registered); https://www.isrctn.com/ISRCTN37530113.

International Registered Report Identifier (IRRID): DERR1-10.2196/24057

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KEYWORDS

obsessive-compulsive disorder; cognitive behavioral therapy; e-mental health; children; adolescents; cognitive; behavioral; pediatric

Introduction

Background

Pediatric obsessive-compulsive disorder (OCD) is a relatively common, severe, and debilitating condition [1], leading to substantial impairment in family, academic, and social functioning [2,3] and reduced quality of life [4]. Cognitive behavioral therapy (CBT) is the treatment of choice [5,6], and its effectiveness has been extensively demonstrated [7-9]. However, treatment for pediatric OCD is limited by several problems.

First, not all children benefit sufficiently from treatment. In general, after standardized CBT, average symptom improvement is about 50%, with large individual differences [10,11]. The combination of CBT with pharmacotherapy is an option for partial responders and nonresponders, but recent studies have cast doubts on the additional effect of medication [12,13]. Furthermore, use of medication entails several disadvantages, such as possible adverse effects, a heightened chance of relapse by discontinuation, and unknown effects in the long term [14]. This highlights the need for new ways to improve treatment for pediatric OCD.

Second, there are organizational and practical barriers to treatment. Particularly in remote areas, CBT is not always available, and in many places, there has been a long tradition of a shortage of experienced therapists and long waitlists for treatment [15-18]. Practical problems with scheduling, treatment associated costs, disorder-specific symptoms that restrict mobility, shame, and stigma can further limit accessibility to treatment [16,19-22].

In parallel, the use of digital technology in child mental health care is rapidly increasing [23]. Technologies (computers, internet, mobile devices, and apps) offer a unique opportunity to address several limitations associated with traditional treatment, such as access, suitability, expense, and stigma. In addition, new technologies can be appealing to children and adolescents, which may increase treatment compliance and motivation.

Several types of technology-based CBT (tCBT) programs for OCD have been developed and implemented, including online bibliotherapy, online self-help therapy, therapist-supported computerized CBT, smartphone apps, traditional CBT delivered via telephone or videoconferencing, and combinations of these forms [22,24-27]. Preliminary evidence shows that these programs yield positive effects overall. A meta-analysis on tCBT for OCD, which was based on eight randomized controlled trials (N=420, including youth, n=31), showed a large effect size for tCBT (*d*=1.18, CI 0.80-1.56) [25]. Moreover, tCBT was found to be superior to control conditions (waitlist and active controls, *d*=0.82), and no difference was found in efficacy between tCBT and traditional therapist-delivered CBT [25]. Results from a recent systematic review on tCBT for pediatric OCD (N=96) indicated that tCBT can be a feasible and acceptable treatment for youth with OCD [24].

However, tCBT for OCD is still in its infancy. Current evidence is limited by small numbers of trials, small sample sizes, methodological shortcomings, and focus on adults in most studies. In addition, tCBT programs vary greatly in format, duration, intensity, length, and their specific aims, making it hard to draw firm conclusions. This stresses the need for further research, especially in children with OCD.

In this protocol, we propose an *enhanced* cognitive behavioral therapy (eCBT) package for pediatric OCD, integrating modern internet technology and traditional CBT, in order to improve treatment response as well as user friendliness.

eCBT for Pediatric OCD

eCBT is an innovative treatment package for children and adolescents with OCD, which has been developed by academic OCD experts, clinicians, information technology and media developers, and service users. eCBT integrates modern technology with well-validated principles of CBT, with the aim to address some challenges faced by traditional therapy. eCBT employs the Norwegian [28] and Dutch [29] treatment manuals for CBT for pediatric OCD. For both protocols, effectiveness has been demonstrated [11,30]. Equivalent to traditional CBT, eCBT contains psychoeducation, exposure with response prevention (ERP), cognitive interventions, and relapse prevention. Parents are actively involved in the treatment. eCBT enhances traditional CBT by offering treatment at home via a webcam in addition to face-to-face sessions, more frequent therapist contact, and an app system to support and monitor treatment. Taking into account the shortage of experienced therapists and high societal health care costs, total therapist time for eCBT is kept equivalent to traditional CBT.

Treatment Components

The following five closely linked components are integrated in the eCBT treatment process: videoconferencing sessions in combination with face-to-face sessions, an app system, a psychoeducation tool, and frequent online ratings with direct feedback to the patient. We describe these components in more detail below.

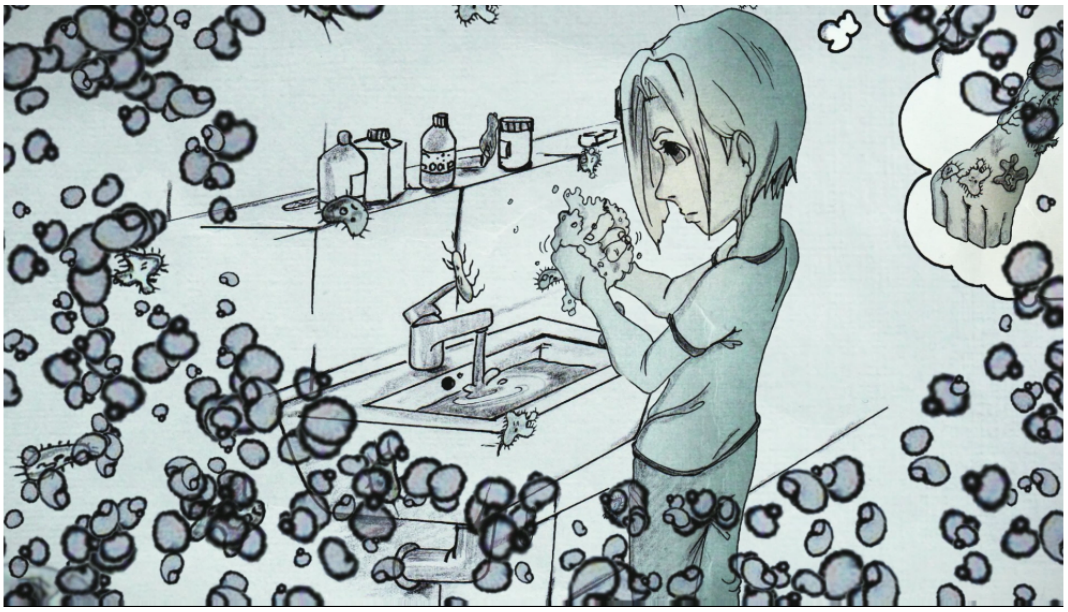
eCBT combines face-to-face treatment sessions with videoconferencing sessions from home. During the videoconferencing sessions, therapists assist children in ERP exercises at home or at other places that elicit OCD symptoms. The videoconferencing sessions aim to improve the ecological validity of the treatment and to encourage generalization of CBT principles by extending treatment from the therapist's office to settings in which the problems naturally occur. In addition, treatment at home may be more convenient and may reduce travelling time, costs, and stigma. Children and therapists have access to the video-teleconferencing software via their smartphones, using Cisco Webex Teams [31]. Face-to-face sessions, allowing for full contact, may facilitate the building of therapeutic alliance and may provide the therapist with other information since observations are not limited to the scope of the webcam.

The app system consists of a smartphone app for children, a smartphone app for parents, and a web-based application for therapists on the computer, which are all interconnected. The main goals of the app system are to increase motivation and treatment adherence, and to encourage parents' involvement in the treatment process. The app system further contributes to personalizing treatment to individual needs. The app provides information about OCD and CBT (psychoeducation videos), supports and structures ERP exercises at home, and closely monitors treatment progress. The web-based application for therapists has a coordinating and monitoring function. The app can be used in the treatment sessions together with the therapist and independently at home. Multimedia Appendix 1 provides an overview of the app system.

The app system is fully integrated in the treatment process, starting in the first session with the psychoeducation tool. The psychoeducation tool contains four video stories showing animated narratives of children with OCD. The aim is to provide information about OCD and treatment (CBT), to increase insight in an attractive and accessible way, to give recognition to a patient's struggle with OCD and take away shame, and to provide hope and motivation for treatment. The videos, displaying cartoons voiced over by a child or a parent, show how OCD has interfered in the lives of these children and their families, and show their experiences with treatment. The tone is positive and encouraging. The portraits represent children of different ages and both sexes, with different OCD symptomatology to facilitate recognition and identification with one of the portraits. Figure 1 displays a picture of one of the video stories. Multimedia Appendix 2 provides a description of the stories.

The app is also used to facilitate listing and monitoring of OCD symptoms. OCD symptoms can be entered via the therapist application during the treatment sessions or directly in the child and parent apps. Symptoms are scored on a subjective units of distress (SUD) scale. The three symptoms identified by the child and parents as most important are marked, forming the *top problems* measure that is used for idiographic patient-guided assessment of treatment progress [32]. Parents can make a list of the child's symptoms from their perspective, for example, in case of young children who are not able to list the symptoms themselves and in the case of different views on the symptoms between parents and the child. This approach allows the therapist to get a more complete picture of the OCD and keep parents involved, and it may facilitate discussion when the child and parents disagree, opening the way to a shared vision.

Figure 1. Psychoeducation tool.



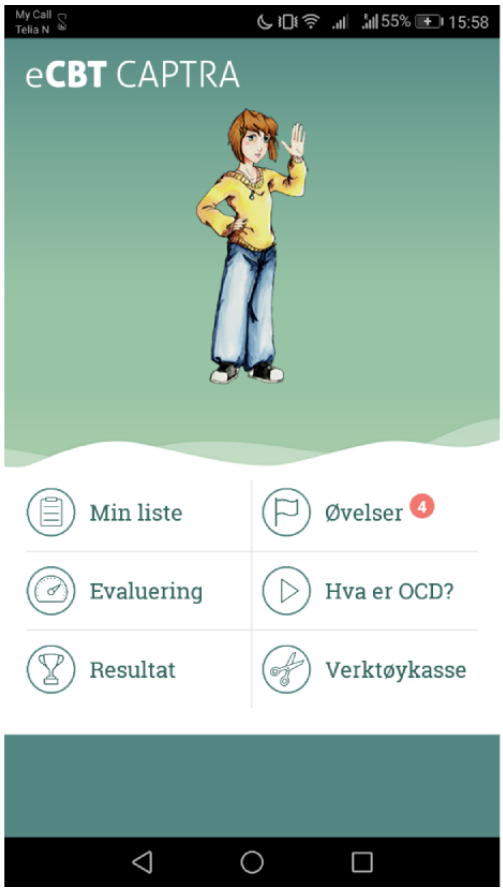
The app further contains a feature to structure and support ERP exercises at home. During the treatment sessions, ERP exercises are described in the app and can be displayed at any moment in the child and parent versions of the app. The child can receive daily reminders for the ERP exercises. When the child activates an ERP exercise in the app, the description of the exercise appears, followed by a button to confirm the start and end of the exercise, and finally, an evaluation question ("How much discomfort did you have during the exercise?"; visual analog scale [VAS]). The app contains a virtual reward system for the

number of completed ERP exercises to keep the child motivated. The description of the ERP exercises in the parents' app keeps parents informed and may facilitate parents to support the exercises. Therapists can add, modify, and monitor exercises via the therapist application.

The child can build a personal support and relapse prevention plan via the app. Any kind of support (ie, coping strategies and tools for dealing with distress) in overcoming OCD can be added to the "toolbox" in the form of text, images, pictures, and video and audio files. The toolbox is a working file that is continuously supplemented and refined throughout the treatment. At the end of the treatment, an individualized relapse prevention plan is added to the toolbox. This plan can be exported to a PDF file, allowing for a paper version of the plan as well.

The child and parents are encouraged to daily rate OCD severity and overall psychological well-being using short idiographic ratings in the app with direct feedback to the patient and the therapist (Multimedia Appendix 3). In addition, the three OCD-related problems identified by the child and parents as most important (*top problems* measure) are evaluated weekly in the app. Reminders can be set for completing the ratings. Results (visually displayed in graphs showing progress during the last week and last 6 months) are directly accessible via the child and parent apps, since direct feedback to patients may enhance motivation and thereby treatment effect [33]. In addition, the outcomes provide the therapist with actual information. Signs of noncompliance can be monitored regularly, and early steps can be taken to address problems. Figure 2 displays a screenshot of the app.

Figure 2. Screenshot of the app for children.



Treatment Process

eCBT covers a 14-week treatment period. The first part of the treatment (weeks 1-5) consists of weekly face-to-face sessions, equivalent to traditional CBT. Regular face-to-face sessions allow the therapist to start therapy in full contact with the child and the parents in order to build therapeutic alliance and establish treatment principles. However, as soon as the child starts with ERP exercises at home (week 2), an additional videoconferencing meeting is scheduled, resulting in two appointments with the therapist per week. During the videoconferencing sessions, the therapist guides the child while carrying out an ERP exercise at home or at another location if applicable. In this way, the therapist can provide extra support to the child when performing ERP exercises and solve problems directly. In the second part of the treatment, from week 6 onwards, the frequency of the face-to-face sessions is reduced from weekly to once in 2 weeks, since the treatment principles are expected to be established by this time and the main focus becomes continuation of ERP exercises. From this point, two videoconferencing sessions (guided ERP at home) and one face-to-face session are scheduled in a 2-week period. This schedule offers more frequent therapist contact than the usual weekly sessions in traditional CBT and provides the therapist with extra tools to ensure adequate execution of ERP exercises in a natural environment.

In the first face-to-face session (week 1), the therapist provides psychoeducation about OCD and treatment (CBT), augmented

with the psychoeducation tool in the app. The eCBT concept is introduced, including an explanation of the app system. The therapist starts with an OCD symptom inventory, which will be completed during the coming weeks. The child as well as parents identify the three most important OCD-related problems (*top problems* measure). In the coming week, the child and/or parents report OCD symptoms in the app. They also start with ratings via the app. The therapist discusses the outcomes of the ratings during the face-to-face sessions. In the next session (week 2), the therapist and child establish a symptom hierarchy, and ERP exercises are set up. The first ERP exercise is practiced together in the session and will be further practiced at home. An appointment is made for a videoconferencing session later that week to guide the ERP exercise at home. In the third face-to-face session (week 3), the therapist evaluates the ratings (app) with the family and discusses the first experiences with practicing ERP at home. A new ERP exercise is selected (or the previous ERP exercise is adapted) to be practiced during the coming week. The new ERP exercise is first practiced during the session and will be further practiced at home. Based on clinical considerations, the therapist may introduce cognitive interventions (eg, challenging dysfunctional thoughts) during this session. Cognitive interventions are not mandatory but can be used to support the ERP exercises and increase motivation. The manual provides for different cognitive interventions, including guidelines for when to apply these interventions, allowing the therapist to customize the treatment to the child's needs, capacities, and preferences. The face-to-face session will be followed by a videoconferencing session (guided ERP at home) later that week. From this point, the face-to-face sessions have the same structure and include evaluating the ratings and the ERP exercises practiced at home, preparing new ERP exercises, practicing ERP exercises in the session, and introducing optional cognitive interventions. From week 4, the child works on a personal support plan, which is supported by the "toolbox" feature in the app. The "toolbox" will be continuously supplemented and refined during the treatment. At the end of the treatment (weeks 12-14), an individualized relapse prevention plan is added to the toolbox. Multimedia Appendix 4 provides an overview of the treatment.

Research Protocol

The research protocol (version March 2020) describes an open study to explore the acceptability, feasibility, and effectiveness of eCBT for pediatric OCD.

Aims and Hypotheses

The aim of the study is to explore whether eCBT is (1) a feasible intervention in terms of treatment drop out; (2) an acceptable intervention; and (3) an effective intervention for children and adolescents with OCD in terms of positive treatment outcomes and showing noninferiority to traditional CBT (Nordic Long-term OCD Treatment Study [NordLOTS]) [11] for the primary outcome measure (Children's Yale-Brown Obsessive-Compulsive Scale [CY-BOCS]).

We hypothesize that (1) preterm treatment drop out will be equivalent or lower than that found for traditional CBT (≤10%) [11]; (2) eCBT will be positively evaluated by children and their parents; (3) there will be a considerable reduction in OCD symptoms after treatment; and (4) the treatment outcome (CY-BOCS) for eCBT will show noninferiority to traditional CBT (NordLOTS) [11].

Methods

Study Design and Sample Size

This study is an open trial using a historical control design to explore the feasibility, acceptability, and effectiveness of eCBT in children and adolescents with OCD. To examine noninferiority of eCBT to traditional CBT, the treatment outcome for eCBT (CY-BOCS) will be compared to data collected in the NordLOTS [11]. The intended sample size is 30 participants.

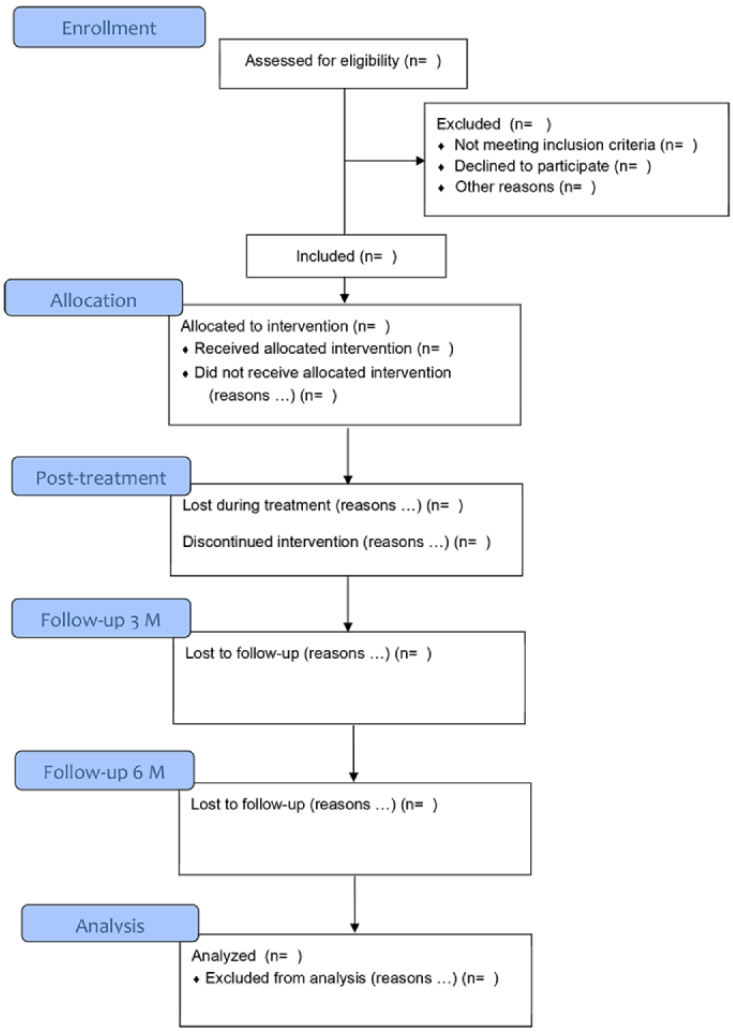
Study Setting and Recruitment

Children who visit the outpatient clinic of the Department of Child and Adolescent Psychiatry at St. Olavs University Hospital (Trondheim) or at BUP Klinikk (Aalesund), and meet the study's eligibility criteria are informed about the study and asked to consider participation. They receive the opportunity to ask questions and have a reasonable amount of time for consideration. Consenting patients are enrolled in the study. During the intake procedure, a qualified professional confirms OCD diagnosis and comorbid disorders using a semistructured interview (Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version [K-SADS-PL]) [34] if not completed prior to the trial. A standardized questionnaire is used to collect information about demographics and symptom/treatment history.

Study Procedures

All participants receive eCBT. For participants not having a smartphone and for those using an iPhone, an Android smartphone will be lent for the purpose of the study. Concurrent medication is allowed and will be reported during the study. Ongoing psychological treatment for OCD other than eCBT is not allowed. Participants can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a participant from the study for urgent medical reasons. The following stop rules for study participation are applied: (1) problems other than OCD requiring acute other treatment (eg, severe depression and suicidal ideation) and (2) severe increase in OCD symptoms and insufficient response to eCBT treatment. Figure 3 shows the flow diagram of the study.

Figure 3. Flow diagram.



Participants

To be eligible for study participation, a participant must meet all of the following criteria: (1) age 7-17 years (inclusive); (2) primary Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 diagnosis of OCD; and (3) CY-BOCS score ≥16.

A potential participant meeting any of the following criteria will be excluded from participation: (1) a psychiatric comorbidity that has a higher treatment priority than OCD and makes participation clinically inappropriate (eg, primary anorexia nervosa, depression with suicidality, and psychosis); (2) mental retardation (if suspected based on the level of functioning, or in the presence of neuropsychiatric comorbidity, an IQ test is performed); and (3) insufficient understanding of the Norwegian language.

Assessments

Assessments are performed pretreatment and posttreatment, and at 3- and 6-month follow-ups. A 12-month follow-up assessment is envisioned.

Outcome Measures

Outcome measures for treatment acceptability, feasibility, and effectiveness are specified below. Table 1 provides an overview of the assessments. Acceptability involves the following: Client Satisfaction Questionnaire-8 (CSQ-8) [35], primary outcome; a treatment evaluation questionnaire for children and their parents composed of the User Experience Questionnaire (UEQ) [36], and qualitative and quantitative treatment-specific questions; a modified version of the Barriers to Treatment Participation Scale (BTPS) [37], child and parent version (for the aim of this study, we shortened the questionnaire, added a child version, and adapted some items to increase the fit to the eCBT treatment package); and a short qualitative interview examining clinicians' treatment satisfaction and their suggestions to improve the treatment. Feasibility involves the following: preterm treatment drop out, primary outcome; and number of eligible participants that rejected/accepted eCBT. Effectiveness involves the following: CY-BOCS [38], primary outcome; Child Obsessive-Compulsive Impact Scale-Revised (COIS-R) [39]; and Family Accommodation Scale for OCD–Self-Rated Version (FAS-SR) [40]. Comorbidity/psychological well-being involves the following: Strengths and Difficulties Questionnaire (SDQ) [41]; Child Behavior Checklist (CBCL) [42]; Youth Self-Report Questionnaire (YSR) [42]; Screen for Child Anxiety-Related Emotional Disorders-Revised (SCARED-R) [43,44]; Mood and Feelings Questionnaire (MFQ) [45]; KINDL-R [46]; Children's Global Assessment Scale (CGAS) [47]; and Clinical Global Impressions Scale-Severity/Improvement (CGI-S, CGI-I) [48].

Other study parameters include the following: study-specific *treatment integrity forms* completed by the therapist following each treatment session and the Trimbos/iMTA Questionnaire for Costs associated with Psychiatric Illness (TiC-P) [49].

Table 1. Overview of assessments.

Assessment	Pretreatment	During treatment	Posttreatment	Follow-up 3 months	Follow-up 6 months
CY-BOCS[a]	IE[b]	N/A[c]	IE	IE	IE
CGI-S[d]	IE	N/A	IE	IE	IE
CGI-I[e]	N/A	N/A	IE	IE	IE
CGAS[f]	Therapist	N/A	Therapist	Therapist	Therapist
COIS-R[g]	Child and parent	N/A	Child and parent	Child and parent	Child and parent
FAS[h]	Parent	N/A	Parent	Parent	Parent
CBCL[i]	Parent	N/A	Parent	N/A	Parent
YSR[j]	Child (≥11 years)	N/A	Child (≥11 years)	N/A	Child (≥11 years)
SCARED[k]	Child and parent	N/A	Child and parent	Child and parent	Child and parent
MFQ[l]	Child and parent	N/A	Child and parent	Child and parent	Child and parent
SDQ[m]	Child and parent	N/A	Child and parent	Child and parent	Child and parent
KINDL	Child and parent	N/A	Child and parent	Child and parent	Child and parent
CSQ-8[n]	N/A	N/A	Child and parent	N/A	N/A
Treatment evaluation questionnaire	N/A	N/A	Child and parent	N/A	N/A
BTPS[o] (modified version)	N/A	N/A	Child and parent	N/A	N/A
TiC-P[p]	Parent	N/A	Parent	Parent	Parent
Session integrity form	N/A	Therapist	N/A	N/A	N/A

[a]CY-BOCS: Children's Yale-Brown Obsessive-Compulsive Scale.
[b]IE: independent evaluator.
[c]N/A: not applicable.
[d]CGI-S: Clinical Global Impressions Scale-Severity.
[e]CGI-I: Clinical Global Impressions Scale-Improvement.
[f]CGAS: Children's Global Assessment Scale.
[g]COIS-R: Child Obsessive-Compulsive Impact Scale-Revised.
[h]FAS: Family Accommodation Scale for obsessive-compulsive disorder.
[i]CBCL: Child Behavior Checklist.
[j]YSR: Youth Self-Report Questionnaire.
[k]SCARED: Screen for Child Anxiety-Related Emotional Disorders.
[l]MFQ: Mood and Feelings Questionnaire.
[m]SDQ: Strengths and Difficulties Questionnaire.
[n]CSQ-8: Client Satisfaction Questionnaire-8.
[o]BTPS: Barriers to Treatment Participation Scale.
[p]TiC-P: Trimbos/iMTA Questionnaire for Costs associated with Psychiatric Illness.

Data Management

All hard-copy forms and informed consent forms will be stored in a secured facility. Protection of participant identity will be guaranteed by assigning study-specific unique participant codes. Only the principle investigator (NS) and the executive investigator (LBE) have access to the key for unique study IDs. Codes will be used to conceal identities in all external communications. Rechecks or later use of the data will be possible using the anonymized data file. Later use of the data will only be possible with consent of the participant. Information (raw data) will be stored for 10 years.

Regular reports are sent to the funding agency. The study is not monitored or audited by an independent party.

Safety Procedures

Children and parents are encouraged to report the occurrence of adverse events or undesirable treatment effects to their therapists or to the investigator. Therapists report this information in the treatment integrity forms and contact the research team if needed. In addition, a member of the research team (BW) will discuss the occurrence of adverse events and undesirable treatment effects with the therapists at regular times. The investigator will report all serious adverse events that logically could be expected to be related to study participation or eCBT treatment to the sponsor without undue delay after obtaining knowledge of the events.

In case a participant's condition deteriorates seriously during treatment, the therapist will perform an immediate assessment of the symptoms and will discuss this with the investigator to determine necessary actions.

The additional risk related to study participation for participants is assessed as negligible compared to regular treatment. eCBT follows the treatment principles of CBT, which is the evidence-based treatment for pediatric OCD. In addition, treatment progress and signs of noncompliance are monitored regularly, and immediate steps can be taken when problems are detected. In case of faltering technology (app or webcam), the therapist can be contacted by telephone, email, or face-to-face appointment. Patients can terminate treatment participation at any time and switch to regular treatment if desired. Risks related to technology and security cannot be excluded (ie, hacked data or spyware compromising patient confidentiality). However, security measures are undertaken. Data gathered with the app are stored on a secured server.

Statistical Analysis

Regarding feasibility and acceptability, descriptive statistics will be provided as follows: CSQ-8, treatment evaluation questionnaire, and modified BTPS for treatment acceptability, and preterm treatment drop out and number of eligible participants that rejected/accepted eCBT for treatment feasibility.

Regarding effectiveness, the treatment effect is expressed as percentage symptom improvement based on the CY-BOCS, the percentage of patients with OCD symptoms in the clinical range (CY-BOCS ≥ 16) and in remission (CY-BOCS ≤ 12), and the percentage of treatment responders (≥35% symptom reduction on the CY-BOCS plus CGI-I rating of 1 or 2 "[very] much improved") [50]. Effect size (*d*) is calculated by the mean difference in the CY-BOCS score before and after eCBT divided by the SD of the difference in the score before and after eCBT. We will run a series of linear mixed models with treatment outcome (CY-BOCS, CGAS, COIS-R, FAS-SR, CBCL/YSR, SCARED, and MFQ) as the dependent factor and time as the independent factor. An independent *t* test will be performed to compare the treatment outcome (difference in the CY-BOCS score before and after treatment) in this study with the treatment outcome reported for the NordLOTS [11].

In terms of other study parameters, for treatment adherence, treatment integrity forms are evaluated by two raters independently, and Cohen kappa will be calculated. To get an impression of treatment costs, outcomes for the TiC-P (related to the SDQ) will be described.

In case of missing assessments, all possible attempts will be made to contact participants.

For feasibility and acceptability analyses, missing data will be described. Acceptability analyses will be conducted on cases having complete data on these measures after treatment.

Regarding treatment outcome, an algorithm for handling missing data is integrated in linear mixed model analyses. Cases with missing data at baseline will be excluded from analyses.

Sample Size

As the intervention concerns an innovative treatment, the study is primarily aimed at studying acceptability and feasibility. For this goal, a power calculation cannot be performed.

To explore noninferiority of eCBT to traditional CBT (as delivered in the NordLOTS), we will use a historical control design. A power calculation (noninferiority margin set at 4 points on the CY-BOCS) shows that 21 participants per treatment arm would be sufficient to show noninferiority (80% power).

Results

The study has been approved by the Regionale komiteer for medisinsk og helsefaglig forskningsetikk (REK 2016/716/REK nord) and has been registered in the ISRCTN registry (ID: ISRCTN37530113). The study will be conducted according to the principles of the Declaration of Helsinki (version October 19, 2013; WMA, 2013) [51] and in accordance with the Medical Research Involving Human Subjects Act (WMO) and Good Clinical Practice (GCP) standards.

Multimedia Appendix 5 provides a summary of the trial registration data. Informed consent will be obtained prior to enrollment in the study. Inclusion started on September 04, 2017. Data collection is ongoing. The results will be published in peer-reviewed academic journals, presented at scientific conferences, and communicated to the participants and patient organizations. International Committee of Medical Journal Editors (ICMJE) criteria on contributorship and authorship are applied.

Discussion

This study is the first step in testing the acceptability, feasibility, and preliminary effectiveness of eCBT. In case of positive results, future steps include improving the eCBT treatment package based on feedback from service users, examining cost-effectiveness in a randomized controlled trial, and making the package available to clinicians and other service providers treating OCD in children and adolescents.

Although eCBT has not been developed with the intention to overcome all barriers to treatment, we aim to improve treatment response by offering a more focused application of CBT

principles in a user-friendly way. A future step would be to examine which approach works best for which patients.

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Conflicts of Interest

None declared. For the sake of completeness, LHW reports personal fees from Bohn Stafleu van Loghum, Houten, the Netherlands (publisher), outside the submitted work, and BW reports personal fees from Gyldendal Akademisk forlag, Olso, Norway (publisher), outside the submitted work.

Multimedia Appendix 1
Overview of the app system.
[PDF File (Adobe PDF File), 59 KB - resprot_v9i12e24057_app1.pdf]

Multimedia Appendix 2
Psychoeducation tool: stories.
[PDF File (Adobe PDF File), 60 KB - resprot_v9i12e24057_app2.pdf]

Multimedia Appendix 3
Questions for monitoring treatment progress via the app system.
[PDF File (Adobe PDF File), 74 KB - resprot_v9i12e24057_app3.pdf]

Multimedia Appendix 4
Enhanced cognitive behavioral therapy: treatment overview.
[PDF File (Adobe PDF File), 99 KB - resprot_v9i12e24057_app4.pdf]

Multimedia Appendix 5
Summary of trial registration data.
[PDF File (Adobe PDF File), 98 KB - resprot_v9i12e24057_app5.pdf]

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Abbreviations

BTPS: Barriers to Treatment Participation Scale
CBCL: Child Behavior Checklist
CBT: cognitive behavioral therapy
CGAS: Children's Global Assessment Scale
CGI-I: Clinical Global Impressions Scale-Improvement
CGI-S: Clinical Global Impressions Scale-Severity
COIS-R: Child Obsessive-Compulsive Impact Scale-Revised
CSQ-8: Client Satisfaction Questionnaire-8
CY-BOCS: Children's Yale-Brown Obsessive-Compulsive Scale
eCBT: enhanced cognitive behavioral therapy
ERP: exposure with response prevention
FAS-SR: Family Accommodation Scale for OCD–Self-Rated Version
K-SADS-PL: Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version
MFQ: Mood and Feelings Questionnaire
OCD: obsessive-compulsive disorder
SCARED-R: Screen for Child Anxiety-Related Emotional Disorders-Revised
SDQ: Strengths and Difficulties Questionnaire
tCBT: technology-based cognitive behavioral therapy
TiC-P: Trimbos/iMTA Questionnaire for Costs associated with Psychiatric Illness
UEQ: User Experience Questionnaire
YSR: Youth Self-Report Questionnaire

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Original Paper

Integrating Key User Characteristics in User-Centered Design of Digital Support Systems for Seniors' Physical Activity Interventions to Prevent Falls: Protocol for a Usability Study

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Abstract

Background: The goal of user-centered design (UCD) is to understand the users' perspective and to use that knowledge to shape more effective solutions. The UCD approach provides insight into users' needs and requirements and thereby improves the design of the developed services. However, involving users in the development process does not guarantee that feedback from different subgroups of users will shape the development in ways that will make the solutions more useful for the entire target user population.

Objective: The aim of this study was to describe a protocol for systematic analysis and prioritization of feedback from user subgroups in the usability testing of a digital motivation support for fall-preventive physical activity (PA) interventions in seniors (aged 65 years and older). This protocol can help researchers and developers to systematically exploit feedback from relevant user subgroups in UCD.

Methods: Gender, PA level, and level of technology experience have been identified in the literature to influence users' experience and use of digital support systems for fall-preventive PA interventions in seniors. These 3 key user characteristics were dichotomized and used to define 8 (ie, 2^3) possible user subgroups. The presented method enables systematic tracking of the user subgroups' contributions in iterative development. The method comprises (1) compilation of difficulties and deficiencies in the digital applications identified in usability testing, (2) clustering of the identified difficulties and deficiencies, and (3) prioritization of deficiencies to be rectified. Tracking user subgroup representation in the user feedback ensures that the development process is prioritized according to the needs of different subgroups. Mainly qualitative data collection methods are used.

Results: A protocol was developed to ensure that feedback from users representing all possible variants of 3 selected key user characteristics (gender, PA level, and level of technology experience) is considered in the iterative usability testing of a digital support for seniors' PA. The method was applied in iterative usability testing of two digital applications during spring/summer 2018. Results from the study on the users' experiences and the iterative modification of the digital applications are expected to be published during 2021.

Conclusions: Methods for systematic collection, analysis, and prioritization of feedback from user subgroups might be particularly important in heterogenous user groups (eg, seniors). This study can contribute to identifying and improving the understanding of potential differences between user subgroups of seniors in their use and experiences of digital support for fall-preventive PA interventions. This knowledge may be relevant for developing digital support systems that are appropriate, useful, and attractive to users and for enabling the design of digital support systems that target specific user subgroups (ie, tailoring of the support). The protocol needs to be further used and investigated in order to validate its potential value.

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KEYWORDS

eHealth; mobile health; internet-based interventions; physical activity; exercise; older adults; gender; user feedback; user involvement; user-centered design

Introduction

Background

The goal of user-centered design (UCD) is to understand the users' perspective and to use that information to shape more effective solutions [1]. UCD gains access to users' needs and requirements and thereby improves the solutions' design and increases their functionality, usability, and quality [2,3]. UCD can reduce the users' need for support, decrease development costs, and increase user satisfaction and safety [4]. However, involving users in the development process does not guarantee that feedback from different subgroups of users will equally shape the development in such a way that the developed solution becomes useful for the entire user population for which it was intended. This study describes a method that enables systematic tracking of feedback from user subgroups in usability testing of digital support for fall-preventive physical activity (PA) in seniors (adults aged 65 years and older). The aim of the method is to support the development of a digital support system that is useful for different subgroups of users.

Digital Support for Improved Health in Seniors

Digital support systems—for example, mobile apps or web-based services—have the potential to strengthen and complement existing health care resources. There is evidence indicating that digital support can be effective in somatic care [5]. The internet is also an important source for acquiring disease-specific knowledge in chronic care management [6]. In 2019, approximately one-fifth of the population in the European Union was 65 years or older, and more than 5% of the population was 80 years and older [7]. The proportion of individuals aged 80 years and older is expected to more than double within the next 80 years. Furthermore, approximately 80% of the population aged 80 years and older suffers from at least one chronic condition [8]. Provision of digital support to improve health in the growing population of seniors is therefore increasingly important.

It is well established that PA has a positive impact on health and well-being. For example, physically active people have lower rates of lifestyle-related diseases (including coronary diseases, high blood pressure, type 2 diabetes, colon and breast cancer, and depression) and exhibit higher levels of functional health and better cognitive function [9]. Despite this knowledge, physical inactivity is an increasing global health burden [9].

Involvement of Seniors in the Development of Digital Support Systems

User involvement in the development of digital support systems is an evolving area. A review on development of fall-detection systems concluded that seniors are never involved throughout the whole development process and seldom involved in the early and end stages of development [10]. The authors emphasize that early user involvement, focusing on the users' needs and preferences, is important for improving the seniors' level of technology acceptance. There is a great variation regarding which users are involved in UCD and how they are involved. Moreover, reporting on the procedures used for the selection and recruitment of users is often lacking [11].

Seniors' interest in and use of the internet is associated with sociodemographic factors including gender, age, and socioeconomic status [12-15]. Moreover, seniors use the internet for different purposes: while some use it solely for practical things, such as financial purposes, searching for information, and emailing, others use it for additional purposes, such as gaming and social interaction [16]. In addition, seniors have different needs and preferences for digital health care support, partly driven by their own experiences with health care [13]. The described diversity in the older population challenges the UCD because involving certain users does not entail that their feedback will represent views of the entire target population. There is a need to increase the understanding of user subgroups' needs and contribution in UCD processes in order to involve representatives of relevant stakeholders in the development.

Purpose of the Study

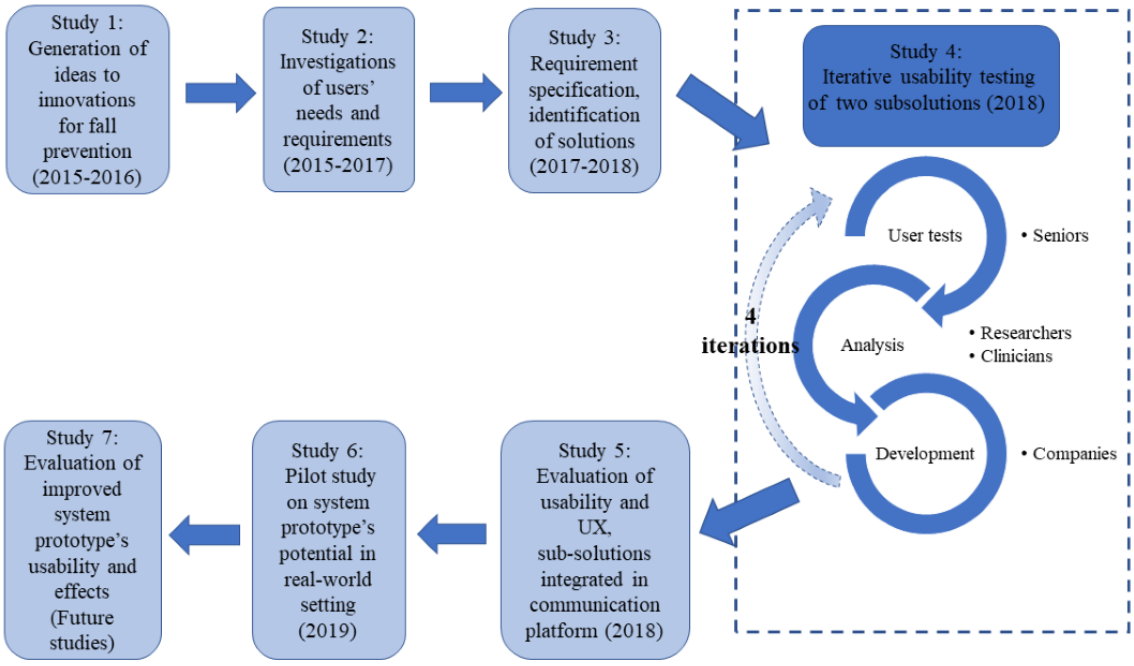
The aim of this study was to describe a protocol for systematic analysis and prioritization of feedback from user subgroups in the usability testing of digital support systems to motivate fall-preventive PA in seniors. This protocol can help researchers and developers to systematically exploit feedback from relevant subgroups in UCD.

Methods

Overview of the UCD Process and Included Studies

This project is based on a UCD model [1] and the key principles described by Gulliksen et al [17], including early user involvement. An overview of the UCD process is presented in Figure 1. The protocol described in this article is used in study 4 (Figure 1).

Figure 1. Overview of the user-centered design and the 7 studies (where study 7 represents several future studies) of the development of digital support for fall-preventive physical activity interventions in seniors. This protocol describes a method for systematic tracking of feedback from user subgroups used in study 4. UX: user experience.



Identification of Key User Characteristics

Three key user characteristics have been identified in the literature to influence seniors' experience of fall prevention, PA, and technology use: (1) gender, (2) PA level, and (3) level of technology experience. Gender was selected because a gender-based difference exists in PA behavior, falls incidence, and consequences from falls; men and women have different fall risk factors, both short- and long-term [18]. Compared to men, women are more prone to falling, sustain more fall-related injuries [19,20], and report fear of falling more frequently [21,22]. Men and women also differ in their exercise habits and reasons for exercise [23]: women are less likely than men to be regularly physically active [24] and tend to prefer different types of PA [25]. Gender has also been identified as crucial for understanding technology use [26]. PA level and level of technology experience were also selected because seniors with lower PA levels and less experience with technology might represent less engaged users of digital support services for PA. The 3 key user characteristics are integrated in the collection and analysis of user feedback.

Definition of User Subgroups From Possible Combinations of Key User Characteristics

By dichotomizing the 3 key user characteristics, 8 (ie, 2^3) possible user subgroups were defined. The participant's PA level and level of technology experience were classified as "higher" or "lower," respectively, according to the user's self-reported PA level and level of technology experience in the questionnaire on user characteristics (Multimedia Appendix 1). Participants who reported spending at least 3 hours/week performing moderate-intensity activities during a regular week (questions 1 and 2, respectively, on PA level in Multimedia Appendix 1) were classified as having a higher PA level, while participants who reported spending less than 3 hours/week performing moderate-intensity activities were classified as having a lower PA level. The threshold was chosen based on the PA guidelines for the adult population, which recommend at least 150 minutes/week of moderate-intensity aerobic PA [9]. The cutoff for higher level of technology experience was set to using a mobile phone and/or computer/tablet often for purposes including calls, texting, emails, and surfing the internet, as reported by participants (questions 3 and 4 on level of technology experience in Multimedia Appendix 1). This cutoff was chosen to ensure that participants had experience in surfing the internet. The participant's gender was classified as man or woman according to the participant's self-reported gender in the questionnaire (Multimedia Appendix 1).

Examples of subgroups were men with a lower PA level and higher level of technology experience and women with a higher PA level and lower level of technology experience.

Coding of Individual Users According to User Subgroups

The assignment of each participant to 1 of 8 subgroups was identified by analysis of the questionnaire on participant characteristics (Multimedia Appendix 1). Each participant's user subgroup was visualized on all templates for processing and analysis of data generated by the specific participant.

Usability Test Procedure

During the iterative testing (Figure 1, study 4), the participants tested and evaluated prototype versions of the digital support (2 applications) in 4 test cycles. Each participant performed the tests individually with a researcher. Qualitative and quantitative

data on use and use experience were collected during and after the test sessions.

Table 1 presents an overview of the methods for data collection, processing, and analysis, and concretization of improvements applied in each test cycle. Steps 1 to 3 were included in the method for systematic tracking of user subgroups' feedback and they are described in detail below.

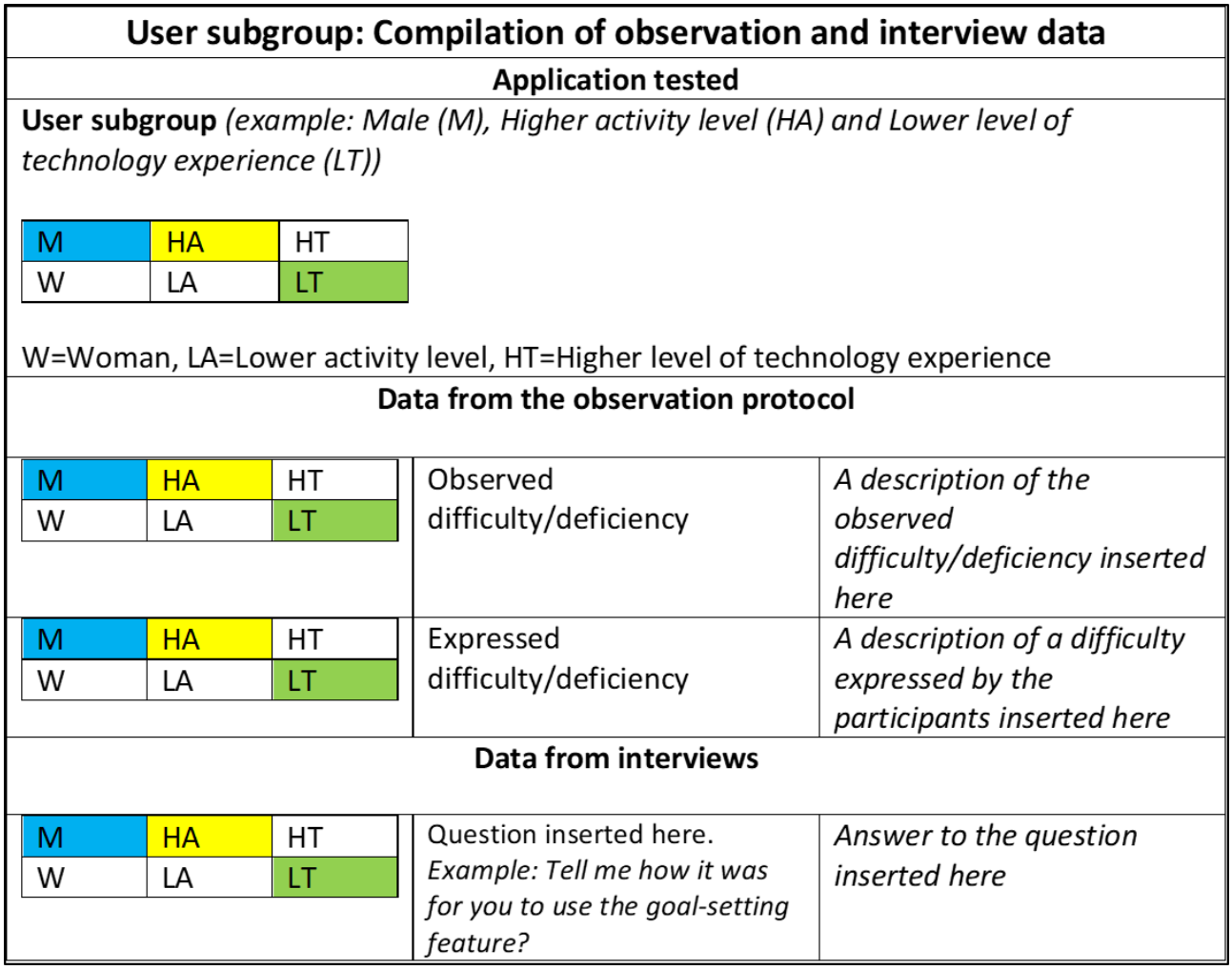
Table 1. Overview of the data collection, processing, and analysis, as well as the concretization of improvements in the usability testing, highlighting the 3 steps included in the subgroup method.

Research phase	Description of actions and the 3 steps included in the subgroup method
Data collection	Multiple sources of mainly qualitative data on participants' management and experiences of the applications: • questionnaire on user characteristics (Multimedia Appendix 1) • observation protocol (Multimedia Appendix 2) • written interview and user rating documentation (Multimedia Appendix 3) • audio recording
Data processing	Summary of observations and answers to rating and interview questions for each user Step 1: Identification of difficulties and deficiencies in the applications and the user subgroups experiencing them • compilation of difficulties/deficiencies from data collected on participants' experiences • paper strips, containing 1 experienced difficulty/deficiency each, tagged with the participant's user subgroup
Data analysis including prioritization of difficulties/deficiencies to be rectified/improved	Step 2: Clustering of difficulties and deficiencies • thematic analysis, by sorting the paper-strips manually • labeling themes to reflect the difficulty/deficiency tagged with an aggregation of user subgroups Step 3: Prioritization based on user subgroup representation, importance and impact
Concretization of improvements	Concretization of actions to be taken for prioritized improvements

Step 1: Identification of Difficulties and Deficiencies in the Applications and the User Subgroups Experiencing Them

The data on difficulties/deficiencies in the applications collected during test sessions is compiled in a predefined template (Figure 2). In the template, each row documents one identified difficulty/deficiency tagged with the user subgroup of the participant (colored to improve visualization of different key characteristics). One template is completed for each participant. The template can be expanded by the addition of as many new rows as needed.

Figure 2. The template used in step 1 for the compilation of observation and interview data.



User subgroup: Compilation of observation and interview data

Application tested

User subgroup *(example: Male (M), Higher activity level (HA) and Lower level of technology experience (LT))*

M	HA	HT
W	LA	LT

W=Woman, LA=Lower activity level, HT=Higher level of technology experience

Data from the observation protocol

M HA HT / W LA LT	Observed difficulty/deficiency	*A description of the observed difficulty/deficiency inserted here*
M HA HT / W LA LT	Expressed difficulty/deficiency	*A description of a difficulty expressed by the participants inserted here*

Data from interviews

M HA HT / W LA LT	Question inserted here. *Example: Tell me how it was for you to use the goal-setting feature?*	*Answer to the question inserted here*

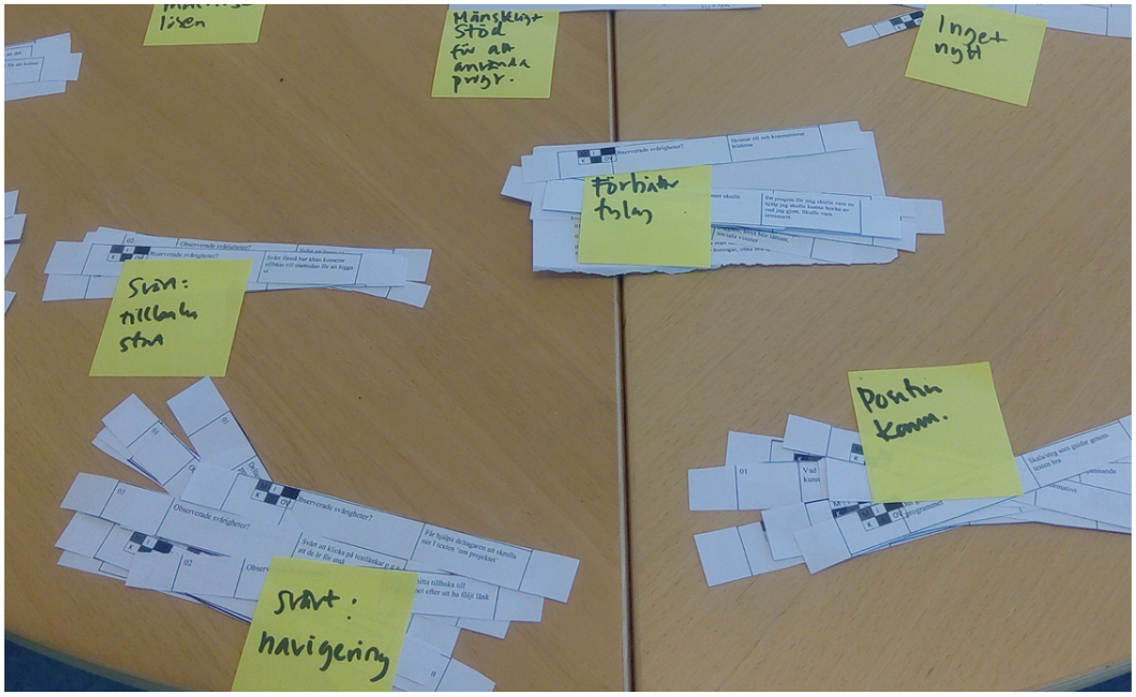
After compiling data on observed or expressed difficulty/deficiency for all participants, the templates are printed out on paper and cut into paper strips. Hence, each strip contains one observed/expressed difficulty/deficiency tagged with the participant's user subgroup.

The main results from this step are paper strips containing observed/expressed difficulty/deficiency identified during the usability testing tagged with user subgroup.

Step 2: Clustering of Difficulties and Deficiencies

All paper strips from step 1 are analyzed qualitatively. Any qualitative method can be used, for example the thematic analysis described by Braun and Clarke [27]. The paper strips are sorted manually according to similarity in the difficulty or deficiency they reflect and subsequently labeled (Figure 3).

Figure 3. Thematic analysis and clustering of the paper strips. Each cluster is labeled according to the difficulties/deficiencies it reflects.



The main results from this step are themes describing deficiencies/difficulties in the digital applications tagged with an aggregation of user subgroups that all participants experiencing the difficulties belonged to (hereafter denoted "user subgroup aggregation"). For example, if participants from the two user subgroups "men with lower PA level and higher level of technology experience" and "women with higher PA level and higher level of technology experience" express the same deficiency, the resulting theme (ie, deficiency) is tagged with the user subgroup aggregation (ie, "men and women with lower and higher PA level and higher level of technology experience").

Step 3: Prioritization Based on User Subgroup Aggregation, Importance, and Impact

Themes reflecting deficiencies/difficulties in the applications tagged with aggregated user subgroups (identified in step 2) are further grouped according to the feature they occur in (eg, navigation, goal setting, or feedback). All features with identified deficiencies/difficulties tagged with user subgroup aggregations are summarized in a prioritization template (Table 2).

Prioritization of difficulties/deficiencies to be improved or rectified prior to the next test cycle is based on the following aspects: (1) whether the user subgroup aggregations represent all or most of the 8 possible user subgroups (ie, if both men and women with higher and lower PA levels and levels of technology experience have experienced the deficiency); (2) whether the deficiency can be related to the participants' ratings of user experience or perceived value for support in fall-preventive PA interventions of different features, if applicable (this can be interpreted as "performance" and "effort expectancy", two constructs important for the acceptability and usability of technology according to the unified theory of acceptance and use of technology [28]); and (3) whether the deficiency has high impact on the solution's purpose and usability. Previous research has suggested that issues that are both brought up by users and have a large impact on the overall purpose of a solution should be considered in development [29]. The researchers' assessment of aspects (1) to (3) for each deficiency is documented in a prioritization template (Table 2).

The main result from this step is a list of prioritized difficulties/deficiencies to be improved before the next test cycle or saved for later.

Table 2. The template used in step 3 for prioritization of difficulties and deficiencies to be improved or rectified, including a mock result.

Features	Deficiency	User subgroup aggregation experiencing deficiency						Prioritization			When to be improved?	
		M[a]	W[b]	HA[c]	LA[d]	HT[e]	LT[f]	All user characteristics represented?	Related to low ratings?[g]	High impact on the solution?	Now	Later
Goal set	Concepts difficult to understand	✓	✓	✓	✓	✓	✓	Yes	No	Yes	✓	
	Difficult to set a realistic PA goal[h]	✓	✓	✓	✓	✓		No	No	Yes		✓

[a]M: man.

[b]W: woman.

[c]HA: higher activity level.

[d]LA: lower activity level.

[e]HT: higher level of technology experience.

[f]LT: lower level of technology experience.

[g]The participants' answers to the rating questions, on a 100 mm visual analog scale (see Multimedia Appendix 3 for more details).

[h]PA: physical activity.

Results

This paper describes a novel approach to systematically track user subgroups' feedback in usability testing of digital support systems. The method will ensure that feedback from users representing all possible variants of 3 selected key user characteristics (gender, PA level, and level of technology experience) are shaping the iterative development of digital support systems. An overview of the key activities in the subgroup tracking method is summarized in Table 3.

Table 3. Presentation of main activities in the method for identifying key user characteristics and systematic tracking of user subgroup feedback.

Research phase	Description of main activities in the subgroup method
Preparation	Identification of key user characteristics • based on previous research and/or theory relevant for the focus area of the digital support system Definition of user subgroups from possible combinations of key user characteristics • dichotomization of the key user characteristics Coding of individual users according to user subgroup • visualization of subgroup on the templates used for data collection, processing, and analysis
Data processing	Identification of difficulties and deficiencies in the applications and the user subgroups experiencing them • compilation of difficulties/deficiencies from data collected on users' experiences • paper strips containing an experienced difficulty/deficiency tagged with the user's subgroup
Data analysis	Clustering of difficulties and deficiencies • thematic analysis, by sorting the paper strips manually • labeling themes to reflect the difficulty/deficiency tagged with an aggregation of user subgroups Prioritization based on user subgroup aggregations, importance, and impact

The method was applied in a study approved by the regional ethics committee in Uppsala, Sweden (Dnr 2018/044). In this study, the method was used in usability testing of two digital applications to motivate PA in seniors during spring/summer 2018. Results from the study on the users' experiences and the iterative modification of the digital applications are expected to be published in 2021. The study will provide further insights into the potential of this novel approach for ensuring that needs and preferences of different user subgroups are captured and considered in a UCD process. Moreover, the results are expected to contribute new knowledge on how digital support for PA needs to be modified to fit the heterogeneous population of seniors.

Discussion

Tracking of Subgroups' Feedback in UCD

The method presented in this study provides a structured way to document and exploit feedback from different user subgroups in iterative development of new solutions, exemplified here by digital support systems for fall-preventive PA interventions in seniors. Involving seniors in technology development has been suggested as an important component for improving technology acceptance [10]. Moreover, physical inactivity is an increasing global health burden, and it is well documented that older age groups are less active than younger individuals [24] and that PA is important for improving health [9]. Moreover, although

inclusiveness is an important design goal, discrimination is a common deficiency of digital support systems [14]. For example, gender inclusiveness and equality are important in system design, since the two aspects influence users' behaviors, both online and offline [15,26]. GenderMag [30] is a systematic method for illustrating and tracking gender differences in software development by the use of personas. The method has proven effective for finding and fixing gender-inclusiveness deficiencies in software applications [31] and has been reported to be appreciated in practice [32]. Research on how to prevent discrimination and strengthen inclusiveness of digital support systems needs further attention.

In addition to increasing gender inclusion, the method presented in this study aims at ensuring that the feedback of users with varied self-reported technology experience and PA levels is shaping the development of digital support systems. The aim of integrating these perspectives is to encourage participation of persons who, because of lower levels of technology experience or PA, might have low interest in participating in UCD studies of technical solutions supporting PA. However, other user characteristics might also be of relevance when involving seniors in UCD studies. For example, Vandekerckhoven et al [11] suggested that creativity and communication are relevant and important user characteristics to consider in UCD studies.

Limitations

In this study, the users' gender, PA level, and level of technology experience were identified as relevant key user characteristics to define the subgroups to track in UCD studies. It could be argued whether these are the most critical key user characteristics to consider and if additional subgroups are to be included in order to support the development of digital support systems that fits the whole heterogenous target population. For example, fall history might be relevant to consider, since previous falls have been identified as a risk factor for new falls in both men and women [18] and it is vital to promote fall-preventive PA interventions in persons with increased fall risk. Moreover, users' level of technology experience and internet use are related to age [16,33]: younger seniors (mean age less than 70 years) use the internet the most and older seniors (mean age 73 years) use the internet the least [16]. Furthermore, older seniors have more problems with activities in daily living and experience worse health than younger seniors [16]. However, this study used internet experience instead of age as a key user characteristic. To ensure that both younger and older seniors are involved in the UCD process, seniors representing different ages should be recruited.

Other examples of user characteristics that might be relevant for defining user subgroups include level of education and socioeconomic status [12,33], as well as personal qualities such as the level of communication and creativity [11]. However, in order to make the method feasible, the number of subgroups considered needs to be limited. This is accomplished by selecting user characteristics that are critical for the aim of the technical solution and can be dichotomized. In this study, 3 key user characteristics were selected based on the literature, and by dichotomizing them, 8 (ie, 2^3) possible user subgroups were defined. The method represents a pragmatic approach, which is needed in UCD for balancing the quantitative research paradigm (requiring involvement of large user groups and thereby not feasible in UCD) and the qualitative research paradigm (focusing on one specific user subgroup and thereby not useful for an entire heterogenous population). However, further research is needed to validate if the key characteristics selected in this study are purposeful for creating a solution that is attractive and useful for the intended users of digital support systems for fall-preventive PA interventions for seniors.

Conclusions

User involvement alone does not guarantee that feedback from different user subgroups is correctly shaping the development of digital support systems and resulting in a solution that is useful for the whole intended user population. Further attention is needed on methods for systematic tracking of user subgroups' feedback to ensure that new systems and services are designed for the entire target user population. Also, new knowledge is needed on how to select users to be involved in UCD processes. The method presented in this study elucidates and documents potential differences between how different user subgroups contribute to the development. This may clarify whether new users need to be added to the process, either to increase the contribution of specific user subgroups or to involve new subgroups.

Our hope is that this protocol will be used for systematic analysis and prioritization of user subgroups' feedback in the development of new digital systems. The protocol may help to identify and improve the understanding of potential differences between subgroups of seniors in use and experiences of digital support for fall-preventive PA interventions. This new knowledge can be of great importance in future research to develop systems that are relevant, useful, and attractive to the heterogenous population. Moreover, it can facilitate tailoring solutions toward specific user subgroups. However, the protocol needs to be further used and evaluated to validate the potential value of the method and the purposefulness of the selected key user characteristics.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Questionnaire on demographics, physical activity level, and level of technology experience to be completed by the participants.
[DOCX File , 58 KB - resprot_v9i12e20061_app1.docx]

Multimedia Appendix 2
Observation protocol to be completed by the researcher during the test.
[DOCX File , 14 KB - resprot_v9i12e20061_app2.docx]

Multimedia Appendix 3
Interview guides for the 4 test cycles in the usability test.
[DOCX File , 66 KB - resprot_v9i12e20061_app3.docx]

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Abbreviations

PA: physical activity
UCD: user-centered design

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Protocol

Emotional Bias Modification for Individuals With Attention Deficit Hyperactivity Disorder: Protocol for a Co-Design Study

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Abstract

Background: Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder with a worldwide prevalence rate of 5%. Individuals with ADHD often tend to have difficulties with emotional regulation. The advances in experimental psychology have led to the discovery of emotional biases. Targeting emotional biases could potentially help improve the core symptoms of irritability and short-temperedness among these individuals. Emotional biases refer to the preferential allocation of attention toward emotional stimuli. A recent study reported the presence of emotional biases among individuals with ADHD when they compared individuals with ADHD with those without. Gamification technologies have been explored to help diminish the repetitiveness of the task and increase the intrinsic motivation to train. These inconsistent findings of the impact of gaming on the effectiveness of mobile interventions call for further work to better understand the needs of patients (users) and health care professionals.

Objective: The aim of this research study is to collate health care professionals' perspectives on the limitations of the existing task, and to determine if gamification elements could be incorporated, to refine the conventional intervention.

Methods: A qualitative research approach, that of a focus group, will be used. Health care professionals from the Department of Development Psychiatry, Institute of Mental Health, Singapore will be invited to participate in this qualitative research. During the focus group, participants are to comment on the limitations of the existing emotional bias intervention; recommend strategies to improve the intervention; and provide their perspectives pertaining to the use of gamification to improve the intervention.

Results: We expect that the study will be completed in 12 months from the publication of this protocol.

Conclusions: To our best knowledge, this is perhaps one of the only few studies that have attempted to explore emotional biases among adolescents with ADHD.

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KEYWORDS

emotional bias; cognitive biases; ADHD; child psychiatry

Introduction

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder with a worldwide prevalence rate of 5% [1]. Individuals afflicted with ADHD typically have a constellation of symptoms, characterized by that of hyperactivity, impulsivity, and inattention. The presence of these symptoms often leads to significant psychosocial impairments, for example, that of academic achievements. Individuals with ADHD often tend to have difficulties with emotional regulation too [2]. Because of their inherent difficulties with emotional regulation, these individuals tend to be short-tempered and irritable. The advances in experimental psychology have led to the discovery of emotional biases. Targeting emotional biases could potentially help improve the core symptoms of irritability and short-temperedness among these individuals. Emotional biases refer to the preferential allocation of attention toward emotional stimuli [2]. Emotional biases are most found among individuals who have the combined subtype of ADHD. Children with ADHD-C typically have difficulties not only in emotional processing, but also in comprehension of others' emotional state, recognition of facial emotions, matching emotional stories, and orientating toward emotional cues [2]. The theoretical approach suggests that these individuals typically have altered top–down processes that are typically responsible for executive planning, inhibition, and cognitive control [2].

The Stroop task has most commonly been used for the assessment and modification of emotional biases and biases related to interference control. In the Stroop task, participants are required to name the colors of the words, while ignoring the semantics of the word. There are limitations to the standard Stroop task, as very often the stimuli are not relevant to individuals with ADHD, and this might affect the assessment for and the modification of such biases. The Dot-probe or visual probe task is an alternative paradigm that was first described by Macleod et al [3]. In the Dot-probe task, participants are presented with 2 stimuli on a screen simultaneously. For individuals with ADHD, these stimuli are usually associated with emotional valence. For example, one of the stimuli might be that of anger expression, whereas the corresponding stimulus is that of a neutral expression. The stimulus would then disappear, and the participant must indicate the position of the probe that comes on. The reaction time that the participant takes to indicate a response following the disappearance of the stimulus is used in the computation of the baseline biases, and in the estimation of how much the bias has been modified. It is expected that individuals with ADHD would react faster when probes replace a stimulus with a positive emotional valence, as compared to probes that replace a stimulus with a negative emotional valence.

The effectiveness of cognitive biases has been well investigated especially among children and adolescents. Krebs et al [4] examined in their review how modification of negative interpretative biases could negate anxiety symptoms among children and adolescents. They identified a total of 26 studies, with each study including individuals up to the age of 18 and reported that cognitive bias modification had moderate effects in reducing negative and positive interpretative biases (Hedges g was 0.70 and 0.52, respectively) [4]. They also reported that bias modification resulted in a small, yet significant reduction of anxiety, with an effect size of 0.17 (Hedges g) [4]. Others have also investigated the utility of cognitive bias modification for hostile interpretative biases [5], and found successful effects of bias modification on hostility. With regard to emotional bias, Cremone et al [6] in their recent study reported the presence of emotional biases among children with ADHD when they compared children with ADHD with those without. In their study, they found that emotional biases were mediated by factors such as the amount of sleep children had. Other studies [7,8] have reported the presence of emotional biases/interference control issues among children with ADHD.

One of the challenges inherent in cognitive bias assessment and modification interventions relates to the laborious nature of these interventions, given that numerous repeats of the trials are required to be undertaken. Serious games and gamification technologies have been applied for mental health interventions. In a previous review, Fleming et al [9] reported the 6 major types of applied games for mental health: exergames, virtual reality, cognitive behavioral therapy (CBT)–based serious games, CBT gamification, biofeedback, and entertainment computer games for mental health, with each having a variable of increasing engagement and some rationalizing the serious purpose of engagement features. Some examples to indicate the role of games in mental health are "SPARX," an avatar-based video game for CBT, and "JOURNEY," another video gaming tool to support adolescents depression, which are found have a significant impact in decreasing the adolescent depressive symptoms [9]. Some of the gaming interventions have been evaluated which highlighted that serious games could help improve neuropsychological rehabilitation [10] and that gamification helps improve engagement in the short and long term, promote self-empowerment, and improve the existing skills [11]. The systematic review by Lau et al [12] indicated that serious games could help improve psychiatric symptoms with an effect size of 0.55. There is thus a possibility in considering such technologies for emotional biases intervention, given that such interventions are to be catered for a child and adolescent population. Gamification technologies might also help diminish the repetitiveness of the task and increase the intrinsic motivation to train. These inconsistent findings of the impact of gaming on the effectiveness of mobile interventions call for further work to better understand the needs of patients (users) and health care professionals. Most of these prior interventions have been developed by academics or software developers. The study by Hopia et al [13] reported the perceptions of the end users such as health care professionals and mental health service users on the usage of gamified interventions. Although the views in the study indicated the potential usability of these interventions, these were more generalized. As the interventions could vary according to the type and nature of the specific disorder, there is a need to explore the perceptions of stakeholders belonging to the respective specialties. With the increased recognition of participatory action design research in the recent years [14], such methods could be used to improve existing interventions to suit the needs of

patients, and to address existing limitations in various interventions.

The aim of this research study is to collate health care professionals' perspectives on the limitations of the existing task, and to determine if gamification elements (Table 1) could be incorporated, to refine the conventional intervention. By undertaking this research, we seek to answer the following research questions: (1) What are the perspectives of health care professionals on existing gaming interventions for ADHD; (2) What are the perspectives of health care professionals on a conventional emotional bias modification task?; (3) Would gamification strategies be appropriate, and which gaming strategies are deemed to be the most appropriate? We have decided to sample health care professionals first, to better the existing conventional emotional bias modification paradigm.

Table 1. Overview of gamification approaches [15].

Gaming approach	Description
Economic gamification techniques	
Marketplace and economies	Providing gamers with a virtual currency that allows them to deal in the game.
Digital rewards	These include badges, game currency, game points, virtual goods, and powers or abilities.
Real-world prizes	Provides gamers with options to exchange in-game credits for real-world prizes such as vouchers or other forms of goods and services.
Social gamification techniques	
Avatar	Allows individuals to choose a virtual character to represent oneself.
Agent	A virtual character that guides or provides instructions to the user.
Competition	Allows individuals to compete with other players or with each other.
Teams	Game that involves several individual players, allowing them to interact and form relationships.
Parallel communication systems	Allows individuals to communicate with one another.
Social pressure	Ability of game to pressurize individuals to perform in a certain task, so that he or she will be invited to subsequent events.
Performance oriented	
Feedback	Spoken, visual, or auditory feedback about user's performance.
Levels	Information on the stage of a game one has attained.
Secondary game objectives	Secondary goals that reward the player upon completion.
Ranks of achievement	Measurement of character development.
Leaderboards	Allows for comparisons with other players.
Time pressure	Predetermined time limits for task completion.
Embedding focused	
Narrative context	A storyboard or stories that guide the development of the character.
3D environment	3D models of objects that parallel the real world.

Methods

Study Design

For the purposes of this research, a qualitative research approach (focus group) will be used. We will also adopt some principles from participatory action research, which is a form of research that uses systematic inquiry, along with the participation of the relevant stakeholders. This helps to refine educational processes or effecting a social intervention.

Study Setting

We seek to invite health care professionals from the Department of Development Psychiatry, Institute of Mental Health, Singapore to participate in this qualitative research. The purpose of including health care professionals is mainly due to their expertise in the treatment of children/adolescents with ADHD. A diverse group of participants will be recruited, as the group comprises not only psychiatrists, but also psychologists and occupational therapists. It is expected that psychiatrists will comment on how this intervention will complement their existing pharmacological interventions, and psychologists and occupational therapists will comment on how this intervention will supplement or complement existing psychological approaches.

Sample Size

A total of 8 participants will be recruited for the study. The participants will include 3 psychiatrists, 3 psychologists, and 2 therapists for the focus group. To recruit the participants, the principal investigators (MZ and RV) will approach the head of the department to seek approval if an email could be circulated among the department to inform about the study. Participants willing to voluntary participate in the study could reply to the principal investigators' email. The principal investigators will

liaise with the participants regarding the date and time of the study.

Details of the Planned Focus Group

All participants who provide their consent for the study will be asked to complete a baseline demographic questionnaire. This questionnaire will collate information about their age, gender, and their years of experience in child psychiatry/treatment of children with psychiatric disorders. Following the completion of the questionnaire, the study team members will email all the participants and identify a common date and time in which the focus group could be conducted. The duration of the focus group discussion is expected to last between 1.5 and 2 hours.

Both principal investigators will facilitate the focus group and record field notes. At the start of the focus group discussion, participants will be informed about the rationale of the project as well as the specific objectives of the sessions. Participants will be reassured that their comments are confidential, and will be told that their comments will be audio-recorded. Participants will be shown some examples of existing gaming interventions in the published literature for the treatment of ADHD symptoms. Participants are asked to comment on the advantages and the limitations of these interventions. In the event that participants do not feel comfortable in commenting, they are also provided with written materials, for them to note down their comments. Following the completion of this phase, participants are shown examples of cognitive bias modification interventions, and specifically, an example of an emotional bias modification intervention. Participants are asked to comment on the benefits of such a form of intervention, identify limitations, and suggest possible methods to overcome the limitations. Following this, participants are shown a list of gamification techniques, and the facilitators (MZ and RV) will explain to them more about the specific gamification techniques. Participants will be asked if the inclusion of such techniques would be appropriate for the existing application.

Data Analyses

The workshops will be audio-recorded and transcribed verbatim subsequently. The principal investigator MZ will listen to the audio recordings of the workshop and develop a coding frame. Two separate researchers will also review and code the transcripts. The codes will then be reorganized into themes. NVivo version 12.0 will be used in the analysis.

Data Management and Monitoring

No participant-related identifiers will be captured on the hard copy questionnaires. All the completed hard copy forms and the informed consent forms will be stored in a secured facility, under lock and key. The audio recordings of the workshop will be transferred onto a local secured computer for storage and the recording will also be removed from the recording device. The password of the local computer will be changed frequently, and only the principal investigator (MZ) will have access to the local computer. All the records and audio recordings will be kept for 6 years after the completion of the study.

Adverse Events

Any adverse events that occur during the conduct of the study will be reported to the domain-specific research board according to the local institutional policy.

Ethical Approval

The study has been approved by the Ethical Review Board of Nanyang Technological University Singapore (IRB-2020-03-058). The data obtained could be potentially used to develop the novel prototype that suits the needs of the stakeholders.

Results

We expect that the study will be completed in 12 months from the publication of this protocol. The findings arising from this study will be published in academic journals, and presented at both local and international conferences.

Discussion

To our best knowledge, this is perhaps one of the only few studies that have attempted to explore emotional biases among individuals with ADHD. The utilization of participatory action design research, in the design and conceptualization of a co-designed application, is novel, and helps to ensure that the conceptualized application is based on evidence. While the perspectives of health care professionals are critical in bettering the existing conventional task, and ensuring that it maintains the evidence base, it is nevertheless important to seek out the perspectives of the service user/individuals with ADHD. We intend to undertake this as soon as we have completed the existing study.

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Authors' Contributions

MZ, RV, and DF jointly conceptualized the study. MZ wrote the initial draft, which was revised by RV. DF provided critical inputs to the final manuscript. All authors read and approved the manuscript prior to submission.

Conflicts of Interest

None declared.

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Abbreviations

ADHD: attention deficit hyperactivity disorder
CBT: cognitive behavioral therapy

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Protocol

Mining Electronic Health Records to Promote the Reach of Digital Interventions for Cancer Prevention Through Proactive Electronic Outreach: Protocol for the Mixed Methods OptiMine Study

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Abstract

Background: Digital behavior change interventions have demonstrated effectiveness for smoking cessation and reducing alcohol intake, which ultimately reduce cancer risk. Leveraging electronic health records (EHR) to identify at-risk patients and increasing the reach of digital interventions through proactive electronic outreach provide a novel approach that may increase the number of individuals who engage with evidence-based treatment.

Objective: This study aims to increase the reach of digital behavior change interventions by implementing a proactive electronic message system for smoking cessation and alcohol reduction among a large, at-risk population identified through an acute hospital EHR.

Methods: This protocol describes a 3-phase, mixed-methods implementation study to assess the acceptability, feasibility, and reach of a proactive electronic message system to digital interventions using a hospital's EHR system to identify eligible patients. In Phase 1, we will conduct focus group discussions with patients and hospital staff to assess the overall acceptability of the electronic message system. In Phase 2, we will conduct a descriptive analysis of the patient population in the hospital EHR regarding target risk behaviors and other person-level characteristics to determine the project's feasibility and potential reach. In Phase 3, we will send proactive messages to patients identified as smokers or risky drinkers. Messages will encourage and provide access to behavior change mobile apps via an embedded link; the primary outcome will be the proportion of participants who click on the link to access information about the apps.

Results: At the time of initial protocol submission, data collection was complete, but analysis had not begun. This study was funded by Cancer Research UK from April 2019 to March 2020. Health Research Authority approval was granted in June 2019.

Conclusions: Increasing the reach of digital behavior change interventions can improve population health by reducing the burden of preventable death and disease.

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KEYWORDS

EHR; electronic health record; smoking cessation; alcohol reduction; proactive outreach; proactive messages; electronic messages

Introduction

Cigarette smoking and risky alcohol consumption, both modifiable behaviors, are among the leading causes of cancer and other diseases [1,2]. Increasing the reach of evidence-based interventions that effectively help people quit smoking and drink less can improve population health by reducing the burden of preventable death and disease.

In 2018, 14.7% of adults 18 years and older in the United Kingdom smoked cigarettes (16.5% among men vs 13.0% among women), which is equivalent to roughly 7.2 million people [3]. Although cigarette smoking has steadily declined since 2011, disparities exist in smoking rates by age, socioeconomic status, employment status, and ethnicity, in addition to location-based disparities [3]. In England, smoking led to 77,800 deaths and 489,300 hospital admissions in 2018 [3]. By 2035, reducing tobacco use to under 5% across all socioeconomic groups in the United Kingdom would prevent 35,901 new cases of tobacco-related cancers, 28,997 cases of chronic obstructive pulmonary disease, 24,854 cases of stroke, and 7594 cases of coronary heart disease [4].

Alcohol consumption above 14 drinks/week for men and women, referred to herein as risky drinking, is known to increase risk of alcohol-related harm [5]. In the United Kingdom, 28% of men and 14% of women, accounting for 21% of adults 16 years and older, drank alcohol at risky levels in 2019 [6,7]. In 2018, there were 7551 alcohol-related deaths in the United Kingdom, which is equivalent to 11.9 deaths/100,000 population [8]. Similar to cigarette smoking, disparities exist in alcohol-related deaths by gender, age, location, socioeconomic status, employment status, race, and ethnicity [8]. Further, the comorbidity of tobacco and alcohol use is well documented and results in higher dependency and exacerbated adverse health consequences compared to those experienced by sole users of either tobacco or alcohol [9].

Scalable public health interventions are necessary to reduce the impact of tobacco use and risky drinking. Digital health interventions have demonstrated effectiveness for promoting smoking cessation and reducing alcohol use [10-15]. The availability of digital health interventions has rapidly increased over the past decade fueled by scientific interest, commercial investment, and public demand for these interventions [16-18].They can overcome psychological and logistical barriers (eg, stigma, cost, time) that impede the reach of traditional behavioral interventions (eg, in-person or group counselling).Their demonstrated effectiveness, combined with their scalability to reach large populations at a relatively low incremental cost per user, has the potential to achieve high population health impact [10,19,20].

One approach for distributing digital interventions to reach members of the population is to leverage electronic health records (EHRs). Originally intended to replace paper documents on patients' medical histories, EHRs are now widespread in health care systems, driven by evidence of their positive impact on health care quality and efficiency [21,22]. In the United Kingdom, adoption of EHRs in general practices is nearing saturation, whereas adoption in secondary care is not as widespread. [23]. Studies have documented the use of EHR-based electronic communication with patients to improve service outcomes such as attendance rates, vaccination rates, and cancer screening [24-27]. Similarly, studies have documented benefits of EHR-based reminders, decision support systems, performance feedback, and easy referral to services in supporting physicians' duties in screening and treating patients [28-40].

Previous studies have used EHRs to identify subgroups of patients and then proactively connect them with counselling, removing a barrier to reach by eliminating the need for clinician referral [38,39,41,42]. For example, Haas and colleagues [41] identified smokers of low socioeconomic status through a hospital EHR and contacted them using interactive voice response to deliver treatment. They found that patients who participated in proactively offered telephone counselling were more likely to quit smoking than those who did not [41]. Similarly, Fu et al [42] found that offering tobacco cessation treatment to smoking veterans identified through an EHR increased quit rates compared to participants who received only usual care. Taken together, these results suggest that proactive outreach of behavioral interventions to patients who have been identified through EHRs is an acceptable and effective strategy for increasing the reach of health services. Less evidence exists regarding the acceptability or effectiveness of proactively offering patients fully digital interventions. In one study, Abroms et al [43] found that, among smokers, a digital treatment offering was acceptable and had higher reach than one that involved phone counselling. If acceptable, such an approach would leverage the scalability of digital interventions to deliver treatment at lower costs than approaches that rely exclusively or in part on traditional in-person or telephone counselling.

This 3-phase, mixed methods implementation study aims to implement and assess the acceptability, feasibility, and reach of an EHR-based system for identifying at-risk adults and promoting digital interventions. The design is guided by the taxonomy of implementation outcomes described by Proctor et al [44]. Specifically, adults who smoke cigarettes or drink

alcohol at risky levels will be identified from a hospital's EHR and sent proactive electronic messages that promote mobile apps endorsed by Public Health England for smoking cessation and alcohol drinking reduction: "SmokeFree" [45] and "Drink Free Days" [46]. In Phase 1, formative research on the acceptability of the electronic message system will be conducted through focus groups. In Phase 2, feasibility of the approach will be assessed through descriptive analysis of patient records in the EHR. Finally, in Phase 3, patients identified through the EHR will receive a message via email, text message (SMS), or patient portal that contains a link to access the app appropriate for their risk profile. The primary outcome of Phase 3 is the proportion of patients who follow an embedded link in the message to access the app. Our hypothesis is that proactive electronic messages will engage a clinically meaningful proportion of at-risk patients in digital interventions for health behavior change, defined here as ≥5%.

Methods

Setting

The project will take place at West Suffolk NHS Foundation Trust (WSFT), a provider of acute and community services to a population of around 300,000 people based in Bury St. Edmunds, Suffolk, United Kingdom. WSFT is one of 17 acute National Health Service (NHS) Trusts that are internationally recognized providers of exceptional and efficient NHS care via world-class digital technology and information, known as a Global Digital Exemplar [47].

The WSFT EHR system—Cerner Millenium, locally named "eCare"—includes records for all outpatients and inpatients registered with the hospital. Smoking and alcohol data are captured in the Activity of Daily Living Nursing assessment and a bespoke Lifestyle Screening form completed by nurses and doctors at the time of admission to hospital [48]. The EHR also contains contact information, demographics, and other health data such as chronic disease status.

Phase 1: Acceptability

Overview

Acceptability has been defined as "the demonstrable willingness within a user group to employ information technology for the tasks it is designed to support" [49]. Focus groups are a qualitative method to collect in-depth information about participants' opinions, attitudes, and beliefs around a specific topic [50] and are thus suited for acceptability studies. In this phase, we will conduct 6 focus groups onsite at WSFT to measure patient and stakeholder acceptability and preferences of using EHRs to identify at-risk patients and send them electronic messages that promote behavior change mobile apps.

Participants

Participants, both patients and hospital staff, must be at least 18 years of age. Patients must self-identify as smokers and/or individuals who regularly consume alcohol. We will recruit participants who drink alcohol at any level (not just risky levels) to avoid alienating patients who do not recognize they are drinking at risky levels or those who do not wish to identify as such. We will attempt to balance participants by gender and age.

Data Collection

Topic guides will be based on Perceived Attributes of eHealth Innovations [51] and the diffusion of innovation theory [52], which can explain and predict an intervention's acceptability and potential for adoption [51,53]. Specifically, we will focus the topic guide on 3 constructs central to the Perceived Attributes of eHealth Innovations and diffusion of innovation theory—relative advantage, complexity, and compatibility. These 3 attributes were selected for their alignment with the larger construct of acceptability (our Phase 1 focal point), and we will focus equally on these 3 attributes in terms of question intensity and analysis. To the extent that participant discussions are responsive to these attributes, we do not intend to prioritize one attribute over another.

We will conduct 3 focus groups with patients: one with patients who smoke tobacco, one with patients who drink alcohol, and a third with patients who smoke tobacco and drink alcohol. In addition to questions about the acceptability of the electronic message system, we will ask patients about their preferences for message modality (email, SMS, online patient portal, other), opinions about the content of messages (see Multimedia Appendix 1 for sample messages), and any potential unanticipated consequences.

We will also conduct 3 focus groups with hospital staff: one with health care professionals who undertake lifestyle screening, one with EHR administrative staff (eg, information analysts, information technologists, communications staff), and a third with senior managers in the eCare team. In addition to questions about the acceptability of the messages, we will ask hospital staff to identify any technical, legal, privacy, ethical, or medical challenges or concerns they foresee in implementing the proposed system within the hospital's EHR.

Procedures

We will recruit patients via the WSFT website and through a volunteer organization that supports research studies at the hospital. Hospital staff will be recruited via intranet, email newsletter, word of mouth, and a monthly corporate briefing. Patients and staff members who express interest in the focus groups will be emailed an information sheet and a consent form. Participants must sign the consent forms prior to any research activity. Participants in the patient focus groups will complete a brief, anonymous, demographic form similar to the demographic characteristics data recorded in the EHR (see Phase 2). Patients will be offered a £25 (US $34) voucher as a token of appreciation.

Each focus group will include approximately 6-8 participants and last approximately an hour. All focus groups will be audio-recorded. A professional transcription service will transcribe the audio recording verbatim, and all personal identifying information will be removed.

Analytic Plan

Qualitative coding software NVivo will be used to organize the themes in the transcripts [54]. Focus groups will be coded by

one researcher, and coding will be cross-checked by a second independent researcher. Researchers will meet regularly to discuss the coding and any discrepancies will be resolved collaboratively. Framework analysis will be used to analyze the data, guided by the Perceived Attributes of eHealth Innovations [51]. We will also use inductive analysis where themes will be identified from the data [55]. Data from the focus groups will inform messaging decisions in Phase 3. For example, results from the focus groups will determine whether messages are sent via SMS, email, or patient health portal and the framing of the message content in order to maximize acceptability and minimize any concerns.

Phase 2: Feasibility

Overview and Data Collection

Feasibility assesses whether the methods and procedures of a proposed study will work before implementing it on a large scale [56]. We will work with hospital information analysts to identify the proportions of patients who smoke, drink alcohol at risky levels, or both in the hospital's EHR. Obtaining information about the patient population will inform the planned segmentation in Phase 3. Specifically, we will mine the EHR for the following key data fields: risk profile, contact information, demographic characteristics, chronic or past health conditions, and screening recency. The risk profile is categorized as (1) exclusive smokers, (2) exclusive risky alcohol drinkers, and (3) dual smokers and drinkers. Contact information includes an email address, a mobile phone number, or a record of access to the online patient portal. Demographic characteristics include gender, age, ethnicity, and level of economic deprivation (Index of Multiple Deprivation using post code). Chronic or past health conditions include hypertension, high cholesterol, heart disease, chronic kidney disease, stroke, chronic obstructive pulmonary disorder, asthma, diabetes, dementia, cancer, arthritis, schizophrenia, bipolar and/or other psychosis, and depression and/or anxiety. Screening recency is the date on which tobacco and alcohol use status was most recently assessed.

Analytic Plan

We will use descriptive statistics to tabulate the frequencies and percentages of patients with valid data in each of the aforementioned key fields. Availability of contact information, demographics, health conditions, and screening recency will be stratified by risk profile. Distributions will be compared with chi-squared tests and logistic regression analyses. No personally identifiable information nor patient-level data will be available to the study team. The study team will provide table shells to the hospital-based information analysts, who will aggregate the data onsite and return deidentified results to the study team, consistent with hospital policies. Findings from Phase 2 will inform the viability of the proposed 3 risk profile groups to be examined in Phase 3. A sample size of 383 will be needed for each risk profile to produce a 95% confidence interval of ±5%, assuming a population proportion of 50% and a population size of 100,000 [57]. While we plan to conduct Phase 3 regardless of the true EHR population size as revealed in Phase 2, this statistic provides a benchmark for interpreting results. Furthermore, although not an outcome for the proposed study, findings from Phase 2 will be shared with hospital staff to identify any potential gaps in completeness of records and to suggest potential changes to hospital protocols to improve their completeness.

Phase 3: Reach

Overview

The reach of a public health intervention can be defined as "The proportion and representativeness of individuals who are willing to participatein a given initiative, intervention, or program." [58]. In this phase, we will send proactive electronic messages to at-risk patients who have visited the hospital in the past year, encouraging them to access behavior change apps that support smoking cessation and alcohol reduction. The primary outcome will be the click rate on the link embedded in these messages. We will tailor messages to each participant's risk profile (ie, smoker, risky drinker).

Participants

All identified smokers and risky drinkers for whom contact information is available will be eligible to receive messages, except for patients <18 years old; patients on the End of Life Pathway; pregnant women, as their data are held in a separate database and governed by separate hospital policies; and patients who have opted out of receiving messages from the hospital.

Procedures

The final content and modality of the messages will be based on the acceptability and feasibility findings from Phase 1, and the final number of participants will be based on the feasibility findings from Phase 2. Eligible patients will be sent messages containing a link to a webpage hosted by the NHS where participants can download a free behavior change app relevant to their risk profile. These apps include "SmokeFree" and "Drink Free Days," both of which are promoted by Public Health England as part of their "OneYou" campaign [45,46]. The apps are available for iOS and Android devices.

A data privacy impact assessment has been performed to assess the risk posed by processing patients' data in order to send communications promoting behavior change apps [59]. Each participant will receive at least one initial message and another reminder message if they do not click the link in the initial message; the total number of messages will be determined by the results of Phase 1. To capture and track click rates, each message-embedded link will contain a tracking code that is unique to its recipient. Information technologists at the hospital will use the tracking codes to identify which participants clicked through to access the NHS webpage.

Approximately 1 week after the intervention messages have been sent, participants will receive a message inviting them to complete an anonymous follow-up survey. The survey will collect information on their experience of receiving the message, to further inform acceptability. As in Phase 1, survey items in Phase 3 will be based on the Perceived Attributes of eHealth Innovations and will examine 3 acceptability constructs: relative advantage, simplicity, and compatibility [51]. Patients who complete the survey will be entered into a prize draw to win £250 (US $338) high street vouchers.

Measures

With the exception of the primary outcome (ie, click rate of the link), all study measures are defined within the WSFT EHR system. For behavioral risk status, smokers are defined by a single item labelled "Does the patient smoke?", and risky drinkers are defined by the hospital as those with an Alcohol Use Disorders Identification Test–Consumption version (AUDIT-C) score between 5 and 10 [60]. Demographics include gender, age, ethnicity, and Index of Multiple Deprivation. Health conditions include hypertension, high cholesterol, heart disease, chronic kidney disease, stroke, chronic obstructive pulmonary disorder, asthma, diabetes, dementia, cancer, arthritis, schizophrenia, bipolar and/or other psychosis, and depression and/or anxiety. The primary outcome for Phase 3 is the click-through rate of the links embedded in the messages. In other words, the outcome is the proportion of participants who click the message link to access a behavior change app, with the numerator being the number of individuals who clicked the link and the denominator being the number of individuals who received the message.

Analytic Plan

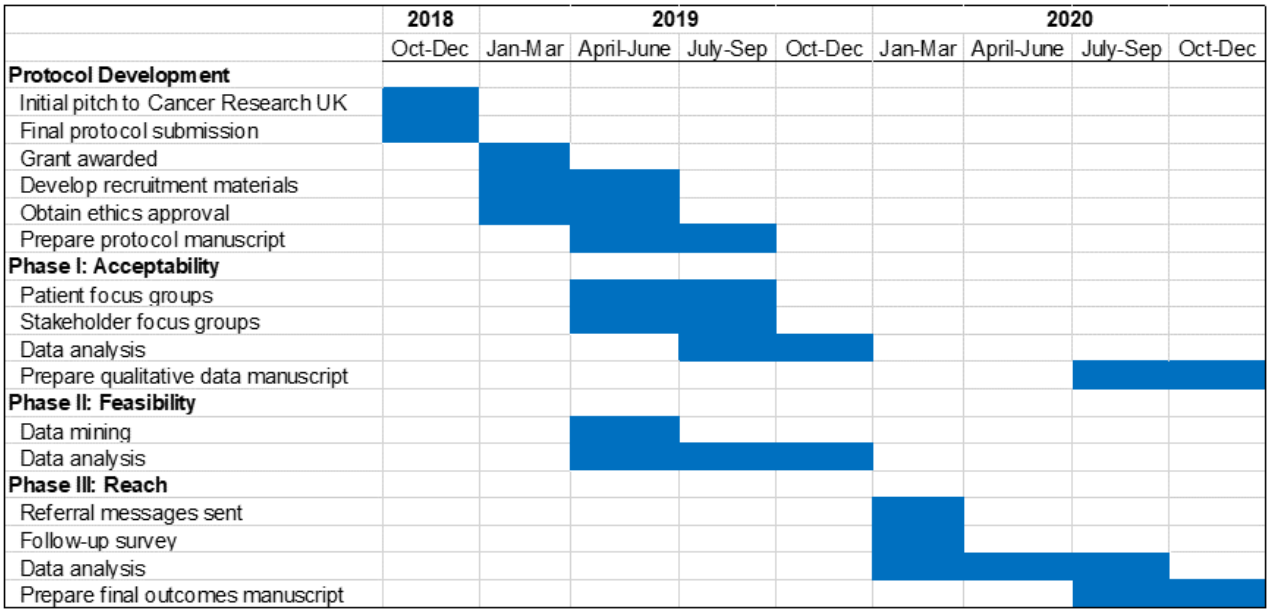
We will use logistic regression analysis to model the likelihood of clicking on the message-embedded link within each risk group, with demographics and health condition statuses entered as covariates. The logistic regression approach will support comparison of effect sizes as the relative risk, a metric that is familiar and easily interpretable across the health sciences. Additional analyses will explore the click rate stratified by risk group and sociodemographic characteristics to investigate health disparities, if any.

We determined a priori that 5% would be a clinically meaningful proportion of users clicking on the message-embedded link. This value was selected based on feasibility determined by prior research [39]. Although relatively modest in absolute terms, 5% of the total number of smokers or risky alcohol drinkers within the NHS EHRs would represent many people. We hypothesize that 5% is attainable based on similar studies in which patients identified through an EHR responded to a quitline referral [39,43] or proactive telephone calls offering telephonic coaching [41] and on email marketing campaign industry standards of click-through rates of 2%-5% [61]. This includes those whose mobile phone numbers are invalid (eg, message undeliverable) and therefore unable to receive the messages.

Ethics Approval

We will seek ethical approval from the NHS Research Ethics Committee and the Health Research Authority. All communications with patients in Phase 3 will come from the hospital, rather than the study team, and only patients who have consented to receive health communications from the hospital are eligible to be included in the study. We have already received authorization to use EHR data from the WSFT Information Governance Team via a data protection impact assessment form [59] (approval date: September 20, 2019). The study timeline is presented in a Gantt chart (see Figure 1).

Figure 1. Gantt chart of study timeline.



Results

This study was funded by Cancer Research UK from April 2019 to March 2020. NHS Research Ethics Committee and Health Research Authority approvals were granted in June 2019. At the time of the original submission of this protocol manuscript, data collection was complete, but analyses had not begun. Analysis of phase 3 data was extended beyond the end of the study, due to prioritization of COVID-19 activity.

Discussion

Increasing the reach of digital behavioral health interventions can improve population health by reducing the burden of preventable death and disease. This 3-phase study protocol describes an implementation strategy that aims to increase

exposure to digital-based treatment for smoking cessation and alcohol reduction among a large, at-risk population identified through a hospital's EHR. While future research is needed to assess what proportion of users who click a link subsequently enroll in treatment, this study will provide empirical estimates of an important first step on that pathway. Specifically, we aim to use electronic communications to promote Public Health England's behavior change mobile apps to secondary care patients who smoke or drink alcohol at risky levels. The implementation strategy [62] is designed to be scalable, such that the study protocol can be readily and economically translated to an automated system for immediate implementation within a hospital EHR system.

This study is one of the first to integrate digital behavior change interventions with an EHR system. This study will contribute to the literature by providing valuable data on the acceptability, feasibility, and reach of such integration. The study will advance the dissemination of digital health interventions, expand the use of EHR beyond the individual patient, and provide a model for implementation and adaptation to other health care systems. Finally, a fully automated screening and proactive outreach system to digital behavioral interventions will preserve human resources for cases that need special attention, such as patients who need personal follow-up calls to enroll in behavioral change interventions or patients who may require in-person behavioral counselling such as smokers from special populations such as HIV patients or those with mental illness.

Future directions include follow-up studies to determine optimal message content, frequency, and other communication meta parameters to yield higher click rates. Similarly, follow-up studies should explore group differences in patient preferences for engaging with electronic communications about behavior change support. Other future directions include deeper integration of interventions with EHRs, for example dynamically tailored interventions based on clinician-initiated changes to a patient's EHR or reporting information bidirectionally from a digital intervention back to the EHR for clinician review. Finally, follow-up studies on implementation fidelity and adaptability to health care systems nationally and worldwide are needed.

Limitations

The proposed study takes place at a Global Digital Exemplar Trust, a world leader in digital technology and health records. This infrastructure might not be available at other hospitals. The intervention is based on the use of electronic communication (email, SMS, online patient portal) and directs patients to download mobile apps for behavioral interventions; patients who are not connected to the internet or do not own smartphones are unlikely to benefit from such approaches. Race/ethnicity and socioeconomic status are important determinants of smoking and alcohol drinking behaviors; however, the sample for the current study is limited by the hospital population.

Conclusion

This implementation study will add valuable insights to sparse literature on using EHRs to expand the reach of digital interventions for cancer prevention. The ultimate goal of the research is to reduce cancer incidence on a population level by addressing cancer risk behaviors such as cigarette smoking and drinking alcohol at risky levels. Results will guide future studies on wider-scale implementation.

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Authors' Contributions

All authors conceived of the study and protocol. MA and SE drafted the manuscript. All authors reviewed and edited the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Focus group example messages.
[DOCX File , 279 KB - resprot_v9i12e23669_app1.docx]

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Abbreviations

EHR: electronic health record
NHS: National Health Service
WSFT: West Suffolk NHS Foundation Trust

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Protocol

The Role of Stress and Genital Immunity in Sexual Trauma and HIV Susceptibility Among Adolescent Girls and Adult Women (The THRIVE Study): Protocol for a Longitudinal Case-Control Study

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Abstract

Background: The relationship between sexual violence and HIV risk has been extensively documented through social and behavioral research; however, the underlying biological mechanisms are poorly understood.

Objective: The purpose of the THRIVE (Trauma and HIV Risk: Investigating Stress and the Immune Disruption of the Vaginal Environment) Study is to examine the impact of sexual trauma due to sexual violence on HIV susceptibility through dysregulation of soluble inflammatory and anti-inflammatory and anti-HIV biomarkers in the female genital tract and dysregulation of the hypothalamic-pituitary-adrenal axis among adolescent girls and adult women.

Methods: The THRIVE Study is a longitudinal case-control study conducted in San Diego, CA, among a racially diverse sample. Cases are adolescent girls (aged 14-19 years) or adult women (aged 20-45 years) who have experienced forced vaginal penetration by a phallus perpetrated by a man within the past 15 days. Controls are adolescent girls or adult women who have engaged in consensual vaginal sex with a man within the past 15 days. At baseline and 1- and 3-month follow-up study visits, participants undergo a urine-based pregnancy test; venipuncture blood draw for HIV, C-reactive protein, adrenocorticotropic hormone, and progesterone testing; a 45-min interviewer-administered computer survey; and cervicovaginal lavage to measure proinflammatory and anti-inflammatory and anti-HIV soluble immune biomarkers. After each study visit, participants self-collect saliva specimens (upon waking, 30 min after waking, and 45 min after waking) at home for 3 consecutive days, which are later assayed for cortisol and dehydroepiandrosterone sulfate. Participants receive compensation at each study visit and for the return of saliva specimens, and a list of local medical and support services. Study procedures use trauma-informed care methods, given the sensitive nature of the study and enrollment of women in the acute phase after sexual trauma. All research staff and investigators adhere to ethical principles and guidelines in the conduct of research activities. Data will be analyzed for descriptive and inferential analyses.

Results: The recruitment of participants is ongoing. The publication of the first results is expected by late 2021.

Conclusions: The THRIVE Study will provide foundational knowledge on how sexual trauma due to sexual violence increases susceptibility to HIV acquisition via alterations in cervicovaginal immune regulation and the psychobiology of the stress responses. These findings will inform future research on mechanistic models of in vitro and in vivo injury and cervicovaginal wound healing processes, which may lead to the development of nonvaccine biomedical HIV prevention products for girls and women.

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KEYWORDS

sexual trauma; sexual violence; forced sex; HIV risk; stress; genital immunity; adolescent girls; adult women; United States; case-control; longitudinal

Introduction

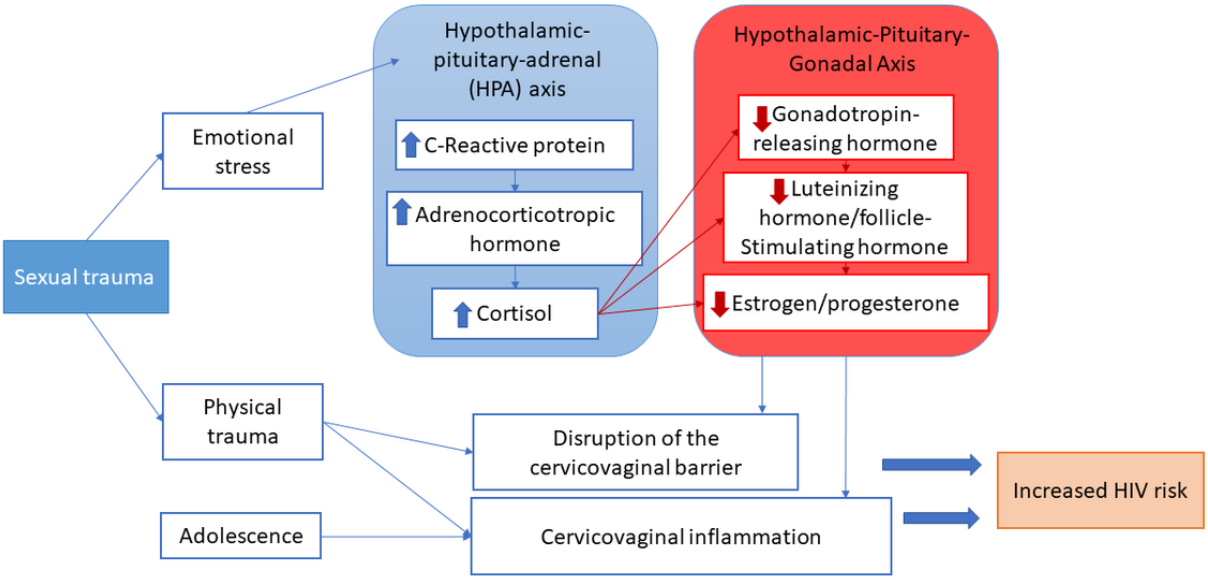
Background

In the United States, racial and ethnic- and age-related disparities in the intersecting epidemics of sexual violence and HIV are paramount [1-4]. The type of sexual violence most often implicated as a risk factor for HIV acquisition is forced sex, defined as unwanted or nonconsensual penetrative sex that occurs through the use of violence, physical force, or threats thereof [1,5]. Although national statistics highlight equivalent lifetime prevalence rates of forced sex (a form of sexual violence) for Black and White women (21%) and lower rates among Latinx women (14%) [5], multiple US community-based studies have documented a forced sex lifetime prevalence rate as high as 38%-54% for Black women [6-8] and 21%-38% for Latinx women [9-11]. More severe forms of sexual trauma due to forced sex or sexual violence have also been reported among Black and Latinx women [12,13]. Among women who have experienced rape, 40% were raped before the age of 18 years and 79% were raped before the age of 25 years [5]. Specific to HIV infection, women account for 20% of all new HIV infections in the United States, of which 22% occur in adolescent girls and adult women between the ages of 13 and 24 years [14]. Women of color account for most of the incident and prevalent HIV infections and HIV-related deaths among women in the United States [14]. The likelihood of a woman being diagnosed as having HIV in her lifetime is significantly higher for Black (1 in 54) and Latinx (1 in 256) women than for White women (1 in 941) [15].

The sexual- and drug-related behavioral pathways linking sexual violence and HIV susceptibility have been extensively documented [1,2,16]. However, the biological mechanisms driving increased HIV susceptibility following a forced sex incident are understudied, despite documentation of plausible pathways [1,17-19]. A potential pathway is that following trauma due to sexual violence, there is immune dysregulation in the female genital tract (FGT) secretions (ie, cervicovaginal inflammation) that may increase HIV susceptibility (Figure 1) [19-21]. These changes may be due to rough or violent, nonconsensual vaginal or anal intercourse; genital injuries, such as abrasions, tears, and microlesions in the epithelium of the vagina, cervix, or anal regions; sexually transmitted infections (STIs) that cause cell death; mucosal inflammation; and local activation of CD4+ T cells, which may increase the likelihood of HIV transmission [17,19,22]. The production of proinflammatory cytokines as a result of sexual trauma may be disrupted and delay wound repair [18], further compromising the vaginal and anal epithelium [19]. Adolescents may face compounded risk as a result of the immaturity of the FGT and incomplete development of the vaginal, ectocervical, and cervical epithelia [23].

Moreover, as a result of the psychological consequences of intense sexual trauma, individual differences in the effects on the reactivity and regulation of the hypothalamic-pituitary-adrenal (HPA) axis have the potential to affect the innate and adaptive immune system in the FGT [24], further influencing HIV susceptibility (Figure 1) [25-27]. High and variable levels of HPA axis activation also have consequences for the secretion of estrogen and progesterone through effects on the gonadotropin-releasing hormone [28]. The pubertal stage, shifts in emotional lability, increased levels of hormones, and rapid brain development in adolescents render them particularly susceptible to the adverse effects of stress [28].

Figure 1. Conceptual model for the THRIVE Study. THRIVE: Trauma and HIV Risk: Investigating Stress and the Immune Disruption of the Vaginal Environment.



Sexual trauma may affect the normal stress response (1) immediately via the sexual trauma incident, (2) by the physical and psychological violence that accompanies sexual trauma, and (3) via continued retraumatization and re-experiencing of the sexual trauma after the incident [29,30]. HPA dysregulation has been documented in acute and chronic sexual abuse victims [25,31,32], and it is suggested that alterations in the HPA axis functioning may occur relatively proximate to the traumatic event and correlate with hyperarousal symptoms [26]. Trauma-induced changes in the regulation of the HPA axis may manifest for years after the original trauma or stressor [33]. Chronic and sustained activation of the HPA axis in response to stress can lead to abnormal levels of reproductive hormones, which also has the potential to influence the immune system [17,34]. Specifically, traumatic stress promotes a proinflammatory profile [35], which may increase susceptibility to HIV, either directly by cortisol binding to receptors on immune cells or indirectly by disrupting the regulation of cytokines [18,34].

The pronounced racial and ethnic disparities in sexual violence and HIV highlight the importance of considering potential racial and ethnic group differences in the underlying biological mechanisms. Women of color experience chronic stress because of social and cultural factors (eg, discrimination, medical mistrust, and immigration status) [36,37]. In addition, low socioeconomic status and ethnic minority status are associated with increased psychosocial stress and elevated circulating concentrations of C-reactive protein (CRP), a marker of chronic inflammation, which may indicate preexisting immune dysregulation that could be exacerbated by sexual trauma [37,38]. Furthermore, there are observed differences between Black and White or Latinx women with regard to genes associated with inflammation and antimicrobial immunity [39].

Given the lack of understanding of the biological pathways contributing to the relationship between sexual violence and increased HIV susceptibility, it is critical to explore the potential biological mechanisms at play. This is particularly important given the increased risk of sexual violence and HIV independently among adolescents and women of color, and the possible compounding effect of biology with society and culture.

Objectives

The primary aim of the THRIVE Study is to assess the impact of sexual trauma on the FGT immunity in adolescent girls and adult women by evaluating (1) the disruption of genital immune biomarkers after sexual trauma and (2) the functional loss of anti-HIV immunity against laboratory-adapted and transmitter/founder (T/F) strains of HIV in genital secretions after sexual trauma. The secondary aim is to assess the impact of sexual trauma on HPA axis dysregulation in adolescent girls and adult women by evaluating (1) correlations between the dysregulated HPA axis and genital immune biomarkers and (2) correlations between the dysregulated HPA axis and functional loss of anti-HIV immunity in genital secretions. Finally, the third aim is to examine whether risk factors linked to sexual trauma, including sexual risk behaviors, substance use, and mental health, influence HPA axis dysregulation and FGT immunity in adolescent girls and adult women after sexual trauma.

Methods

Study Design

The THRIVE (Trauma and HIV Risk: Investigating Stress and the Immune Disruption of the Vaginal Environment) Study is a longitudinal case-control study among girls and women aged 14-45 years, with baseline and 1- and 3-month follow-up study

visits. Cases include adolescent girls aged 14-19 years (n=30) and adult women aged 20-45 years (n=30) who have experienced vaginal sexual trauma within the past 15 days. Controls include adolescent girls aged 14-19 years (n=30) and adult women aged 20-45 years (n=30) who have engaged in consensual sex within the past 15 days. The goal is to recruit an ethnically diverse (ie, Black, White, Latinx, and Asian) sample of English- or Spanish-speaking adolescent girls and adult women in each study group.

Study Population

Inclusion criteria for the THRIVE Study are (1) biologically female; (2) HIV negative at baseline; (3) either aged 14-19 (adolescent girls) or 20-45 (adult women); (4) having experienced forced vaginal penetration by a phallus, perpetrated by a man, within the past 15 days (cases) or having engaged in consensual sex via vaginal penetration within the past 15 days (controls); and (5) ability to provide informed consent (if aged 18 years and older), or ability to provide informed assent (if under the age of 18 years). Exclusion criteria are (1) currently pregnant or breastfeeding, (2) use of douches or other vaginal products within 15 days before baseline, (3) cognitive impairment that would limit participation in study procedures, and (4) for cases, consensual vaginal penetration between the experience of forced vaginal penetration and baseline study visit.

Study Procedures

Recruitment and Screening

Recruitment methods for the THRIVE Study include a three-pronged approach to facilitate the sampling of an ethnically diverse study population. First, we conduct passive recruitment of hard-to-reach populations (ie, adolescents and women of color) through targeted flyer distribution, using a recruitment theme of empowerment and capitalizing upon current movements in women's rights. Canvassing activities focus on neighborhoods in San Diego County, where more than 10% of the population is Black or Latinx, and areas with a high incidence of sexual violence. Second, we use rigorous outreach methods for passive recruitment through print and social media, including advertisements in local newspapers and a robust presence on Facebook and Instagram, an accessible branded website, and the creation of spaces within social media for sharing, advocacy organizing, and engaging with the THRIVE Study. Finally, we partner with ancillary support agencies (eg, rape crisis centers, mental health providers, community centers, and housing services), community centers, and health clinics to passively recruit through flyer distribution and to actively recruit or refer via agency employees (eg, providers, social workers, case managers, and advocates) who have direct interaction with potential participants. Potential participants who are interested in the THRIVE Study are given the study contact information to call or email study staff or provide verbal permission for collaborating organizations to provide their contact information to the THRIVE Study staff.

Girls and women interested in participating in the study are either screened for eligibility over the phone by study staff or complete a 5-min web-based screening survey, which is then reviewed by study staff for eligibility. Participants provide digital or verbal consent to screen before responding to the screening questions. Screening questions include demographics, sexual violence history, consensual sexual behavior history, pregnancy and breastfeeding status, and ability and willingness to participate in at-home saliva sample collection following each study visit. After completion of the screener, girls and women are notified of their eligibility status. Eligible and interested participants are scheduled to attend the baseline study visit. Ineligible participants are informed that their eligibility status may change, and if interested, they are invited to rescreen in the future.

Study Visits

At the baseline visit (duration of 1.5-3 hours), participants provide written informed consent (adult women) or assent (adolescent girls) and complete study activities. At baseline and 1- and 3-month postbaseline visits, participants complete the study activities, receive US $50, and are provided with a list of local health and support resources and transportation assistance. Following each study visit, participants complete 3 days of at-home self-collection of saliva specimens. Participants have the choice to deliver the saliva specimens or have the study staff retrieve them. Following retrieval of each of the saliva specimen collection periods, participants receive an additional US $35.

At each study visit, participants undergo (1) a urine test, (2) venipuncture blood sample collection, (3) an interviewer-administered quantitative survey, and (4) a cervicovaginal examination. Biological biomarkers and survey measures are listed in detail in Tables 1 and 2, respectively. Following each study visit, participants self-collect saliva specimens at home for 3 consecutive days. All study staff are trained on research methods, data collection, confidentiality, trauma-informed care, safety and security protocols, protection of human subjects, and mental health first aid. Trained and licensed clinical staff collect all biological specimens and interpret the test results.

Table 1. Biological sample biomarkers.

Biological sample and biomarker	Test or method	Source of the protocol
Dipstick pregnancy test		
hCG[a]	Sure-Vue	Manufacturer
Venipuncture blood draw		
HIV 1/2 antibody and p24 antigen	CMIA[b]	UCSD[c] Health Clinical Laboratories
Progesterone	ECLIA[d]	UCSD Health Clinical Laboratories
C-reactive protein	Latex immunoturbidimetry	UCSD Health Clinical Laboratories
ACTH[e]	ECLIA	ARUP[f] Laboratories
Vaginal swabs		
Candida, Gardnerella, and Trichomonas	Affirm VPIII Ambient Temperature Transport System	Manufacturer
Chlamydia trachomatis (Chlamydia) and *Neisseria gonorrhoeae* (Gonorrhea)	Cobas CT/NG[g]	Manufacturer
Cervicovaginal lavage		
IL[h]-1α, IL-1β, IL-6, IL-8, TNF-α[i], MIP3α[j], SLPI[k], elafin, and β-defensin 2	ELISA[l] (R&D Systems and PeproTech)	Ghosh et al [40] and Lahey et al [41]
Passive drool saliva samples		
Cortisol and DHEA-S[m]	ELISA (SalivaBio and Salimetrics)	Granger et al [42] and Wilde et al [43]

[a]hCG: human chorionic gonadotropin.

[b]CMIA: chemiluminescent microparticle immunoassay.

[c]UCSD: University of California, San Diego.

[d]ECLIA: electrochemiluminescence immunoassay.

[e]ACTH: adrenocorticotropic hormone.

[f]ARUP: Associated Regional and University Pathologists.

[g]CT/NG: *Chlamydia trachomatis* or *Neisseria gonorrhoeae*.

[h]IL: interleukin.

[i]TNF-α: tumor necrosis factor-alpha.

[j]MIP3α: macrophage inflammatory protein-3α.

[k]SLPI: secretory leukocyte peptidase inhibitor.

[l]ELISA: enzyme-linked immunosorbent assay.

[m]DHEA-S: dehydroepiandrosterone sulfate.

Table 2. Exposure and outcome measures: quantitative survey.

Variable group and measures	Source of measures
Demographic characteristics[a]	
Race and ethnicity	N/A[b]
Nativity	N/A
Sexual orientation	N/A
Marital status	N/A
Number of children	N/A
Educational attainment	N/A
Student status	N/A
Employment status	N/A
Living situation	N/A
Socioeconomic status	N/A
Mental health history	
PTSD[c] (preassault)[d]	PC-PTSD[e] [44]
Depression (preassault)[d]	CES-D[f] [45]
Perceived stress (preassault)[d]	PSS[g] [46]
Resilience	Connor-Davidson Resilience Scale [47]
Lifetime of traumatic events[a]	Lifetime Events Checklist [48]
Previous experiences with battering	Women's Experiences with Battering Scale [49]
Sociocultural factors[a]	
Gender role beliefs	Gender Role Beliefs Scale [50]
Sexual relationship power	Sexual Relationship Power Scale [51]
Discrimination	Extended Everyday Discrimination Scale [52]
Medical mistrust	GBMMS[h] [53]
Law enforcement mistrust	Adapted from GBMMS
Medical history	
Current symptoms	Created for the THRIVE[i] Study
Diagnosis history[a]	N/A
Use of medications and substances	N/A
Gynecologic and reproductive history	
Menstrual history	Created for the THRIVE Study
STI[j] and HIV testing history	N/A
STI diagnosis and treatment history	N/A
Pregnancy history	National Survey of Family Growth and CDC[k] Reproductive Health Assessment Questionnaire for Conflict-Affected Women [54]
Pregnancy complication history	National Survey of Family Growth and CDC Reproductive Health Assessment Questionnaire for Conflict-Affected Women [54]
Lifetime[a], recent[a], and current contraceptive use	National Survey of Family Growth and CDC Reproductive Health Assessment Questionnaire for Conflict-Affected Women [54]
Sexual behavior history	

Variable group and measures	Source of measures
Sexual debut[a]: age, contraceptive or protective method use, substance use, coercive or forced experience	Created for the THRIVE Study
Recent sexual behavior	N/A
Lifetime[a] and recent sexual partners	N/A
Concurrent sexual partners	N/A
Lifetime[a] and recent sexually violent experiences	Created for the THRIVE Study
Current and former substance use	
Lifetime[a] and recent substance use before sexual activity	N/A
Recent alcohol use behaviors	10-item Alcohol Use Disorders Identification Test [55]
Lifetime[a] and recent drug use behaviors	NIDA[l] Quick Screen and NIDA-Modified Alcohol, Smoking and Substance Involvement Screening Test [56]
Lifetime[a] and recent methods of drug administration	Created for the THRIVE Study
Sexual assault[a,d]	
Perpetrator use of alcohol and drugs	Created for the THRIVE Study
Survivor use of alcohol and drugs (consensual and nonconsensual)	Created for the THRIVE Study
Postassault change[a,d]	
Substance use postassault	Created for the THRIVE Study
PTSD postassault	PC-PTSD [44]
Depression postassault	CES-D [45]
Perceived stress postassault	PSS [46]
Referral assessment	
Assessment of suicidal ideation	Suicide Behaviors Questionnaire-Revised [57]
Assessment of the likelihood of partner homicide	Danger Assessment [58]

[a]Denotes measures collected at baseline (month 0) only.
[b]N/A: not applicable.
[c]PTSD: posttraumatic stress disorder.
[d]Denotes baseline measures asked of case participants only.
[e]PC-PTSD: Primary Care PTSD Screen.
[f]CES-D: Center for Epidemiologic Studies Depression Scale.
[g]PSS: Perceived Stress Scale.
[h]GBMMS: Group-Based Medical Mistrust Scale.
[i]THRIVE: Trauma and HIV Risk: Investigating Stress and the Immune Disruption of the Vaginal Environment.
[j]STI: sexually transmitted infection.
[k]CDC: Centers for Disease Control and Prevention.
[l]NIDA: National Institute on Drug Abuse.

Urine Test

Every participant is asked to provide a urine sample. The urine sample is collected by clinical laboratory staff, and a urine dipstick test (Sure-Vue, Fisher Scientific) is used to test for pregnancy via assessment of human chorionic gonadotropin hormone (Table 1). Participants with a positive test result at baseline are provided with counseling, education on pregnancy options (eg, parenting, abortion, or adoption), and referrals by the study physician or nurse practitioner, and then they are administratively withdrawn from the study. Participants testing positive at a follow-up study visit are provided similar items but are not administratively withdrawn from the study.

Venipuncture Blood Sample Collection

Participants undergo low-volume peripheral blood draws performed by clinical laboratory staff. Blood samples are processed by clinical laboratory staff and sent to the University of California, San Diego (UCSD) Health Clinical Laboratories for testing. All blood samples undergo assaying for serum CRP and progesterone using the immunoturbidimetric latex and chemiluminescence methodology, respectively (Table 1). When possible, study visits are scheduled to facilitate blood draws

between 7 and 10 AM, the time frame in which adrenocorticotropic hormone (ACTH) levels peak. The additional sample is collected in an EDTA tube to be processed and transported to be tested for plasma ACTH at UCSD Health Clinical Laboratories.

HIV Testing

From the low-volume peripheral blood draw, a blood sample is collected, processed for transport, and transported to the UCSD Health Clinical Laboratories for HIV-1/2 antibody and p24 antigen testing, followed by HIV RNA testing if the initial test result is positive or inconclusive (Table 1). Participants who have a positive test result for HIV at baseline are provided with counseling, referrals, and linkage to HIV care by the study physician or nurse practitioner, after which they are administratively withdrawn from the study. Participants with a positive test result for HIV at a follow-up visit undergo the same process but are not administratively withdrawn from the study to capture HIV incidence.

Quantitative Survey

At each study visit, all participants complete a 45-min interviewer-administered computer survey using Research Electronic Data Capture (Vanderbilt University) hosted by the UCSD Altman Clinical and Translational Research Institute. Participants are shown visual analog response cards for measures with Likert response scales to reduce the participant burden. The quantitative survey includes the following 10 domains (Table 2): demographic characteristics, mental health, sociocultural factors, medical history, gynecologic and reproductive history, sexual behavior, substance use, sexual assault, postsexual assault, and referral assessment for suicide risk and potentially lethal relationships. Questions on sexual trauma and postsexual trauma experiences are only asked for case participants. Sexual trauma history questions assess perpetrator and participant use of alcohol and drugs during the incident of sexual violence that met the study inclusion criteria, both consensually and nonconsensually. The section on postsexual assault experiences assesses changes in behaviors and mental health in the time since participant's experiences of sexual violence, including changes in substance use, posttraumatic stress disorder, depression, and perceived stress, and the participant's use of formal and informal support services.

Cervicovaginal Examination

Following the completion of the survey, participants undergo a cervicovaginal examination performed by a female physician or nurse practitioner specialized in infectious diseases and women's reproductive health. This examination includes a visual inspection of the cervicovaginal epithelium to assess current STI symptomology and the collection of vaginal swabs and cervicovaginal lavage (CVL) fluid (Table 1).

STI Testing

Vaginal swabs are collected by rotating a single-use specimen swab along the vaginal epithelium and are used to test for vaginal candida (yeast), gardnerella (bacterial vaginosis), trichomonas, chlamydia, and gonorrhea. For candida, gardnerella, and trichomonas, the Affirm VPIII Ambient Temperature Transport System is used to preserve the sample for testing. Chlamydia and gonorrhea nucleic acid amplification testing is performed using the Cobas CT/NG (*Chlamydia trachomatis* and *Neisseria gonorrhoeae*) testing system. All vaginal swabs are sent to the UCSD Health Clinical Laboratories for testing.

CVL

During the cervicovaginal examination, the study physician or nurse practitioner collects cervicovaginal cells using a disposable speculum lubricated with a water-based lubricant to dilate the cervicovaginal canal. The cervix and ectocervix are bathed with 5 mL of 0.9% saline solution. The saline solution is allowed to pool in the posterior fornix and then aspirated into a syringe. The study physician or nurse practitioner repeats this process 5 times to ensure adequate suspension of cervicovaginal epithelial cells. The CVL fluid is then centrifuged, the supernatant and pellet are separated, and both samples are frozen at −80°C until batch shipment to the George Washington University Milken Institute School of Public Health. Supernatants from CVL samples will be tested for proinflammatory (interleukin [IL]-1α, IL-1β, IL-6, IL-8, and tumor necrosis factor-alpha [TNF-α]) and anti-inflammatory and anti-HIV (secretory leukocyte peptidase inhibitor [SLPI], elafin, β-defensin 2, and macrophage inflammatory protein-3α [MIP3α]) soluble immune biomarkers. These biomarkers will be quantified using enzyme-linked immunosorbent assays from R&D Systems and PeproTech. The functional anti-HIV activity of CVL will be determined using the TZM-bl assay.

Saliva Specimen At-Home Self-Collection

Following the completion of each study visit, participants are instructed on the saliva specimen at-home self-collection process. Saliva is used to measure cortisol and dehydroepiandrosterone sulfate (DHEA-S; Table 1). Participants use a prepackaged kit to self-collect saliva samples at home 3 times a day (upon waking, 30 min after waking, and 45 min after waking) for 3 days following each study visit. The prepackaged kit contains instructions, 3 snack-size bags with cryovial tubes (for each collection day), SalivaBio saliva collection aids, and a log form. Using the passive drool method, pooling saliva at the bottom of the mouth, and then easing it into the collection device directly, participants self-collect at least 1 mL of saliva in each cryovial tube. Samples are stored in a −20°C freezer (or general home freezer) immediately following collection. The log form is used for participants to self-report any deviation from their wake-up schedule, actual collection times, stressors, or unexpected activities (eg, brushing teeth, smoking, and eating). To facilitate ease of sampling and increased adherence, this protocol includes a thorough explanation of collection procedures at each study visit; scheduling of wake-up times; reminder text messages and phone calls; supply of a study mobile phone if the participant does not have a phone, cannot receive messages, or feels unsafe or uncomfortable receiving study messages to her personal mobile phone; and pick up of samples by study staff. The saliva collection protocol is based on previously published recommendations for home-based saliva sample collection, participant preparation, and sample handling [26,42]. On the third day of collection, the study staff travels to participants' residence to pick up the saliva samples. Samples are then batch

shipped (using dry ice) to the University of California Irvine Institute for Interdisciplinary Salivary Bioscience Research, where they are stored frozen at −80 °C until the day of the assay. Samples are assayed in duplicate using commercially available immunoassays for cortisol and DHEA-S, specifically designed for use with saliva, according to the manufacturer's recommended protocols (Salimetrics). The average of the duplicate assays is used in the statistical analysis. Cortisol is measured in micrograms per deciliters and DHEA-S in picogram per milliliters.

Using the waking, 30-min postwaking, and 45-min postwaking samples, the daily cortisol awakening response (CAR) is calculated; using the area under the curve increase to calculate the CAR accounts for the change over time in cortisol with respect to baseline, which is the waking sample in this study. Next, we compute the mean between the 3 days for an average CAR for each participant. The average CAR will be used for the study analyses [59].

Safety Protocol

Due to the highly sensitive nature of this study and the acute phase following sexual trauma during which cases are enrolled in the study, the THRIVE Study has taken additional measures to develop and implement a safety protocol. This protocol outlines the information on how to respond to sensitive circumstances that may arise during study appointments, including mandated reporting of child abuse, expected and unexpected adverse events, including extreme emotional distress and suicidal ideation, and identification of a participant in an abusive relationship or at risk of homicide by a violent partner. Within the safety protocol, the staff is trained in ways to address participant sensitivity and trauma and to explain our role as mandated reporters of any incidents of childhood abuse reported during participation in the study. In addition, the safety protocol outlines resources that are distributed to all participants, which include ancillary services for domestic violence (eg, shelter and counseling), legal assistance, substance use, and medical care. Finally, as part of the safety protocol, all women receive counseling on community awareness of sexual violence and partner violence as well as resources to share with their community.

Data Management and Quality Assurance

Several precautions are taken with participant data to protect confidentiality. All participants are assigned a numeric personal identification number, which is used as a reference to the participant on all study data to delink the study databases from personal identifying data. Only a few study personnel have access to deidentified project files and databases, and the lowest level of access acceptable for a staff member's role is only granted after full ethical training and upon the principal investigator's approval. All study materials on paper containing participant information (eg, contact information sheet and signed consent forms) are stored in a locked cabinet in a locked office, accessible by the project coordinator and principal investigators, and within a building with restricted access.

Quantitative deidentified screening data are downloaded on a weekly basis and distributed graphically and in a tabular format to the project coordinator and principal investigators to monitor recruitment, screening, and enrollment of participants. Deidentified biological samples from blood and vaginal swabs are sent to the laboratories at UCSD for assaying or testing of CRP, progesterone, ACTH, HIV, STIs, yeast infections, and bacterial vaginosis; CVL samples are sent to the George Washington University for assaying of proinflammatory (IL-1α, IL-1β, IL-6, IL-8, and TNF-α) and anti-inflammatory and anti-HIV (SLPI, elafin, β-defensin 2, and MIP3α) soluble immune biomarkers; and saliva specimens are transported to the University of California, Irvine, for assaying of cortisol and DHEA-S. Test results from UCSD are delivered deidentified on paper and directly entered into REDCap, whereas test results from the George Washington University and the University of California Irvine are sent deidentified via email to UCSD and securely stored in the OneDrive THRIVE Study folder. Biological specimens are stored for 6 months to allow for retesting, if necessary, and then disposed of as medical hazard waste.

Ethical Conduct of Human Subjects Research Approval

The THRIVE Study has been approved by the UCSD Human Research Protection Program (HRPP; UCSD HRPP Project #181898). The institutional review boards at the George Washington University and the University of California, Irvine, approved reliance agreements from the institutional review board at UCSD. Before working with the THRIVE Study, all UCSD staff received training in the ethical conduct of human subjects research, compliance, and data management via a collaborative institutional training initiative for biomedical research and Health Insurance Portability and Accountability Act (HIPAA). Women 18 years and older who are interested in participating in the THRIVE Study are asked to sign an informed consent form before participating, whereas adolescent girls younger than 18 years are asked to sign an informed assent form. A waiver of parental assent allows for the protection of privacy for young girls, given the sensitive topic of sexual trauma and sexual intercourse, and is in accordance with the UCSD HRPP's recommendations. In addition, it is in consonance with the waiver of parental assent implemented for adolescents receiving services at the rape crisis center, a collaborating recruitment site. All participants are asked to sign a HIPAA authorization form. Finally, a certificate of confidentiality for the THRIVE Study is automatically issued by the funding agency, the National Institutes of Health, to protect identifiable research information from forced disclosure (eg, substance use behaviors).

Data and Safety Monitoring

The THRIVE Study uses a data and safety monitoring plan, which is detailed in a standard operating procedures manual as a reference for secure data collection, management, and monitoring procedures for all study staff. Refresher training sessions for staff are scheduled as needed. All data collected for the THRIVE Study are stored on a secure encrypted drive in a locked office within a secure, locked suite in a clinical research building. Participants' identifying information is stored separately from numeric participant identification numbers. The

linkage between identifying information and study data is maintained through Ripple [60], a HIPAA-compliant secure web application designed for the management of identifying information of participants. Ripple is used only for storing identifiable information of participants and not to capture other research data, ensuring the segregation of personally identifiable information and research data. Adverse events (eg, a breach in confidentiality or privacy and risk of serious and unanticipated harm) and serious adverse events (eg, hospitalization or death because of participation in study-related activities) are monitored by study staff. In the case of such an event, study staff make appropriate referrals to care for the participant, including, but not limited to, warm handoffs with the staff licensed therapist and local mental health resources. Immediately after adverse events, the staff is required to report to the principal investigator. The principal investigator reviews the adverse or serious adverse event and incident report and reports the event within 24 hours of its occurrence to the UCSD HRPP.

In addition, a consultant who is a nurse researcher and an international expert in the area of violence against women, with an emphasis on sexual and intimate partner violence and risk or lethality, is available for meetings and debriefing sessions with staff, as needed. Finally, a data and safety monitoring board convenes 2 times per year to review the progress of the THRIVE Study and assesses adherence to the data and safety monitoring plan. This board comprises a practicing infectious disease clinician, a biostatistician specializing in social epidemiology and HIV, and a public health researcher in HIV prevention and treatment. Recommendations are provided to the study team following each meeting.

Analysis

Aim 1: Understand the Impact of Sexual Trauma on the FGT Immunity

Temporal trends in inflammatory and anti-inflammatory cytokines relative to postsexual trauma will be examined by producing frequency tables and bar graphs by time, age group, and case-control status. Measures of central tendencies and variability will be computed, and corresponding boxplots will be generated. Continuous variables that are not normally distributed will be log-transformed to reduce skew. We will use Student *t* tests and Wilcoxon signed-rank tests to compare continuous variables with *P* values lower than .05, considered significant. Spearman correlation coefficients will be computed to assess potential associations between continuous variables. We will use mixed (random effects) regression to examine the relationship between the case-control groups and the inflammatory and anti-inflammatory cytokines. Separate models will be constructed for adolescent girls and adult women. Models will account for known confounders, including the stage of the menstrual cycle, contraception use, and STI diagnosis after follow-up.

To evaluate the functional loss of anti-HIV immunity against laboratory-adapted and transmitted/founder strains of HIV in genital secretions of adolescent girls and adult women, we will use Kruskal-Wallis tests to compare CVL anti-HIV activity measured by percent HIV inhibition for selected strains, that is, laboratory-adapted R5-tropic virus and 3 mucosal-transmitted clade T/F viruses between case-control status by time. We will conduct two-group comparisons using Mann-Whitney *U* tests. This will be conducted for adolescent girls and adult women. We will also correlate the percent change in anti-HIV activity in CVL with alterations in each inflammatory and anti-inflammatory cytokine to postulate the mechanisms of immune dysfunction.

Aim 2: Assess the Impact of Sexual Trauma on the HPA Axis

The primary variables of interest to address this aim are CAR, DHEA-S to cortisol ratio, and ACTH levels. We will compute cortisol to DHEA-S ratios and follow the analytical methods outlined in aim 1 to examine the impact of sexual trauma on the HPA axis.

To determine the extent to which the HPA axis affects FGT immunity owing to sexual trauma, we will use Pearson correlation coefficient tests to test individual correlation statistics for pairs of the HPA axis (cortisol, ACTH) and FGT immunity variables (IL-1α, IL-1β, IL-6, IL-8, TNF-α, and %HIV inhibition). We will produce a correlation matrix to investigate the dependence between multiple variables at the same time, with correlation estimates measuring the direction and strength of the linear relationship among variables. We will also produce a symmetric scatterplot matrix of the variables as tested as correlations to visually observe the data. These results will be stratified by time and case-control status for adolescent girls and adult women.

Aim 3: Risk Factors Linked to Sexual Trauma Influence HPA Dysregulation and FGT Immunity

We will conduct comparisons between case-control status and independent variables using Pearson chi-square or Fisher exact test for dichotomous variables and *t* test and Wilcoxon rank-sum tests for continuous normally and non-normally distributed variables, respectively. We will use bivariate and multivariate logistic regression to examine associations between case-control status and survey variables (demographics, gynecologic and reproductive history, substance use, sexual behavior, and mental health status) at each time point.

To examine the relationship between (1) case-control status and the inflammatory and anti-inflammatory and anti-HIV mediators (ie, dysregulation of the FGT) and (2) case-control status and CAR and DHEA-S to cortisol ratio (ie, dysregulation of the central and peripheral HPA axis), mixed (random effects) regression models will be used. Separate models will be constructed for adolescent girls and adult women. Models will account for known confounders, including the stage of the menstrual cycle, contraception use, and STI diagnosis after follow-up. Given our small sample size and one of the benefits of using random effects regression models being that we can examine estimated changes for each subject, we will examine both subject-specific trends and population average trends.

Sample Size Considerations

The goal of the THRIVE Study is to provide knowledge and data to facilitate future hypothesis-driven longitudinal research.

As such, the THRIVE Study is an exploratory hypothesis-generating study rather than a hypothesis-testing study. The sample size was determined based on previous studies that have examined the immune microenvironment and wound healing in the female reproductive tract, with total sample sizes ranging between 18 and 77 women [18,40,41]. Given this range, we decided upon a sample size of 30 per case-control group in each age group (adolescent girls and adult women). Furthermore, our power calculation supported this decision. With 30 girls and 30 women in each group, there will be 82% of power to detect a standardized effect size for comparing with any 2 time point means of 0.75 with a two-sample *t* test and α=.05, 2-sided. As an example of detectable effect size, it is estimated that the standard deviation for SLPI, an anti-inflammatory and anti-HIV biomarker, is 26,000 units [41] so that mean differences of 19,500 and 13,520 units would correspond to a standardized effect size of 0.75 and 0.52, respectively. We expect attrition at the follow-up visits to be between 10% and 15%. However, because the proposed mixed and generalized estimated equations repeated measures approach uses all available data on each participant, these analyses should have very little loss of power because of attrition.

Results

Recruitment Timeline

Recruitment of potential participants began in January 2019, and enrollment of participants began in February 2019. Recruitment efforts began with control participants aged 18 years or older as the least sensitive population to be enrolled in the study. This allowed for iterative consideration of study procedures and participant burden and facilitated streamlining and honing of participant experience before enrollment of under 18 years and case populations. Adult case enrollment began in June 2019; however, active recruitment of cases did not begin until September 2019. Case participants enrolled before September 2019 contact the study based on recruitment materials targeting adult control participants. Recruitment of control and case participants under the age of 18 years began in November 2019. As of January 2020, recruitment and enrollment efforts have yielded screening of 557 potential participants and enrollment of 50 participants, including 8 case participants and 42 control participants.

Screening and Enrollment

Of the 557 potential participants screened, 60.1% (335/557) had enough information to be classified into a study group: 74.3% (249/335) adult controls, 20.9% (70/335) adolescent controls, 3.3% (11/335) adult cases, and 1.5% (5/335) adolescent cases. Potential participants who screened and indicated a source were recruited through a variety of methods, including social media advertisements (335/468, 71.6%), paper flyers (89/468, 19.0%), referral by friends or family (26/468, 5.6%), and community newspaper advertisements (15/468, 3.2%). It is notable that most participants enrolled to date have been recruited through social media, including 63.1% (157/249) of adult controls, 60% (3/5) of adolescent cases, 64% (7/11) of adult cases, and 80% (56/70) of adolescent cases. With respect to cases, this may allow for access to individuals who may not seek services associated with traditional recruitment locations for recent survivors of sexual violence, such as emergency rooms or rape crisis centers. Of all participants screened, 45.1% (251/557) were classified as eligible, 30.0% (167/557) did not provide enough information to classify their eligibility, 19.0% (106/557) were ineligible, and 1.1% (6/557) declined to complete the screener. Of those eligible, 28.9% (73/253) were contacted and pursued for scheduling. Of those pursued for scheduling, 68% (50/73) were enrolled, 11% (8/73) cancelled before enrollment, and 18% (13/73) declined to enroll. Of the enrolled participants, 6% (3/50) of participants were administratively dropped because of positive STI at baseline. Of participants not administratively dropped or currently progressing through the study, 85% (35/41) have been retained to follow-up 1, and 76% (31/41) have been retained through study completion.

Adult Control Participants

Of the control participants, 62% (26/42) are in the adult group (aged 20-45 years), with a mean age of 27.1 years (SD 7.6). Among adult control participants, 38% (10/26) of participants identify as Black or African American, 31% (8/26) identify as White, and 12% (3/26) as Asian. In addition, 31% (8/26) identify as Hispanic or Latinx (categories are not mutually exclusive). Regarding education, 38% (10/26) of adult control participants have graduated high school or received a General Educational Diploma (GED), 38% (10/26) have completed a bachelor's or associate's degree, and 65% (17/26) are current students. More than half of the adult control participants (14/26, 54%) make less than US $10,000 annually, whereas 100% make less than US $49,999 annually.

Adolescent Control Participants

Of the control participants, 38% (16/42) are in the adolescent group (aged 14-19 years), with a mean age of 18.8 years (SD 0.5). Among adolescent control participants, 6% (1/16) identify as Black or African American, 25% (4/16) identify as White, and 38% (6/16) identify as Asian. In addition, 50% (8/16) identify as Hispanic or Latinx (categories are not mutually exclusive). All adolescent control participants have received a high school diploma or a GED, and 94% (15/16) are current students. Three-quarters of adolescent control participants make less than US $10,000 annually (12/16, 75%), whereas the remainder makes US $19,999 or less annually.

Adult Case Participants

Of the participants, 63% (5/8) are in the adult group (aged 20-45 years), with a mean age of 34.6 years (SD 10.4). Among adult case participants, 80% (4/5) identify as Black or African American and 20% (1/5) as White. In addition, 40% (2/5) identify as Hispanic or Latinx (categories are not mutually exclusive). Regarding education, 60% (3/5) of adult case participants have a high school diploma, GED, or less than a high school diploma, whereas 40% (2/5) have a graduate degree, and 20% (1/5) are current students. Most adult case participants (3/5, 60%) make less than US $29,999 annually, whereas 40% (2/5) make US $50,000 or more.

Adolescent Case Participants

Of the participants, 38% (3/8) are in the adolescent group (aged 14-19 years), with a mean age of 18.3 years (SD 0.6). Among adolescent case participants, 100% (3/3) identify as White and 33% (1/3) identify as Hispanic or Latinx (categories are not mutually exclusive). One (1/3, 33%) of the adolescent case participants has received a high school diploma or GED, and 2 (2/3, 67%) have completed trade or vocational school; 100% (3/3) are current students. Adolescent case participants make less than US $10,000 (2/3, 67%) or US $50,000 or more (1/3, 33%) annually.

Discussion

The intersecting epidemics of sexual violence and HIV in women is a well-described epidemiologic phenomenon that affects physical and mental health [61,62]. The bidirectional relationship between violence and HIV in women provides a clear but complex target for HIV treatment and prevention. In terms of interventions for violence against women, most approaches focus on perpetration by men [63,64]. HIV prevention efforts in women focus on behavioral interventions that draw from theoretical frameworks of self-efficacy and self-empowerment [65] and on the use of HIV pre-exposure prophylaxis (PrEP) [66]. However, current studies suggest that PrEP failure is more common in women, with multiple factors being delineated, including poor adherence [67-69], sex-based differences in the pharmacokinetics and pharmacodynamics of the antiretrovirals used for PrEP [70], and alteration by the vaginal microbiome [71,72]. Despite evidence that sexual violence is also associated with alterations in the immunobiology of the female reproductive tract, which may increase HIV risk [18], very little is understood about the actual pathogenesis. A clearer understanding of the role of the endocrinologic system in the immunobiology of the female reproductive tract will facilitate the development of novel interventions (both behavioral and pharmaceutical) to enhance PrEP efficacy in women. This study represents the first of its kind to comprehensively evaluate the endocrinologic and local immunobiology of female survivors of sexual violence.

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Authors' Contributions

All authors contributed to this paper. JS and MG had a lead role in the study design. JS conducted the literature review and was a major contributor in writing the manuscript, specifically the Background, Objectives, and Methods sections. KA led the implementation of the study and was a major contributor in writing the manuscript, specifically the Methods section and in the development of the figure and tables. MK led the clinical activities of the protocol and wrote the Discussion section of the manuscript. CB, KT, and DG reviewed and substantially edited the manuscript. AW assisted in the development of the protocol. All authors contributed to the refinement of the protocol and approved the final manuscript.

Conflicts of Interest

In the interest of full disclosure, DG is the founder and chief scientific and strategy adviser at Salimetrics LLC (Carlsbad, CA) and SalivaBio LLC (Carlsbad, CA), and these relationships are managed by the policies of the committees on conflict of interest at the University of California, Irvine, and Johns Hopkins University School of Medicine. All other authors have no competing interests to declare.

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Abbreviations

ACTH: adrenocorticotropic hormone
CAR: cortisol awakening response
CRP: C-reactive protein
CVL: cervicovaginal lavage
DHEA-S: dehydroepiandrosterone sulfate
FGT: female genital tract
GED: General Educational Diploma
HIPAA: Health Insurance Portability and Accountability Act
HPA: hypothalamic-pituitary-adrenal a
HRPP: Human Research Protection Program
IL: interleukin
MIP3α: macrophage inflammatory protein-3α
PrEP: pre-exposure prophylaxis
SLPI: secretory leukocyte peptidase inhibitor
STI: sexually transmitted infection
T/F: transmitter/founder
THRIVE: Trauma and HIV Risk: Investigating Stress and Immune Disruption of the Vaginal Environment
TNF-α: tumor necrosis factor-alpha
UCSD: University of California, San Diego

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Protocol

Effect of PARACT (PARAmedical Interventions on Patient ACTivation) on the Cancer Care Pathway: Protocol for Implementation of the Patient Activation Measure-13 Item (PAM-13) Version

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Abstract

Background: The increase in the number of cancer cases and the evolution of cancer care management have become a significant problem for the French health care system, thereby making patient empowerment as a long sought-after goal in chronic pathologies. The implementation of an activation measure via the Patient Activation Measure-13 item (PAM-13) in the course of cancer care can potentially highlight the patient's needs, with nursing care adapting accordingly.

Objective: The objectives of this PARACT (PARAmedical Interventions on Patient ACTivation) multicentric study were as follows: (1) evaluate the implementation of PAM-13 in oncology nursing practices in 5 comprehensive cancer centers, (2) identify the obstacles and facilitators to the implementation of PAM-13, and (3) produce recommendations for the dissemination of such interventions in other comprehensive cancer centers.

Methods: This study will follow the "Reach, Effectiveness, Adoption, Implementation, and Maintenance" framework and will consist of 3 stages. First, a robust preimplementation analysis will be conducted using the Theoretical Domains Framework (TDF) linked to the "Capability, Opportunity, Motivation, and Behavior" model to identify the obstacles and facilitators to implementing new nursing practices in each context. Then, using the Behavior Change Wheel, we will personalize a strategy for implementing the PAM-13, depending on the specificities of each context, to encourage acceptability by the nursing staff involved in the project. This analysis will be performed via a qualitative study through semistructured interviews. Second, the patient will be included in the study for 12 months, during which the patient care pathway will be studied, particularly to collect all relevant contacts of oncology nurses and other health professionals involved in the pathway. The axes of nursing care will also be collected. The primary goal is to implement PAM-13. Secondary factors to be measured are the patient's anxiety level, quality of life, and health literacy level. The oncology nurses will be responsible for completing the questionnaires when the patient is at the hospital for his/her intravenous chemotherapy/immunotherapy treatment. The questionnaires will be completed thrice in a year: (1) at the time of the patient's enrollment, (2) at 6 months, and (3) at 12 months. Third, a postimplementation analysis will be performed through semistructured interviews using the TDF to investigate the implementation problems at each site.

Results: This study was supported by a grant from the French Ministry of Health (PHRIP PARACT 2016-0405) and the Lucien Neuwirth Institute of Cancerology of Saint-Etienne, France. Data collection for this study is ongoing.

Conclusions: This study would improve the implemented targeted nursing interventions in cancer centers so that a patient is offered a personalized cancer care pathway. Furthermore, measuring the level of activation and the implementation of measures intended to increase such activation could constitute a significant advantage in reducing social health inequalities.

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KEYWORDS

oncology; nursing; implementation science; PAM-13; patient activation; REALM-R; health literacy; mixed method

Introduction

Background

The increase in the number of cancer cases and the evolution of cancer care management have been generating a shift toward chronicity since many years. This phenomenon poses a significant problem for the French health care system [1,2]. As the number of patients treated as outpatients increases, the duration of hospitalization decreases and the care pathways become more complex [1,3,4]. The first 2 French cancer plans have given a structure to the field of cancer care in the domains of both treatment and research [5,6]. The objective of the 2014-2019 French cancer plan was to improve the interfaces between the different fields of interventions for a smoother transfer of innovation and for more fluidity in cancer care pathways [1]. However, the French health care system is centered on acute care whether it involves the management of benign acute diseases combining simple technical procedures or a multitude of complex interventions to treat the severity of acute diseases [7]. One can therefore comprehend the difficulty of integrating chronic care into hospitals in terms of its organization and due to certain attitudes adopted by caregivers. Three types of interventions were identified as part of the research conducted within our health services and performance research team, the objective of which is the performance of the provision of care and the performance of the patient pathway: (1) intervention to improve patient navigation (patient navigation) [8], (2) intervention to support and improve health literacy [9,10], and (3) intervention to support and improve patient empowerment during care (patient empowerment) [11]. These 3 types of interventions are considered to be evidence-based since they have been assessed in an experiential or quasi-experiential context to optimize the care pathway.

Types of Interventions

Patient Navigation

According to the patient navigation experience developed by Harold Freeman in 1990 in Harlem for breast cancer screening, the aim of “Nurse Navigation” in the United States or “Pivot Nurses” in Canada is to better guide patients through a complex care pathway [12,13]. The principle of navigation serves to eliminate barriers having an adverse effect on the quality of care in all phases of prevention, detection, treatment, and posttreatment [14-17]. In France, patient navigation was implemented in oncology clinics with the national initiative of cancer coordination nurses in accordance with the 2009-2013 French Cancer Plan [17]. However, not all French hospitals employed navigation nurses.

Health Literacy

The term “health literacy” is based on the definition given by Sørensen, since it is an accepted reference at the European level [18]. She defines health literacy as “the knowledge, skills, motivation, and ability of an individual to identify, understand, evaluate, and use health information when making decisions in the health care, disease prevention, and health promotion contexts to maintain or improve the quality of life” [18]. It has been established that doctors often communicate ineffectively with their patients by providing them with explanations that are theoretically beyond their comprehension, leading to a relatively low health literacy. The most affected areas include the general context, explanations of the patient’s state of health, and treatment methods [19]. Research has objectively demonstrated that when doctors provide their patients with useful health information while also responding to patients’ emotions, the latter express a greater sense of control and hope, which has a direct positive impact on their quality of life as well as on their chances of survival [20]. It therefore seems evident that clear communication adapted to the patient is essential in the management of care for patients with cancer. After all, patients must assimilate a sum of complex explanations in order to make informed decisions about their treatment options and management of their symptoms [21]. Specifically, in oncology clinics, being mindful of patients’ needs in terms of health literacy is an important aspect of treatment since it results in care that is both focused and safe [22]. Furthermore, various studies indicate that a low level of health literacy can have an impact on the following parameters [23,24]: (1) readmission and recourse to hospitalization, (2) problems understanding medical prescriptions, (3) increase in adverse effects, (4) less awareness regarding prevention, (5) higher prevalence of health risk factors, (6) low autonomy in chronic disease management, (7) poor health outcomes, (8) less effective communication with health care professionals, (9) increased health care costs, and (10) poor general health and increased mortality.

The REALM-R (rapid estimate of adult literacy in medicine-revised) is a health literacy test that was developed to evaluate patients in a clinical setting [25]. Bass et al provided evidence to support the validity and reliability of a shortened version of the REALM [26]. Grandjacquot recently adapted it in the French language and the test proved effective in detecting inadequate levels of health literacy [27].

Patient Empowerment

This process was developed in the United States of America and Canada with the concept of activation and has not yet been widely applied in France. It is defined as a process of knowledge acquisition, skill development, and self-esteem development, thereby enabling the patient to be an actor or to engage in a proactive manner for his or her health care [28,29]. The Patient Activation Measure (PAM) was developed by Hibbard et al to assess knowledge, skills, and confidence in managing health [30,31]. This questionnaire can be used at different times of care [31,32]. The PAM-13 item (PAM-13) is the shortened version of the PAM. It is actually used in several contexts of disease and in many countries around the world [31,33-39]. In particular, Prey et al have demonstrated its reliability and validity while using it with inpatient individuals in oncology clinics [40]. The PAM-13 is used to determine the patient's score and activation level [41]. Four activation levels are defined: "believes active role important" (level 1), "confidence and knowledge to take action" (level 2), "taking action" (level 3), and "staying the course under stress" (level 4). A validated French version is available (Multimedia Appendix 1).

In general, the lower the level, the more passive the patients behave in regard to their health; the higher the level, as measured by the PAM-13, the more proactive patients are with regard to their health. In all probability, the latter group would commit to improving their health behaviors [38,42]. The importance of the patient's role in self-management of chronic illness, including making daily decisions about treatment, physical activity, or diet, has been increasingly recognized [43,44]. A high activation level can result in improved health-friendly behaviors [45], appropriate use of the health care system [42,46], a critical perspective and participation in decision-making processes with stakeholders in the health care system [42], improved management [47] and better control of chronic diseases [48,49], and a reduction in health care costs [50]. Patients with a high activation level generally manifest less misguided practices of care and better treatment adherence [46,51]. This concept of commitment can be initiated and applied to treatment and to the management of services and establishments or health policies [52].

Objective of This Study

We believe that effective action in cancer care requires progressive patient empowerment. Several studies have illustrated the role doctors play in the patient activation process [53-56]. However, nearly all such studies have focused on basic care, with the general practitioner positioned as the "gatekeeper." Hospitals and their staff can contribute to improving health-related behaviors and mobilizing their patients [57,58]. Nevertheless, in comprehensive cancer centers, the modulation of activation is likely varied and more complex because these facilities differ in terms of the specificities of nursing specialties they offer. Nursing positions and the provision of supportive care in oncology clinics can vary greatly depending on the hospital; for example, there are nurse navigators, nurse educators, dieticians, oncopsychologists, osteopaths, physiotherapists, hypnotherapists, and nurses specialized in tobacco cessation. We can suppose that the patients' activation is therefore largely modulated by the type of nurse and supportive care implemented within the hospital. Therefore, we can also assume that these varying cancer care pathways also lead to different results when considering vulnerabilities, access to specific measures, quality of life, and, consequently, patient activation. The World Health Organization has stated that although certain patients will be able to mobilize their own resources and succeed in coping with the situation, thereby eventually becoming (pro)active, others will need to be guided by their caregivers [59]. The implementation of an activation measure via the PAM-13 by navigation nurses or other registered nurses would highlight the patients' needs [60].

We are aware of the need to perform a periodic screening to identify new patient needs that emerge over time and adapt nursing measures to these needs that arise in the course of the cancer care pathway [61,62]. In addition, van Houtum et al suggest that patient activation is not a stable parameter in patients with chronic disease [63]. Greene et al provide a longitudinal measurement of PAM in order to better understand the timing of the activation process [41]. In France, the first results of the Observatory on Patient Expectations of the Unicancer Group, and more recently, findings of the new 2014-2019 Cancer Plan III (Objectives 2 and 7), underlined the need to shift current practices of care toward a more holistic view of the patient with cancer [1].

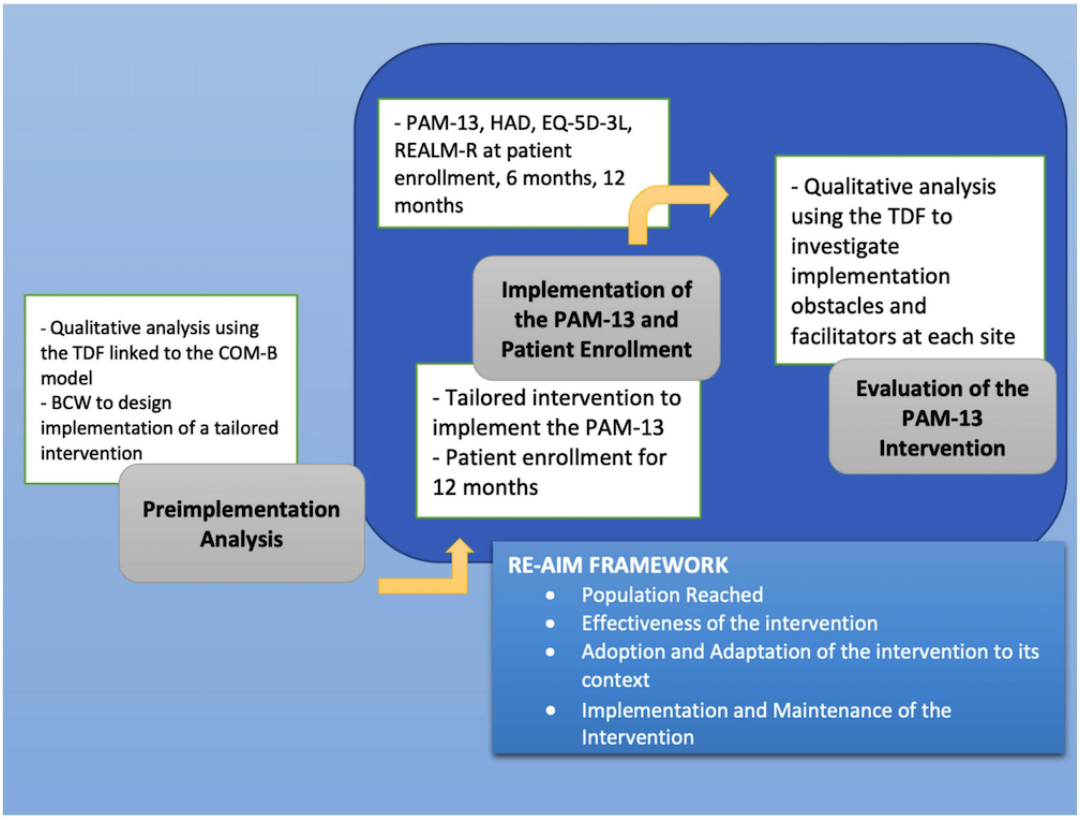
The PARACT (PARAmedical Interventions on Patient ACTivation) multicentric study aims to (1) evaluate the implementation of PAM-13 in oncology nursing practices in 5 comprehensive cancer centers, (2) identify the obstacles and facilitators to the implementation of PAM-13 at the different sites, and (3) produce recommendations for the dissemination of the intervention in other comprehensive cancer centers.

Methods

Implementation Study

This is an implementation multicentric study. The PARACT study is part of the realistic evaluation of an intervention as described by Pawson and Tilley following Campbell's work [64]. This approach favors multisite and multidisciplinary assessments to study the interactions of context-mechanism-outcomes configurations. This type of evaluation makes it possible to adapt the interventions according to the results observed, while considering the context. The assessment selected for this study will therefore be multidisciplinary, combining public health teams and human and social sciences teams. The aspect of navigation in establishments will be assessed in accordance with current recommendations [65]. The patient will act as his/her own control. Given that we are conducting a study of an implementation that is complex, the study will follow the RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) framework. The implementation process will consist of 3 stages (Figure 1).

Figure 1. Overall design of the PARACT (PARAmedical Interventions on Patient ACTivation) multicentric study.



1. First, a robust preimplementation analysis will be performed by using the Theoretical Domains Framework (TDF) linked to the COM-B (Capability, Opportunity, Motivation, and Behavior) model to identify the obstacles and facilitators to implementing new nursing practices in each context. Then, using the Behavior Change Wheel, a strategy for implementing the PAM-13 will be personalized, depending on the specificities of each context, in order to encourage acceptability by the nursing staff involved in the project. This preimplementation analysis will be carried out via a qualitative study through semistructured interviews.
2. Once this step is complete, the second step of enrolling patients in the study can begin. The patient will be included in the study for a period of 12 months. During his or her involvement, the patient care pathway will be studied, particularly to collect all relevant contacts of oncology nurses and other health professionals involved in the cancer care pathway. The axes of nursing care will also be collected. The primary goal is PAM-13. Secondary factors to be measured are the patient's level of anxiety according to the Hospital Anxiety and Depression (HAD) scale, the assessment of patients' quality of life as measured by the European Quality of Life-5 Dimensions-3 Level (EQ-5D-3L) questionnaire, and the level of health literacy using the REALM-R. The oncology nurses in charge of treating the patient in the cancer care pathway will be responsible for completing each of the questionnaires when the patient is at the hospital for his/her intravenous chemotherapy or immunotherapy treatment. The questionnaires will be completed 3 times in the course of 1 year: (1) at the time of the patient's enrollment in the study, (2) at 6 months, and (3) at 12 months.
3. Finally, at the end of the study period and patient follow-up, a postimplementation analysis will be performed through semistructured interviews, using the TDF to probe implementation problems at each site. Four implementation elements will be measured within the framework of RE-AIM: reach the population (R), effectiveness of the intervention (E), adoption and adaptation of the intervention to its context (A), and maintenance of the intervention (M) [66].

Research Design

Step 1: Preimplementation Analysis

Qualitative data will be collected in the form of individual semistructured interviews, with oncology nurses involved in setting up and conducting PAMs in different comprehensive cancer centers. This qualitative phase will take place before implementation. According to Malterud, qualitative research offers strong potential to understand a problem in all its dimensions from all angles and to study a phenomenon not yet documented. In addition, the production of qualitative data is essential to be able to question the caregivers' representations [67]. It will enable us to assess the evolution of the perceptions of the nurses' teams concerned in this study, the activation of the patients, the perception of their own roles, and their perceived and actual implications in this project. Ten

semistructured interviews will be scheduled at each center. The special feature of TDF is that it specifically questions individual motivation and capacity factors, in addition to taking into account the physical and social environment of the context concerned by the implementation [68]. We will perform a qualitative analysis based on TDF to (1) build the semistructured interview grid [68,69], (2) conduct a qualitative analysis [70], (3) diagnose obstacles and facilitators to implementation [68], (4) draw up the intervention to ensure better acceptability, linking the TDF to the COM-B model and then to the Behavior Change Wheel [69].

Qualitative data will be analyzed in order to generate themes, that, in poststudy findings, can be associated with the TDF [68,69,71-74]. Specifically, we will apply the methodology framework proposed by Braun and Clarke [75].

1. Familiarization with the data: This phase involves reading and rereading the data to become immersed and intimately familiar with its content.
2. Generating initial codes: This phase involves generating succinct codes that identify important features of the data that might be relevant to answering our research question. It involves coding the entire data set, and after that, collating all the codes and all relevant data extracts together for later stages of analysis. Nvivo 11 pro software (QSR International) will be used to perform the analyses.
3. Searching for themes: The collection of codes will be worked on in pairs with a PhD researcher in sociology to validate a comprehensive interpretation and a grouping of code elements into themes.
4. The resulting themes will be compared to the TDF domains, independently by 2 researchers, and then compared and discussed. Items that could not be included in the TDF framework will be thematized separately.
5. Finally, a more refined coding will be used for each part of the verbatim used to illustrate the themes.

The COREQ (consolidated criteria for reporting qualitative research) will guide the reporting of the qualitative analysis [76].

Step 2: Implementation of the PAM-13 and Patient Enrollment

Number of Subjects Needed

As this is an implementation study, it is not possible to calculate a sample size required to respond to an efficacy hypothesis. The goal is to observe how many patients will be involved in the measurement of PAM-13 in real life. It is therefore not possible at this juncture to determine a set number of patients to be reached before ending the study.

Nevertheless, in order to stay within the confines of the study budget, it seems reasonable to limit the number of enrollments to approximately 150 patients per center in order to have a sufficient understanding of the implementation of the PAM-13 in the different facilities. A total of up to 600 patients will be included in the 5-site study (up to 150 patients per site). Two establishments will include a maximum of 75 patients per site.

We will implement the PAM-13 at each center and the study may begin enrolling patients, as outlined below.

Screening and Inclusion

The oncologists, and, as a priority, the cancer nurse navigator (if the establishment employs one) or an oncology care nurse involved in the announcement of the diagnosis, and finally, a registered nurse at the choice of the investigator of the different investigative centers will suggest patients who meet the inclusion criteria to participate in the PARACT study. First, the procedure and aim of the study will be explained to the patient, and then, he or she will be given a consent form to sign. Patients will have a period of reflection of at least half an hour—seemingly sufficient—considering the extremely low risk factor of participating in the PARACT study. The patients' inclusion must be completed within 15 days of the consultation to announce the cancer pathology. The patient will be included in the study for a period of 12 months. During his or her involvement, the patient care pathway will be studied, particularly to collect all relevant contacts of oncology nurses and other health professionals involved in the cancer care pathway. Axes of nursing care will also be collected. The primary goal is PAM-13. Secondary factors to be measured are the patient's level of anxiety according to the HAD scale, the assessment of patients' quality of life as measured by the EQ-5D-3L questionnaire, and the level of health literacy by using the REALM-R screening instrument. The oncology nurses in charge of treating the patient in the cancer care pathway will be responsible for completing each of the questionnaires when the patient is at the hospital for his/her intravenous chemotherapy or immunotherapy treatment. The questionnaires will be completed 3 times in the course of 1 year: (1) at the time of the patient's enrollment in the study, (2) at 6 months, and (3) at 12 months.

Patient Inclusion Criteria

The inclusion criteria for this study are as follows. The patient must be at least 18 years of age upon enrollment. The patient with cancer must have an estimated life expectancy of at least one year. The patient must be undergoing treatment involving intravenous chemotherapy or immunotherapy for any cancer or both of them as outlined in the decision of the multidisciplinary concertation meeting. The patient must be affiliated with a health insurance policy or entitled to social security coverage.

Patient Exclusion Criteria

Patients are excluded from this study for any of the following reasons. The patient has declined to participate. The adult patient is protected under legal guardianship or curatorship. The patient is unable to understand the procedure of the study. The patient has presented prior documentation indicating cognitive or psychiatric disorders. The patient does not understand the French language.

Validity and Reliability of the Questionnaires

The PAM-13 was developed by Hibbard et al to assess knowledge, skills, and confidence in managing health [30,31,77]. It is used in several contexts of disease and in many countries around the world [31,33-39]. Specifically, Prey et al have demonstrated its reliability and validity with inpatient

individuals in oncology [40]. The validated French version will be used. The HAD scale will be used to measure the evolution of patients' anxiety [78]. The United Kingdom National Health Service and French National Authority for Health recommend its use to assess anxiety and depression among inpatient individuals. Its reliability and validity are widely recognized [78-80]. The EQ-5D-3L is a validated tool for measuring the quality of life [81]. Several studies have been published and have provided evidence to support the validity and reliability of the EQ-5D in studies of cancer [82]. This self-questionnaire explores 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and worry/pressure. The REALM-R test validated in French will be used to measure the level of patients' health literacy. Bass et al provided evidence to support the validity and reliability of the shortened version of the REALM, which is named as REALM-R [26]. Grandjacquot recently adapted it in the French language, and it proved effective in detecting inadequate levels of health literacy [27].

Step 3: Evaluation of the Implementation

First, at the end of the inclusion period and patient follow-up, a postimplementation analysis through semistructured interviews using the TDF to investigate implementation obstacles and facilitators at each site will be performed. The same sample and qualitative analysis methodology as that relating to the preimplementation analysis will be used.

Second, 4 implementation outcomes will be measured. These outcomes would have been collected over the entire study by using the RE-AIM [66]. See overview of the implementation outcomes from the RE-AIM (Multimedia Appendix 1).

Statistical Analysis

Design

The analyses will be performed using R 3.2.5 (R Foundation [83]) software. The characteristics of the patients will be described using the following statistics: for quantitative variables, number of available data, means, standard deviation, median, quartile 1, and quartile 3; and for qualitative variables, absolute and relative frequencies (expressed as percentage). To calculate patient activation, the guidelines provided by Insignia Health will be followed [84]. Activation will be measured quantitatively at enrollment, at 6 months, and at 12 months. The difference will be calculated between the baseline measurement and the 12-month measurement for all patients at each center. The mean of this difference will be compared between the comprehensive cancer center that employs a nurse navigator and each of the 4 other facilities. Activation will also be compared according to its evolution during the 12 months of follow-up by using a mixed linear model. The variables influencing the difference in the activation score will be included in this model. The search for factors influencing the activation level will be carried out using the following methods:

1. Initially, univariate analysis with chi-squared tests (or Fisher exact if the conditions are not met) for qualitative variables and Student two-sided *t* test (or Wilcoxon test if the conditions are not met) for quantitative variables will be performed.
2. Subsequently, multivariate analysis with all exploratory variables with a significance threshold lower than 0.2 will be introduced into the multivariate model. The interactions between the variables will be ensured in advance. If an interaction is detected, the choice of the variable to be introduced will be made based on clinical relevance. The choice of the best multivariate model will be made using a selective downward procedure on the Akaike information criteria.
3. Health literacy will be assessed via the score obtained by the REALM-R (a score <6 demonstrating a low health literacy score). The before/after health literacy increase will be assessed using a McNemar chi-square test using the score qualitatively (threshold at 6). A logistic regression model with random effect will be used in the multivariate analysis to eliminate any confounding factors with the same methodology as described above. The same methodology will be applied to the HAD scale (threshold at 11). The analysis of quantitative scales such as the EQ-5D-3L or the confidence level will be performed with matched (or otherwise Wilcoxon) Student tests between inclusion and M12. Random multivariate linear models will be implemented to adjust for any confounding variables. For the EQ-5D-3L, analyses of time until deterioration can be implemented if necessary.

Degree of Statistical Significance

The results will be considered significant at the 5% threshold.

Methods for Considering Missing, Unused, or Invalid Data

No imputation of missing values will be performed.

Ethical Considerations

Declarations indicating that the research will be conducted in accordance with the protocol and good practice and legislative and regulatory provisions are in force. The protocol is in accordance with the principles of ethics established by the 18th World Medical Assembly (Helsinki 1964) and the amendments established at the 29th (Tokyo 1975), 35th (Venice 1983), 41st (Hong Kong 1989), 48th (Somerset West 1996), 52nd (Edinburg 2000), 54th (Washington 2002), and 59th World Medical Assembly (Seoul 2008) and reviewed at the 64th World Medical Assembly (Fortaleza 2013). The protocol will be conducted in accordance with the International Conference of Harmonization guidelines of Good Clinical Practice.

Results

This study was supported by a grant from the French Ministry of Health (PHRIP PARACT 2016-0405) and the Lucien Neuwirth Institute of Cancerology of Saint-Etienne, France. Patients' data collection for this study has been ongoing since 2018.

Discussion

The purpose of this project is to implement the PAM-13 within oncology nursing practices at 5 comprehensive cancer centers. To our knowledge, no measurement of patient activation has

been used in routine practice or has been experimented in cancerology in France. Analyzing the impact of nursing intervention through such a measure, depending on the type of facility, could lead to strengthening some of them, modifying care practices, and enabling better patient management. In the end, this evaluation via the PAM-13 should allow for a greater understanding of the contribution of these specific nursing interventions of care, the objective being to confirm better activation of the patient in establishments that use a combined set of measures.

The use of an activation measure would constitute a major change in the management of patients with cancer. As the patient's activation is evolutive, the implementation of targeted nursing interventions would increase the activation. A number of programs have demonstrated their ability to increase the level of patient activation [85-87]. They generally focus on the acquisition of new skills by patients and support a sense of ownership of their health. These different research studies showed that peer support, changes in the patient's social environment, coaching, and health education courses have been deemed valuable [85-87]. Furthermore, measuring the level of activation and the implementation of measures intended to increase the level of activation would constitute a significant advantage in reducing social health inequalities [88]. Indeed, different studies having implemented this type of intervention have shown that the patients who experience the lowest activation levels are those who tend to show the greatest increase in the activation level [46]. This may be partially due to a "ceiling" effect; not much improvement can be made in patients who already demonstrate high levels of activation. However, this also shows that effective interventions can help disengaged patients become proactive toward their health [85,89,90].

Finally, we assume that studying the implementation of a tool for measuring the degree of activation of the patient of nursing practices in oncology would enable a dynamic evaluation of changes in the patient's cancer care pathway in order to optimize the latter. The implementation methodology using the RE-AIM evaluation framework would specify the real-life efficiency of the PAM-13, the different adaptations of the centers that have implemented it routinely, the key success factors and pitfalls to avoid, and the various parameters impacting its efficiency [66]. Due to the study and its resulting detailed and analytical description of the contents of the use of the PAM-13 in the comprehensive cancer center concerned, we will produce recommendations for the dissemination of such an intervention in order to manage the deployment of an activation measurement for all new patients with cancer at any requesting facility.

In conclusion, this study of implementation conducted at 5 French comprehensive cancer centers could help define a new strategy for sustaining patients' empowerment in the cancer care pathway. The use of a PAM would constitute a notable change in the management of patients with cancer. Systematic integration of the measure should make it possible to implement targeted oncology nursing interventions, strengthening some of them in order to offer patients a personalized cancer care pathway adapted to their needs. Indeed, with the arrival of immunotherapy combinations, it appears essential to focus on patients' empowerment in the management of their medical care. Moreover, the measurement of the level of activation and the implementation of measures to strengthen such activation would constitute a significant advantage in reducing social health inequalities.

Acknowledgments

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Authors' Contributions

FC and EV conceived the study. All authors were involved in the design of the PARACT study. RR is the chief investigator of the study. EV is the project manager. WBE is the clinical research manager, managing ethics, multicentric monitoring, and study recruitment. CM is the institutional person of reference of the PARACT study. EV wrote the first draft of the paper, and all authors provided critical input and revised drafts. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Overview of the implementation outcomes from the RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) framework.
[DOCX File , 16 KB - resprot_v9i12e17485_app1.docx]

Multimedia Appendix 2
SPIRIT checklist.
[PDF File (Adobe PDF File), 74 KB - resprot_v9i12e17485_app2.pdf]

Multimedia Appendix 3
Peer-review reports from DGOS-France, translated in English.
[PDF File (Adobe PDF File), 30 KB - resprot_v9i12e17485_app3.pdf]

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Abbreviations

COM-B: Capability, Opportunity, Motivation, and Behavior
EQ-5D-3L: European Quality of Life-5 Dimensions-3 Level
HAD: Hospital Anxiety and Depression
PAM-13: Patient Activation Measure-13 item
PARACT: PARAmedical Interventions on Patient ACTivation
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
REALM-R: rapid estimate of adult literacy in medicine-revised
TDF: Theoretical Domains Framework

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Proposal

Mitigating Health Risks to Reopen a Clinical Research Laboratory During the COVID-19 Pandemic: A Framework

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Abstract

Background: The COVID-19 pandemic has led to many countries implementing lockdown procedures, resulting in the suspension of laboratory research. With lockdown measures now easing in some areas, many laboratories are preparing to reopen. This is particularly challenging for clinical research laboratories due to the dual risk of patient samples carrying the virus that causes COVID-19, SARS-CoV-2, and the risk to patients being exposed to research staff during clinical sampling. To date, no confirmed transmission of the virus has been confirmed within a laboratory setting; however, operating processes and procedures should be adapted to ensure safe working of samples of positive, negative, or unknown COVID-19 status.

Objective: In this paper, we propose a framework for reopening a clinical research laboratory and resuming operations with the aim to maximize research capacity while minimizing the risk to research participants and staff.

Methods: This framework was developed by consensus among experienced laboratory staff who have prepared to reopen a clinical research laboratory.

Results: Multiple aspects need to be considered to reopen a clinical laboratory. We describe our process to stratify projects by risk, including assessment of donor risk and COVID-19 clinical status, the COVID-19 status of the specific sample type, and how to safely process each sample type. We describe methods to prepare the laboratory for safe working including maintaining social distancing through signage, one-way systems and access arrangements for staff and patients, limiting staff numbers on site and encouraging home working for all nonlaboratory tasks including data analysis and writing. Shared equipment usage was made safe by adapting booking systems to allow for the deployment of cleaning protocols. All risk assessments and standard operating procedures were rewritten and approved by local committees, and staff training was initiated to ensure compliance.

Conclusions: Laboratories can adopt and adapt this framework to expedite reopening a clinical laboratory during the current COVID-19 pandemic while mitigating the risk to research participants and staff.

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KEYWORDS

clinical laboratory; risk assessment; COVID-19; SARS-CoV-2; framework; research; risk; lab; safety

Introduction

The novel coronavirus SARS-CoV-2, causing the disease COVID-19, emerged from China in December 2019 with the World Health Organization declaring the outbreak a public health emergency of international concern on January 30, 2020. Since then, many countries have implemented lockdown measures with only essential work allowed. This has impacted many workplaces, including laboratories, which have had to suspend research. With lockdown measures being gradually eased, many laboratories are now preparing to reopen. Reopening clinical research laboratories in the wake of COVID-19 presents a particular challenge because many patients' biological samples are likely to have an unknown SARS-CoV-2 status at the time of sampling. The Advisory Committee on Dangerous Pathogens have classified SARS-CoV-2 as a HG3 (Hazard Group 3) pathogen [1]. This requires specific procedures to be implemented under stringent safety approval processes. Many laboratories will not meet the specific requirements needed to handle and process samples that are COVID-19 positive or have unknown status. The transmission risks and pathogenicity of this virus is still unclear. However, there is growing scientific evidence on many aspects of the virus biology, and this has helped to inform public health measures including the reopening of workplaces.

SARS-CoV-2 is capable of human to human transmission, with aerosol transmission of the virus also documented [2-4]. The virus is mainly spread through inhalation of respiratory droplets produced when an infected individual coughs or sneezes [5-7]. Respiratory droplets can also contaminate surfaces, and as such, fomite transmission can occur. Current evidence indicates that the virus may survive up to 72 hours on stainless steel and plastic with a half-life of approximately 5.6 hours and up to 24 hours on cardboard and up to 4 hours on copper [4]. However, whether the virus is still capable of causing infection over this time course has yet to be demonstrated. The half-life of SARS-CoV-2 in aerosols was shown to be approximately 1.2 hours [4]. To prevent spread, current government guidelines specify a social distance from persons not from the same household of 1-2 meters and encourage regular hand washing for at least 20 seconds in soapy water [8].

The clinical symptoms of COVID-19 are varied, ranging from no symptoms (asymptomatic) and those mimicking a common cold to a severe respiratory disease including pneumonia and progression to acute respiratory distress syndrome. Early symptoms of COVID-19 are characterized by one or more of the following: a persistent cough, a fever, and a change in or loss of taste and/or smell [9,10]. Current government guidelines state that if one of more of these symptoms is experienced, a person must self-isolate for 14 days. Evidence suggests a temporal pattern of viral shedding with viral load at its highest shortly after disease onset with a gradual decrease over time [11,12].

To date, the evidence on the role of asymptomatic carriers in SARS-CoV-2 transmission is unclear. However, the virus has been detected in individuals who do not exhibit any symptoms of the disease [13]. Until more is known, it is important to consider the possible risk of asymptomatic carriage when assessing the risks to individuals within a workplace. In the laboratory setting, it may not be possible to test patients prior to biological sample donation.

Levels of viral RNA (ribonucleic acid) detected in blood samples appear to be low [14]. In a study carried out on 307 blood samples from patients with COVID-19, only 1% tested positive via polymerase chain reaction (PCR). No viral RNA was detected in urine samples from the same patients [15]. These sample types therefore pose a lower risk to individuals handling them compared to respiratory tract samples. Bronchoalveolar lavage fluid specimens and sputum samples showed the highest viral loads detected with 93% and 72% of samples with a positive PCR result, respectively [15]. Upper respiratory tract samples, nasal swabs, and pharyngeal swabs have been routinely used for testing during the COVID-19 outbreak. A study comparing viral detection in nasal swabs and saliva samples in persons not displaying any obvious clinical signs of COVID-19 found that not only was the virus detected in saliva samples, but that the cycle threshold (Ct) values were lower than that of throat swabs from the same individuals, suggesting that viral load may be higher in saliva than in throat swab samples. Individuals testing positive by saliva samples later went on to develop clinical symptoms [16].

To date, no confirmed transmission of the virus has been confirmed within a laboratory setting. However, laboratory work must be altered, and the appropriate processes and procedures need to be put in place to ensure a safe working environment if samples are of positive or unknown COVID-19 status.

SARS-CoV-2 is easily destroyed by alcohol [17] and soap [18] due to disruption of the protein envelope. Therefore, handwashing remains an extremely effective way of breaking fomite transmission; 70% ethanol is an effective disinfectant within a laboratory setting.

There remain considerable uncertainties in reopening clinical research laboratories that process human samples and have a disease-based focus. Resuming laboratory activities including sample taking and processing requires consideration of a number of risks, which, broadly speaking, can be divided into:

- Risks to the research participant (in attending the clinical laboratory setting and being close to research staff or other research participants)
- Risks to the research staff (from exposure to patients, processing samples, and working with others in a laboratory facility)

This paper provides a suggested framework that may inform how clinical laboratory operations can be resumed with the aim to maximize research capacity while minimizing the risk to research participants and staff.

Methods

This framework was developed by consensus among experienced laboratory staff who have prepared to reopen a clinical research laboratory. Staff included 1 consultant in

respiratory medicine and professor of acute and respiratory medicine, 1 respiratory registrar, and 8 immunologists working in a translational laboratory.

Results

Project Classification and Risk Assessment

To allow resumption of research as quickly but safely as possible, studies/projects should be stratified into categories by risk. This includes the participants' demographics, medical history (with relevant bodies providing definitions of the levels of risk depending on disease area and severity [19,20]) and the likely COVID-19 status of the sample (positive, negative, or unknown). Ethically approved protocols may require amendments to incorporate these factors to mitigate risk where possible. It is also important to consider the status of the building that participants will be entering (hot, cold, or mixed site), and their ingress and egress routes through the facility. We recommend a risk assessment for every participant, which includes consideration of their medical history, likelihood of having COVID-19 (based on screening questionnaires), and the samples to be collected.

Assessment of Donor Risk and COVID-19 Clinical Status

Clinical research often requires samples from individuals presenting with existing medical conditions, which may predispose them to a more severe outcome if infected with SARS-CoV-2 [21-23]. These include demographic factors such as age [23,24], ethnicity [18], and smoking status [24-26]. It is important to identify which potential donors are high risk prior to attending clinical or research spaces in accordance with current government guidelines and initially prioritizing research participation for those deemed at less risk, if possible.

Some participants will have a COVID-19 swab taken as part of their routine care (such as those admitted to hospitals or where directed by clinical care pathways). Where the participant is known to have COVID-19 infection, the risk to staff and the participant from donating samples are known and can be mitigated with appropriate personal protective equipment (PPE) and HG3 laboratory processing. Where COVID-19 is highly suspected clinically but not confirmed by SARS-CoV-2 swab, we recommend treating the sample as though positive, as per national guidelines.

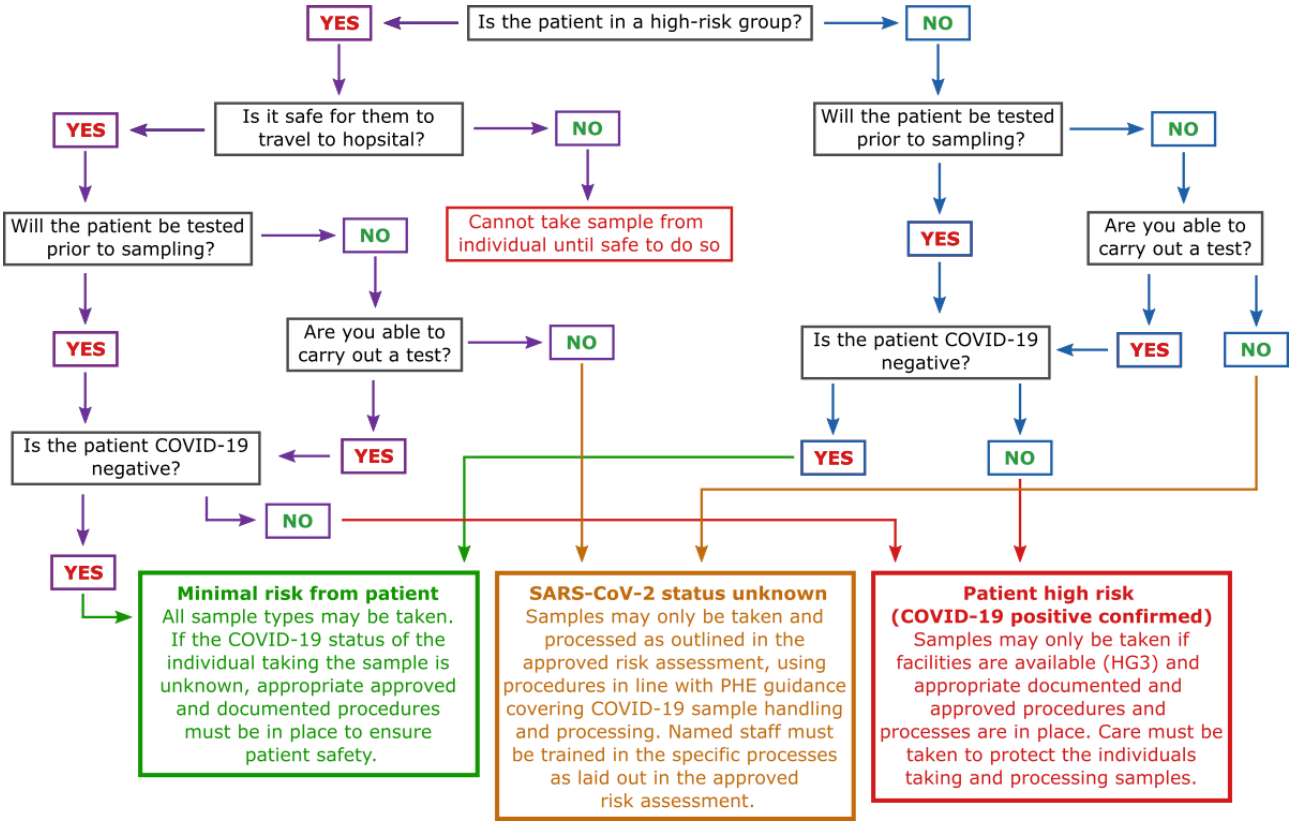
A negative swab cannot fully exclude COVID-19 infection due to the false-negative rates, but when combined with a low clinical suspicion of COVID-19 infection, could be assessed as "COVID-19 unlikely" in status, although many laboratories would still suggest using enhanced category 2 (Cat2+) for processing.

In some instances, the COVID-19 status of the participant will be unknown (with no swab taken). Screening questionnaires to identify and avoid participants with potential COVID-19–related symptoms may help mitigate risk further, and following that, if clinical suspicion is low, Cat2+ processing should still be considered.

We propose a simple workflow (Figure 1) to aid in stratifying donor groups by risk and capacity of the laboratory for handling high-risk pathogens.

In brief, research donors may be screened remotely by an appropriately trained health care professional prior to presenting at the clinic to determine medical conditions, which may increase risk and active symptoms or known exposure to COVID-19. An example of this is presented in Multimedia Appendix 1. Once the health care professional is reassured that the individual is not an obvious risk, they may be invited to attend the clinic. Upon arrival, the individual should be reassessed to identify characteristic COVID-19 symptoms and signs such as an elevated temperature. If resources allow, individuals presenting both with or without clinical symptoms may be tested using an approved and recommended test such as PCR to confirm COVID-19 status, in the understanding that the time between swab and result may necessitate multiple patient visits to the research department. In the event that a test is not available or feasible, samples from patients with low clinical suspicion of COVID-19 may be taken for research. However, the appropriate PPE and procedures must be followed when taking samples which then must still be treated with caution during processing as asymptomatic carriage is common [13].

Figure 1. Donor risk flow diagram. Patients are first assessed by phone by a health care professional in the form of a questionnaire. If the patient is unable to be tested for COVID-19, the sample must be processed as status unknown according to Public Health England (PHE) guidance. If the patient can be tested and the test is returned negative, it is safe to assume minimal risk and proceed according to local risk assessments. If the test is returned positive, samples can only be taken if Hazard Group 3 (HG3) facilities are available and proceed according to local risk assessments.



COVID-19 Status of Sample and Risk Assessment

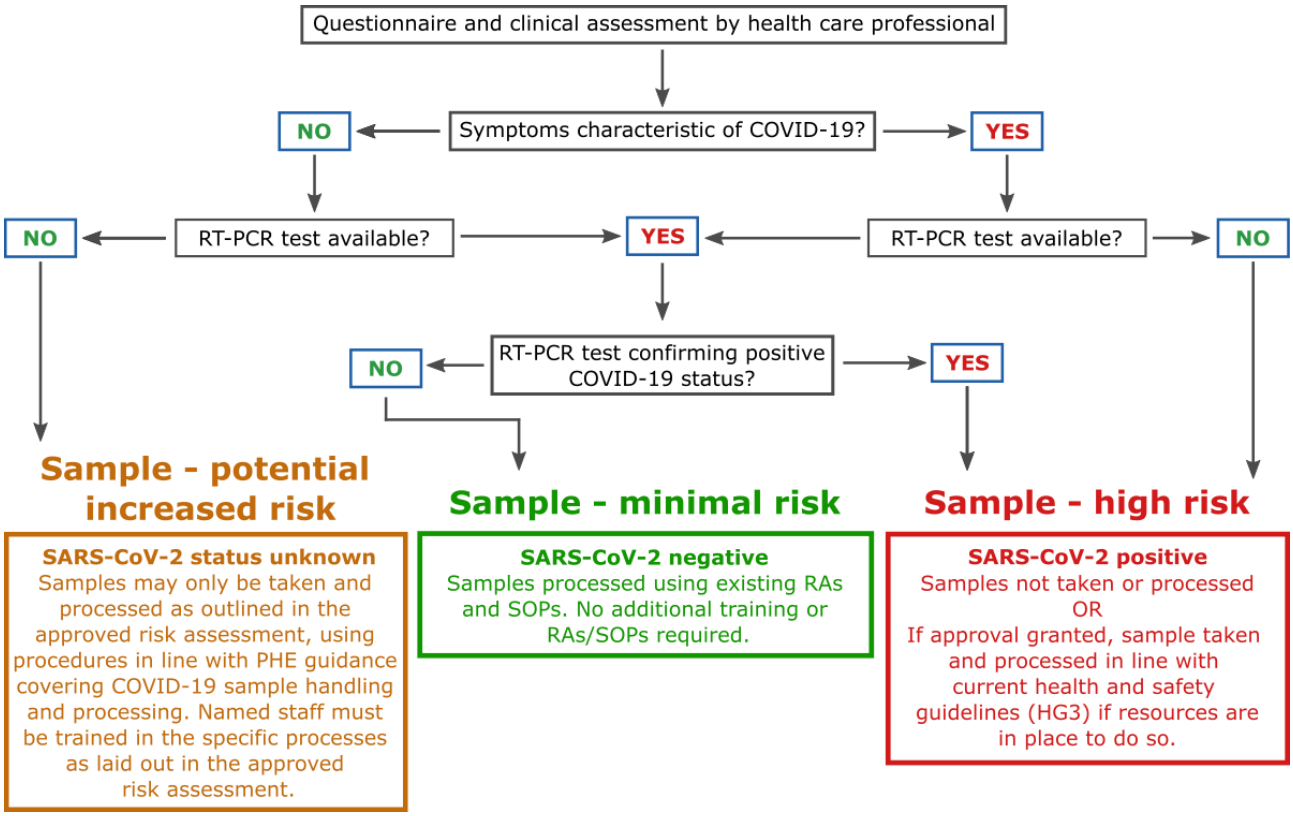
SARS-CoV-2 has been detected in several different clinical sample types, including blood, feces, and respiratory specimens (Table 1). Risk assessments for taking samples such as phlebotomy should be reviewed, amended, and approved before study resumption. Assessing the risk of each sample is imperative, and we propose a tricolor risk alert system as demonstrated in the flow diagram in Figure 2.

Table 1. Viral detection and cultivation of live virus in clinical samples to date.

Sample type	Virus detected by PCR[a]	Live virus cultivated	Reference
Nasal swab	Yes	Yes	Yang et al [27]; Wang et al [15]
Throat swab	Yes	Yes	Yang et al [27]; Wang et al [15]
Saliva	Yes	Yes	To et al [11]
Sputum	Yes	Yes	Yang et al [27]; Wang et al [15]
Bronchoalveolar lavage	Yes	Yes	Yang et al [27]; Wang et al [15]
Lung tissue	Yes	Yes	Wang et al [15]
Feces and rectal swab	Yes	No	Wang et al [15]; To et al [11]
Urine	Yes	No	To et al [11]
Blood	Yes	No	To et al [11]; Wang et al [15]
Sperm	Yes	No	Li et al [28]

[a]PCR: polymerase chain reaction.

Figure 2. Clinical laboratory flow diagram for assessing sample risk. Individuals are first assessed by phone by a health care professional in the form of a questionnaire. If no clear risk is identified, patients may present at a clinic. Here, they will undergo a clinical observation to assess for characteristic symptoms of COVID-19. If resources allow, they may then undergo testing for the virus. The information will identify the risk of a particular patient sample and will inform decisions as to which samples can be taken and which can be processed safely. HG3: Hazard Group 3; PHE: Public Health England; RA: risk assessment; RT-PCR: reverse transcription-polymerase chain reaction; SOP: standard operating procedure.



All samples with an unknown COVID-19 status (even if the risk is assessed as low; eg, whole blood sample from donor who has no clinical symptoms) should be processed under Cat2+ conditions, including use of a class II or class I microbiological safety cabinet in a category 2 laboratory but under aerosol tight conditions. Such procedures are specified in the risk assessment example in the online supplement. Any samples taken out of the cabinet should be placed inside at least two levels of containment. Samples used for processes performed outside of a microbiological safety cabinet such as flow cytometry or RNA extraction should first be inactivated or fixed by an approved and tested method such as 4% paraformaldehyde [25]. This should be documented in standard operating procedures and risk assessments. Any procedures involving the possible production of aerosols such as pipetting, vortexing, flow cytometry, and centrifugation should be risk assessed and the appropriate, approved procedures implemented. Samples may only be processed if the infrastructure and experience of staff allows for it.

Cells from samples of unknown COVID-19 status must not be put into culture as this may inadvertently result in amplification of the virus if it is present [29-31].

High-Risk Patients and Samples

Any sample from an individual with confirmed COVID-19 must be classified as high risk and treated as such. The highest viral loads have been detected in respiratory specimens [15], and as such these samples are deemed high risk if the COVID-19 status of the patient is positive or unknown. This includes bronchoalveolar lavage, sputum, and lung tissue samples [31], and therefore we recommend only processing lung tissue if the patient has been screened for COVID-19 and has been confirmed negative or low risk. All high-risk samples must be processed at category 3 level using appropriate containment. If such containment or trained staff are not available, such samples should not be taken or processed. New risk assessments should be written and official safety approval granted before working with high-risk specimens.

High-Risk Patients and Lower-Risk Samples

Viral presence in blood and urine has been shown to be varied; however, current evidence suggests that the virus is not always detectable in the blood or urine of COVID-19–confirmed cases. When it is, levels are low with no current evidence of infectivity from these samples. These sample types are therefore at a lower risk than respiratory samples. These samples can be processed within the context of amended risk assessments and official safety approval and in line with current safety guidelines, which will inform laboratories of the containment level required. Under current guidelines, this mandates Cat2+ conditions, operating under aerosol-free conditions at all times.

Low-Risk Patients

Samples taken from individuals with a confirmed COVID-19 negative test result are deemed to pose no added risk. As such, these samples can be processed and handled under the standard laboratory operating procedures with risk assessments and safety

approval already in place. No further action is needed beyond the requirement to make the workplace safe as indicated below. Where the status of a patient is unknown, but clinical suspicion is low, we recommend processing within Cat2+ conditions, operating under aerosol-free conditions at all times.

Preparing the Laboratory for Safe Working

Social distancing is vital in a pandemic as discussed in a recent systematic review and meta-analysis by Chu et al [32], where a physical distance of 1 meter reduced the risk of betacoronavirus transmission by 82% and that every additional 1-meter increase in social distance doubled the relative protection. To prevent the risk of transmission between persons and through fomites, adherence to current government social distancing guidelines is necessary. Outlined below are several actionable suggestions to increase the safety of the workforce and to help staff to maintain distancing while maximizing research capacity.

Signage, One-Way Systems, and Access Arrangements

In order to maintain social distance within the laboratory/workplace, clear rules and signage should be put into place as follows:

- Clear signage and demarcations: signs on doors to laboratories, equipment rooms, offices, and toilets to indicate the number of persons inside at any given time. This will ensure that the capacity of the room is not exceeded and will allow persons to only enter the room if the capacity has not already been met. Signage may also indicate which specific working groups occupy a room at any given time. This can be in the form of a magnetic board or white board.
- A knock and call system: a knock and call procedure may be adopted for entering certain areas such as toilet areas.
- One-way systems around the building: if the layout of the workplace allows for this, one-way systems with clear signage will prevent individuals passing each other and will enable staff to maintain social distance while moving around the building. If the layout of the building does not allow this, the corridors may be split in two with directional traffic on each side. Directional systems must be clearly marked.
- Restricted access: it may be desirable to limit access to only specifically trained staff members to be on site. This will ensure that only authorized persons may gain access to the site. Staff should have their staff ID exhibited clearly at all times.

Identifying High-Risk Staff, Limiting Staff Numbers on Site, and Encouraging Working From Home

In order to reduce the risk to staff of catching and spreading the virus, clear rules must be put in place as follows:

- Identifying high-risk staff: there is clear evidence that certain groups of people are at a higher risk of severe illness if they contract COVID-19. In order to protect staff, it is essential to identify any individual who may fall into a high-risk category such as pregnant women or individuals with underlying medical conditions. Prior to returning to work, such individuals must have a meeting with their line manager to discuss potential hazards and work options. They must follow the current government recommendations on shielding of high-risk groups. This may mean that such staff members are temporarily moved onto other projects that only require working from home until it is safe for them to return to the laboratory. Alternatively, if space allows, designated work areas may be provided to avoid contact with other staff members.
- Encouraging working from home: unlike many other workplaces, laboratory work cannot be done from home. However, work such as data analysis, experiment planning, stock ordering, and writing should be done at home where possible. In the event that data analysis requires a specific software, piece of equipment, or there is limited access due to data security, procedures must be followed to make staff members safe as outlined below.
- Limiting the number of staff on site: in order to maintain social distancing, numbers of staff members on site will need to be reduced. This can be done by a combination of facilitating working from home where possible, by implementing a rota system and by prioritizing projects.

Work Pods, Rotas, and Shared Working Strategies

In order to meet social distancing guidelines, clear rules must be put in place as follows:

- Creating working groups (pods): restricting work activity to only occur within a small group of staff will limit spread amongst workers if an outbreak in the workplace does occur. Where possible, staff should be split into pods, whereby only members of each pod can occupy the laboratory or work space together at one time. When pods switch, all common areas must be cleaned. In the event that one member of a pod becomes ill and displays characteristic symptoms of COVID-19, all members of the pod must self-isolate until they have had a test confirming that they do not harbor the virus. Only then may they return to work. Splitting staff members into pods means that if one pod is required to isolate, other pods may continue to work. This helps to maintain research capacity and protects workers.
- Implementing work rotas and shift patterns: in order to meet social distancing rules and to maintain work pods, rotas will need to be established. Frequently changing requirements are common in translational research. As such, work rotas will need constant management to meet as many requirements of staff members as possible without breaking the pod system. We have found a daily rota split into two sessions (8:15 AM to 1 PM and 1:15 PM to 6 PM) is the best option for maximum flexibility. A short time period in between pod switchover will ensure that individual pods do not come into contact with each other when entering and exiting the building. On some days, a pod may take up both sessions. Time must be allocated at the end of each shift to allow for cleaning of the work area to prepare for the arrival of the next pod.
- Teamwork and work sharing: teamwork will be essential in order to complete work within the allotted time frame, as staff may require help from team members. Collaborative experiments will be more common. For example, researchers in Pod A could process blood samples, isolate,

and prepare cells during the first shift, and researchers in Pod B could carry out functional assays on these cells during the second shift.
- Experimental planning: all researchers recognize that time management is a key skill that must be employed to efficiently plan a working day. However, as mentioned above, staff will need to adhere to strict timelines. Therefore, time management and experiment planning will be the key to efficient working. Experimental plans must be made and agreed in advance to allow for rota organization.

Equipment Usage

In order to ensure a safe working environment using shared equipment, clear rules must be put in place as follows:

- Equipment booking systems: to ensure social distancing is maintained, equipment usage should be booked in advance. If online systems are not available for this, a simple shared calendar will meet this need. Only one person should use equipment at any one time and social distance measures must be put in place around the equipment area. Extra time must be added in for each session to allow for equipment cleaning, plus an extra 15 minutes [33] to allow any aerosols to settle before the next person enters the space.
- Removal of nonessential shared equipment: any nonessential equipment such as coffee machines or microwaves in communal areas should be removed.
- Equipment cleaning: all equipment should be wiped down with 70% ethanol before and after use. Cleaning of equipment should be documented to ensure that it is done and to indicate to the next person that the area is clean.
- Equipment maintenance: procedures must be put in place for equipment repair or maintenance. Engineers must only be allowed on site to attend to equipment if it is safe for them to do so. Such individuals must not come into contact with any staff members unless it is absolutely necessary.

PPE and Hand Gel Stations (Staff Hygiene)

In order to limit the risk of transmission, clear rules and signage must be put in place as follows:

- Appropriate PPE as stated in the local risk assessment should always be worn. In the event that social distancing is not possible, masks and goggles may be required. In these instances, a risk assessment should be written and approved and appropriate PPE identified.
- Personal PPE such as lab coats and goggles should be stored separately to prevent cross contamination.
- It may be beneficial to provide hand sanitizers around the workplace. This will encourage staff members to keep their hands clean and therefore help to reduce fomite transmission.

Amended Standard Operating Procedures and Risk Assessments

In order to ensure sample types are handled safely, changes to operating procedures must be made as follows:

- All local risk assessments and standard operating procedures should be reviewed and, if required, amended and reapproved by local committees. All clinical samples should be assessed as recommended in the previous section.
- It is important that samples that are COVID-19 confirmed or of unknown COVID-19 status are stored and labeled appropriately.
- Designated sample reception areas are needed. In order to ensure safety, designated sample reception areas should be established for samples that are COVID-19 positive or those with an unknown COVID-19 status. Such areas should be clearly marked. Appropriate waste receptacles, PPE donning and doffing areas, and disinfectants should be available at these stations. Individuals working in such areas must wear the appropriate PPE as stated in the documentation and the location of the reception area must be selected with social distance measures in mind.

Work Checks

It is important to have a record of which staff members are on site at any given time. This information will be required if an outbreak does occur in the workplace in order to carry out contact tracing and to ensure all the appropriate staff self-isolate if required. It is important to ensure that all staff members adhere to the local rules laid out with appropriate checks conducted to emphasize best practices.

Discussion

These proposed flowcharts and working patterns are suggested to identify and mitigate risk to research participants and staff during the COVID-19 pandemic. The central components of these guidelines are based on advice from Public Health England and the UK government but can be adapted as needed.

Authors' Contributions

EMW, AEJ, LD, KPY, AAF, MJH, HAC, DAS, ES, KBRB, and AS wrote the paper. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Risk assessment.
[PDF File (Adobe PDF File), 358 KB - resprot_v9i12e22570_app1.pdf]

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Abbreviations

Cat2+: enhanced category 2
Ct: cycle threshold
HG3: Hazard Group 3
PCR: polymerase chain reaction
PPE: personal protective equipment
RNA: ribonucleic acid

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Protocol

Long-Term Outcomes of the Good School Toolkit Primary School Violence Prevention Intervention Among Adolescents: Protocol for a Nonrandomized Quasi-Experimental Study

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Abstract

Background: Violence against children in schools is a global public health problem. There is growing evidence that school-based interventions can be effective in reducing violence against children in schools. However, there is little evidence on the long-term impact of such interventions. The Good School Toolkit, developed by Raising Voices, a Uganda-based nonprofit organization, is a whole-school violence prevention intervention that aims to change the operational culture of primary schools. In 2014, the Good School Toolkit was evaluated through a cluster randomized controlled trial (Good Schools Study) and found to reduce teacher-to-student and student-to-student violence.

Objective: This protocol describes quantitative analyses to explore long-term outcomes of the Good School Toolkit intervention among adolescents in Uganda, including the extent to which it is associated with peer-violence victimization (primary outcome) and peer-violence perpetration, intimate-partner violence, acceptance of teacher-violence, equitable gender attitudes, agency, self-regulation, peer connectedness, social assets, psychological assets, and retention in school (secondary outcomes).

Methods: This is a nonrandomized quasi-experimental 4-year follow-up study of adolescents who attended the 42 Good Schools Study primary schools in 2014; 21 schools initiated the Good School Toolkit intervention during the trial from 2012, and 19 schools initiated the intervention after the trial (during the later delivery phase) from 2015; 2 schools did not implement the intervention. Students in the final school grade (Primary 7) during 2014 of the 19 primary schools in the later delivery phase are expected to have left school prior to toolkit delivery in 2015. Wave 1 data were collected in 2014 from 3431 grade Primary 5 to Primary 7 school students aged 11-14 years; these students were followed up in 2018-2019 when aged 16-19 years and invited to participate in the Wave 2 survey. Data were collected in face-to-face interviews by trained Ugandan field researchers. Toolkit exposure groups are defined as exposed during the Good Schools Study trial (from 2012), as exposed during later delivery (from 2015), or not exposed including those expected to have completed Primary 7 prior to later delivery or from the 2 schools that did not implement the toolkit. Associations between outcomes at Wave 2 and toolkit exposure groups will be analyzed using mixed-effect multivariable logistic and linear regression models for binary and continuous outcomes, respectively. This analysis is exploratory and aims to generate hypotheses on if, and under what circumstances, the toolkit influences later adolescent outcomes.

Results: Data collection was completed in August 2019.

Conclusions: To our knowledge, this is the first long-term follow-up study of adolescents exposed to a school-based violence-prevention intervention in sub-Saharan Africa. If the intervention reduces violence and improves other outcomes in later adolescence, then this study supports primary school interventions as key to achieving long-term population impacts. The pattern of effects will inform where reinforced or additional interventions are needed.

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KEYWORDS

violence; long-term follow-up; whole-school; intervention; adolescents; Uganda; resilience; non-randomised

Introduction

Background

Globally, over 1 billion children experience violence every year [1]. In Uganda, 75% of 18- to 24-year-old individuals report violence in their childhood [2], and over half of ever-married women report physical violence from an intimate partner in their lifetime [3]. Violence against children that occurs in school is a global public health problem that takes many forms. It may include physical, emotional, and sexual violence and involve different perpetrators and power dynamics [4]. In Uganda, similar to in other resource-constrained settings, the majority of primary school students have experienced physical violence from a teacher, and almost half have experienced physical, emotional, or sexual violence from a fellow student [5-7]. Negative health, social, and economic outcomes among those who experience violence in childhood have been well described [8]. Furthermore, experiencing violence as a child may lead to a "cycle of violence" with increased aggressive behavior and greater risk of boys perpetrating violence and girls experiencing intimate-partner violence later in life [9]. Uganda's Demographic and Health Survey 2016 indicated that, nationally, 84% of primary school–aged children attend some primary school [3], and 60% of those who complete primary school transition to secondary education [10]. The extent and consequences of violence call for urgent effective violence prevention strategies that can protect against childhood violence and reduce the risk of future violence by supporting positive transitions through adolescence into adulthood [11,12].

Long-Term Effects of School-Based Violence Prevention Interventions

Evidence from high-resource settings suggest that some school-based violence-prevention interventions show promising long-term effects on violence outcomes 3 or more years later [13,14]: Safe Dates, delivered to the eighth-grade students in the United States, reduced dating violence 4 years later [15]; Learning Together, in UK secondary schools, reduced bullying victimization at 36 months [16]; Gatehouse Project, a social-inclusion intervention in Australian secondary schools, reduced risky behavior (a composite measure that included interpersonal violence) after 4 years [17]; Aban Aya Youth Project, a social-emotional program delivered to Grade 5 to 8 students in the United States, reported a reduced rate of increase in violent behavior among boys over 4 years [18]; and Positive Action, a multiple-risk behavior intervention in Hawaii and US eliminatory schools, which reported reduced violent behavior after 3 to 6 years [19,20]. The majority of these interventions have been delivered in secondary schools through a variety of approaches, and outcomes are assessed when students are still in school [13]. Effective pathways from primary school interventions to long-term violence reductions are less understood in resource-constrained contexts. To our knowledge, no whole-school intervention that acts on reducing teacher-to-student violence has been evaluated in terms of long-term impacts after adolescents transition out of primary school.

The Good School Toolkit Intervention

The Good School Toolkit, a violence against children–prevention intervention, was developed by Ugandan nonprofit organization Raising Voices and is freely available for download on their website [21]. It is a complex school-wide intervention that addresses multiple actors and behaviors and was designed to be locally adapted. The intervention is school-led through 2 appointed teacher and student protagonists. Materials are provided along with over 60 interactive and accessible activities that engage the whole school as they sequentially complete the 6 core steps (Textbox 1).

Textbox 1. Good School Toolkit steps [21].

Step One: Your Team & Network

- Schools identify key protagonists at school and create their Good School Committee to build school-wide support for the process (precontemplation)

Step Two: Preparing for Change

- Baseline measurements gather information on each schools' starting point, and school leaders cultivate interest among parents, the community and local education officials (contemplation)

Step Three: Good Teachers & Teaching

- A school-wide reflection on teacher-student relationships provides a renewed sense of teacher roles, increased professional support, and new approaches for positive student engagement (preparing for action)

Step Four: Positive Discipline

- Schools reflect on how violence manifests and establish a new school culture by exploring positive disciplinary methods to create students who believe in themselves (action).

Step Five: Good Learning Environment

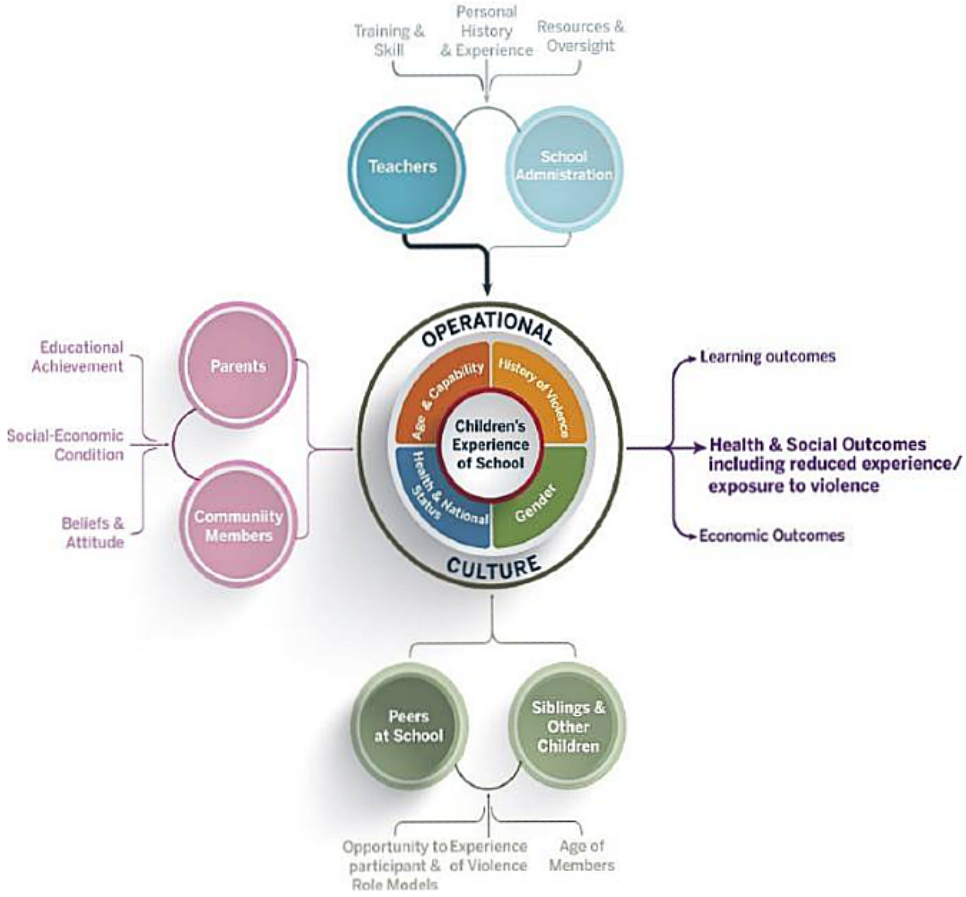
- Schools reflect on what a good learning environment looks like and work with all stakeholders to foster a psychological sense of safety and inclusion (maintenance of action)

Step Six: Good Administration & the Future

- The work of the preceding steps is celebrated and consolidated through reflection and transfer of leadership to the school administration (consolidated gains)

Figure 1 summarizes the toolkit programmatic theory of change [22]. The intervention aims to positively transform operational culture within primary schools. Raising Voices conceptualizes school operational culture as consisting of 3 domains drawn from Moos' [23] interpretation of the social-ecological framework: (1) psychological, referring to attachment, belonging, identification with—and attitudes toward—the school; (2) relational, referring to interpersonal relationships between teachers and students and between students; and (3) structural, referring to policies, administrative infrastructure, and capacity [24].

Figure 1. Good School Toolkit programmatic theory of change.



The Good School Toolkit is one of the few school interventions with a demonstrated impact of reducing school violence in a resource-constrained setting, including teacher-to-student violence [25]. The Good Schools Study included a cluster randomized controlled trial [26,27], qualitative study [28], process evaluation [29], and economic evaluation [30]. During the trial, conducted in Luwero district in Uganda from 2012-2014, the toolkit was delivered to 21 intervention schools that were compared with 21 wait-list control schools. The trial found that the toolkit reduced the relative risk of past-week teacher-to-student physical violence by 42% [27]. Secondary trial analysis found that the toolkit reduced teacher-to-student past-week physical, emotional, or sexual violence (adjusted odds ratio [OR] 0.41, 95% CI 0.26-0.64) and any student-to-student past-week physical, emotional, and sexual violence (adjusted OR 0.70, 95% CI 0.51-0.96) [31,32]. Subsequently (from 2015), the toolkit was delivered to 19 of the wait-list control schools. While the intervention remained the same (see Table 1), during later delivery the intervention was implemented by *resource persons*, trained and supported by Raising Voices, rather than the Raising Voices program team.

Table 1. The Good School Toolkit intervention delivered during the trial and later delivery to study schools.

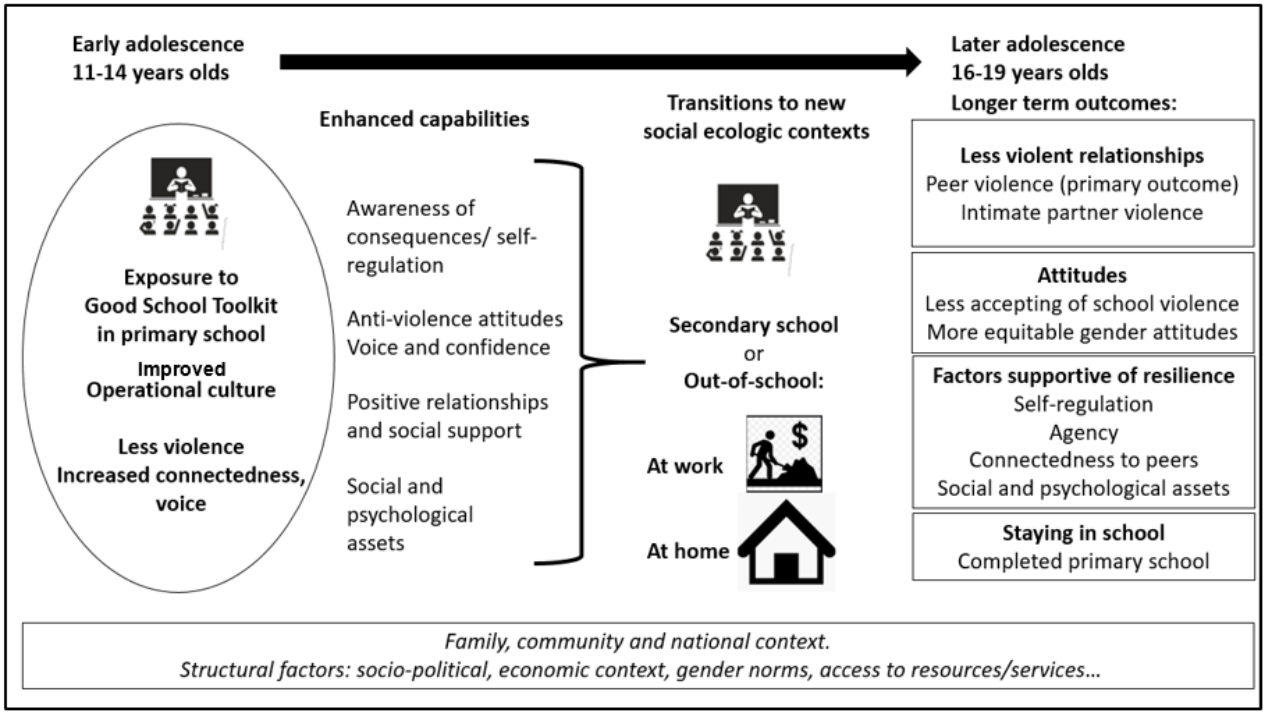
TIDieR [33] guideline	Description of the toolkit
Brief name	Good School Toolkit
Why	The goal of the toolkit was to transform the operational culture at the school level such that violence against children is prevented. The toolkit draws on the Transtheoretical Model [34] and contains behavior change techniques that have been shown to be effective in a variety of fields [35] and have been included in interventions to change teacher behavior in primary schools [36,37] and reduce perpetration of intimate partner violence [38].
What-materials and content	The toolkit materials consist of books, booklets, posters, and facilitation guides for about 60 different activities. These activities are related to creating a better learning environment, respecting each other, understanding power relationships, using nonviolent discipline, and improving teaching techniques. All materials are publicly available online. Specific behavior change techniques for staff, students and administration included setting school-wide goals, developing action plans with specific dates for deliverables, encouraging empathy by facilitating reflection on experiences of violence, providing new knowledge on alternative nonviolent discipline, and providing opportunities to practice new behavioral skills. Schools were encouraged to self-monitor their progress according to their action plans. Reinforcement of new information and ideas, feedback on progress, and modeling of new techniques and behaviors were provided by visits from the Raising Voices team and also within the school by protagonists to their peers as they gained new knowledge and skills. Children actively participated and formed committees and groups related to different activities. Schools rewarded the successful achievement of their goals and action plan deliverables by creating celebrations. Social support for behavior change was also created because the intervention engaged multiple groups within a school (teachers, administration, students, and also parents) to change ideas and attitudes.
What-procedures	Following a school's agreement to participate, an inception visit of 2 hours was held, where Raising Voices introduced the toolkit to all school staff. Once the schools were committed to implementing the toolkit, at least 2 staff protagonists were identified who attended a 3-day residential workshop. During this workshop, the protagonists became familiar with the toolkit and developed an action plan for their school. Raising Voices staff members then provided direct one-on-one support and mentorship to key staff protagonists students and at least 2 key student protagonists in each school to carry out the action plan. The toolkit itself has 6 steps, which were designed to be implemented in sequence to guide schools through a systematic process of change. Protagonists could choose which activities they implemented but should complete a minimum number from each step before moving on to the next.
Who provided	Delivery to trial schools: Raising Voices program staff members were trained facilitators and advocates and had received approximately 100 hours of training with individualized coaching support to understand the ideas and content of the toolkit. Later delivery to schools: Raising Voices resource persons were experienced consultants, usually working within the education sector who received at least 20 hours of training and then subsequent individualized coaching support by Raising Voices program staff to understand the ideas and content of the toolkit and how to provide support to school-based protagonists. The key protagonists in each school were 2 teachers who receive 3-day residential workshop based training and ongoing support.
How	During the intervention, Raising Voices staff or resource persons provided direct one-on-one support in the form of in-person visits and telephone calls to staff protagonists, and in-person visits to student protagonists. Staff and student protagonists conducted face-to-face activities with other staff and students in their school, mainly in groups. Children and staff members encouraged others to form, lead, and join groups for various intervention activities.
Where	Activities with students and staff were conducted in schools. Some activities involved creating a better school environment by painting murals on school walls and hanging codes of conduct in visible places; however, the intervention does not require any physical infrastructure.
When and how much	Raising Voices staff made in-person visits to protagonists in each school quarterly and telephoned school staff members approximately monthly, although this varied slightly depending on need. The toolkit itself was designed to be implemented flexibly, and there was no prescribed number of activities or set schedule upon which they should be implemented. However, schools should proceed in sequence and conduct a minimum number of activities, which depends on the stage, prior to progressing to the next stage.
Tailoring, modifications, fidelity	The toolkit was specifically designed to be flexible and adaptable to individual schools. To ensure more uniformity during the trial, Raising Voices staff visited each school at least once per school term, conducted a 3-day residential workshop with all teacher protagonists, met with protagonists to review progress after 1 to 2 terms of implementation, and held meetings with protagonists so they could learn from each other.

Long-Term Effects: Conceptual Framework

A schematic that illustrates mechanisms through which the Good School Toolkit may achieve long-term effects is shown in Figure 2. The Good Schools Study's quantitative and qualitative findings suggested that the toolkit intervention improved the schools' operational culture and enhanced student capabilities, including improvements in student-teacher relationships; fostered attitudes that were less accepting of teacher violence; enhanced emotional support from peers;

allowed enhanced school-connectedness; and improved self-regulation, voice, and motivation [28,31,39-41]. We hypothesize that students who experienced the toolkit intervention during their primary education (ie, were exposed to a supportive culture and less violence in a safer school environment) are less likely to drop out of school and therefore are retained in the education system for longer. Furthermore, we hypothesize that students' enhanced capabilities—brought about by the toolkit intervention—can be retained through the transition out of primary school into new environments, equipping adolescents with individual skills supportive of resilience. Through these positive changes brought about by exposure to the toolkit intervention, we hypothesize that adolescents will have attitudes that are less accepting of violence, will be more gender-equitable, and will be less likely to perpetrate or experience peer and intimate partner violence in later adolescent relationships.

Figure 2. Schematic illustrating the toolkit intervention long-term effects conceptual framework.



Adolescents' interactions within supportive social ecologies are important for both positive development and resilience [39,42]. Environments outside of primary school are also likely to influence adolescents' trajectories, in particular, family support, economic pressures, and violence experienced outside of school. As adolescents transition out of primary school, experiences in new secondary schools, the workplace, and domestic contexts are expected to affect adolescents' outcomes. While enhanced capabilities may support Ugandan adolescents in navigating risk of violence and collectively advocate for change, this is largely limited by gender-related vulnerabilities within shifting risk environments [43]. In addition, adolescents' negotiations and need for support, resources, and services may not be met by family, school, workplace, or the community systems, which are all subject to wider structural factors [44]. Consequently, the economic and sociopolitical contexts, gender norms, and access to safe secondary education or employment are expected to influence adolescents' opportunities for positive adaptations and agency in Uganda [45].

Research Questions

We aim to evaluate long-term effects of the Good School Toolkit, specifically whether exposure to the toolkit intervention in early adolescence is associated with (1) less violent relationships in later adolescence, including peer-violence victimization (primary outcome), peer-violence perpetration, and intimate-partner violence victimization among female adolescents and perpetration among male adolescents; (2) lower acceptance of teacher violence and more equitable gender attitudes in later adolescence; (3) factors supportive of resilience in later adolescence (enhanced agency, self-regulation, peer connectedness, and social and psychological assets); and (4) increased retention in school.

Methods

Design

The proposed quantitative analysis makes use of the variation in the Good School Toolkit intervention delivery to create a nonrandomized quasi-experimental design, comparing outcomes across levels of toolkit exposure. This analysis is exploratory and aims to generate hypotheses on if, and in what circumstances, the toolkit influences later adolescent outcomes. To better understand how context and structural factors may influence later outcomes, further quantitative and qualitative analysis is planned and will be informed by this analysis.

Sampling, Intervention Delivery, and Survey Assessments

The original Good Schools Study trial sampling is fully described elsewhere [26]. In summary, we used the 2010 list of 268 government and nongovernment primary schools in Luwero district, obtained from the Ministry of Education. Eligibility criteria were school size (>40 Primary 5 students) and having no existing interventions. Of 151 eligible primary schools that were identified and stratified into 3 groups based on the student male to female ratio (>60% girls, >60% boys, or approximately even), 42 schools were randomly selected proportional to the size of stratum. All selected school headteachers agreed for their school to participate. After the trial baseline survey in 2012, stratified block randomization was used to allocate schools to receive the intervention immediately or to be wait-listed to receive the intervention after the end of the trial (Figure 3). Stratified randomization was used to ensure balance regarding the following key factors: baseline violence, whether the school was urban or rural, and a qualitative assessment of the likelihood of attrition throughout the trial. For both the trial baseline (in 2012) and endline (in 2014), for cross-sectional surveys, a simple random sample of up to 130 Primary 5 to Primary 7 students per school were invited to consent for a survey interview, and if there were <130 Primary 5 to 7 students then all were invited. Figure 2 describes the timing of the Good School Toolkit delivery and survey assessments. The trial baseline survey data were collected across the 42 schools in 2012 (n=3706, 77% survey response). In 2014, after 18 months of Good School Toolkit implementation in the 21 intervention schools, trial endline data were captured across the 42 schools (n=3820, 93% survey response). Of the students surveyed at the trial endline, 90% (n=3431) agreed to be followed up. These individuals constituted our Wave 1 sample for this study and analysis. The Good School Toolkit intervention was subsequently delivered to 19 of the 21 wait-list control schools from 2015, by which time the Primary 7 students were expected to have left primary school, and 2 wait-list control schools declined to implement the toolkit. Wave 1 adolescents were traced, and Wave 2 survey data collected during 2018 and 2019. A full description of data collection procedures and methods for our Wave 2 survey are reported elsewhere [46].

Figure 3. Good School Toolkit exposure by calendar year and across school grade. Boldface school grade denotes school grade at Wave 1 survey. Grey shade indicates students' expected Toolkit intervention exposure, showing grades and duration of exposure. *At Wave 1 all cohort adolescents were students in primary school grades P5-P7 (approx. aged 11-14) and at Wave 2 cohort adolescents are expected to be either in secondary school grades (S2-S5) or no longer attending a school (approx. aged 16-19).

	Year and school grade (if in school)						
Year:	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018/19**
Survey:	**Base-**		**Wave**				**Wave**
Toolkit intervention exposure groups	**line**		**1**				**2**
1) Trial arm							
21 schools, estimated 50% of Wave 2 sample							
Grades Primary 5 to Primary 7 (P5-P7) at		P4	**P5**	P6	P7	S1	S2/S3
Wave 1		P5	**P6**	P7	S1	S2	S3/S4
		P6	**P7**	S1	S2	S3	S4/S5
2) Wait-list control arm							
21 schools, estimated 50% of Wave 2 sample							
2.1) Later delivery: 19 schools, grades			**P5**	P6	P7	S1	S2/S3
P5 and P6 at Wave 1, estimated 31% of Wave			**P6**	P7	S1	S2	S3/S4
2 sample.							
2.2) No exposure: 19 schools, grade P7			**P7**	S1	S2	S3	S4/S5
at Wave 1 and two schools that did not take-up							
the intervention, estimated 19% of Wave 2							
sample.							

Ethics and Consent to Participate

The Contexts of Violence in Adolescence Cohort (CoVAC) study, which encompasses this long-term follow-up, was approved by the London School of Hygiene and Tropical Medicine (6183 and 14768), University of London, Institute of Education, Research Ethics Committee (1091), Uganda Virus Research Institute and Uganda National Council of Science and Technology ethics committees (SS2520 and SS4722). All adult participants and emancipated minors complete voluntary informed written consent procedures prior to involvement in the study. For adolescents under 18 years old who are not emancipated minors, caregivers are provided with information about the study and can verbally opt their children out of participation and, if the caregiver has not opted-out the adolescent, the adolescent provides voluntary informed written assent prior to involvement in the study. Consent procedures have been approved by all ethics committees. During Wave 2, survey referral was offered to adolescents based on predefined criteria agreed with service providers that related to the severity and timing of violence and/or mental health concerns reported. All were offered counseling regardless of what they disclosed. Wave 1 [26] and Wave 2 [46] protocols, including methods and referral procedures [47], are fully documented elsewhere.

Good School Toolkit Exposure Measures

Primary

Participants in 21 trial intervention schools and those in the 21 wait-list control schools are categorized as the original study arms (1) trial and (2) wait-list control. Further subcategories defined within the wait-list control are adolescents who were attending Primary 5 or 6 in the 19 later delivery schools as the (2.1) later delivery exposure group; adolescents who attended one of the schools that did not implement the toolkit or who were attending Primary 7 in one of 19 later delivery schools at Wave 1 (as these students are expected to have left school prior to intervention delivery) as the (2.2) no exposure group (Figure 3).

Secondary

Adolescent Good School Toolkit exposure will be further defined using the following data: number of years exposed; time elapsed since exposure; age at exposure; individual survey responses to 2 exposure survey questions on role and participation in the Good School Toolkit intervention; and Raising Voices' staff assessments of school implementation. Raising Voices' assessments were captured during in-school visit observations by program staff across 39 schools in 2017 using a standardized scorecard developed by Raising Voices (data were not captured in one trial intervention school that reported they had discontinued the intervention and the 2 wait-list control schools that did not implement the intervention). We will use methods such as exploratory factor analysis to create composite exposure groupings; methods and construction of exposure measures will be fully documented [48,49]. For example, school implementation intensity, length of time exposed, and time since exposure may be used to generate high-, medium- and low-exposure groupings.

Study Outcome Measures

Study outcome measures are summarized in Table 2.

Table 2. Summary of the study outcome measures.

Outcomes	Measure construct	Source
Violence outcomes:		
Primary outcome:		
Peer violence victimization: Self-reported experience of any physical, emotional, and sexual violence between adolescent peers, in the last 12 months.	Question items on physical (6 items), emotional (4 items), and sexual violence (4 items) experienced from a peer, constructed as a binary outcome. Positive response to 1 or more of the 16 items coded=1, negative to all items coded=0. Binary outcomes will also be constructed separately by violence type (physical, emotional, and sexual). A peer is defined as students, coworkers, or community members of a similar age.	Questions adapted from the International Society for the Prevention of Child Abuse and Neglect Child Abuse Screening Tool-Child Institutional [50].
Secondary outcomes:		
Peer violence perpetration: Self-reported use of physical and emotional violence between adolescent peers, in the last 12 months.	Questions items on physical (2 items) and emotional violence (3 items) use against a peer, constructed as a binary outcome. Positive response to 1 or more of the 5 items coded=1, negative to all items coded=0. Binary outcomes also constructed separately by violence type (physical and emotional). A peer is defined as students, coworkers, or community members of a similar age.	Questions adapted from the International Society for the Prevention of Child Abuse and Neglect Child Abuse Screening Tool-Child Institutional [50]
Intimate-partner violence victimization: Self-reported experience of physical, emotional, and sexual intimate-partner violence among ever partnered adolescent women, in the last 12 months.	Question items on physical (3 items), emotional (8 items), and sexual violence (4 items) experienced from a partner, constructed as a binary outcome. Positive response to one or more of the 15 items coded=1, negative to all items coded=0. Binary outcomes also constructed separately by violence type (physical, emotional, and sexual). Intimate partners include boy/girlfriends, husbands/wives, and casual dating partners.	Adapted from the World Health Organization multicountry study on women's health and domestic violence against women [51], and the Conflict in Adolescent Dating Relationships Inventory [52,53]
Intimate-partner violence perpetration: Self-reported use of physical and emotional intimate-partner violence, among ever partnered adolescent men, in the last 12 months.	Question items on physical (2 items) and emotional (3 items) violence use constructed as a binary outcome. Positive response to one or more of the 5 items coded=1, negative to all items coded=0. Binary outcomes also constructed separately by violence type (physical and emotional). Intimate partners include boy/girlfriends, husbands/wives, and casual dating partners.	Adapted from the World Health Organization multicountry study on women's health and domestic violence against women [51], and the Conflict in Adolescent Dating Relationships Inventory [52,53]
Attitudes outcomes:		
Student acceptance of teacher violence	3 items will be constructed as a continuous outcome. Each response option will be assigned a score of 0–3. Scores summed and modeled as continuous score range 0 (low) to 9 (high acceptability)	Measure from the Good Schools Study [41]
Adolescents attitudes toward gender relations	18 items will be initially explored as one construct to generate a continuous outcome. Response options numerally coded 0-3 and individual scores calculated, ranging from 0-54. Attitudes toward domestic violence from Gender Equitable Men subscale 5 items will be explored as a continuous outcome and as single question items.	Gender Equitable Men scale, Uganda version [54]
Outcomes supportive of resilience:		
Agency	13 items, 3 independent dimensions, Internality (4 items), Powerful Others (4 items), and Chance (5 items). Each subscale will be initially explored as separate continuous outcome measures, response options will be assigned a score 0-3, summed and modeled as continuous scores.	Adapted Internality, Powerful Others, and Chance measure of locus of control, short-form
Self-regulation	13 items will be initially explored as one construct (one continuous outcome), and further explored as a 2-dimensional measure, with restraint and impulsivity modeled as separate continuous outcomes [55,56].	Brief Self-Control Scale [57]
Social assets	Continuous outcome, 8 items with response options: 0 not true, 1 somewhat true, and 2 certainly true. scores summed and modeled as continuous score range 0-16	Constructed from subsets of the Strengths and Difficulties Questionnaire [58,59]

Outcomes	Measure construct	Source
Psychological assets	Continuous outcome, 7 items, reverse coded: 2 not true, 1 somewhat true and 0 certainly true. Response options assigned a score 0-2, range: 0-14	Constructed from subsets of the Strengths and Difficulties Questionnaire [58,59]
Peer connectedness	2 items, continuous outcome generated, response options numerally coded 0-3 and individual scores calculated, range 0-6.	Questions adapted from scales used in adolescent health behavior surveys [60] and used in Good Schools Study. Response options: all the time, most of the time, sometimes, or never
Retention in school outcomes		
Staying in school	Last school grade completed will be assessed in relation to current age and grade at Wave 1, for example, binary outcomes: completion of grade Primary 7 (yes=1, no=0), transition to secondary school measured as completion of grade Secondary 1 (yes=1, no=0)	Not applicable

The primary outcome is peer violence victimization. A peer is defined as students, coworkers, or community members of a similar age. Adolescents' self-reported experience of peer violence in the last year will be measured using an adapted subset of questions from the International Society for the Prevention of Child Abuse and Neglect Child Abuse Screening Tool—Child: Institutional [61]. Questions were previously piloted and used in the Wave 1 survey [32]. For this analysis, peer violence is defined as violence from students, coworkers, or community members of a similar age. Experience of past-year peer violence will be constructed as a composite binary measure, with positive responses to one or more question items on acts of physical, emotional, and sexual violence coded as 1, and no acts coded as 0.

Secondary violence outcomes will be constructed as single and composite binary measures—as described above—for the primary outcome. Secondary violence outcome measures include past-year self-reported use of peer violence, girls' experience and boys' use of intimate-partner violence, measured using question items from the WHO multicountry Study on Women's Health and Domestic Violence [51] and Conflict in Adolescent Dating Relationships Inventory [52,53,62] adapted and used during Wave 1. Intimate partners include boy/girlfriends, husbands/wives, and casual dating partners. Self-reported intimate-partner violence will be explored as a combined measure and separately by violence type (emotional, physical, and sexual).

We will measure attitudes toward teacher violence with a 3-item measure developed for the Good Schools Study and used during the Wave 1 survey [41]. A shortened 18-item Gender Equitable Men scale, previously validated among Ugandan adolescents [54], will be used to measure gender-equitable attitudes. Question items and subsets of questions, including attitudes toward domestic violence, will be explored as single items and composite outcomes. Response options for all attitude questions are on a 4-point Likert-type scale.

Factors supportive of resilience will be measured, including peer connectedness [41], social assets, and psychological assets [63], these 3 measures had adequate internal consistency at Wave 1 [58,59,64]. The response options were on a 3-point scale for the asset questions and a 4-point Likert-type scale for the connectedness questions. Furthermore, we will explore using the Internality, Powerful Others, and Chance measure of locus of control, as a proxy measure of agency [65,66], and the Brief Self Control Scale [57,67], as a proxy to measure self-regulation. As neither Internality, Powerful Others, and Chance nor Brief Self Control Scale measures have been validated among Ugandan adolescents, questions were forward and backward translated by bilingual researchers, concepts were reviewed by a user group of Ugandan adolescents, wording was iteratively adapted through cognitive interviews with 8 to 15 adolescents, and the questions were pilot tested before inclusion in the Wave 2 survey questionnaire. If the outcomes measures for either have low internal consistency (Cronbach $\alpha<.65$) then exploratory factor analysis will be considered to generate factors scores and groupings.

To measure retention in school, we will capture last school grade completed and assess this in relation to expected grade based on school grade at Wave 1 and current age.

Potential Confounders and Effect Modifiers

The following factors have been identified a priori as potential confounders or effect-modifiers to the exposure-outcome relationships of interest: biological sex and the number of meals eaten the previous day (as a proxy for socioeconomic status that is expected to be associated with staying in the study school throughout intervention delivery and associated with later violence outcomes). In addition, and as appropriate for specific exposure-outcome relationships, the following variables have been identified as potential effect-modifiers or confounders measured at Wave 1: school grade, family connectedness, and experiences of violence outside of school [68,69].

Power to Detect a Difference

We anticipate that our trial exposure group will be 50% (n=1201), and no exposure group 19% (n=456), of the total Wave 2 sample (assuming a conservative 70% follow-up, 2402/3431). We estimate 50% [2] of our no exposure group will report past-year experiences of physical, emotional, or sexual violence from a peer at Wave 2. In this case, the smallest difference we can detect between no exposure and trial exposure groups, assuming 70% follow-up, an α of .5 and power of .8, would be an 8% difference between groups (OR 0.73).

Data Management

All Wave 1 and Wave 2 survey data were captured, transmitted, and stored on a secure server using Open Data Kit. Raising Voices school-level implementation assessment data were initially captured on standardized Excel (Microsoft Inc) spreadsheets scorecard. All data will be transferred to Stata 15 (StataCorp LLP) for all data management processes and analysis. A data set containing Wave 1 data (2014) will be individually linked with Wave 2 data (2018-2019) and merged with school-level aggregate data from the Good Schools Study baseline survey (2012) and Raising Voices school-level program implementation assessment scorecard data (2017), to create one data set for analysis.

Analysis Plan

Adolescents' sociodemographic characteristics will be described for Wave 1 and Wave 2 and by intervention-exposure groupings. Descriptive statistics for continuous variables will include the number of observations, mean, and standard deviation (or median and interquartile range as appropriate). Categorical variables will be presented as numbers and percentages. We will formally test for differences in characteristics between those who participated in Wave 1 and 2 compared to Wave 1 only (eg, age, sex, number of meals eaten the day before, school grade, and original study arm). We will account for clustering by original primary school (by using the Stata *Svy* command) and Taylor linearized variance estimation to calculate standard errors, present corrected person chi-square for categorical data, and associated *P* values and 95% confidence intervals. Together, these will be considered as evidence toward differential attrition [70].

Regression Analysis Strategy

All analysis is exploratory and hypotheses generating rather than testing. To explore if the intervention influences later outcomes, we will compare across the trial and no exposure groups (1 vs 2.2) and original study arms (1 vs 2) first including all 42 schools and then repeated, dropping the 2 nonimplementation schools. To further explore differences between levels of exposure, we plan to compare between trial and the later delivery groups (1 vs 2.1) and across secondary exposure groupings (Figure 3). We will account for clustering by including original study primary school as a random effect in mixed-effect regression models [71]. Binary outcomes will be analyzed using mixed-effect logistic regression, with effect size presented as odds ratios. Continuous outcomes will be analyzed using mixed-effects linear regression, with effect size presented as mean difference. All unadjusted and adjusted analyses will include baseline school-level mean of outcomes, where available [72]. Adjusted models will additionally include covariates identified as potential confounders. All measures of effect will be presented with 95% confidence intervals and *P* values. Size and direction of effect will be considered along with *P* values when assessing the strength of associations [70]. Appropriate methods will be used to analyze numeric outcomes that are not normally distributed. For example, bias-corrected 95% confidence intervals will be estimated using nonparametric bootstrapping. The presence of effect modification will be assessed by comparing models fitted with and without an interaction term. Likelihood ratio tests with *P* values<.1, along with the direction and size of effect for each group, will be considered as evidence for or against modification. If there is evidence of modification, then stratum-specific effects will be calculated [73].

For self-reported exposure, propensity score–matching will be used to account for the likelihood that self-reported exposure is confounded by an individual's propensity to report exposure. We will estimate what factors predict toolkit exposure using regression analysis [29], then calculate predicted probability of exposure and group adolescents with similar propensity scores. The analysis will compare outcomes across these propensity score exposure groups, including the score as a covariate in regression models [72].

For the primary peer-violence victimization outcome, we will present unadjusted and adjusted mixed-effect logistic regression models exploring the association between intervention exposure measures and peer-violence victimization.

For the secondary outcomes, we will present unadjusted and adjusted mixed-effect logistic or linear regression models exploring the association between intervention exposure measures and secondary outcomes. The effect of intervention exposure on secondary outcome measures will be assessed by the size of effects and accompanying *P* value and 95% confidence intervals, as well as expected direction and consistency across results.

Results

Data collection started in 2014 (Wave 1) and data collection was completed in 2019 (Wave 2). Data analysis has not been conducted.

Discussion

Principal Findings

This is the first study that evaluates the long-term impacts of an effective primary school violence-prevention intervention in a resource-constrained setting, where the majority of adolescents transition out of school after primary education. Guided by our conceptual framework, we plan to explore how long-term effects on violence and other outcomes may vary across schools and adolescents to build a picture of what works and for whom. This analysis will shed light on the generalizability of effects to inform intervention strengthening, future targeting, and generate hypotheses on potential transferability to other contexts. For instance, if there are no long-term impacts on retention in school, violence outcomes, or factors supportive of resilience, then this will suggest that further efforts are required to reinforce and sustain positive effects. Findings might point toward the need for complementary interventions in secondary schools or targeting family support and the home environment. Little is known about whether capabilities gained in primary school can be maintained through transition into new schools or the workplace, nor whether experiencing improved relationships and school connectedness in a safer primary school environment can positively influence future peer and intimate relationships among older Ugandan

adolescents. Our findings will highlight important areas for further qualitative and quantitative inquiry to better understand how school interventions shape violence and other outcomes through adolescent transitions.

Limitations

This protocol focuses on adolescent long-term outcomes, therefore, whether the intervention is maintained in primary schools and the influence of secondary school environments on outcomes are questions beyond the scope of the analysis. Our quasi-experimental nonrandomized design utilizes the trial delivery and later delivery of the intervention to schools and makes use of an unexposed comparison group that arose from the process and timing of delivery. As in other nonrandomized studies, confounding is of concern, as comparison groups differ regarding factors other than exposure to the intervention. To address this, we have a documented conceptual framework, plan to control for potential observed confounding in our analyses, and will consider the consistency of effects when interpreting results [74]. We expect to gain further insight into the toolkit's long-term effectiveness by comparing effects across original study arms in addition to across other exposure groupings.

This is an unblinded study, where both participants and researchers—including those leading the analysis—are aware of the intervention delivery. Selection bias may be introduced at Wave 1 as 10% of students in the original trial endline did not agree to follow-up. Differences in retention at Wave 2 could be associated with our outcomes of interest or with toolkit exposure, we will test for differences and, where possible, apply appropriate statistical methods to take account for such differences.

Conclusion

This analysis will be the first to examine the long-term effects of a whole-school violence-prevention intervention in a resource-constrained setting. If results are positive, this indicates that primary school interventions are promising platforms to institute lasting widespread change. This is especially relevant to alleviate the burden of many adverse outcomes of early exposure to violence in Uganda and other countries.

Acknowledgments

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Authors' Contributions

KD and JP designed the CoVAC study, with substantive input from DN. LK drafted this manuscript with substantive direction and input from KD and EA. LA, SN, DN, CB, HAW, JS, JP, KA-E, MN, JN, and AM commented critically on the manuscript. KD, JP, and DN are co–principal investigators on the CoVAC study. All authors read and approved the final manuscript.

Conflicts of Interest

DN (Raising Voices) developed the Good School Toolkit, SN and KA-E were previously employed by Raising Voices, and JN, AFM, MN are currently employed by Raising Voices. All other authors declare no conflict of interest.

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Abbreviations

CoVAC: Contexts of Violence in Adolescence Cohort study
OR: odds ratio
WHO: World Health Organization

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Protocol

A Brazilian Cohort of Patients With Immuno-Mediated Chronic Inflammatory Diseases Infected by SARS-CoV-2 (ReumaCoV-Brasil Registry): Protocol for a Prospective, Observational Study

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Abstract

Background: Patients with immune-mediated rheumatic diseases (IMRD) are at increased risk of infections, including significant morbidity and high mortality. Considering the potential for unfavorable outcomes of SARS-CoV-2 infection in patients with IMRD, several questions were raised regarding the impact of COVID-19 at the start of the pandemic.

Objective: This paper presents the protocol of a study that aims to prospectively evaluate patients with IMRD and a confirmed COVID-19 diagnosis (using criteria provided by the Brazilian Ministry of Health).

Methods: The study comprised a prospective, observational cohort (patients with IMRD and COVID-19) and a comparison group (patients with only IMRD), with a follow-up time of 6 months to evaluate differences in health outcomes. The primary outcomes will be changes in IMRD disease activity after SARS-CoV-2 infection at 4 time points: (1) at baseline, (2) within 4-6 weeks after infection, (3) at 3 months after the second assessment (±15 days), and (4) at 6 months (±15 days). The secondary outcomes will be the progression rate to moderate or severe forms of COVID-19, need for intensive care unit admission and mechanical ventilation, death, and therapeutic changes related to IMRD. Two outcomes—pulmonary and thromboembolic events in patients with both IMRD and SARS-CoV-2 infection—are of particular interest and will be monitored with close attention (clinical, laboratory, and function tests as well as imaging).

Results: Recruitment opened in May 2020, with 1300 participants recruited from 43 sites as of November 2020. Patient recruitment will conclude by the end of December 2020, with follow-up occurring until April 2021. Data analysis is scheduled to start after all inclusion data have been collected, with an aim to publish a peer-reviewed paper in December 2020.

Conclusions: We believe this study will provide clinically relevant data on the general impact of COVID-19 on patients with IMRD.

Trial Registration: Brazilian Registry of Clinical Trials RBR-33YTQC; http://www.ensaiosclinicos.gov.br/rg/RBR-33ytqc/

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KEYWORDS

COVID-19; SARS-CoV-2; prospective study; immune-mediated rheumatic diseases; registry; Brazil; inflammatory; chronic disease; cohort; immunology; infection rate; mortality; morbidity

Introduction

Background

COVID-19 was declared a pandemic on March 11, 2020, by the World Health Organization [1], and on February 26, 2020, Brazil became the first Latin American country to have a confirmed case of COVID-19 [2]. More than 4 million cases and over 130,000 deaths have been confirmed in Brazil as of July 31, 2020 [3].

Patients with immune-mediated rheumatic diseases (IMRD) are at increased risk of infections, including significant morbidity and high mortality [4]. It is worth emphasizing this is a complex binomial with many factors involved, such as disease activity, age, comorbidities, and drugs (eg, glucocorticoids; conventional synthetic, specific target or biological disease–modifying antirheumatic drugs; and immunosuppressants) [5]. Considering a possibly unfavorable evolution of SARS-CoV-2 infection in patients with IMRD, a number of questions has been posed regarding the impact of COVID-19 at the start of the pandemic, including withdrawal or spacing of medications, hospitalization, need of mechanical ventilation, and mortality rate [6-8].

Some Italian, American, French, and Chinese databases have started to demonstrate that the risk of poor outcomes is quite similar to the general population and could be linked more closely with comorbidities and aging than IMRD itself [9-11]. However, there are controversial data, especially regarding mortality rates [12,13]. More recently, a systematic review and meta-analysis showed the prevalence of COVID-19 to be 0.011 (95% CI 0.005-0.0025), which was significantly higher than that of the comparison group [14].

Considering Brazil as a continental country and with relevant regional and socioeconomic differences, as well as discrepancies concerning basic sanitation and access to public and private health care systems, it is important to generate data related to disease activity, treatment management, and survival curves in patients with both IMRD and COVID-19.

Aims

This paper presents the protocol for the ReumaCoV-Brasil Registry (Brazilian Registry of Patients with Immuno-mediated Chronic Inflammatory Diseases Infected by SARS-CoV-2). This trial was registered with the Brazilian Register of Clinical Trials (RBR-33YTQC) on June 1, 2020.

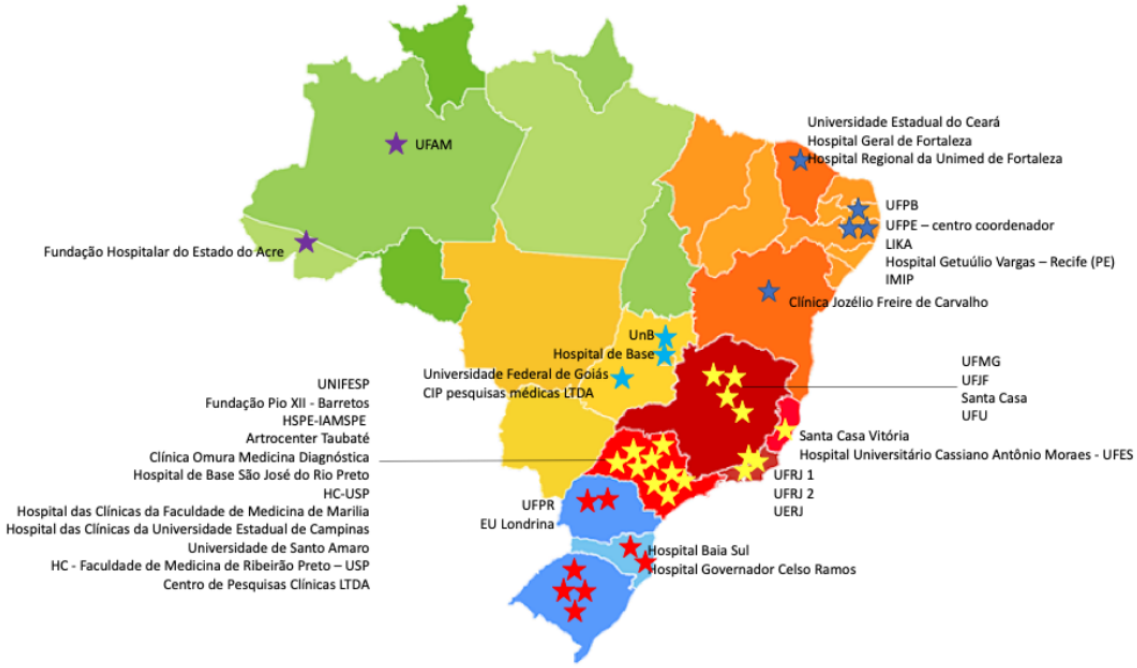
The primary objective is to prospectively evaluate patients with IMRD who had COVID-19, according to the Brazilian Ministry of Health criteria [15] (Multimedia Appendix 1), and to compare them to a control group of IMRD patients without a COVID-19 diagnosis.

The inclusion phase started on May 20, 2020, with the recruitment of patients from 43 centers in 5 regions of the country (Textbox 1 and Figure 1), and will run through November 30, 2020, considering that Brazil is still undergoing community viral transmission. An invitation to participate in this study was sent to all rheumatologists affiliated with the Brazilian Society of Rheumatology. Most invitees were employed at academic centers or private offices.

Textbox 1. Participating research sites in Brazil.

- Hospital das Clínicas, Universidade Federal de Pernambuco
- Artrocenter Clínica Médica – Unidade Taubaté, São Paulo
- Centro de Pesquisas Clínicas, São Paulo
- Clínica Jozélio Freire de Carvalho, Bahia
- Clínica Médica do Hospital Baia Sul, Santa Catarina
- Clínica Omura Medicina Diagnóstica, São Paulo
- Faculdade de Ciências da Saúde de Barretos, São Paulo
- Fundação Hospitalar do Estado do Acre
- Fundação Universidade Estadual do Ceará
- Hospital da Secretária da Saúde do Distrito Federal – Instituto Hospital de Base do Distrito Federal
- Hospital das Clínicas da Faculdade de Medicina da USP, São Paulo
- Hospital das Clínicas da Faculdade de Medicina de Marilia, São Paulo
- Hospital das Clínicas da Universidade Estadual de Campinas, São Paulo
- Hospital das Clínicas da Universidade Federal de Goiás
- Hospital das Clínicas da Universidade Federal de Uberlândia, Minas Gerais
- Hospital das Clínicas, Faculdade de Medicina de Ribeirão Preto – USP, São Paulo
- Hospital das Clínicas, Universidade Federal de Minas Gerais
- Hospital de Base, Fundação Faculdade Regional de Medicina São José Do Rio Preto, São Paulo
- Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul
- Hospital de Clínicas, Universidade Federal do Paraná
- Hospital dos Servidor Público Estadual de São Paulo
- Hospital Geral de Fortaleza, Ceará
- Hospital Getúlio Vargas, Pernambuco
- Hospital Governador Celso Ramos, Santa Catarina
- Hospital Moinhos de Vento, Porto Alegre
- Hospital Nossa Senhora da Conceição, Rio Grande do Sul
- Hospital Regional da Unimed de Fortaleza, Ceará
- Hospital Santa Casa de Misericórdia de Vitória, Espírito Santo
- Hospital São Lucas da PUCRS, Pontifica Universidade Católica do Rio Grande do Sul
- Hospital São Paulo, Universidade Federal de São Paulo
- Hospital Universitário Clementino Fraga Filho (1), Universidade Federal do Rio de Janeiro
- Hospital Universitário Clementino Fraga Filho (2), Universidade Federal do Rio de Janeiro
- Hospital Universitário de Londrina, Universidade Estadual de Londrina, Paraná
- Hospital Universitário Lauro Wanderley, Universidade Federal da Paraíba
- Hospital Universitário, Universidade Federal de Juiz de Fora, Minas Gerais
- Instituto de Medicina Integral Professor Fernando Figueira, Pernambuco
- Laboratório de Imunopatologia Keizo Asamy, Pernambuco
- Santa Casa de Misericórdia de Belo Horizonte, Minas Gerais
- Universidade de Brasília, Distrito Federal
- Universidade de Santo Amaro, São Paulo
- Universidade Estadual do Rio de Janeiro
- Universidade Federal de Ciências da Saúde de Porto Alegre, Rio Grande do Sul
- Universidade Federal do Amazonas

Figure 1. A nationwide task force, comprising 43 centers from 5 geographic regions in Brazil (see full organization names in Textbox 1).



Over the course of 6 months, participants will be questioned regarding disease activity, clinical manifestations of COVID-19 (complaints; evolution [eg, need for hospitalization, intensive care unit, or mechanical ventilation; or death]; time from infection to resolution; epidemiologic, demographic, and socioeconomic data), concomitant medications management, social distancing, flu vaccination, survival curves, and mortality rates.

The secondary objectives will include assessing the autoantibodies profile (rheumatoid factor, anti–cyclic citrullinated peptide [anti-CCP], anti–citrullinated protein antibody, antinuclear antibody, anticardiolipin immunoglobulin [Ig] G and IgM), as well as immunoglobulins (IgM, IgG, and IgA) and the serologic conversion rate for SARS-CoV2 (IgG and IgM).

Methods

Study Design

ReumaCoV-Brasil is a multicenter, observational, prospective registry implemented to monitor adult IMRD patients with a confirmed diagnosis of COVID-19, according to the Brazilian Ministry of Health criteria [13].

Using a nationwide sampling strategy, it is a 2-phase study: (1) cross-sectional evaluation (inclusion) with information about previous or current symptoms of COVID-19 and clinical characteristics at baseline, which can be performed via telephone call (preferred due to social distancing measures) or by a face to face visit, if possible; and (2) prospective follow-up concerning the IMRD characteristics with 2 face to face visits, every 3 months (3-month and 6-month assessments), after viral infection.

Participants and Eligibility Criteria

Regardless COVID-19 diagnosis, eligible patients include those aged 18 years or over with a prior diagnosis of IMRD, according to the American College of Rheumatology or European League against Rheumatism criteria, including rheumatoid arthritis [16,17], systemic lupus erythematosus [18,19], Sjögren syndrome [20], systemic sclerosis [21], inflammatory myopathies [22], axial spondyloarthritis [23-25], enteropathic arthritis [26], psoriatic arthritis [27], sarcoidosis [28], antiphospholipid syndrome [29], Behçet disease [30], mixed connective tissue disease [31], Takayasu arteritis [32,33], giant cell arteritis [34], ANCA (antineutrophil cytoplasm antibodies)-associated vasculitides [35-38], and juvenile idiopathic arthritis in adults [39]. In addition, a third group will also be evaluated, consisting of non-IMRD patients with COVID-19 infection.

The exclusion criteria included the presence of other primary immunodeficiency diseases, past organ or bone marrow transplantation, neoplasms within the last 5 years, current chemotherapy, HIV diagnosis, and thymus diseases. The controls will be patients with IMRD but without a diagnosis of COVID-19, matched for sex, age, and IMRD type. The exclusion criteria stated above will apply to the control group as well.

Considering the moderate to severe forms of COVID-19 as the dependent variable and an estimated rate at 20%, according to the current literature, as well as the proportion of 1 case for 1 control and an error α=5% and β=20%, the sample calculation was approximately 576 IMRD patients with positive COVID-19 and 576 IMRD patients without COVID-19 [1,2,8].

Clinical Data and Outcomes

When an IMRD case is identified, the patient will be invited to participate in the study and will be enrolled after reading and

signing the informed consent form (Multimedia Appendix 2). The clinical form (Multimedia Appendix 3) will be filled at baseline and at 3- and 6-month follow-up using the REDCap platform. Each researcher (principal investigator and 4 additional subinvestigators for each center) will have a unique and personalized login and password to access this platform. The REDCap platform will be frequently monitored in order to ensure data quality.

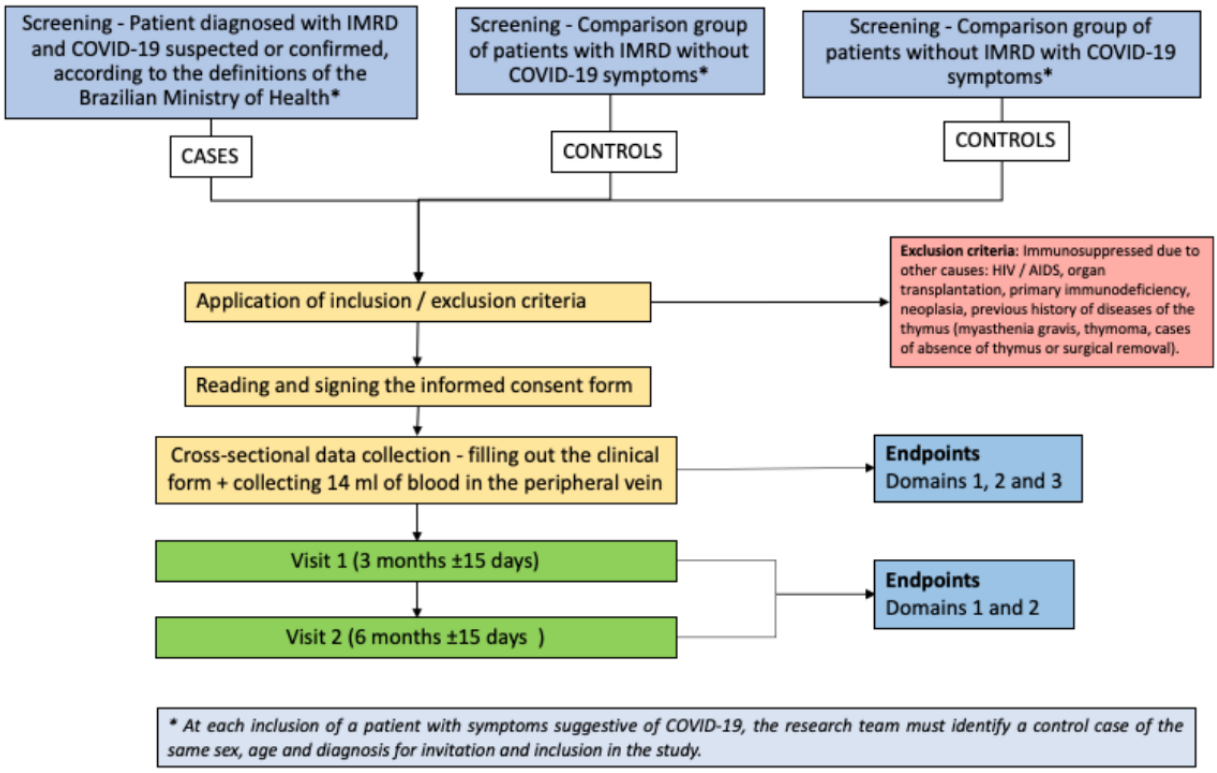
The primary outcomes will be changes in IMRD activity after SARS-CoV-2 infection at 4 time points: (1) baseline; (2) within 4-6 weeks after SARS-CoV-2 infection; (3) 3 months after inclusion in the study (±15 days); (4) 6 months after inclusion (±15 days) (Table 1 and Figure 2). If the patient is unavailable to perform a face to face visit at baseline because of social distancing, the physician may use clinical data from within the last 6 months (a period of time without any evidence for COVID-19).

Table 1. ReumaCoV-Brasil procedures[a].

Procedure	Visit 1 (inclusion)		Visit 2 (face to face) – 3 months (±15 days) after visit 1	Visit 3 (face to face) – 6 months (±15 days) after visit 1
	Phone call – immediately after COVID-19 diagnosis	Face to face – within 4-6 weeks after inclusion		
Informal consent	✓			
Inclusion and exclusion criteria	✓	✓		
Signed informed consent		✓		
Clinical data	✓	✓	✓	✓
Disease activity assessment	✓	✓	✓	✓
Lab exams		✓		

[a]The same procedures will be adopted for the control group.

Figure 2. Study flowchart.



The disease activity assessment will be performed using a global patient assessment and physician assessment, using a numerical visual scale (0-10), as well as specific and validated disease activity measurements or prognostic factors related to systemic vasculitis (Textbox 2). In addition, the type of organ or tissue with systemic prior involvement (eg, the renal, lung, heart, or nervous system [central or peripheral]; hematological, gut, eye, vessels, skin, mucous, and other extra-articular manifestations)

will be assessed. For musculoskeletal complaints, including muscle (fatigue, pain, weakness, and myopathy) and joint (arthritis, enthesitis, and dactylitis), endpoints will also be evaluated. The secondary outcomes assessed will be the progression to moderate or severe forms of COVID-19, need for intensive care unit admission and mechanical ventilation, and death.

Textbox 2. Specific and validated disease activity measurements and prognostic factors.

1. Rheumatoid arthritis
2. Clinical Disease Activity Index [40]
3. Axial spondyloarthritis
4. Ankylosing Spondylitis Disease Activity Score-C-Reactive Protein [41]
5. Ankylosing Spondylitis Disease Activity Score-Erythrocyte Sedimentation Rate [41]
6. Bath Ankylosing Spondylitis Disease Activity Index [42]
7. Psoriatic arthritis
8. Psoriasis Area Severity Index and nail disease [43]
9. Disease Activity in Psoriatic Arthritis [44]
10. Minimal Disease Activity [45]
11. Systemic erythematous lupus
12. Modified Systemic Erythematous Lupus Disease Activity Index [46,47]
13. Sjögren syndrome
14. European League Against Rheumatism Sjögren's Syndrome Disease Activity Index [48]
15. Systemic sclerosis
16. Rodnan score [49]
17. Raynaud’s phenomenon and digital ulcers
18. Behçet disease (BD)
19. Behçet’s Disease Current Activity Form [50]
20. Inflammatory myopathies
21. Manual Muscle Testing in 8 muscles [51]
22. Health Assessment Questionnaire [52]
23. Systemic vasculitis
24. Birmingham Vasculitis Activity Score, version 3 [53]
25. Five-Factor Score [54]

Details about previous lab exams will also be recorded, such as erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, anti-CCP, antinuclear antibody, anti-ENA (extractable nuclear antigen), anti–double-stranded DNA, human leukocyte antigen B27, complement, anticardiolipin IgG and IgM, ANCA, and cryoglobulins.

The secondary outcomes will be related to COVID-19 itself, such as hospitalization, need of intensive care unit, mechanical ventilation, time from onset of symptoms or hospitalization to development of severe acute respiratory syndrome (SARS), outcome after SARS (improvement or death), laboratory changes (renal function, hemoglobin, leucocytes, lymphocytes, platelets, ferritin, albumin, D-dimer, fibrinogen), and pharmacological (hydroxychloroquine, azithromycin, glucocorticoids, heparin, antibiotics, intravenous immunoglobulin, tocilizumab), experimental (convalescent plasma, extracorporeal membrane oxygenation), and supportive treatments. Moreover, information about changes in IMRD treatment (withdrawal, dosage reduction or addition) and new autoimmune manifestations will be also recorded for all patients.

Two outcomes—pulmonary and thromboembolic events in patients with both IMRD and SARS-CoV-2 infection—are of particular interest and will be monitored with close attention and entail the collection of more data (clinical, lab, function tests, and imaging, when appropriate) because they have been reported as an important aspect of moderate and severe forms of COVID-19, and heparin and direct oral anticoagulants are used to manage them. Considering that some researchers have shown antiphospholipid autoantibodies in patients from the general population without IMRD, another secondary endpoint is to evaluate these aspects as well as to verify if patients with IMRD could have more thromboembolic events compared to the third group (patients without IMRD) [55,56].

The explanatory variables will be age, sex, geographic localization, race, education level, profession, employment

situation, comorbidities, IMRD details (disease activity, time since diagnosis, level of damage), concomitant medications, and COVID-19 symptoms (eg, fever, cough, dysgeusia, anosmia, myalgia, fatigue, expectoration, shortage of breath, headache, dizziness, diarrhea, nausea, vomiting), time of infection, municipality, and vaccination against the flu.

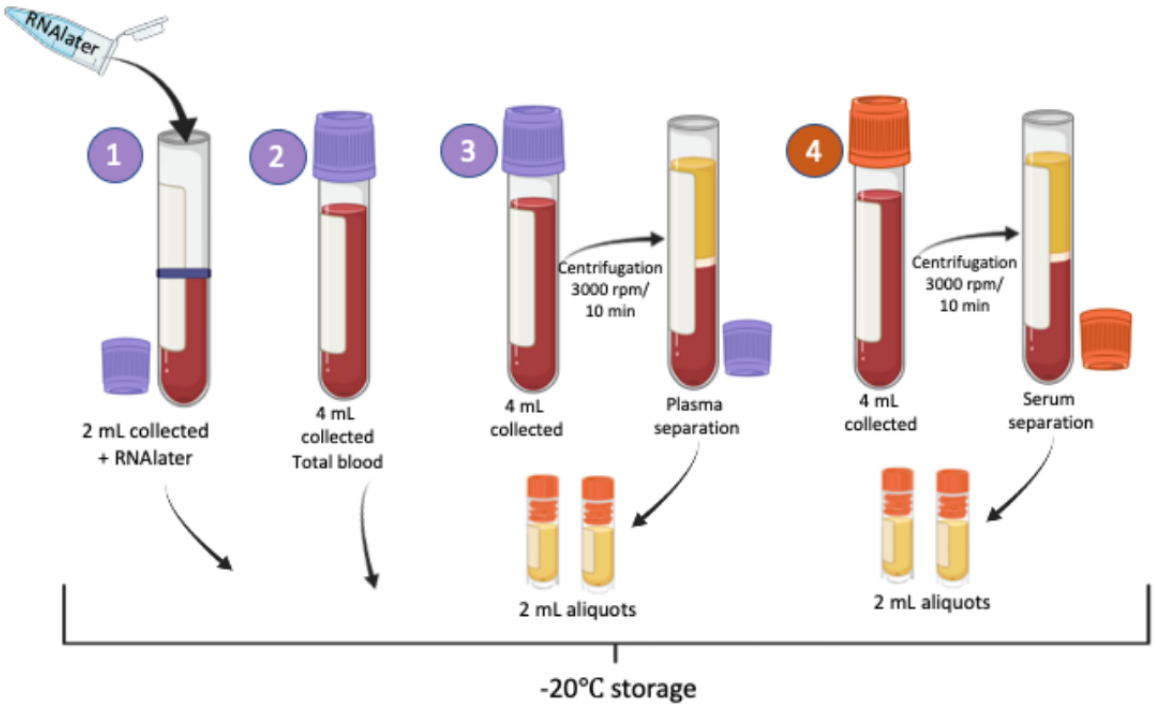
If IMRD patients without symptoms of COVID-19 enrolled in the control group test positive for anti–SARS-CoV-2 antibodies (IgM and/or IgG) after scheduled lab exams at baseline, they will be considered as having COVID-19 and will be moved from the control group to the intervention group (asymptomatic group).

Lab Data Collection

A total of 14 mL of blood will be collected for further lab testing, according to the protocol described in Figure 3. The blood will be centrifuged at 3000 rpm with the serum being separated and stored at –20 °C at each participating center and will be sent to the Hermes Pardini Laboratory posteriorly via one-way shipping. The anti–SARS-CoV-2 antibodies (IgM and IgG) will be evaluated by ELISA (enzyme-linked immunosorbent assay; Euroimmun), using plasma aliquots, according to the manufacturer's recommendations. Rheumatoid factor, anti-CCP, antinuclear antibody, anticardiolipin (IgG and IgM), and immunoglobulins (IgM, IgG, and IgA) will be tested using serum aliquots and pre-established protocols.

The total blood tube and another tube with RNAlater added will be shipped to the Keizo Asami Immunopathology Laboratory, located at the Federal University of Pernambuco and maintained at –80 °C (Figure 3).

Figure 3. Blood collection and storage protocol: The blood from the peripheral vein will be collected in a total of 16 ml: 3 EDTA tubes, one with 2 ml and two with 4 ml and 1 dry tube with separating gel. To the first EDTA tube, where 2 ml of blood was collected, 2 ml of RNAlater will be added for later storage. The second EDTA tube will be stored with total blood. The third EDTA tube will be centrifuged for plasma separation, along with the dry tube, for serum separation. Serum and plasma will be divided into 2 ml aliquots and frozen at -20ºC, together with the tube where RNAlater was added, and the EDTA tube containing whole blood.



Data Management and Monitoring

The data will be collected by appropriate and trained health care staff, particularly rheumatologists from public and private backgrounds. In addition, 4 study coordinators will provide regular assistance and training regarding data quality. Regular data inspection and quality control will be performed throughout the lifetime of the study. Research sites will retain identifiable study data securely. The data custodians will work together to establish a suitable trial data repository for the anonymized study data set following the conclusion of primary and secondary data analysis. Anonymization will ensure patients' privacy and adherence to the previously mentioned guidelines.

Endpoints

The study's endpoints are as follows:

- Domain 1: changes in disease activity and modifications in lab exam results
- Domain 2: outcomes concerning moderate and severe forms such as hospitalization rate, need for intensive care unit and mechanical ventilation, total hospitalization time, and death; date of a major serious event (death, hospitalization, survival curve)
- Domain 3: humoral response regarding anti–SARS-CoV-2 antibodies and autoantibodies related to IMRD.

Statistical Analysis

The data will be analyzed in a descriptive way using absolute and relative frequencies for categorical variables and quantitative measures (mean, median, quartiles, minimum and maximum values, and standard deviation) for numerical variables. The normality of the data will be verified using the Kolmogorov-Smirnov test.

The chi-square association test will be used to assess any differences among the endpoints, or the Fischer exact test for small samples. The linear associations among variables will be evaluated using the Pearson correlation or Spearman, when appropriate.

For the evaluation of the behavior of clinical variables between 2 or more points in time by group, analysis of variance (ANOVA) will be used, with repeated measures to be made. In case of nonnormality of the data, the averages of the groups at each time point will be compared using the Kruskal-Wallis nonparametric test. To compare the means between the groups, the Wilcoxon nonparametric test will be used.

The comparison between the means of numerical variables with normal distribution will be verified through the Student *t* test. In case of violation of the assumption of normality, the Mann-Whitney nonparametric test will be used.

Adjusted multiple linear regression models will be used to assess the simultaneous effects of sex, age, time of disease, disease activity, comorbidities, concomitant medications, and other confounding variables, according to the group and predefined outcomes. For dichotomous dependent variables, a logistic regression model will be preferred. Survival analysis models, including log rank and Kaplan-Meier tests, adjusted for confounding variables, will be developed to assess the main outcomes over time. The time defined as the end date will be the date of a major event, such as illness with confirmation or suspicion of infection, hospitalization, or death.

SPSS, version 20 (IBM Corp), will be used in all analyses, and a P value <.05 will be defined as significant.

Results

Ethics Approval and Regulatory Considerations

The results of this research will be presented in an aggregated form, guaranteeing confidentiality and ensuring that there are no risks to patients' well-being and care. This protocol was approved by the Brazilian Committee of Ethics in Human Research on April 5, 2020 (CAAE 30186820.2.1001.8807; number: 3.933.204), and registered on the Brazilian Registry of Clinical Trials (RBR-33YTQC) on June 1, 2020. The project is in the data collection phase, which is expected to end in May 2021.

Data Availability and Materials

The data are owned and held by the Brazilian Society of Rheumatology (Sociedade Brasileira de Reumatologia). Data can be obtained upon request.

The authors will ensure safe and proper conduct of the study, in agreement with the International Conference on Harmonization Guideline for Good Clinical Practice and the Declaration of Helsinki [57], and reserve the right to audit all study documents and standard operating procedures at the coordinating center and research sites.

Discussion

The ReumaCoV-Brasil is a Brazilian registry of rheumatic patients with COVID-19, supported by the Brazilian Society of Rheumatology. This study was designed to provide more information on epidemiological data and specific outcomes in Brazilian patients with IMRD across the country. In addition, the immunophenotyping may help us to understand the different outcomes according to genetic background and host response [58,59]. With an unprecedent design and a real-life perspective, particularly focused on disease activity before and 6-month follow-up after COVID-19 diagnosis, ReumaCoV-Brasil will add new evidence regarding the complex interaction between SARS-CoV-2 and IMRD. In addition, our database will be linked to other national databases for enhancing the magnitude of captured data and to avoid missing data. However, some limitations may occur, such as potential biases, including notification of more severe cases and lack of confirmatory tests (SARS-CoV-2 RNA [ribonucleic acid] real-time polymerase chain reaction) in asymptomatic patients or with nonsevere forms. In addition, our data will allow comparisons with other international registries and provide enhanced knowledge about similarities and differences across countries. Another relevant point is related to case definitions that varied among countries and could contribute to the differences in the case fatality rates in affected regions. A clear definition of a COVID-19 case is crucial for management, tracking of clinical illness, and to inform the quarantine measures and social distancing during the COVID-19 outbreak [60]. For our registry, we choose suitable criteria to avoid problems concerning outcome definitions. We believe this study will provide clinically relevant data on the general impact of COVID-19 on patients with IMRD.

Acknowledgments

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Authors' Contributions

All authors contributed equally in all phases of the protocol design, as well as in the preparation and revision of this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Definitions of symptomatic suspected and confirmed cases and asymptomatic cases of COVID-19, according to the Brazilian Ministry of Health criteria.
[PNG File , 190 KB - resprot_v9i12e24357_app1.png]

Multimedia Appendix 2
Informed consent form (in portuguese).
[PDF File (Adobe PDF File), 238 KB - resprot_v9i12e24357_app2.pdf]

Multimedia Appendix 3
Clinical form - generate using the REDCAp (Research Electronic Data Capture) platform (available from: http://www.project-redcap.org).
[PDF File (Adobe PDF File), 425 KB - resprot_v9i12e24357_app3.pdf]

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Abbreviations

ANCA: antineutrophil cytoplasm antibodies
ANOVA: analysis of variance
anti-CCP: anti–cyclic citrullinated peptide
ELISA: enzyme-linked immunosorbent assay
ENA: extractable nuclear antigen
Ig: immunoglobulin
IMRD: immune-mediated rheumatic diseases
RNA: ribonucleic acid
SARS: severe acute respiratory syndrome

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Protocol

Impacts of a New Supermarket on Dietary Behavior and the Local Foodscape in Kisumu, Kenya: Protocol for a Mixed Methods, Natural Experimental Study

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Abstract

Background: Access to healthy food is considered a key determinant of dietary behavior, and there is mixed evidence that living near a supermarket is associated with a healthier diet. In Africa, supermarkets may contribute to the nutrition transition by offering both healthy and unhealthy foods and by replacing traditional food sellers. In Kisumu, Kenya, a planned hypermarket (ie, a supermarket combined with a department store) will form the basis for a natural experimental evaluation.

Objective: The aim of this study is to explore the impacts of a new hypermarket on food shopping practices, dietary behaviors, physical activity patterns, and body composition among local residents and to identify concurrent changes in the local foodscape. We also aim to explore how impacts and associations vary by socioeconomic status.

Methods: We employ a mixed methods, longitudinal study design. Two study areas were defined: the hypermarket intervention area (ie, Kisumu) and a comparison area with no hypermarket (ie, Homabay). The study is comprised of 4 pieces of primary data collection: a quantitative household survey with local residents, a qualitative study consisting of focus group discussions with local residents and semistructured interviews with government and private sector stakeholders, an audit of the local foodscape using on-the-ground data collection, and an intercept survey of shoppers in the hypermarket. Assessments will be undertaken at baseline and approximately 1 year after the hypermarket opens.

Results: Baseline assessments were conducted from March 2019 to June 2019. From a total sampling frame of 400 households, we recruited 376 of these households, giving an overall response rate of 94.0%. The household survey was completed by 516 individuals within these households. Across the two study areas, 8 focus groups and 44 stakeholder interviews were conducted, and 1920 food outlets were geocoded.

Conclusions: This study aims to further the understanding of the relationship between food retail and dietary behaviors in Kenya. Baseline assessments for the study have been completed.

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KEYWORDS

food retail; food environment; supermarket; natural experiment; diet; Africa

Introduction

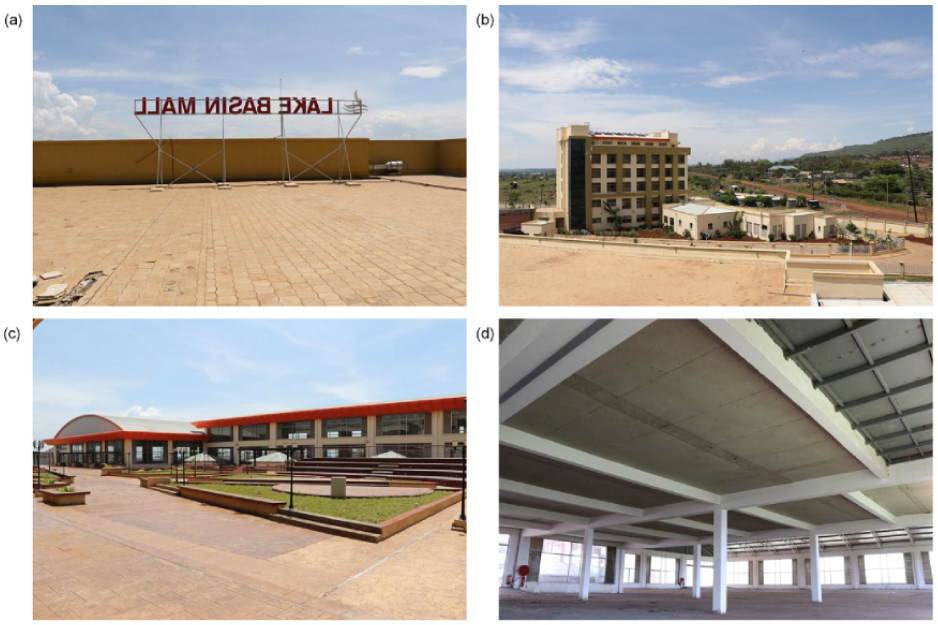
Dietary behavior is complex and shaped by multiple interacting factors, including policy, built, and social environments [1]. Access to healthy food is considered a key determinant of dietary behavior, and some evidence suggests, albeit inconsistently, that residential proximity to a supermarket is associated with a healthier diet [2]. In high-income countries, there is mixed evidence that the establishment of a new supermarket influences health-related outcomes among local residents [3-5]. A review indicated inconsistent evidence that new supermarkets improve fruit and vegetable consumption and no evidence for changes in BMI or self-rated health [3]. However, further reviews of research from predominantly high-income countries suggested that interventions that involved manipulating the price or availability of products within grocery stores could increase the purchasing of healthier foods [6,7].

Evidence on the relationship between supermarkets, food purchasing, diet, and health is drawn mostly from high-income countries. There is an inadequate understanding of dietary behaviors and their drivers in low- and middle-income countries (LMICs). It is particularly important to understand dietary behaviors in these settings because of the ongoing nutrition transition that is typified by a movement away from traditional staples toward the consumption of cheap and highly processed food [8]. This is responsible, in part, for the emerging "triple burden of malnutrition," whereby undernutrition and micronutrient deficiency coexist with obesity at population, household, and individual levels [9]. In Africa, the structure of the food retail market is changing rapidly as large supermarket chains expand into urban settings [10]. Supermarkets may play a key role in driving the nutrition transition through increasing the availability of processed food, though they may also sell healthy food cheaply or facilitate access to a wider range of foods [10,11]. Due to economies of scale, supermarkets are often able to sell items more cheaply than local traders and have been shown to displace smaller or informal local food outlets frequented by low–socioeconomic status (SES) households, generating or entrenching inequalities in food access and health [10].

Kenya is a low-income [12] East African country with a population of approximately 50 million [13]. Kenya is experiencing an escalating burden of noncommunicable disease and obesity [14,15], which is related, in part, to changing local diets. Kenya has a prospering supermarket sector [11], accounting for approximately 10% of the share of grocery sales at the national level, with a higher share in urban centers [16]. Evidence from Kenya suggests that living near, or shopping at, a supermarket increased the consumption of processed food at the expense of unprocessed food [11,16] and was associated with a higher BMI and metabolic syndrome in adults [16-18] but a lower probability of being underweight in children [17].

A new hypermarket (ie, a supermarket combined with a department store) is currently under construction at Lake Basin Mall in Kisumu, Western Kenya (see Figure 1). The mall, funded through a public-private partnership and currently planned to be the largest in Western Kenya, is located approximately 5 km from the central business district of the city of Kisumu, the seat of Kisumu County. The mall will house other amenities, such as an amphitheater, doctors' offices, cafeterias, a gym, and office spaces. Lake Basin Mall is in close proximity to a higher-SES residential area but also close to lower-SES informal (ie, slum) settlements. It is situated along a busy highway that opens up the western part of Kenya, runs past Kisumu International Airport, and continues on toward Uganda's Northern Transport Corridor, a popular destination for Kenyan traders in commodities such as fish, fruit, cereals, and animal feed.

Figure 1. Images showing (a and b) the Lake Basin Mall site, (c) a scene from within the mall, and (d) the hypermarket site.



The opening of the hypermarket provides an opportunity to examine potential impacts on dietary behaviors among residents of Kisumu living nearby and on the local foodscape, using a natural experimental design [19], as well as the opportunity to

explore whether impacts are distributed unequally or inequitably. Impacts will be examined relative to the town of Homabay in Homabay County, a neighboring comparison area where no hypermarket is planned. As such, the overall purpose of this study is to address the following research questions:

1. What are the individual, household, and population impacts of the new hypermarket at Lake Basin Mall on food shopping practices, dietary behaviors, physical activity patterns, and body composition among local residents across different SES groups?
2. How has the local foodscape changed, do these changes relate to the new hypermarket at Lake Basin Mall, and how are they experienced by local residents?

Methods

Design

This is a protocol for a mixed methods, natural experimental study [20] that will use a combination of quantitative and qualitative research methods to evaluate changes in dietary and health behavior coupled with furthering an understanding of the drivers and impacts of these changes. As is typical for natural experimental studies, the intervention will not be under the control of researchers, and intervention assignment will not be randomized or blinded.

The study is comprised of four core pieces of primary data collection:

1. A longitudinal quantitative household survey with local residents.
2. A longitudinal qualitative study consisting of focus group discussions with local residents and semistructured interviews with government and private sector stakeholders.
3. A longitudinal audit of the local foodscape using on-the-ground data collection.
4. A cross-sectional intercept survey of shoppers in the hypermarket.

The baseline data collection took place in 2019, before the anticipated opening of the hypermarket. The follow-up data collection is anticipated to take place in 2021, approximately 1 year after the hypermarket opens, which should provide sufficient time for shopping habits to adjust after an initial period where use of the hypermarket may be atypical. Assessments will ideally be seasonally matched (ie, they will take place at a similar time at both the intervention and comparison sites) to account for seasonal variation in behaviors. Should this not happen, seasonality will be addressed in the analysis. Modest incentives will be used to increase retention and to compensate for time spent participating in the study. The incentives include transport reimbursement, refreshments, and bars of soap as tokens of appreciation. If households subsequently move to outside the study areas, they will still be eligible for the follow-up assessment. Depending on attrition, we will also consider the possibility of recruiting a new sample of households from the study areas at follow-up.

Setting

The study is set in Kisumu County and Homabay County in Western Kenya. Kisumu County has a population of 968,909, and Homabay County has a population of 963,794. Two study areas were defined: the hypermarket intervention area (ie, Mamboleo, Kisumu) and a comparison area with no hypermarket (ie, Sofia, Homabay). These areas were delineated using existing spatial census data, field visits, and local knowledge of the study investigators. A 2-km radial buffer was drawn around the hypermarket and matched according to population density with a 2-km radial buffer around another landmark in the comparison area. Therefore, both study areas are 2 km in size, by radius, and the two areas lie approximately 100 km apart.

Though we aimed to ensure similar aggregate socioeconomic characteristics and broadly similar topographical and food retail characteristics apart from the presence of a hypermarket, the sites are still somewhat heterogeneous. The intervention site may be considered urban and the comparison site maybe be considered periurban. However, both areas include a mix of lower- and higher-SES areas, both informal and formal settlements; both areas have a similar number of supermarkets and encompass the main shopping street; and both areas have major roads. Both areas are located on the shores of Lake Victoria, a freshwater lake and the traditional ancestral lands for the Luo ethnic community of Kenya; thus, they share similar cultural practices.

Eligibility

Household Survey

Households living in one of the local study areas at baseline are eligible for the household survey. Individuals are considered household members if they regularly share meals, live together, and pool their monetary resources. A maximum of 5 adults, aged 18 years or over, in the household, including the head of household and the person who is usually responsible for food purchasing, will be eligible to complete interviewer-administered questionnaires and anthropometric measurements. The household head is the adult member of the household who is accepted and recognized by the other household members as the head, which implies a prominent role in making decisions that concern the household. Additionally, a maximum of 5 children, aged between 5 and 17 years, in the household will be eligible to complete anthropometric measurements. Households where either the head or the person responsible for food purchasing is under the age of 18 years will be excluded from the study.

Focus Groups

Adult householders from each of the local study areas who took part in the household survey will be eligible to participate in subsequent focus group discussions. These will be disaggregated into male and female as well as lower- and higher-SES groups. This was considered necessary to address any social, economic, cultural, or class issues that may impede free discussion. The focus group discussions will be conducted in local community halls owned by churches, local businesses, or the county government.

Stakeholder Interviews

Eligible stakeholders of interest include county government officers from the health, trade, agriculture, and infrastructure departments. Local administration representatives include the county commissioner and representatives of this office. Members of the Lake Basin Development Authority who developed the mall and hypermarket as well as representatives from the local food retail sector, such as the market master, are also considered important stakeholders. Other important local representatives include the motorcycle taxi (ie, boda boda) and fishing industries as well as local faith and religious leaders who are influential in the community.

Shopper Intercept Survey

Once the hypermarket is open, shoppers will be eligible to answer questions on their shopping habits and will be intercepted while they shop.

Intervention

The intervention under study is the new hypermarket at Lake Basin Mall and its associated changes to the local foodscape. At the group level, the intervention dose is operationalized as the geographical proximity to the new mall (ie, living in either the intervention or comparison area). At the individual level, the intervention dose is operationalized according to whether the individual shops at the new hypermarket.

Outcomes

The primary outcomes are as follows:

1. Change in the self-reported percentage share of monthly household food expenditure from supermarkets between baseline and follow-up.
2. Changes in the number and type of local food outlets between baseline and follow-up.

The secondary outcomes are as follows:

1. Change in self-reported, monthly, household food expenditure, in Kenyan shillings, between baseline and follow-up.
2. Change in self-reported household food security between baseline and follow-up.
3. Change in self-reported individual dietary diversity (ie, number of food groups consumed on the previous day) between baseline and follow-up.
4. Change in measured individual body composition (ie, BMI in kg/m^2) between baseline and follow-up.
5. Change in self-reported individual well-being between baseline and follow-up.
6. An understanding of the changes that have occurred and how their effects have been experienced.

Sample Size

The primary outcome is the percentage share of the monthly household food expenditure from supermarkets. With reference to a previous study on supermarkets and food purchasing in Kenya [18], a baseline sample of 250 households—125 intervention and 125 comparison households—was estimated to allow the detection, with 95% confidence and 80% power, of a difference between intervention and comparison groups of 5% in expenditure share, while allowing for a 50% attrition rate between baseline and follow-up. Therefore, we aimed to recruit 300 households at baseline in 2019 to ensure adequate statistical power. While we did not anticipate 50% attrition, we used this as an upper limit to ensure we recruited an adequate number of households at baseline.

Sampling and Recruitment

Household Survey

In each of the study areas, we consulted with local community health volunteers. In the Kenyan health system, community health volunteers represent the first basic level of care. The majority of these volunteers have completed 8 years of primary education and are elected or nominated by their communities to serve them in a voluntary capacity on health-related matters under the community health strategy [21]. A community health volunteer typically works in a village with about 100 households and is supervised by community health extension workers, who are government employees [22]. Community health volunteers visit households monthly to collect general health indicators and often work with partners in their respective areas. They are assumed to know the households well in terms of living standards.

We engaged with 20 community health volunteers from the intervention area and 20 from the comparison area. Each community health volunteer provided a household list from their area, for a total of about 2000 households per study area. In addition, community health volunteers classified each household as low, medium, or high SES. These classifications were broadly based on asset-based measures used in previous household surveys conducted in LMICs [23], in particular, focusing on housing characteristics (eg, material of dwelling floor and roof and main cooking fuel) and access to basic services (eg, electricity supply, source of drinking water, and sanitation facilities), modified for the local context.

Using a geographic information system (GIS), we plotted a quadrant from the center of each study area to demarcate the area into four subareas—northeast, northwest, southeast, and southwest— and plotted three radii of 500 m, 1 km, and 2 km from the center. Each household in the sampling frame was classified by quadrant, distance from the center, and SES. A stratified random sample of households was drawn from these three strata—400 in total (200 in the intervention area and 200 in the comparison area)—to account for refusal to participate.

Study teams consisting of two field workers, guided by a local community health volunteer, will knock at the doors of eligible households to make an initial approach and recruit households to participate in the household survey.

Focus Groups

Following completion of the household survey, a purposive sample of participants will be drawn for the resident focus groups. We will aim for a diverse sample that mirrors the basic demographic characteristics of the survey sample and includes a mixture of lower- and higher-SES participants, those living in formal and informal settlements, both males and females, and a range of ages. Householders will be approached and

recruited by the same field worker teams using contact details provided during the household survey. We aim to conduct four focus groups in each study area, split by gender and SES.

Stakeholder Interviews

We will use existing relationships combined with snowball sampling to identify and recruit a range of stakeholders to participate in semistructured interviews, including mall developers and managers as well as members of the county government, including the trade executive, the health executive, the planning executive, and the local ward representative. We will give preference to those directly involved in the decision making and development of the mall and aim to interview at least 6 stakeholders per study area.

Shopper Intercept Survey

Once the hypermarket is open, a minimum of 20 shoppers will be recruited while they shop to answer a short survey.

Assessment

Household Survey

At baseline and follow-up, participants will complete a household and an individual questionnaire. The household questionnaire will be completed by the head of household and by the person who is usually responsible for food purchasing and will assess the following variables:

1. Demographic variables for each individual in the household (ie, age, sex, relationship to head of household [eg, wife or child], ethnicity, education, and occupation).
2. Characteristics of the household (ie, housing tenure and quality, access to electricity and water, appliance used for cooking, refrigerator ownership, car ownership, and duration of residence in the area).
3. Household food purchasing in the previous month, including sources of food, types of food retail accessed, and amount of money spent at different types of food retailers and overall.
4. Number of trips made to purchase food and modes of transport used in the previous month.
5. Household food security, based on the Food and Agriculture Organization's Food Insecurity Experience Scale [24].

The individual questionnaire will be completed by each eligible adult, aged 18 years or over, and will assess the following variables:

1. Dietary diversity using an unquantified 24-hour dietary recall and following the approach described by the Food and Agriculture Organization and the United States Agency for International Development's Food and Nutrition Technical Assistance III Project [25]. In order to calculate a dietary diversity score, the range of foods and drinks consumed will be classified into 10 core food groups: grains, white roots, tubers, and plantains; pulses; nuts and seeds; dairy; meat, poultry, and fish; eggs; dark green leafy vegetables; other vitamin A–rich fruit and vegetables; other vegetables; and other fruit.
2. Physical activity, using the World Health Organization Global Physical Activity Questionnaire [26].
3. Well-being, using two items from the abbreviated version of the World Health Organization Quality of Life instrument [27].
4. Social connectedness, using 3 items from the Social Provisions Scale [28].

Following this, all eligible participants in the household, both adults and children, will complete anthropometric measurements (ie, height, weight, and waist circumference) using standard procedures. A tape measure, stadiometer, and calibrated scales will be used. Each measurement will be taken in duplicate.

Assessments will last approximately two hours and will be conducted on different days of the week in order to capture both weekdays and weekends on the dietary recall. Although, ideally, multiple dietary recalls would be used, in order to minimize participant burden we will undertake a single dietary recall to describe the range of food groups consumed on the recall day. A field worker will administer questionnaires by interview with the aid of an electronic tablet, preprogrammed with prompts and validation rules to help limit missing data and ensure data quality. All field workers will be educated at the degree level in a related field (eg, health sciences) and will attend a minimum of five days of training covering all elements of the primary data collection, including a dedicated session on administering dietary recalls facilitated by a nutrition researcher. Following the training, field workers will have access to bespoke training resources.

Focus Groups

At baseline and follow-up, focus groups will be oriented around understanding what influences people's food practices and exploring the role of the hypermarket within the local foodscape. We will explore the day-to-day experience of food, including travel to procure food and the influence of family and community members. We will also investigate the connection people make between food, health and well-being, and the environment.

The focus groups will be held at local venues, such as community church halls or appropriate business outlets; will be conducted by two facilitators; and will last approximately two hours. Focus groups will be held for male and female participants as well as for lower- and higher-SES participants separately. Each focus group will start with a short introduction to the project, described as research on the food local people eat and how they get it. Using a topic guide, the facilitator will help to guide and explain the questions, a second facilitator will take notes, and the discussions of each focus group will be tape-recorded. The audio recordings will be transcribed verbatim and, if applicable, translated into English.

Stakeholder Interviews

At baseline, stakeholder interviews in the intervention area will be oriented around determining how decisions to invest in and situate the mall and hypermarket were made as well as projected impacts in relation to food prices and variety, other food outlets in the area, food supply chains, and health among the local people. At follow-up, interviews will focus on the implementation of the intervention and any important short-term outcomes. In the comparison area, stakeholder interviews at

both time points will focus more broadly on the impacts of the changing local foodscape.

The interviews will be held at a location convenient to the stakeholder, likely their place of work. Semistructured interviews will be conducted by two facilitators according to a topic guide and will last for approximately one hour. The interviews will be tape-recorded; the audio recordings will then be transcribed verbatim and, if applicable, translated into English.

Foodscape Audit

At baseline and follow-up, systematic on-the-ground data collection will be undertaken to geolocate and categorize food outlets in each of the local study areas. Teams of field workers will systematically walk around the study areas, coding the location and types of establishments and taking photos of food outlets. Data collection will be undertaken using electronic tablets. In addition, we will explore the availability and accuracy of existing data, such as county records of licensed food sellers.

Shopper Intercept Survey

At follow-up, shoppers in the hypermarket will be intercepted while they shop and asked a set of standard questions covering basic demographics, the items being purchased on the shopping trip, the mode of transport used to get there, and the main reasons for using the hypermarket. A field worker will administer the survey by interview with the aid of an electronic tablet. It is anticipated that each survey will take 5 to 10 minutes.

Data Management

The study will be conducted in accordance with relevant current policies, standard operating procedures, and regulatory requirements for data protection, storage and security, and secure data sharing across sites at the Kenya Medical Research Institute and the University of Cambridge. Each participant will be assigned a unique registration number. A master list linking each participant registration number to identifying details will be stored separately from the deidentified data. There will be secure storage of both paper (ie, locked filing cabinet) and electronic (ie, password-protected database) data at the Kenya Medical Research Institute. Electronic data will be stored on a secure server at the Kenya Medical Research Institute.

Quantitative Data

For the household survey, foodscape audit, and shopper intercept survey, data will be captured electronically using preprogrammed forms with existing prompts, codes, and validation rules to help limit missing data and ensure data quality using the mobile app CommCare (Dimagi). Additional quality control checks will be undertaken once these quantitative data are collated in the database.

Raw survey data will be collected, stored, and backed up on restricted-access CommCare cloud servers. Raw data sets will be downloaded by a data manager onto local password-protected computers for additional backup and management. Data cleaning will be undertaken using Stata software (StataCorp), in which data will be checked for inconsistencies, variables manipulated, and new variables derived. A cleaned data set will be generated and stored locally alongside cleaning and analysis files. Cleaned, deidentified data sets will be shared between institutions according to local ethical approval and the terms of a formal data sharing agreement.

Qualitative Data

For the qualitative focus groups and stakeholder interviews, all transcripts will be checked for accuracy by specially trained qualitative coders prior to analysis. Transcripts will then be imported into NVivo software (QSR International) for coding.

Analysis Methods

Household Survey

For all quantitative analyses, the level of statistical significance will be set as $\alpha<.05$. All participants who provide data will be included in analyses, and we will not impute missing data. Net changes between baseline and follow-up will be computed, and significance tests will be conducted using a method appropriate to the distribution of the data. Differences in means will be compared using *t* tests or analyses of variance for normally distributed variables, while medians will be compared using the Wilcoxon rank-sum test or the Kruskal-Wallis test for skewed data. We will further undertake multivariable regression analyses adjusted for important covariates, using models appropriate to the distribution of the data and accounting for clustering by household. For binary outcomes, we will explore the use of logistic regression models, and for continuous outcomes we will consider linear regression models and negative binomial or zero-inflated generalized linear models. Regression estimates and 95% confidence intervals will be reported.

Focus Groups and Stakeholder Interviews

The qualitative focus groups and semistructured interviews will be analyzed by a team of qualitative coders using thematic analysis. Double-coding of selected transcripts will be used to facilitate this process. Researchers will develop a codebook based on *a priori* themes from the topic guides, and new codes may also emerge. All codes will be combined into a master codebook, and this will be used for analysis.

Foodscape Audit

Food outlets will be counted and categorized (eg, restaurant, kiosk, and supermarket) descriptively. Simple change scores will be calculated. Geospatial information will be imported into a GIS and used to inform analyses exploring distance between households and food outlets as well as density of food outlets.

Shopper Intercept Survey

Intercept survey data will be analyzed using descriptive statistics. This data will be collected once the hypermarket has opened.

Mixed Methods Analysis

To integrate the study findings, a mixed methods, sequential explanatory design will be used. This design consists of two distinct phases: quantitative followed by qualitative [29]. Quantitative data will be analyzed first and take priority in the design. Following this, qualitative data will be analyzed to help explain, or elaborate on, the quantitative results. The methods will be mixed at the analysis stage. This has similarities to the

approach of following of a thread [30,31], where a question or theme taken from one research phase is carried across another phase. This proposal differs slightly from a traditional explanatory design in that the data collection will take place in parallel, but the analysis will take place sequentially.

The primary reason for mixing the methods is to offset the strengths and weaknesses of each method to provide greater insight than could be gleaned from either method alone. For example, the quantitative thread benefits from larger numbers but does not provide insight into how or why outcomes are brought about. By contrast, the qualitative data will provide complementarity via the explanation, elaboration, and illustration of the results from the quantitative method, but is limited by the smaller sample size. The two approaches are intended to answer different questions: *how* (ie, quantitative thread) and *why* (ie, qualitative thread). The qualitative thread will allow for some exploration of potential causal inference and mechanisms that would not otherwise be possible from the quantitative design. In addition, the qualitative thread will provide insight into the local context and give some indication of the potential generalizability of findings.

Knowledge Exchange and Dissemination

Knowledge Exchange

It is anticipated that findings from this study will be relevant for a range of policy areas, including nutrition, health and health inequalities, economic development, urban planning, agriculture, and food supply. Findings will be directly relevant to decision makers in the local study areas. In addition, given the similarity between this development and others taking place in low- and middle-income contexts, as well as wider considerations of health and economic or urban development, there is scope for considerable generalizability of these findings.

There will be 3 key windows for knowledge exchange within the study:

1. An initial stakeholder mapping phase will be an opportunity to understand the landscape of the public and private decision makers involved in this process as well as their needs and practices in terms of evidence provision and use.
2. The stakeholder interviews will provide opportunities to further develop this understanding as well as stakeholder perspectives on health and economic development.
3. The dissemination phase will involve sharing the results with the above actors in a way that reflects our increased understanding of their perspectives. Beyond the local stakeholder, we will also engage with national, regional, and international decision makers.

Key messages for our knowledge exchange will be guided by the research findings. The methods for dissemination will be guided by what is likely to be most effective for the relevant stakeholders.

Dissemination

Findings will be communicated to study participants through activities such as meetings based on the principle and approaches of *Baraza*—informative or deliberative public meetings held in communities in Kenya—and other existing networks and forums that can engage widely within communities. We will communicate study findings through academic publications and conference presentations. In addition, we will pursue a number of nonacademic outputs, activities, and events, including the production of lay summaries, blogging and social media, communicating via news media, and further *Baraza*-style meetings for different community and stakeholder audiences.

Monitoring

Data Monitoring and Auditing

This study forms part of the Global Diet and Activity Research Group and Network (the Network). The Network has a Steering Group comprised of senior investigators across the participating sites, which meets every 6 weeks. The Network Steering Group will act as a study steering committee, providing general oversight and advice on scientific and operational issues. Because of the low-risk nature of the study and the lack of a researcher-manipulated intervention, there will be no formal data monitoring committee for this study. There are no planned interim analyses or stopping guidelines. Minimal monitoring will be undertaken by a member of the investigative team to verify that study procedures are undertaken in accordance with the protocol by communicating deviations where they occur and taking action to prevent recurrence, auditing the completeness of consent forms, and auditing the accuracy and completeness of study data.

Harms

This is considered a minimal-risk study as defined by the local ethics committee. As such, a formal process of adverse event monitoring will not be implemented. However, if any member of the study team becomes aware of a serious adverse event (ie, its occurrence leads to hospitalization, death, or permanent disability or is life threatening), it will be reported to the principal investigator, who will report this to the local ethics committee according to the committee's standard procedures.

Ethics

Ethical approval has been received from the Kenya Medical Research Institute Scientific and Ethics Review Unit (reference KEMRI/SERU/CGHR/174/3730). Important protocol modifications will be updated in the study protocol and a new version released. Protocol amendments will be approved by the Kenya Medical Research Institute Scientific and Ethics Review Unit.

All study participants will read an information sheet and provide written informed consent prior to any study procedures taking place. Participants aged 18 years or over who cannot read and write may thumb-print their consent after the document has been read to them in the presence of their chosen witness. All participants aged 18 years or over who are able to write will sign the consent forms. Parents or guardians will sign consent forms on behalf of their children who are under 18 years of age. An assent form will also be signed by children who are under 18 years or age, or a thumbprint will be given if they cannot read or write, after information has been read to them. The consent and assent forms will be translated into Luo and

Kiswahili, the local language and national language, respectively.

Data will not be copied, removed, or disclosed to anyone outside the collaborating investigators and approved study staff. Approved staff will be given password-restricted access to the data. All participants are entitled to request the details of any personal data relating to them. Confidentiality will be maintained by storing consent forms separately from deidentified data, which will use registration numbers. Deidentified data will be shared between the Network partners under the terms of a formal collaboration and data sharing agreement. Identifiable data will be stored at the Kenya Medical Research Institute only and will not be shared.

Results

As of December 2020, we have undertaken initial stakeholder mapping and completed the baseline assessment. The follow-up assessment, data analysis, and publication are anticipated to take place in 2021.

Initial Stakeholder Mapping

In November 2018, stakeholders were identified and a meeting convened in each of the study areas. In Kisumu (ie, the hypermarket area), the meeting was attending by 32 stakeholders, including representatives from the Ministry of Health, the Lake Basin Development Authority, the county health department, trade and agriculture departments, faith and religious leaders, community health volunteers, and the private food retail and transport industries. In Homabay (ie, the comparison area), the meeting was attended by 19 stakeholders mostly representing the county health department. Investigators briefly described the study and chaired an open forum discussion in which stakeholders could reflect on aspects relevant to them.

Baseline Assessment

We undertook baseline assessments in Kisumu (ie, the hypermarket intervention area) in March 2019 and in Homabay (ie, the comparison area) in June 2019. From a total sampling frame of 400 households, we recruited 376 of these, giving an overall response rate of 94.0%. This exceeded our target of recruiting 250 households at baseline. Numbers of respondents completing each element of the assessment are reported in Table 1. We met or exceeded target sample sizes for all elements of the assessment.

Table 1. Baseline assessment conducted in 2019.

Assessment	Kisumu (ie, hypermarket area), n (%)	Homabay (ie, comparison area), n (%)
Household survey		
Households (N=376)	180 (47.9)	196 (52.1)
Individuals (N=516)	260 (50.4)	256 (49.6)
Focus groups (N=8)	4 (50)	4 (50)
Stakeholder interviews (N=44)	21 (48)	23 (52)
Foodscape audit: outlets geocoded (N=1920)	1008 (52.5)	912 (47.5)

Discussion

Overview

In this paper, we report the protocol for a mixed methods, natural experimental study evaluating the impacts of a new hypermarket on dietary behavior and other related outcomes among local residents in Western Kenya. In addition, we aim to develop a broader understanding of the impacts of a rapidly changing local foodscape, the meaning that local people attribute to these changes, and local people's food practices more generally. A number of reflections on study design and conduct arising from this study are likely to be of interest to those undertaking similar work.

Practical Challenges of Natural Experimental Designs

A defining feature of natural experimental designs is that the intervention of interest is not controlled by researchers, which can raise practical challenges for evaluation. Since the timing of the intervention is not under researcher control, it can be difficult to complete baseline assessments in the interval between the identification of the natural experiment opportunity and the implementation of the intervention. Equally, if an intervention is delayed, it can be difficult to complete an evaluation within the time constraints of research funding. In this study, the opening of the Lake Basin Mall and the hypermarket has been delayed. The baseline assessment has been completed, allowing detailed quantitative and qualitative exploration of associations between food retail, including supermarkets, and the outcomes of interest, which is an important contribution to the broader goal of understanding the role of food retail in shaping dietary and other health behaviors.

Natural Experimental Designs in Low- and Middle-Income Contexts

To date, much of the evidence from research on supermarkets, and studies using natural experimental designs, is drawn from high-income countries. However, the evidence generated from these types of studies tends to be at least somewhat specific to the context, and it is unlikely that findings from high-income countries would be completely generalizable to LMICs. In particular, key differences in LMICs include resource constraints from the individual to the governmental level, the co-occurring burden of infectious disease, and, particularly for research on diet, the nutrition transition and triple burden of malnutrition. It is likely that the identification of generalizable causal

relationships from natural experimental studies will rely on the cumulation of studies across different contexts [20,32]. It is, therefore, important that evidence from a range of different contexts, including LMICs, forms part of this corpus of work.

Conceptualizing Exposure in Natural Experimental Designs

With natural experimental designs, the delineation of exposed (ie, intervention) and unexposed (ie, comparison) groups is required in order to take advantage of the variation in exposure generated. This is not always straightforward and depends on the research question and putative causal chain. For example, the use of area-based exposures is often used [33], encompassing individuals within a defined geographical area. Graded individual-level exposures can also be considered, commonly operationalized as distance to the intervention of interest. In this study, we operationalized a group-level exposure as living in either the hypermarket intervention area (ie, Kisumu) or comparison area (ie, Homabay). The group-level comparison was intended to capture both direct and indirect impacts of the hypermarket, independent of whether the individual actually shopped there, possibly via associated changes to local food retail. We also used an individual-level exposure, operationalized according to whether the individual shopped at the new hypermarket. This was intended to allow for the detailed evaluation of direct impacts among shoppers.

The use of controlled comparisons is intended to account for confounders. However, it is acknowledged that comparison groups in natural experimental studies are typically imperfect and not akin to those achieved through randomization. Groups that are broadly similar across a range of important demographic, environmental, and behavioral variables are often the best that can be achieved. In this study, we acknowledge that our comparison area differed in some respects to the intervention area; nevertheless, this design will still allow researchers to account for measured confounding. The possibility of unmeasured confounding related to other concurrent changes is a core limitation of this study and of natural experimental designs in general.

Strengths and Limitations

This is one of very few studies examining how changes in the food environment relate to changes in behavior and health in LMICs. The strengths of the study include the use of established and validated quantitative methods and the collection of complementary qualitative data, making this a unique data set for this setting. We particularly focus on inequality and the potential for differing impacts in different SES groups. The limitations of this study relate mainly to the general limitations of natural experimental designs and are discussed in detail in the previous section.

Conclusions

This study aims to further the understanding of the relationship between food retail and dietary behaviors in Kenya. Baseline assessments for the study have been completed.

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Conflicts of Interest

None declared.

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Abbreviations

GIS: geographic information system
LMICs: low- and middle-income countries
NIHR: National Institute for Health Research
SES: socioeconomic status
The Network: Global Diet and Activity Research Group and Network

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Protocol

Physical Activity, Nutritional Habits, and Sleep Behavior Among Health Profession Students and Employees of a Swiss University During and After COVID-19 Confinement: Protocol for a Longitudinal Observational Study

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Abstract

Background: SARS-CoV-2, a novel coronavirus strain, has resulted in the COVID-19 pandemic since early 2020. To contain the transmission of this virus, the Swiss Federal Council ordered a nationwide lockdown of all nonessential businesses. Accordingly, students and employees of institutions for higher education were informed to continue their academic programs through home-office settings and online lectures.

Objective: This longitudinal survey aims to evaluate various lifestyle habits such as physical activity, nutritional habits, and sleep behavior among students and employees of a Swiss University of Applied Sciences during a 2-month period of confinement and social distancing due to the COVID-19 pandemic and 1 year thereafter.

Methods: This paper describes a protocol for a retrospective and prospective observational cohort study. Students and employees of Bern University of Applied Sciences, Department of Health Professions, were invited to anonymously complete a web-based survey during the COVID-19 confinement period. This will be followed by a second survey, scheduled 1 year after the lockdown. Information on various lifestyle aspects, including physical activity, nutritional habits, and sleep behavior, will be collected using adaptations of existing validated questionnaires.

Results: This longitudinal study started during the government-ordered confinement period in Switzerland in mid-April 2020 and will end in mid-2021.

Conclusions: The findings of this survey will provide information about the impact of confinement during the COVID-19 crisis on the physical activity, nutritional habits, and sleep behavior of students and employees of a Swiss institute.

Trial Registration: ClinicalTrials.gov NCT04502108; https://www.clinicaltrials.gov/ct2/show/NCT04502108

International Registered Report Identifier (IRRID): DERR1-10.2196/25051

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KEYWORDS

healthy lifestyle; pandemic; public health; universities; COVID-19; SARS-CoV-2

Introduction

On March 11, 2020, the World Health Organization declared COVID-19 as a pandemic. Thereafter, on March 16, 2020, the Swiss Federal Council declared the pandemic as an extraordinary situation in accordance with the Epidemics Act from midnight of March 16, 2020, until April 19, 2020, during which stringent measures were introduced. All so-called

"nonessential businesses" had to be closed, as well as schools of all levels, including universities and universities of applied sciences. The Swiss Federal Council called upon the members of the public to avoid all unnecessary social contact and to remain at home in order to maintain safe physical distance from other individuals, and as such, to contain the pandemic. This so-called extraordinary situation was extended further, and on May 11, 2020, most of the emergency packages were withdrawn.

These lockdown orders were immediately followed by the Head of the Bern University of Applied Sciences (BFH). Classroom teaching (ie, in lecture halls, classrooms, and skills rooms) was no longer possible, and students and employees were asked to remain at home and continue their work in home-office settings. During this period of confinement, social distancing, and working from home-office, lecturers were asked to switch to digital technologies to ensure continuation of various educational programs during the second half of the Spring 2020 academic semester and the upcoming Spring 2020/21 semester. The lifting of these strict COVID-19 measures is being closely monitored. The Swiss Federal Council can impose new restrictions in case of a sudden increase in new COVID-19 cases.

Lifestyle habits such as physical activity, nutritional habits, and sleep behavior of university lecturers and students during such an extraordinary period of confinement and social distancing have not been studied to date. However, there is ample evidence describing the positive effects of adequate physical activity as well as the negative effects of physical inactivity on human health [1-6]. During this nearly 2-month-long lockdown period, all sports infrastructure in Switzerland was forced to close. Although regular access to fitness clubs and sports facilities was no longer possible, individuals were allowed to continue walking, jogging, and cycling. Food shops, however, remained open during this confinement period, and Swiss residents were allowed to go outside for food supply while adhering to the recommended preventive measures (eg, maintaining safe physical distance). The positive relationship between healthy nutritional habits as well as good sleep behavior and improved human health has been well documented in the literature [7-9].

Because the COVID-19 pandemic is caused by a novel coronavirus strain, and vaccination and effective treatment options are currently lacking, it is difficult to predict how the pandemic will develop. Increased knowledge about lifestyle habits of students and employees of the Department of Health Professions (DHP) at BFH (BFH-DHP) during such an extreme confinement situation may help Heads and Deans of academic institutions to inform or counsel their students and employees during a similar situation, or in case of another outbreak, in the future. However, owing to the uniqueness of the ongoing COVID-19 crisis and its societal impact, such knowledge is currently lacking.

This longitudinal observational study will examine the impact of COVID-19 confinement on lifestyle habits such as physical activity, nutritional habits, and sleep behavior among students and employees of the BFH-DHP (Switzerland) during the 2-month confinement period and social distancing and 1 year after confinement.

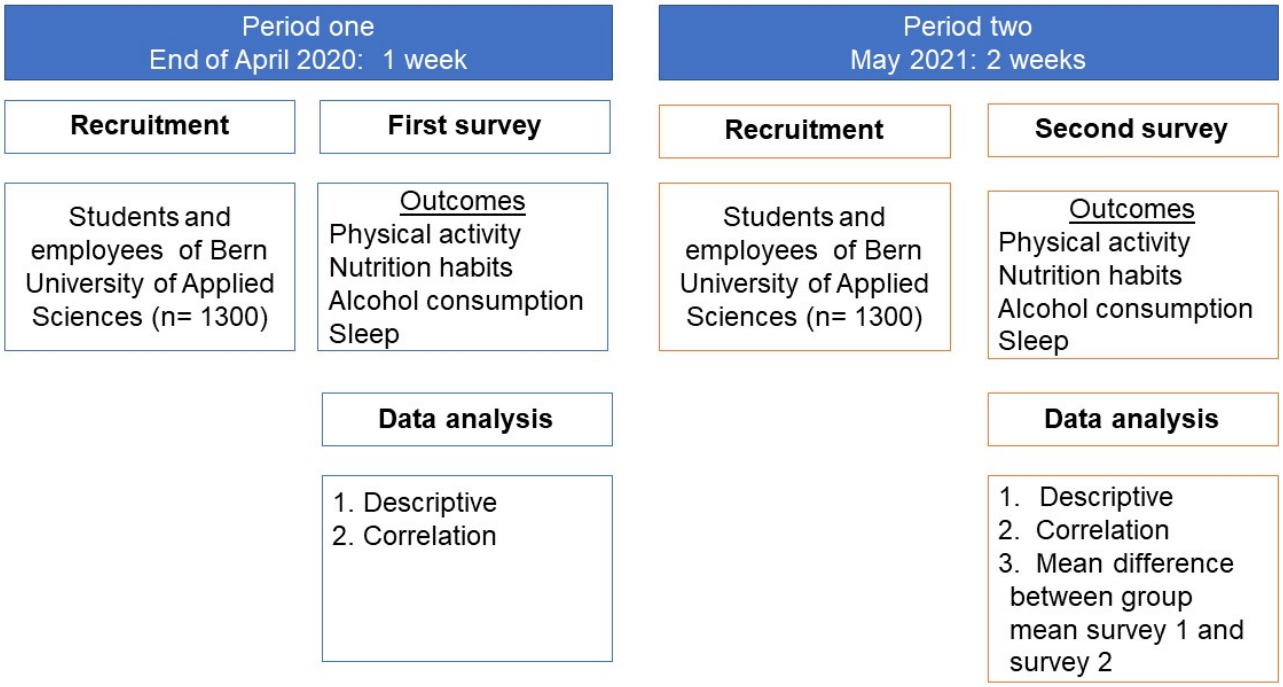
Methods

Study Setting

This study follows a cohort study design and will be carried out at BFH-DHP in Switzerland. Figure 1 illustrates the flow diagram for the research design used in this study. This project is an interdisciplinary cooperation involving colleagues from the Departments of Nutrition and Dietetics and Physiotherapy of BFH-DHP. The contents of the survey will be developed at an interprofessional level.

This cohort study comprises 2 defined study periods: The first study period was in the end of April 2020, when the Swiss Federal Council declared the COVID-19 pandemic as an "extraordinary situation." The first study was cross-sectional, consisting of an anonymous web-based survey. For the first survey, a questionnaire was sent to the staff and students of all 4 divisions of the institute during the COVID-19 confinement period. The participants' responses were anonymous, in accordance with the data privacy policy of Switzerland [10]. Participants were not allowed to provide any personal information or other sociodemographic characteristics and living status. Participants could stop and exit the survey at any stage before completion. Anonymous survey procedures are known to yield higher disclosure rates of sensitive or stigmatizing information than nonanonymous procedures. Moreover, higher disclosure rates have traditionally known to be associated with more accurate results than lower disclosure rates [11].

Figure 1. Flow diagram of the study.



The second survey will be conducted in May 2021; this survey will aim to collect information on the sociodemographic and living status of the participants. The time period for the first survey was 1 week and that for the second survey has been set to 2 weeks.

One researcher (SR) was responsible for the preparation of the electronic version of the first survey in April 2020 (during the full-confinement period); the same researcher will also complete implementation of the survey as a follow-up in May 2021. This study has been registered at ClinicalTrials.gov: NCT04502108.

Ethical Approval and Consent to Participate

Prior to the planning of this protocol, the Dean of the Health Department of BFH was informed about the survey, and he approved this study. This cohort study will be performed following the ethical principles of the Declaration of Helsinki. In the introductory section of the survey, eligible participants (staff and students) were informed that the survey is voluntary and anonymous and that no medical data is requested. Participants could also contact the researchers for any information or further questions. Finally, participants were explicitly asked to provide informed consent for participation electronically, by clicking a button at the start of the electronic survey. The second survey will follow the same procedure outlined above. The evaluation system software we intend to use in this study does not allow for any tracing of the respondents.

The cantonal Ethics Committee of Bern is responsible for this research project. The main task of the ethics committees of Switzerland is to examine and approve applications for research projects in the field of human research. The committees evaluate projects that fall under the following definition from Article 2 of the Federal Act on Research involving Human Beings: “This Act applies to research concerning human diseases and concerning the structure and function of the human body, which involves: persons; deceased persons; embryos and foetuses; biological material; and health-related personal data.” We sought clarification from the Ethics Committee of Bern on whether this research project falls within the scope of the Human Research Act and/or to request a written statement in case the project does not need approval by the committee. We thus verified that this study does not need an approval from the ethics committee (Reference number: Kantonale Ethikkomission Bern, KEK Bern, Req-2020-00909).

Recruitment

This cohort study aims to recruit at least 80% of the 1300 students and employees of BFH-DHP. The recruitment strategy comprised the following procedure: in consultation with and support of the director of BFH-DHP, an invitational letter will be sent via email to all students and employees during the first (April 2020) and second (May 2021) study periods.

Eligibility Criteria

All students (N=1300; 88% female and 12% male) enrolled in programs at the Bachelor of Science and Master of Science levels as well as all academic and nonacademic employees of BFH-DHP are eligible and will be invited to participate in this comprehensive, web-based survey. BFH-DHP runs these educational programs in the fields of nursing, nutrition and dietetics, midwifery, and physiotherapy. Individuals that are not employed or enrolled at the university will not be eligible for this study.

Outcomes

Primary Outcome (Physical Activity)

The validated German version of the international physical activity questionnaire-short form (iPAQ-SF) [12] will be used to assess the participants’ physical activity over the last 7 days.

Seven items of the questionnaire will evaluate the number of days participants performed intensive and moderate physical activities and walking activities and the time (hours and minutes) spent per day in performing the exercises at those intensities. The primary outcome variable will be total physical activity expressed as metabolic equivalents of task in minutes per week (METs/week), which is calculated as the sum of 3 physical activities (ie, walking activity and moderate and intensive physical activities). For the categorical division into the 3 activity levels (low, moderate, and high), definitions from published evaluation guidelines will be used.

Secondary Outcomes

Nutritional Habits

The valid German version of the Mediterranean diet screener (bMDSC) [13] will be used to assess the participants' nutritional habits and adherence to the Mediterranean diet. Participants will be asked to report their adherence to the recommended consumption frequency of 15 selected food items during the past year: (1) use of olive oil for cooking; (2) use of olive oil as salad dressing; (3) daily intake of cooked vegetables; (4) daily intake of raw vegetables; (5) daily intake of fruits; (6) daily intake of red meat or sausages; (7) intake of butter and bread for breakfast or dinner; (8) intake of soft drinks or sweetened drinks on the previous day; (9) attention to nutritional fiber intake; (10) weekly intake of legumes, chickpeas, and beans; (11) intake of fish 1-2 times per week; (12) consumption of nuts at least at 3 days per week; (13) preference of white meat over read meat; (14) intake of rice or pasta with vegetable sauce as part of the diet; and (15) consumption of French fries on the previous day [14]. Response categories will be "Yes" or "No." All questions will be scored "1" if answered with "Yes," except questions (6), (7), (8), and (15) that will be scored "1" if answered as "No." Scores will be summed, and a higher score will indicate better adherence to the Mediterranean diet.

Alcohol Intake

Daily consumption of wine, beer, and spirits (liquor) will be evaluated and measured in units (glasses). For instance, how many units (glasses) of wine, beer, and spirits are consumed per day?

Sleep

Sleep behavior will be evaluated and measured as number of hours of sleep and quality of sleep via the following question: How well do you sleep? Possible answers include "No sleep problems," "Sleep quality could be improved," and "important sleep problems."

Assessment Methods

First Survey

The questionnaire was sent via the institute's email system to all eligible staff and students during the 2020 COVID-19 confinement period. A brief introduction section prefaced the questionnaires to explain the survey objectives. The survey was open during a brief, 1-week period to assure a full-confinement snapshot. Automated reminders were sent at least 2 times during this period. Submitted survey responses have been stored on the institute's "evaluation system software," from where data can be merged and extracted in an Excel spreadsheet for further analyses. As this data management will be fully automated, no special quality control procedures other than regular plausibility control measures (eg, range checks) are planned.

Second Survey

The same questionnaire that was used in the first survey will be sent to all eligible staff and students of BFH-DHP about 1 year later (ie, Spring 2021) during the period of "new normality." The survey will be open during a 2-week period, and automated reminders will be sent to all participants. Because the process will be completely anonymous, the question "Did you volunteer to participate in the same survey last year?" will be added to the questionnaire. This question will allow to extract a set of participants that filled out both surveys and further perform group comparison analyses of lifestyle habits during confinement and under conditions of "new normality." Furthermore, the second survey will include additional questions on gross anthropometric characteristics (ie, height and weight), sociodemographic characteristics, living status, gender, age, household size, changes in smoking habits, and quality of life.

Data Collection

This electronic survey will be conducted anonymously using the "evaluation system software" of BFH-DHP (EvaSys, Electric Paper EvaluationssystemeGmbH), which is typically used for quality control of lectures, seminars, and other educational products. The validated iPAQ-SF and bMDSC questionnaires will be transferred within the EvaSys-framework to assess participants' physical activity and nutritional habits. Additional questions on alcohol consumption and sleep behavior will also be added to the survey.

The first survey will be conducted electronically. After closing of the 1-week survey period by the end of April 2020, the data collected will be merged and automatically extracted into an Excel spreadsheet for further analyses. The first survey will be analyzed as a cross-sectional study, in accordance with the official guidelines to analyze iPAQ-SF and adapted bMDSC. The survey results will be subjected to analyses as described in the Statistical Analyses section.

The second survey in May 2021 will also be analyzed as a cross-sectional study using the same procedures as used for the analysis of the first survey in 2020. In addition, a subgroup analyses of participants who volunteered in both surveys will allow for group comparison (during confinement versus after confinement).

Data Management

Data management will be performed on the BFH-DHP server. The EvaSys system will automatically store data collected from all study participants as comma separated variables (.csv) files. All data files will be imported and merged to a single data file in Excel (2018; Microsoft Corp).

Data cleansing will be performed by one researcher (JT) who will check and solve for example dot-comma decimal signs incompatibilities and to control plausibility of the data (ie, range checks). The iPAQ-SF data-cleansing guidelines will strictly be adhered to, that is, participants with incomplete (missing)

data or those who responded "don't know" will be removed from the analyses.

Data analyses will be carried out in 2 steps. First, data on physical activity, nutritional habits, alcohol consumption, and sleeping habits will be separately analyzed. Second, an explorative correlational analysis will be conducted, including only those participants with a complete set of data for all lifestyle habits under evaluation. Subgroup analyses will be conducted to compare differences in the outcomes between health profession divisions or between students' academic levels (ie, BSc and MSc) and employee status.

Statistical Analyses

Parametric and nonparametric statistics will be used to report results from both surveys and to compare survey results with reference values obtained from the general population during pre–COVID-19 conditions. For descriptive analyses, central tendencies will be expressed as means or medians, and variation will be expressed as SD and 95% CI or interquartile ranges (25th and 75th percentiles), respectively. Kruskal-Wallis tests with posthoc Bonferroni corrections will be used to assess differences between independent groups. Results will be presented as frequency tables or as figures with boxplots.

For the explorative correlation analysis, health profession divisions, students' academic level, and employee status will be recoded as follows: nutrition and dietetics = 1, midwifery = 2, nursing = 3, physiotherapy = 4, BSc = 1, MSc = 2, and employee = 3. The Spearman rank order correlation coefficient will be used to assess associations between the different variables under analysis. Results will be presented in a correlation matrix.

Statistical analyses will be conducted using SPSS software (version 26.0; IBM Corp.). Statistical significance will be set at the 5% level of error.

Results

This longitudinal study was started during the lockdown in Switzerland, in mid-April 2020 and will be completed in May 2021. The first phase of the study is underway, and data from 823 participants will be evaluated.

Discussion

This paper outlines the study protocol of the survey conducted among BFH-DHP students and employees to evaluate their physical activity, nutritional habits, and sleep behavior during the 2020 COVID-19 confinement. This protocol has been developed as an interdisciplinary collaboration between faculty members of the Divisions of Nutrition and Dietetics and Physiotherapy.

During the same period, similar initiatives were undertaken by other institutes. For example, a large survey developed by a consortium of many international universities aimed to retrospectively evaluate the changes in lifestyle habits among the general population in context of the COVID-19 pandemic [2,15,16].

One of the strengths of our survey is that it will be short (time needed to complete the survey will be less than 10 minutes), limiting the questions to physical activity, nutritional habits, and sleep behavior within a specific setting of students and employees of BFH-DHP. We believe, this will help the participants place special focus on the current and future multipliers of healthy lifestyle habits and their own personal behavioral changes due to a general lockdown effected as a key countermeasure to combat the spread of the COVID-19 pandemic. Another strength of our survey is its prospective design over a 1-year period. Based on the large sample size comprising eligible staff and students (N>1500) and considering the huge impact of COVID-19–related strict measures on both the staff and students, we expect a reasonable response rate (ie, around 30%). It may be hypothesized that such a confinement period may negatively affect physical activity levels of individuals, in general, and students and employees of BFH-DHP, in particular. In an effort to support the public in maintaining "healthy" physical activity levels, Swiss television channels resumed broadcasting home exercise programs after almost two decades. During this time, popular press reported an increase in the demand for fresh vegetables and fruit, as well as alcoholic beverages. Our survey will aim to verify and, if applicable, quantify such observations and put them in proper context.

The results of this survey may have important public health impacts. They may empower heads of universities and higher education institutions to better prepare, inform, and counsel their students and employees on maintaining healthy lifestyle habits that may prove useful, for example, in case of an upcoming second wave of COVID-19 or a sudden outbreak of a serious new viral epidemic or pandemic in the future. Action plans for workplace health promotions may be developed with a special focus on digital dissemination routes to reach students and employees in their home-office settings.

Several biases can occur in cohort studies, which should be reduced. For instance, a selection bias resulting from the approach used to select or observe study participants, which may influence the relationship between exposure and outcome. To avoid this type of bias, this study will recruit persons from only a single institution, ie, BFH-DHP. Second, an information bias could originate either from the individuals being observed, observers, or instruments used to evaluate the results. In prospective cohorts, information bias can usually be easily avoided since measures can be taken during scheduling by including all variables in the registration forms (instruments) so that no variables of interest are overlooked.

Nevertheless, this study has limitations. The survey does not collect any data about illnesses among participants during the first phase, which could likely influence a change in the targeted behaviors.

Acknowledgments

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Authors' Contributions

JT conceptualized this project and acted as the project manager; HB is the principal investigator of the research group; and SR, JT, and HB designed the study protocol. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

BFH: Bern University of Applied Sciences
bMDSC: brief Mediterranean diet screener
DHP: Department of Health Professions
iPAQ-SF: International Physical Activity Questionnaire-short form

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Protocol

A Nutrition Intervention to Promote the Consumption of Pulse-Based Foods in Childcare Centers: Protocol for a Multimethod Study

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Abstract

Background: Plant-based foods, including pulses (dry beans, lentils, chickpeas, and peas), have gained worldwide attention owing to their health and environmental benefits. Despite high production, the consumption of pulses is low in Canada. Behavior change interventions systematically designed to promote the consumption of pulse-based foods are scarce.

Objective: We describe the utilization of intervention mapping (IM) in the development of a multicomponent nutrition intervention aimed at promoting consumption of pulse-based foods among preschool children in childcare centers in Saskatchewan, Canada.

Methods: The Pulse Discovery Toolkit intervention was developed following the six steps of the IM protocol. Decisions at each step were either based upon literature review, expert consultation, pretesting, or a combination of these. Following the initial phase of the study, which focused on intervention development, phases II and III of the study were concerned with pilot testing and roll-out of the intervention, respectively. In total, one, two, and four childcare centers participated in phases I, II, and III, respectively. A multimethod approach was designed to evaluate the intervention during pilot testing and roll-out.

Results: The application of IM steps 1 to 3 in phase I resulted in the creation of performance objectives at different levels, including at the individual level (preschool children), and the social and environmental levels (parents, early childhood educators, and cooks). These objectives were then used to create a matrix of objectives matching the constructs of the social cognitive theory while taking Piaget cognitive development into consideration. This step was followed by defining program components, implementation, adoption, and evaluation strategies, which were utilized in phases II and III. Data have been collected from 2015 to 2018 and analyzed. The results will be reported elsewhere.

Conclusions: The IM protocol provided a rigorous framework for the development of a multicomponent evidence-based intervention to promote pulse-based foods in childcare centers.

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KEYWORDS

behavior change; childcare center; intervention mapping; nutrition intervention; preschool children; pulse

Introduction

Consumption of plant-based foods has gained attention worldwide for many reasons, including health, environment, and animal welfare. Recognizing the health benefits of plant-based proteins [1-4], the recent release of Canada's Food Guide (2019) and the Planetary Health Diet both emphasize consumption of these foods [5,6]. Pulses (dry beans, lentils, chickpeas, and peas) are excellent sources of plant-based proteins that can improve the quality of diets; additionally, these foods are rich in micronutrients and fiber and low in fat, and have a low glycemic index.

Despite the health benefits and the high production of pulses in Canada, their consumption is low among Canadian adults [7]. Studies have shown that the development of eating behaviors and food preferences begins during the early years (0-5 years of age) [8,9]. Although there is a paucity of data on children's consumption of pulse-based foods at the national level, Mudryj et al [10] reported that only 8.2% of children residing in Manitoba consumed pulses or soy. Additionally, Jarman et al [11] noted that there is a need for improvement in the diets of preschool-age children, with 90% and 35% of preschool children consuming more than 20 g of candy and snacks (such as popcorn, pretzels, and cookies) and 100 g of sugar-sweetened beverages, respectively, each day.

Understandably, the home and family environments have an important influence on children's eating behaviors. However, according to a survey released in 2019, about 52% of Canadian children under 6 years of age were enrolled in childcare centers [12]. Given that children typically eat at least two meals each day in childcare centers, these centers make an ideal venue to engage a large proportion of children for nutrition-related behavior change interventions. Engaging parents to reinforce such center-based nutrition interventions was found to be crucial in achieving the intended goal [13].

It has been argued that consistently exposing children to nutritious pulse-based foods at an early age may help to promote healthy dietary behaviors that can span into adulthood [14]. Implementing such a behavior change is a complex process that requires a systematic approach. The intervention mapping (IM) protocol provides a framework for guiding the design and implementation of multilevel nutrition education interventions. IM has been successfully used to create and promote a healthy diet in several nutrition behavior change interventions that target children aged 3 to 13 years, as well as their parents [15-20]. Interventions designed using such a structured framework to encourage pulse consumption are scarce. This paper describes the utilization of IM in the development of a multicomponent nutrition intervention aimed at promoting consumption of pulse-based foods among preschool children in childcare centers in Saskatchewan, Canada.

Methods

Overview

The study encompassed three phases. Phase I focused on the development of the Pulse Discovery Toolkit (PDTK) intervention (described in IM steps 1-6 listed below), phase II encompassed pilot testing, and phase III included intervention roll-out with minimal support from the research team. In total, one, two, and four childcare centers participated in phases I, II, and III, respectively. Community partners (childcare center directors, early childhood educators, cooks, and parents) were consulted at various points of the study.

Intervention

The PDTK is a multicomponent nutrition education intervention designed using a stepwise IM approach [21] with two theoretical frameworks, namely the Piaget cognitive developmental theory and social cognitive theory (SCT). The six-step process that guided the developmental process is described below.

Step 1: Needs Assessment

The first step in the development process was a needs assessment and an analysis of the problem. This step was completed through stakeholder (educators, parents, researchers, and community partners involved in the field) consultation, informal conversations with childcare center staff, and a literature review.

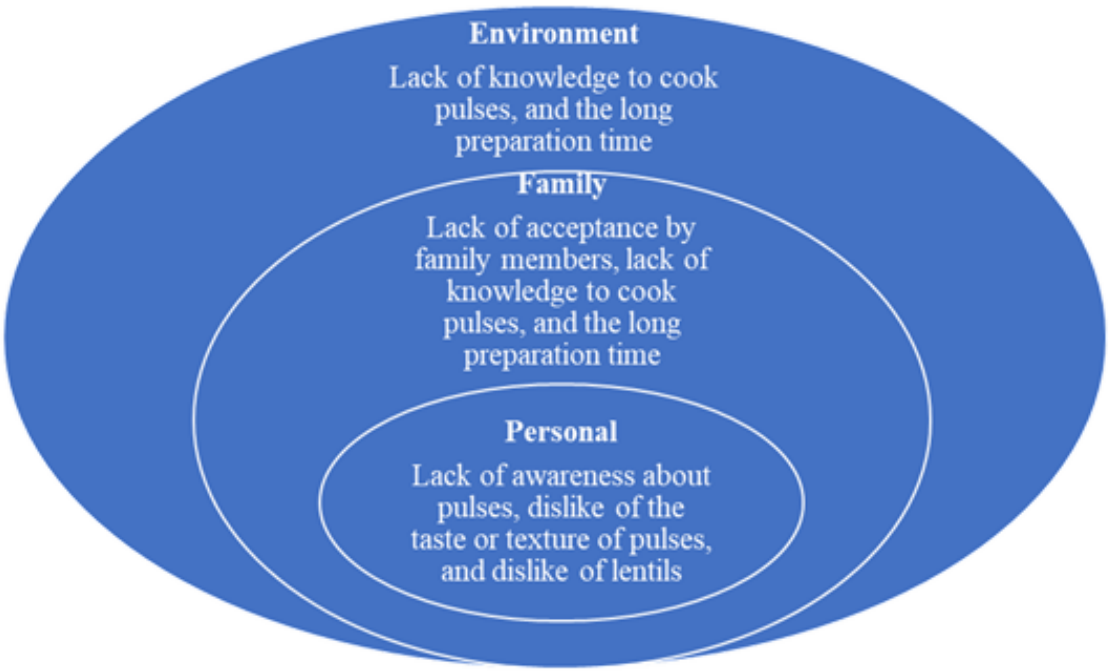
Through the literature review, the consumption of pulse-based foods was explored to elicit additional information on barriers and determinants. Additionally, food-based interventions conducted in childcare settings were reviewed to identify gaps and successes that would be helpful for the development of this intervention. For the stakeholder consultation process, at the beginning of the study, an eight-member multidisciplinary team of researchers, graduate students, and community partners was established to conduct problem analysis, fine-tune the PDTK intervention, and participate in recipe selection and taste testing. Two early childhood educators (ECEs) and preschool children (n=23) from a pretest childcare center in Saskatoon, Saskatchewan, Canada, who were not involved in the pilot study or roll-out study, took part in the development of the PDTK intervention. This pretest site in Saskatoon was chosen owing to its proximity to the University of Saskatchewan campus and willingness to participate in the PDTK development process. Informal discussions were carried out with the pretest childcare center staff on findings obtained from the literature review. The literature review revealed that the emphasis of nutrition interventions targeting preschool children in childcare settings has been on the consumption of fruits and vegetables [22-25]. Furthermore, studies indicated that most effective interventions were multicomponent and involved children, parents, educators, and the food environment [26,27].

Determinants of pulse consumption at individual, social, and environmental levels identified from the literature [28,29] are presented in Figure 1. Very few studies in Canada have

addressed these determinants. A childcare center intervention study conducted by Froehlich Chow et al [30] focused on increasing educators' and cooks' knowledge of pulses that increased their knowledge and utilization of pulse-based foods in these settings.

Recipe books and websites were reviewed to create a matrix of child-friendly pulse-based recipes for lunch and snacks that could be adopted in the intervention using predefined criteria (Multimedia Appendix 1). The Kids Book of Lentils; Pulses; Cooking with Beans, Peas, Lentils and Chickpeas; Lentils for Every Season; The Best of Heart Smart Cooking; and Pulse Canada websites were among the resources reviewed for recipes [31,32]. In addition to pulse-based foods that could be prepared at childcare centers, commercially purchased products, such as puffs, lentil pasta, and biscuits, were also included in the matrix.

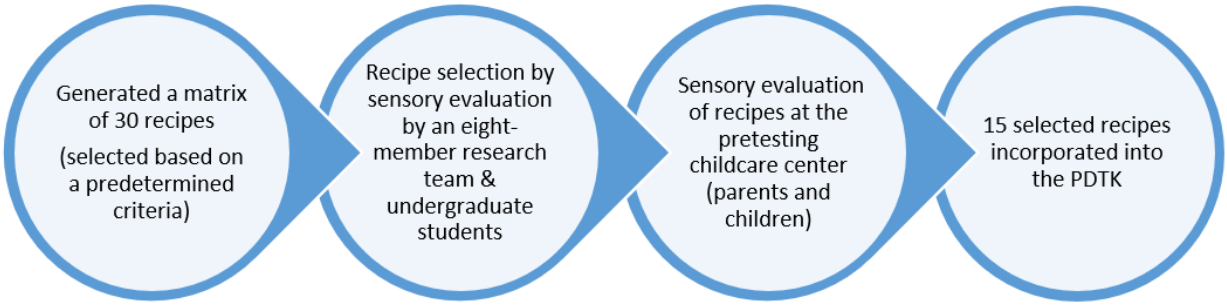
Figure 1. Individual, social, and environmental determinants of pulse consumption among preschool children based on literature review.



The criteria for recipe selection were developed by consulting different guidelines, but mainly focusing on the 2007 Eating Well with Canada's Food Guide and Saskatchewan Ministry of Education's Child Care Regulations [33,34]. Criteria considered during the selection of recipes were as follows: (1) capacity to offer 0.5 to 1 food guide serving, with at least two food groups for mixed dishes; (2) whether the food item could be eaten by children independently; (3) risk of choking; (4) availability of ingredients; (5) risk of allergy; (6) cost of ingredients; and (7) ease of preparation. This initial selection process generated a possible list of 30 pulse-based recipes (Multimedia Appendix 1).

The eight-member team, along with undergraduate nutrition students, preschool children, and their parents in the pretest center participated in sensory evaluation of the recipes at different stages of the PDTK development (Figure 2). Initially, the recipes were evaluated by the eight-member team for taste, appearance, and the likelihood of acceptance in a childcare center. This evaluation resulted in a list of 11 acceptable recipes that could be incorporated without any modifications into the PDTK, as well as a few recipes that would require further modification such as reducing strong flavors, increasing the proportion of pulses, and improving texture. After the recipe modification, students in an undergraduate nutrition class were invited to taste four of the recipes that needed modifications based on the team's evaluation to see if they needed additional adjustments. Further sensory evaluation of selected recipes was then carried out with preschool children at the pretest center to determine their acceptability. A modified method previously used in kindergarten settings was employed for this assessment [35]. Groups of three to five children of similar ages were paired with one researcher. Researchers explained the procedure to the children, and samples of pulse-based foods were presented to them. They could ask for more portions if they wanted. The researchers observed and took detailed notes on whether the children ate all, some, or none of the portions or if they asked for more. The reports from each researcher were used to record how many children tasted the foods, and the results indicated that the majority of children were willing to taste the recipes and expressed their liking. In addition to gathering information on willingness to taste and liking of the pulse-based foods, this process also helped in shaping the final sensory evaluation procedure to be used for the pilot testing project. Parents and their children attending a parent-teacher consultation meeting at the pretesting site also provided an informal evaluation of two of the recipes (lentil smoothie and lentil pizza). Parents tasted the recipes and provided feedback verbally. Most parents indicated that they liked both recipes. Overall, this process served to identify 15 recipes that were incorporated into the PDTK.

Figure 2. Step-by-step recipe selection process for integration into the Pulse Discovery Toolkit intervention.



Step 2: Specifying Program Objectives

Findings from the expert consultation and literature review in step 1 helped to shape the desired objectives of the PDTK intervention. The general program objective was to increase the consumption of pulse-based foods among preschool children in childcare settings. Considering the barriers and determinants related to consumption of pulses by children identified in step 1, the program objective was translated into performance objectives at individual (children), and social and environmental levels (parents, ECEs, and cooks). These are activities that the children, parents, ECEs, and cooks needed to complete to promote behavior change. Parents, ECEs, and cooks were identified as key players who could potentially influence children's food choices [26,36] and were a focus when planning the intervention. The objectives that focused on children, parents, ECEs, and cooks to increase consumption of pulse-based foods among preschool children are presented in Textbox 1.

Textbox 1. Performance objectives of the Pulse Discovery Toolkit intervention at individual (children), and social and environmental levels (parents, early childhood educators, and cooks).

Performance objectives at the individual level (preschool children)

- Name pulses
- Grow pulses
- Identify to which food group pulses belong
- Try pulse-based dishes
- Tell parents about pulses
- Ask for pulses in different settings
- Participate in the preparation of simple pulse-based dishes

Performance objectives at the social and environmental levels (parents, early childhood educators, and cooks)

- Teach children pulse-related concepts
- Prepare pulse-based dishes
- Incorporate pulse-based food in children's menus

Step 3: Selecting Theory-Based Methods and Practical Strategies

Studies have shown that implementing a successful nutrition education intervention requires a theoretical component [37-39]. For the PDTK, two theoretical frameworks were selected to guide intervention development. The frameworks selected for this intervention were the SCT and Piaget cognitive development theory.

The most dominant and extensively used theory for implementing nutrition education programs for children is the SCT [40]. The SCT is known for its comprehensive approach, taking into consideration environmental, personal, and behavioral factors [41], which help to define intervention components [42]. This theory is often chosen because of its "emphasis on approaches that are important to youth, such as positive reinforcement" [42]. The SCT is also considered an effective framework for program development owing to interactions between individuals, their environment, and learning capacity [43]. The constructs of behavioral capability, observational learning, positive reinforcement, and environmental changes were used as guidelines in constructing the PDTK intervention components. Even though the SCT is used as the main theoretical framework, the developmental stage of preschool-aged children makes it difficult to apply all SCT constructs, such as self-evaluation. Recognizing this, the Piaget development theory was used to complement the SCT. The Piaget cognitive development theory offers specific explanations of a child's cognitive development.

The Piaget cognitive development theory highlights play and self-discovery and provides direction in the preparation of age-specific education content. According to Piaget, there are four developmental stages of children, which progress in a linear fashion. The preoperational period, which is most applicable to PDTK development, focuses on children aged 2 to 7 years, is classified as the second stage of a child's cognitive development, and involves the development of symbolic thought and consideration of the world through an egocentric perspective [44]. This stage of development is the most applicable to children during the preschool years, as at this stage, a child cannot use logic or combine ideas and only learns by copying the environment, discovering, questioning, classifying, socializing, and tangibly understanding concepts [45]. This copying of the environment, discovery, and questioning result in a schemata perception that influences children's new experiences [46]. Hence, a new schema can be formed in children's minds about new foods, such as pulses, if they are exposed to them through educational activities.

Taken together, both theories helped to create the project's strategy to encourage children to adopt healthier diets and improve pulse consumption. For example, creating social and environmental changes through constant exposure to pulses and pulse-based dishes was expected to increase preferences for and consumption of pulse-based dishes. Previous studies have shown that repeated taste exposure can influence liking and willingness to consume new foods [47,48]. Subsequently, a matrix of objectives matching the performance objectives defined in step 2 was developed based on the constructs of the SCT while taking children's cognitive development into consideration (Table 1 and Table 2). In addition to the SCT and Piaget cognitive development theory, other theory-based methods were considered and implemented where applicable. These included active learning, sensory learning, and imagery. For example, children were encouraged to actively participate in creating their own pulse-based wrap, taste testing pulse-based buffets, growing pulses in a pot, naming pulses on a picture, and creating crafts using pulses.

Table 1. A matrix of performance objectives for preschool children in the Pulse Discovery Toolkit intervention.

Performance objectives	Knowledge	Skills	Self-efficacy
1. Name pulses	Describe pulses	Identify different types of pulses	Confidence in pulse identification
2. Grow pulses	Describe pulse gardening	Develop gardening skills	Confidence to participate in pulse gardening
3. Identify to which food group pulses belong	Describe the benefits of pulses	N/A[a]	Confidence in pulse identification
4. Try pulse-based dishes	Describe the taste of pulse-based dishes	Describe the taste of pulse-based dishes	Confidence in tasting pulse-based dishes
5. Tell parents about pulses	Describe pulses to parents	Describe pulses to parents	Confidence to discuss about pulses
6. Ask for pulses in different settings	Identify pulses in a variety of places	Practice asking for pulses in a variety of settings	Confidence of pulse selection in a variety of settings
7. Participate in the preparation of simple pulse-based meals	Describe how to prepare pulse-based dishes	Practice food preparation skills	Confidence to participate in preparing simple pulse-based meals

[a]N/A: not applicable.

Table 2. Matrix of performance objectives for parents, early childhood educators, and cooks in the Pulse Discovery Toolkit intervention.

Performance objectives	Knowledge	Skills	Preference
1. Teach children pulse-related concepts	Describe pulses	Demonstrate an ability to teach pulse-related concepts	Teaching children about pulses will mediate pulse-based food intake
2. Prepare pulse-based dishes	Discuss cooking pulses	Demonstrate an ability to cook a variety of pulse-based dishes	Providing pulse-based dishes will help children develop a preference for pulse-based foods
3. Incorporate pulse-based foods in children's menu	N/A[a]	Demonstrate an ability to plan a menu that incorporates pulse-based dishes	Incorporating pulse-based foods into center menus will expose children to different dishes containing pulses

[a]N/A: not applicable.

Step 4. Designing and Organizing the Program

During the fourth step, information obtained in the previous steps was organized into program components. The components of PDTK were designed to target the individual and environmental determinants identified in the previous step of IM. For example, the food service guide, which included a guide to cooking pulses in a childcare center, recipes, and shopping tips, could enhance the environmental conditions and reinforce pulse-related knowledge, thereby impacting purchase and consumption of pulses. The objectives pertaining to the behavior of parents and guardians were facilitated through the development of a newsletter as a mechanism to support their healthy eating behavior. The components of the PDTK

encompassed the following: (1) a 12-week lesson plan, (2) a food service guide for incorporating pulses in the childcare center's menu with an example of a 4-week cycle menu, (3) pulse recipes, and (4) four parent newsletters, which are described in more detail below.

Lesson Plan

The lessons were designed to actively engage children in learning about healthy food choices with a focus on pulses. Though the emphasis was on pulses, the lessons targeted multiple health-related behaviors and domains of wellness. For example, physical health through nutrition and physical activity, mental wellness (self-efficacy and knowledge), and social wellness (problem solving and interacting with others during the lessons). The lesson plans consisted of child-friendly activities and learning objectives. The developed materials, including visual messages, pictures, handouts, worksheets, and exercises, were designed to increase familiarity to pulses. Practical strategies using the objectives defined in step 2 and the selected theories in step 3 were developed (Figure 3).

Figure 3. Matching the lesson plan activities of the Pulse Discovery Toolkit intervention with the social cognitive theory and other theory-based methods.

Food Service Guide

The menu was designed to complement the nutrition education resource with child-tested meals and snacks. To achieve lasting impact, it was planned that students would receive 15 to 20 exposures to pulses through lunches, snacks, and classroom sensory sessions during the 12-week intervention. Taken together, this resource was expected to help address young children's reluctance to try new foods by providing different ideas to promote multiple exposures to pulse-based food products.

Parent Newsletter

Paper-based newsletters were sent home to the children's families as a mechanism to introduce and facilitate pulse use in households (Multimedia Appendix 2). The newsletters included information about the project, the weekly lessons taught to the children, and pulse-based intervention recipes served in the childcare center. The first newsletter was sent to parents at the beginning of the project, while the remaining three were sent monthly.

Step 5: Specifying Adoption and Implementation Plans

This step focused on strategies to promote adoption of the PDTK and the development of an implementation plan. The adoption and implementation strategies included active involvement of primary stakeholders, such as ECEs, cooks, and directors of the childcare facilities. To ensure adoption, each lesson plan and its activities were evaluated for content, flow, and age-appropriateness during the pilot testing of the study. The pilot-testing process would ensure program component evaluation by the major stakeholders.

For implementation and pilot testing, the childcare center was provided with a PDTK manual that incorporated the program components. Additionally, the staff received training in implementing the program. Trained graduate students and ECEs provided the 12 PDTK lessons. The pulse-based foods served for lunch were mainly prepared by the cooks in the childcare center facilities. For pilot-testing, graduate students assisted in the preparation of pulse-based foods used for sensory evaluation. Overall, researchers provided minimal support during the roll-out compared with pilot testing.

Step 6: Evaluation Planning

In this final step, a plan to evaluate the feasibility and impact of the PDTK program was developed. A multimethod approach with both quantitative and qualitative data collection tools was designed. The quantitative approaches to evaluate feasibility and effectiveness included (1) sensory evaluation, (2) plate waste assessment, and (3) pre-post knowledge testing regarding pulses among children. For qualitative data collection, one-on-one semistructured interview guides were developed to elicit detailed information regarding the PDTK intervention from the ECEs and cooks. The ECEs in the pilot testing childcare center were asked to provide qualitative feedback through a predeveloped weekly lesson plan evaluation form. The lesson plan evaluation carried out in phase II pilot testing provided detailed feedback that was used to revise the PDTK before the roll-out in phase III.

Parent Sociodemographic Questionnaire

A 21-item questionnaire was developed using Statistics Canada's Community Health Survey Questionnaire and the Daily Lentils Study [29]. Questions in the parent's questionnaire included, for example, how often their child consumed pulses at home and parents' highest level of education and household income.

Knowledge Assessment Questionnaire

Pretest and posttest assessments of children's pulse knowledge were planned for each intervention site. A pictorial data collection questionnaire was developed, adapted, and pretested for this purpose. This type of pictorial tool has been previously validated and used with children [49,50]. The tool consisted of five questions with various images representing different varieties of pulses. The knowledge test was organized into different pulse categories, and for each category, children were asked to identify or to indicate if they recognized the types of pulses presented. Samples of relevant pulses were also presented to each child during the questioning to assist with this process.

Sensory Evaluation

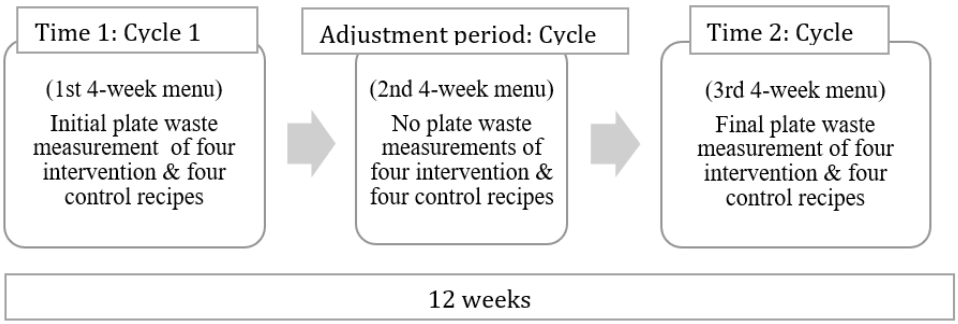
Sensory evaluation of the pulse-based foods in the PDTK was conducted using a three-point facial hedonic scale with ratings of "Yummy," "Yucky," and "Ok" [51]. Evaluations were carried out by graduate students familiar with sensory evaluation techniques. The sensory protocol was adapted from a study conducted by Guthrie et al [52]. Following an introduction of the procedure to participant children in groups, each child's understanding of the scale was assessed on an individual basis using samples of fruits (eg, pineapple, strawberries, honeydew melon, and cantaloupe). Each child was asked to pick the fruit that he or she thought was "Yummy" and asked to select the corresponding face representing the taste of the fruit. In between tasting and rating each sample, the children were asked to rinse their mouths with water. The training was completed when the children were able to understand each facial category properly.

Sensory evaluation of the pulse-based foods by the children was conducted as part of the lesson plan, and during the snack and lunch periods. As part of the lessons, the evaluation was carried out on the following three occasions: during the lessons "Pulse Buffet" (lesson 3), "Let's Make Our Own Food" (lesson 4), and "Pulse Snacks" (lesson 8). Selected recipes were evaluated at two different time points to compare changes in liking after repeated exposures. Preference testing was also conducted on the selected spreads to determine children's liking of the recipes. The procedure included presenting two different samples of spreads (red bean spread and green split pea spread) to the children and asking them to identify which one of the samples they preferred.

Plate Waste

Plate waste measurements of the intervention and control recipes were taken twice during the 12-week intervention as shown in Figure 4. Using each childcare center's 4-week cycle menu, four intervention pulse-based dishes (chickpea spread, three bean quesadillas, lentil pizza, and chicken stir fry) were randomly assigned to weekdays in the menu. The control recipes were chosen from each childcare center's regular menu and designed to fall on the same day of the week as the intervention recipe during the 4-week cycle menu. The foods served to the children were weighed and photographed before and after each meal. No plate waste measurements were taken during the 4-week adjustment period of the second cycle (cycle 2); however, the intervention recipes were incorporated into the menu to increase familiarity with the recipes.

Figure 4. The plate waste measurement cycle in the Pulse Discovery Toolkit intervention.



Information on plate waste was captured using a digital photography weighted plate waste app validated previously [53]. Briefly, a photographed reference of the selected dishes was taken prior to each meal service to provide a pictorial representation (sample) of the food served and eaten by each child. Refuse or discarded food items were also photographed and weighed on a digital scale (Salter Magic Display Electronic Scale 10B55BKEF, Springfield Instruments). To ensure consistency, the same types of plates and utensils were used each day during the data collection period. The amount of food consumed was obtained by subtracting the amount of plate waste from the amount of food served.

Comparison of the Nutrient Composition of the Intervention and Control Recipes

Esha Food Processor Nutritional Analysis Software (version 10.10.00) was used to code and compute the nutrient breakdown for all the intervention and control recipes. The nutrient composition of control recipes (four recipes from each center) and four intervention recipes were compared. Nutrients compared between recipes included kilocalories, protein, fiber, fat, saturated fat, calcium, potassium, sodium, and iron content. In addition, the number of food groups provided by a reference serving for each recipe was determined using the Eating Well with Canada's Food Guide [33]. To calculate the number of servings within each food group, the amount consumed (grams or milliliters) was divided by the value from Canada's Food Guide's reference for one serving of that food group. For example, if a child consumed 15 g of crackers and the reference for crackers is 30 g per serving, the child consumed a 0.5 serving of grain products. If the food item did not fall into one of Canada's Food Guide food groups, it was assumed to belong to the "other" category.

Lesson Plan Evaluation

Process evaluations were administered through a weekly lesson plan evaluation. The lesson plan evaluation forms included questions about the feasibility of the activities and acceptability (ie, if the children were engaged in each lesson), as well as requested suggestions from ECEs about how to improve each lesson. Questions for the lesson plan evaluation were adapted from a previous study conducted by Sharma et al [22] involving a pilot study of preschool-based healthy nutrition and physical activity programs.

ECE, Director, and Cook Interview

A semistructured postintervention interview explored the level of satisfaction with the PDTK program. Questions were adapted from the report by Sharma et al [54]. Interview questions explored topics such as nutrition concepts, children's level of engagement throughout each lesson, and suggestions to improve the nutrition education resource. The cooks' and directors' interview guides were designed to assess the perceived benefits and barriers of cooking pulses and the feasibility of cooking pulse-based dishes. In addition, the questions were designed to generate information regarding PDTK recipes the cooks least enjoyed and most enjoyed cooking. Their perceptions of whether the children liked the pulse-based dishes and whether these dishes should be incorporated into the menus of the childcare centers were also discussed during interviews.

Data Analysis

Quantitative data were analyzed using SPSS version 24 (IBM Corp) and SAS version 9.4 (SAS Institute Inc). SPSS was used to generate descriptive statistics and for paired comparisons. Chi-square and McNemar tests were used for paired nominal data to compare the preindividual and postindividual pulse knowledge scores. Data analysis techniques were adapted from a study conducted by Sigman-Grant et al [55]. A paired sample *t* test was also conducted on spreads (green split pea vs red bean) to determine if there was any difference between sensory acceptance at the beginning and the end of the intervention. SAS was used to generate *t* test and generalized estimating equation model results for plate waste measurements. The consumption proportions were calculated for each of the intervention and control recipes using the following formula: consumption proportion = sum of the amount of all intervention (or control) foods a specific child eats / sum of the amount of intervention (or control) foods given to that specific child. Using aggregate data, an independent *t* test was performed to compare the mean consumption and the mean consumption proportions of both the intervention and control recipes. Results were considered statistically significant if a P value of $<.05$ was obtained.

For qualitative data analysis, the audio recordings of the semistructured interviews were transcribed verbatim. The transcripts were then sent to the interviewees for verification. The verified transcripts were then analyzed in three phases. The first phase involved an initial review of the transcript for common concepts and themes. The process of analysis consisted of reading each individual response to each question several times and highlighting the major ideas that emerged from the transcript. The second phase of analysis consisted of an auditing process, where concepts or themes were reviewed by an independent researcher as a means of verification, to determine

if there was common consensus or disagreement with the themes identified in the initial analytical process. After the verification process, the third phase involved rearranging quotes into the selected thematic categories. Subsequently, comparisons were made between categories to describe the findings [56].

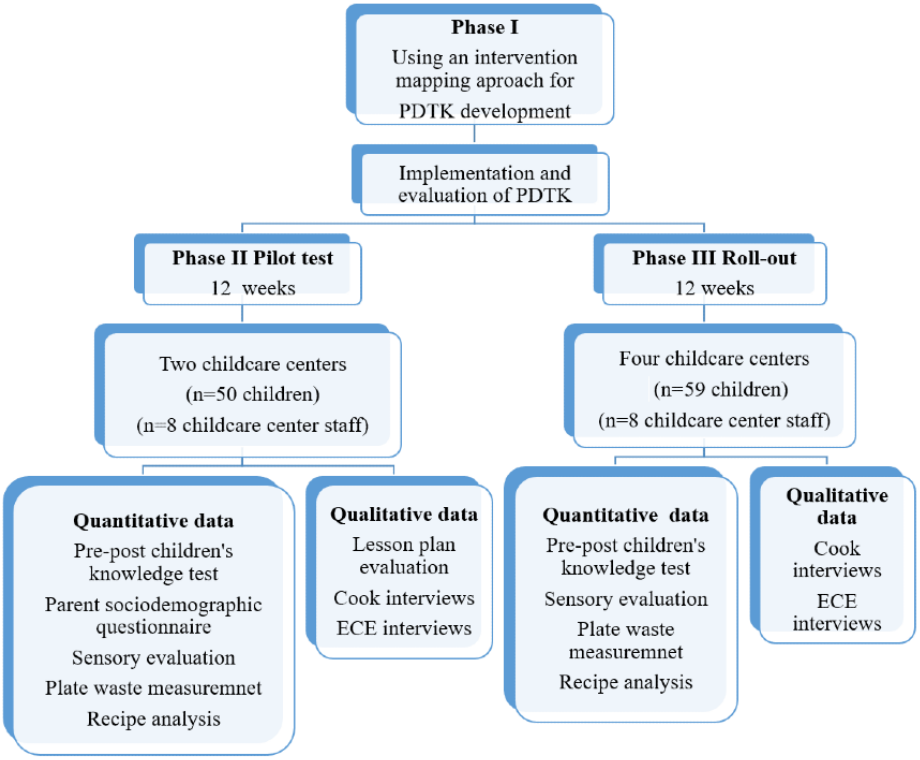
Ethical Consideration

Ethical approval was obtained from the University of Saskatchewan Behavioral Research Ethics Board. Prior to data collection, consent and verbal assent were obtained from parents and children, respectively.

Results

Data have been collected from 140 participants from 2015 to 2018 and analyzed. The results will be reported elsewhere. Figure 5 presents the types of data collected at different phases of the study.

Figure 5. Flow chart showing the development of the Pulse Discovery Toolkit (PDTK) intervention, its implementation, and the evaluation process. ECE: early childhood educator.



Discussion

Overview

Studies have widely documented the health benefits related to the consumption of plant proteins, such as lower risk of cardiovascular disease, lower blood pressure, and improved diabetes management [1,2,4]. However, a recent study underlines the presence of knowledge gaps about plant protein food consumption and the need for food literacy to enhance health [57]. It is reasonable that the introduction of the concept of plant proteins should start at an early age for lasting impact. Pulses are locally produced plant proteins that are poorly consumed in Canada. The PDTK was designed to address the knowledge gap about pulses and provide repeated exposure to pulse-based foods, cooking tips, child-friendly pulse-based recipes, and information for parents though newsletters.

This protocol describes the use of IM in the development of a multicomponent nutrition intervention to promote the consumption of pulse-based foods among preschool children attending childcare centers. Through needs assessment, consumption of pulse-based foods was identified as the behavior targeted for change. This initial step in IM ensured an in-depth understanding of the problem and helped to tailor program components to the findings of the needs assessment in later stages of planning. An important contribution of the IM process was the ability to systematically identify gaps, successes, and determinants before designing program components.

In step 2, the IM process facilitated the selection of determinants and assisted in narrowing the general program objective to objectives changeable at individual, social, and environmental levels (parents, ECEs, and cooks). Changes at the policy level were not assessed as this was beyond the scope of the project. This step facilitated the selection of the most important and modifiable behavioral determinants to ensure a change in behavior. The performance objectives were not only limited to nutrition behaviors, and multiple domains of health were targeted to provide comprehensive intervention. Fernandez et al [58] described this as a critical step in planning as it distinguishes between behaviors and their determinants, and helps establish clear performance objectives.

In the third step, the application of IM facilitated the systematic selection of theories. The available evidence indicates that most theory-based nutrition-related interventions are effective [27]. This step provides a practical decision-making process during

the development of the intervention, which is beneficial to health education program planners [21]. Step 4 focused on creating program components and was instrumental in linking the program components to already identified behaviors and determinants.

IM further assisted in capturing and incorporating the opinions of stakeholders during the development process, hence allowing program planners to plan for adoption and implementation in step 5. The support of stakeholders is crucial for better adoption and scale-up [58]. As discussed in the study by Froehlich Chow et al [30], once ECEs noted that children tasted and liked the pulse-based foods, they were motivated to serve them more often. In the final IM step, a comprehensive evaluation plan was developed.

Limitations

One of the drawbacks of the IM process was that it was time-consuming and complex. Similar limitations have been documented in interventions using IM on related topics [15,59]. Steps 1 to 3, which particularly defined the performance objectives and determinants of pulse consumption and matching with the theoretical framework, required a substantial amount of time. In addition, the process requires going back and forth to ensure all aspects are correctly addressed. Though the SCT has been mostly used to explain the determinants of fruit and vegetable consumption, the selection of the most effective SCT constructs was limited owing to the lack of interventions utilizing the SCT for pulse-based foods in preschool children. The other limitation associated with the SCT, which was owing to the age of the children, was inability to apply all of the SCT constructs. For example, the self-control SCT construct was difficult to design and implement with preschool children. Another limitation in this study is related to parents' engagement, although attempts have been made to engage parents through newsletters. Future research should look for innovative ways to engage parents and increase their involvement in studies in childcare settings.

Conclusion

The six-step IM ensured the development of an evidence-based nutrition intervention. The initial step in the IM process confirmed the need for an intervention targeting pulse-based food consumption. The IM process facilitated the identification of determinants of dietary habits focused on pulse-based food consumption, allowed the use of multiple theoretical frameworks, and assisted the matching of program objectives with the theoretical framework and lesson plan. Although the process was time-consuming, it provided more clarity to various components of the intervention, thereby increasing the intervention's effectiveness potential. To the best of our knowledge, this study is unique as it is the first of its kind to introduce pulse-based foods to young children aged 3 to 5 years through the application of a systematic theory-based IM approach in a childcare setting. Results generated from the evaluation component of this study will guide further improvements of the PDTK intervention.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Matrix of pulse-based recipes and selection.
[DOCX File , 24 KB - resprot_v9i12e22775_app1.docx]

Multimedia Appendix 2
Parents' newsletter.
[DOCX File , 481 KB - resprot_v9i12e22775_app2.docx]

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Abbreviations

ECE: early childhood educator
IM: intervention mapping
PDTK: Pulse Discovery Toolkit
SCT: social cognitive theory

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Protocol

Evaluating the Onset, Severity, and Recovery of Changes to Smell and Taste Associated With COVID-19 Infection in a Singaporean Population (the COVOSMIA-19 Trial): Protocol for a Prospective Case-Control Study

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Abstract

Background: Sudden loss of smell and/or taste has been suggested to be an early marker of COVID-19 infection, with most findings based on self-reporting of sensory changes at a single time point.

Objective: To understand the onset, severity, and recovery of sensory changes associated with COVID-19 infection, this study will longitudinally track changes in chemosensory acuity among people with suspected COVID-19 infection using standardized test stimuli that are self-administered over 28 days.

Methods: In a prospective, case-controlled observational study, volunteers will be recruited when they present for COVID-19 screening by respiratory tract polymerase chain reaction test (“swab test”). The volunteers will initially complete a series of questionnaires to record their recent changes in smell and taste ability, followed by a brief standardized smell and taste test. Participants will receive a home-use smell and taste test kit to prospectively complete daily self-assessments of their smell and taste acuity at their place of residence for up to 4 weeks, with all data submitted for collection through web-based software.

Results: This study has been approved by the Domain Specific Review Board of the National Healthcare Group, Singapore, and is funded by the Biomedical Research Council Singapore COVID-19 Research Fund. Recruitment began on July 23, 2020, and will continue through to March 31, 2021. As of October 2, 2020, 69 participants had been recruited.

Conclusions: To our knowledge, this study will be the first to collect longitudinal data on changes to smell and taste sensitivity related to clinically diagnosed COVID-19 infection, confirmed by PCR swab test, in a population-based cohort. The findings will provide temporal insights on the onset, severity, and recovery of sensory changes with COVID-19 infection, the consistency of symptoms, and the frequency of full smell recovery among patients with COVID-19. This self-administered and cost-effective approach has many advantages over self-report questionnaire–based methods and provides a more objective measure of smell and taste changes associated with COVID-19 infection; this will encourage otherwise asymptomatic individuals who are potential spreaders of the virus to self-isolate and seek formal medical diagnosis if they experience a sudden change in sensory acuity. This broadened case finding can potentially help control the COVID-19 pandemic and reduce the emergence of clusters of infections.

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International Registered Report Identifier (IRRID): DERR1-10.2196/24797

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KEYWORDS

SARS-CoV-2; COVID-19; olfactory dysfunction; gustatory dysfunction; anosmia; ageusia; onset; severity; symptom; infectious disease; dysfunction; protocol; marker; recovery; monitoring; taste; smell

Introduction

Early identification of symptoms associated with SARS-CoV-2, which causes COVID-19, has been recommended to encourage early diagnostic testing and self-isolation and to reduce the risk of community spread of infection. High temperature, continuous dry cough, and fatigue are common clinical symptoms associated with COVID-19 infection; however, numerous recent reports from patients and clinicians worldwide have consistently identified a sudden loss of smell (anosmia) and/or taste (ageusia) as a key early symptom of infection [1-6].

Recent self-report questionnaire data from many countries highlights an association between sudden onset smell and taste loss and COVID-19 infection, with reported incidences of changes in sensory acuity ranging from 11% to >60% [7-13]. A recent systematic review and meta-analysis of studies investigating loss of smell and/or taste with COVID-19 infection reported a pooled prevalence of 52.7% and 43.9% for olfactory and gustatory dysfunction, respectively [14]. Also, Hopkins et al [15] found that 1 in 6 patients reported new onset anosmia as an isolated symptom. The onset of smell and/or taste loss is often abrupt and, unlike other upper respiratory tract infections, it often occurs in the absence of nasal obstruction [13,16]. Importantly, the loss of smell and/or taste occurs early during COVID-19 infection, often before the onset of more established symptoms [8,17-20], and this loss may be an important marker of infection. This finding has prompted many global public health bodies to recommend that individuals who experience sudden changes in sensory acuity should self-isolate and present for diagnostic testing [2-4,21-24].

The majority of published studies investigating smell and taste loss related to COVID-19 have used subjective measurements of smell and taste, specifically self-report questionnaires. In Singapore, there have been anecdotal reports of smell and taste loss with COVID-19 infection [25,26], and in one prospective cohort of patients with COVID-19, it was found that 22.6% experienced acute olfactory loss [27]. The positive predictive value of acute olfactory loss for COVID-19 was 24.1%, and the negative predictive value was 96.5% [27]. Data collected to date have been based largely on self-report questionnaire measures, and there is a lack of objective data on measured smell and taste sensitivity. One study used a validated smell test, the University of Pennsylvania Smell Identification Test (UPSIT), to compare smell acuity in patients diagnosed with COVID-19 with a matched control group; it was shown that 98% of the patient group exhibited some smell dysfunction, scoring significantly lower on the UPSIT compared to controls [28].

In addition, to our knowledge, no longitudinal study has yet been performed to systematically track the onset, severity, and recovery of changes to sensory acuity across the preinfection and postinfection periods of COVID-19, with emerging reports of sustained anosmia among a small proportion of people who have recovered from infection. To date, questionnaire measures alone have been published; these studies relied on self-reporting and may not accurately reflect the true extent of smell and taste changes during COVID-19 infection in the absence of a standardized tool for such measurements. Reliance on self-report questionnaire data and variable approaches could help explain the wide variability in the reported prevalence of olfactory dysfunction with COVID-19 infection (5%-98%) [29]. Therefore, there is a need for objective testing of smell and taste loss in patients infected with COVID-19 using standardized smell and taste stimuli [29-31]. Moreover, due to extensive restrictions on movement, the need to socially distance, and the potential for infection spread with reusable standardized odor and taste test materials, the collection of in-person physical data is challenging. Furthermore, although clinically validated smell and taste assessments are preferred, they are often expensive, and their reuse is not recommended among infected patient populations. Home use sensory tests have been developed to track changes in smell and taste sensitivity using common household items as test stimuli [32,33]. However, these tests rely on participants sourcing and preparing their own test stimuli from available household items; this introduces unwanted stimulus variation, which may present problems for comparability of smell loss across individuals using different stimuli.

The COVOSMIA-19 study will standardize the smell and taste stimuli used by all participants to ensure consistency and provide a disposable, rapid, self-administered home use test, the Singapore Smell and Taste Test (SSTT), to minimize the risk of cross-contamination and infection spread. The trial will enable self-testing for up to 28 consecutive days and will provide a standardized longitudinal assessment of smell and taste function to enable tracking of the onset, severity, and recovery of the sensory changes reported to occur with COVID-19 infection. The standardized smell and taste test will also be compared with self-reported questionnaire measures of smell and taste changes and measured changes to sensory acuity using common household items (an approach previously used by [32]).

The primary objectives of this study are to (1) assess the prevalence of sudden changes in smell and taste sensitivity with COVID-19 infection in a population at risk for COVID-19 infection in Singapore, (2) establish the temporal onset, severity, and recovery of changes in smell and taste sensitivity with COVID-19 infection, and (3) evaluate the efficacy of the SSTT as a rapid, cost-effective, self-administered measure of changes to smell and taste compared to previous measures using household items. The secondary objective of this study is to investigate the effects of loss of smell and taste acuity on food enjoyment and appetite as well as to establish the impact of COVID-19 infection on food-related markers of quality of life.

We hypothesize that loss of smell and taste acuity will be associated with COVID-19 infection, will return upon recovery from infection for the majority of patients, and will result in short-term reductions in appetite, food enjoyment, and food-related quality of life.

Methods

Study Design

The study will track changes in smell and taste with COVID-19 infection using a prospective longitudinal, case-control study design. Participants will be recruited from volunteers presenting at hospitals and hospital facilities across Singapore for COVID-19 screening. After providing informed consent, the study participants will be asked to report on changes in their smell and taste sensitivity in the previous 2 weeks via a series of questionnaires; they will also be asked to prospectively track daily changes in smell and taste acuity using a self-assessment test and a series of questionnaire measures to measure the onset, severity, and recovery of changes in their chemosensory acuity for the next 28 days. A schematic of the study procedure is shown in Figure 1, and the schedule for enrolment and assessment is shown in Table 1.

Figure 1. Frequency of the different test measures for the COVOSMIA-19 clinical trial. GCCRQ: Global Consortium for Chemosensory Research Questionnaire; SNOT-22: Sino-Nasal Outcome Test; SSTQ: Singapore Smell and Taste Questionnaire; SSTT: Singapore Smell and Taste Test.

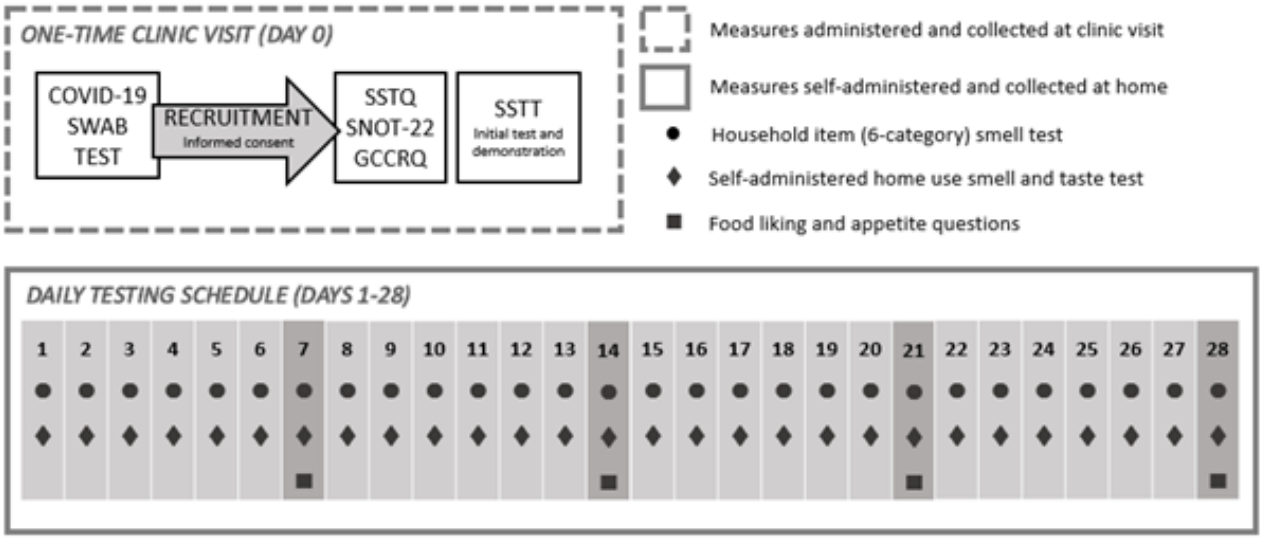

Table 1. Schedule of participant enrolment, intervention, and assessment in the COVOSMIA-19 trial.

Timepoint	Study period						
	Enrollment	In-clinic	At home (4 weeks)				Closeout
	Day 0	Day 0	Week 1	Week 2	Week 3	Week 4	Day 28
Enrollment							
Eligibility screen	✓						
Informed consent	✓						
Procedure							
Questionnaires		✓					
SSTT[a] testing kit demonstration		✓					
Initial SSTT session		✓					
SSTT (daily)[b]			✓	✓	✓	✓	✓
Additional questions (once per week)			✓	✓	✓	✓	
Assessments							
Baseline variables: gender, age, education status, nationality, ethnicity, employment status, smoking status, vaping status, medication, COVID-19 test result		✓					
Primary outcome variables: COVID-19 symptoms (and onset), smell and taste acuity			✓	✓	✓	✓	✓
Secondary outcome variables: appetite, food enjoyment, eating behaviors, nausea, weight, food-related quality of life		✓	✓	✓	✓	✓	✓

[a]SSTT: Singapore Smell and Taste Test.

[b]Participants were asked to complete the SSTT daily from Day 1 to Day 28.

Recruitment Procedure

Participants will be recruited from patients applying to a hospital and its ancillary units for COVID-19 screening by nasal swab polymerase chain rection (PCR) testing. Following their COVID-19 screening, individuals will be approached and invited to participate in this study and to provide informed consent.

Inclusion Criteria for Participants

Participants are required to be aged >21 years, reside in Singapore for the next 28 days, possess a mobile device with a 3G or 4G network, and know how to use mobile apps (ie, a quick response [QR] scanner).

Exclusion Criteria for Participants

Participants will be excluded from the study if they are unable to provide informed consent, are allergic or intolerant to any of the test items (ie, mango fragrance, jasmine fragrance, sugar, salt, coffee powder, or lime powder), are currently pregnant, or do not agree to allow the study team to access their medical records to obtain their COVID-19 infection status (ie, swab test result).

Ethical Approval and Consent to Participate

The study (ref: 2020/00810) has been approved by the Domain Specific Review Board of the National Healthcare Group, Singapore. Written informed consent will be obtained from all eligible participants prior to entry into the study. Any adverse events or unintended effects of the study procedure will be reported to the ethics committee. This information will be given to participants both verbally and in written form (in their copy of the informed consent form) during recruitment. All data will be anonymized through the use of a unique identification number for each participant and will be stored on password-protected computers. Participants will not receive any monetary compensation for their participation in the study.

Any changes to the above protocol will be reported to the Domain Specific Review Board as appropriate. In addition, these changes will be documented on ClinicalTrials.gov. The results of this study will be disseminated through reports, publication of articles in scientific journals, publication of articles for public dissemination, and conference presentations.

Measures

On the day of their COVID-19 swab test (Day 0), after consenting to participate in the trial, participants will complete three questionnaires to document recent changes in their smell, taste, and chemesthetic ability and to detail the frequency of a wide range of nasopharyngeal symptoms. These questionnaires include the Singapore Smell and Taste Questionnaire (SSTQ, Multimedia Appendix 1), the 22-item Sino-Nasal Outcome Test (SNOT-22) [34], and the recently developed Global Consortium for Chemosensory Research questionnaire (GCCRQ) [12]. Participants will receive the Singapore Smell and Taste Test (SSTT, Multimedia Appendix 2), a standardized home use

testing kit to monitor their smell and taste acuity, and will be given a demonstration of the self-assessment procedure that they will complete daily at their place of residence for the following 28 days. All the questionnaires and instructions are available in English, Mandarin, Tamil, and Bengali, and the participants will complete all the measures via Compusense Cloud web-based data acquisition software (Compusense Inc).

The SSTQ

Participants will complete the SSTQ (Multimedia Appendix 1) to record any recent changes in smell and taste and to describe the occurrence of sino-nasal or other COVID-19 symptoms. Participants will rate their current smell and taste sensitivity using the SSTQ (Day 0) to provide a baseline measure for their smell and taste sensitivity. This initial self-report questionnaire will quantify any recent changes in smell and taste acuity and includes questions on the participants' basic demographics, the COVID-19–related symptoms they have experienced, the temporal onset of these symptoms, the smell and taste acuity of the participants, and their appetite-related quality of life (eg, enjoyment of food). See Multimedia Appendix 3 for information on the sources of the questionnaire items.

The SNOT-22

The SNOT-22 will be used to quantify the presence and severity of nasal disorder symptoms [34]. Participants will be provided with a list of 22 symptoms and social and emotional consequences of nasal disorder, and they will be asked to rate the severity of each problem on a 6-point scale from "no problem" to "problem as bad as it can be." This measure has been included to assess symptoms that are commonly associated with nasal disorders and to make a distinction between changes in smell and taste due to nasal disorders and congestion and those associated with COVID-19 infection. Current research suggests that smell and taste loss with COVID-19 infection often occurs without nasal obstruction [13,16]; therefore, we expect participants with smell and taste loss to have a differential prevalence of other common nasal disorder symptoms (eg, blocked nose).

The GCCRQ

The GCCRQ questionnaire was developed and implemented by the Global Consortium for Chemosensory Research to assess whether and how COVID-19 infection affects sense of smell, taste, and chemesthetic sensitivity [12]. Participants are asked about their COVID-19 testing status and symptoms, and they complete 18 items relating to their sense of smell, taste, chemesthetic ability, and food flavors before, during, and after COVID-19 illness. Due to the potential for additional participant burden, the completion of this questionnaire is optional and will not affect the study participation. For participants who complete the GCCRQ, we will ascertain the extent to which the measures obtained using this approach correlate with the measures in the study.

Daily Smell and Taste Testing

The study participants' smell and taste acuity will be prospectively measured for up to 28 days following their clinic visit for COVID-19 testing using the home-based assessment tools detailed in this section. At the start of each daily test session, participants are to report on any changes in their smell and taste acuity by selecting either "improved," "stayed the same," or "worsened" before rating their current sense of smell and taste from "no sense of [smell/taste] at all" to "extremely strong sense of [smell/taste]." Participants will also be asked to "check all that apply" across a list of symptoms they have experienced in the last 24 hours from a list of COVID-19–relevant symptoms.

The SSTT

Participants will be provided with their own standardized home-use smell and taste test that they will complete daily for up to 28 consecutive days (Multimedia Appendix 2). The questioning approach is based on that used in the Yale School of Medicine "Jiffy" Test of mell Sensitivity [35], in which respondents perform a similar procedure with Jif peanut butter.

The SSTT smell test includes two odors—a food odor (mango) and a nonfood odor (detergent)—both of which consist of odor mixtures that have been formulated by an international fragrance manufacturer (Symrise AG). The odor mixtures were chosen to avoid possible specific anosmias to individual odor compounds, and the odors are dosed at the suprathreshold level in specialized odor delivery pens (Otto Hut). Both fragrances have been tested to deliver a suprathreshold odor at a consistent intensity and stability for the duration of the home-use test period. To perform the test, the participants remove the pen lid and place the pen 3 inches from their nose while breathing normally. For each smell, participants will identify the smell and rate the perceived intensity on a visual analog scale (VAS) from "not strong at all" to "extremely strong smell."

For the daily taste test, participants will be provided with small quantities of powder selected to represent the four prototypical tastes: "sweet" (table sugar, NTUC FairPrice), "salty" (table salt, NTUC FairPrice), "bitter" (granulated coffee powder, Nescafé), and "sour" (lime powder, Knorr). The participants will be instructed to take a small amount of each item in a sequential monadic order on the tip of their tongue with a small spoon; they will then be asked to identify and rate the perceived intensity of the taste on a VAS from "not strong at all" to "extremely strong taste" through a web-based questionnaire completed on their smartphone or other device. The participants will be asked to rinse with water between each taste stimulus and will be provided with sufficient taste stimuli for the 28 days of assessment.

Common Household Item Smell Test

For comparison with the SSTT, participants will be asked to complete a daily assessment of smell using household items (see Multimedia Appendix 2). To assess the participants' olfactory sensitivity, we will provide them with 6 categories of common household items. Participants will be asked to choose one odor from a drop-down menu for each category and indicate their perception of it on a scale from "absent" to "heightened." This approach is based on a previously reported self-assessment measure of smell sensitivity using household items [32], with an additional category of stimuli that are particularly high in trigeminal irritation. The items for all categories were adjusted

to include culturally appropriate household items that are common in Singapore.

Additional Questions

Once per week, participants will complete an additional set of questions (Day 7, 14, 21, and 28) relating to their enjoyment of food, appetite, weight, and food-related quality of life (eg, "I no longer enjoy cooking/preparing food"). The goal of this questionnaire is to assess the relative impact of changes in sensory acuity with self-reported appetite and food enjoyment, as it may be related to weight fluctuations observed during the period of infection.

COVID-19 Diagnosis

During study consent, participants will provide access to the outcome of their COVID-19 diagnostic swab test, which will be associated posthoc with the unique identification number linked to the participant questionnaire and daily home-use test data.

Sample Size Determination

This prospective trial will compare the onset, severity, and recovery of smell and taste loss as it relates to COVID-19 infection in a case-controlled prospective clinical trial. To perform our proposed cross-sectional analyses (see Statistical Analyses), we require a minimum sample size of 235 based on a power calculation of the sample size required to conduct a logistic regression. This sample will be used to analyze our primary outcome of whether loss of smell and taste acuity predict the likelihood of testing positive for COVID-19 infection. A sample size of 235 is required to observe an effect at 95% power (with a significance level of 0.05) using Pr(Y=1|X=1) H0=0.20 and an odds ratio of 1.723. This odds ratio was calculated as the smallest effect size of interest (SESOI) below which results would not be practically interesting. Given that it is difficult to draw well-informed sample size estimates from the current research, and that we instead opted to use the SESOI to calculate an estimated odds ratio and this minimum sample size, we will also conduct a sensitivity (posthoc) power analysis to demonstrate the effect sizes our final sample size is powered to detect.

Primary Outcomes

The primary outcomes are (1) to measure the onset, severity, duration, and recovery of changes to smell and taste sensitivity resulting from COVID-19 infection and (2) to assess the efficacy of the SSTT as a simple diagnostic approach. Data will be used to test the association of smell and taste loss with positive COVID-19 infection, measuring changes in sensory acuity from baseline (initial screening, Day 0) to the end of the 4-week monitoring period, to investigate the best predictors of recovery of smell and taste sensitivity. In addition, the primary methodological outcome is a comparison of the consistency and discriminability of self-assessment standardized home use tests compared to both the common household items home use test and the questionnaire-based measures. The findings will inform best practice approaches for future self-assessment of smell and taste acuity among people with suspected COVID-19 infection. This will be measured directly via responses to the daily home-use smell and taste test, complemented by measures from the self-reported questionnaire responses (SSTQ, SNOT-22, GCCRQ).

Secondary Outcomes

The secondary outcomes will include assessment of experienced symptoms and changes in appetite and food-related quality of life over the duration of smell and taste loss and the 4-week follow-up period. This will be assessed via the home-use test questionnaires.

Statistical Analysis

Using a case-control study design for people testing positive (case) or negative (control) for COVID-19 infection, data will be collected on changes in smell and taste loss that have occurred in the 2 weeks prior to the COVID-19 test and on smell and taste acuity changes measured on a daily basis for up to 28 days following the COVID-19 test. The data will be used for descriptive comparisons of the onset, duration, and severity of smell and taste changes with COVID-19 infection and to report on the incidence of these changes among participants testing positive for COVID-19 infection (and those recovering from infection).

Logistic regression analysis will be used to estimate the odds ratio for loss of smell and taste sensitivity as a predictor of testing positive for COVID-19 infection. This will also enable comparison of smell and taste loss as a predictor of COVID-19 infection compared to other symptoms, such as fever and dry cough. Pearson correlations will be used to investigate relationships between smell and taste changes and other symptoms. Time-series analysis of variance (ANOVA) models will be run to investigate temporal changes in smell and taste ratings over time, with baseline ratings in smell and taste acuity corrected for at an individual level. Linear mixed models will be used to test for significant differences in smell and taste acuity between groups, with participants stratified by their COVID-19 infection status.

Factor analyses, using oblique rotation and baseline home-use test responses (conducted in-clinic), will be conducted to assess the internal consistency of our smell and taste test. Adjusted odds ratios will be calculated to investigate the best predictors of recovery of smell and taste acuity postinfection. Linear regression will be run to examine whether responses to the smell and taste test predict responses to the household item odor test (smell) and self-reported taste acuity, respectively. Regression analyses will be conducted to investigate the association between loss of smell and taste acuity and self-reported appetite and food-related quality of life. All statistical analyses will be completed using SPSS (IBM Corporation).

Data Management

Data will be collected on the internet via the CompuSense platform, from which the data will be retrieved and securely stored on a password-protected university computer. These data will be transported into an SPSS file, on which data cleaning and analyses will be conducted.

All participant data will be included in the cross-sectional comparisons, provided the participants have at a minimum undergone COVID-19 swab testing (and we have obtained the

result) and completed the SSTQ, SNOT-22, and in-clinic smell and taste test (SSTT). All remote data collection will use web-based forms with forced choice response questionnaires to encourage adherence to the trial protocol, and each participant will receive daily reminders to complete their home-use smell and taste test and questionnaires. Attrition rates are difficult to estimate a priori; however, participants who provide a low number of completed tests (<25%) will be excluded from the longitudinal analyses investigating the home-use testing procedure. Missing data per analysis will be deleted listwise (ie, the individual's data will be removed from the analysis in question if a single value for any included variable is missing).

Availability of Data and Materials

No data sets are included in this protocol (not applicable). The study materials (Multimedia Appendices 1-3) are provided. According to National University of Singapore guidelines, it is not possible to grant public access to a participant-level dataset. However, in the event of publication of the trial results, a full protocol, study materials, and any relevant statistical code will be made publicly available on the Open Science Framework.

Results

The study (ref: 2020/00810) has been approved by the Domain Specific Review Board of the National Healthcare Group, Singapore. This study is funded by the Biomedical Research Council (BMRC) Singapore COVID-19 Research Fund (Project: 12Al04lg1lA04). All study-related materials, tests, stimuli, and procedures are covered by this funding. Recruitment of participants began on July 23, 2020, and will continue through to March 31, 2021. As of October 2, 2020, 69 participants had been recruited into the study.

Discussion

Study Overview

This study will longitudinally track the onset, severity, and recovery of changes in chemosensory (smell and taste) acuity among people with and without COVID-19 infection (following swab testing) using standardized assessment tools that can be used in a residential setting. The objectives of this study are to confirm the association between sudden changes in smell and taste sensitivity and COVID-19 infection in an at-risk population in Singapore; to establish the temporal onset, severity, and recovery of changes in smell and taste sensitivity with COVID-19 infection; to evaluate the efficacy of the SSTT as an early diagnostic tool; and to investigate the effects of loss of smell and taste acuity on appetite and food-related quality of life.

Using a longitudinal prospective study design, we aim to establish the association of the onset, severity, and recovery of smell and taste changes with COVID-19 infection while also providing an initial validation of a rapid, cost-effective, self-administered, and standardized approach to tracking spontaneous changes to taste and smell sensitivity in both clinical and residential settings. These findings will enable better identification of asymptomatic or pre-symptomatic carriers of COVID-19 infection, encouraging earlier self-isolation and medical consultation. Currently, a small number of studies have objectively tested smell and taste acuity in patients with COVID-19, with the majority of studies relying on subjective self-report measures [29]. Given that one-time self-report measures may underestimate the prevalence of olfactory impairment [36,37] and fail to capture temporal changes in sensory acuity, the COVISMIA-19 study provides an objective measurement of smell and taste loss in a sample of patients with COVID-19 that can encourage earlier self-isolation and medical consultation. Furthermore, current household item tests of smell and taste acuity are often not standardized and are heavily reliant on stimuli availability and volunteer compliance [32,33]. The COVOSMIA-19 approach will provide a short, easy-to-use, self-administered test approach that standardizes the smell and taste stimuli and can be easily completed by participants in their own home.

Study Limitations

There is potential for poor compliance by volunteer participants in completing their daily assessments throughout all 28 days of the assessment period. To mitigate this, all questionnaires and home-use test procedures will be short and easy to complete while maintaining the scientific rigor of the test approach. Similarly, the SSTT test measures focus on detecting changes in "usual" sensory perception, and the stimuli have deliberately been selected to monitor changes in suprathreshold perceptual intensity. As such, the SSTT approach will not provide information regarding changes to smell and taste at the perithreshold level (ie, identification, detection discrimination thresholds) or profile odor identification across a wide range of odor stimuli to identify specific anosmias. Although participants will be texted daily reminders to complete their daily home-use tests, their participation is entirely voluntary, with potential for poor adherence and retention. Our proposed procedure for handling potential missing data scenarios are outlined previously (see the Data Management section).

Study Strengths

A strength of the COVOSMIA-19 study is the longitudinal nature of the participant surveillance and the parallel application of both the questionnaire self-report and standardized test measures for the assessment of loss of smell and taste acuity. Objective measurements of smell and taste acuity are likely to be more reliable [38] and have not yet been used to longitudinally assess smell and taste changes associated with COVID-19 infection. Standardized test stimuli for the home-use test (SSTT) are provided, and longitudinal data collection will be completed remotely via a web-based platform to encourage adherence and facilitate completion of the procedures by the participants in their own home. All test stimuli have been pretested to ensure standardized concentration and stimuli stability and can be used by individuals regularly throughout a period of self-isolation. This approach will both standardize measurement for improved comparison longitudinally and reduce the risk of cross-contamination associated with sharing test measures or attending laboratory testing.

This study will provide new knowledge to increase our understanding of smell and taste losses associated with COVID-19 infection and will evaluate a simple test procedure

for future tracking of these changes among individuals with suspected COVID-19 infection form their own home. Through this study, we aim to better identify individuals who suspect COVID-19 infection but are otherwise asymptomatic or have very mild symptoms, encouraging earlier self-isolation and medical consultation.

Acknowledgments

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Authors' Contributions

CGF is the principal investigator of this study. VT is the study administrator. FS, CGF, VT, and SH contributed to the conceptualization and design of the study. Symrise AG provided advice on the home-use smell test stimuli and provided the test odors. DA, JS, and PT provided guidance and assistance regarding implementing the study in a hospital setting. SS is responsible for recruitment and informed consent data collection within the clinics. FS and CGF were responsible for manuscript preparation, and all authors contributed to editing the final manuscript for publication. Only CGF, VT, SH, and FS will be responsible for conducting the study analyses; therefore, only these individuals will have access to the final trial data set.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Singapore Smell and Taste Questionnaire (SSTQ).
[PDF File (Adobe PDF File), 292 KB - resprot_v9i12e24797_app1.pdf]

Multimedia Appendix 2
Daily smell and taste testing documents.
[PDF File (Adobe PDF File), 543 KB - resprot_v9i12e24797_app2.pdf]

Multimedia Appendix 3
Table S2. Questionnaire items and their sources.
[PDF File (Adobe PDF File), 177 KB - resprot_v9i12e24797_app3.pdf]

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Abbreviations

ANOVA: analysis of variance
BMRC: Biomedical Research Council
GCCRQ: Global Consortium for Chemosensory Research questionnaire
PCR: polymerase chain reaction
QR: quick response
SESOI: smallest effect size of interest
SNOT-22: 22-item Sino-Nasal Outcome Test
SSTQ: The Singapore Smell and Taste Questionnaire
SSTT: Singapore Smell and Taste Test
UPSIT: University of Pennsylvania Smell Identification Test
VAS: visual analog scale

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Corrigenda and Addenda

Correction: Improving Nutrition and Activity Behaviors Using Digital Technology and Tailored Feedback: Protocol for the Tailored Diet and Activity (ToDAy) Randomized Controlled Trial

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Related Article:

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(JMIR Res Protoc 2020;9(12):e25940) doi:10.2196/25940

In "Improving Nutrition and Activity Behaviors Using Digital Technology and Tailored Feedback: Protocol for the Tailored Diet and Activity (ToDAy) Randomized Controlled Trial" (JMIR Res Protoc 2019;8(2):e12782), corrections have been made to the article title and to three places in the text to reflect that the term "LiveLighter" is a registered trademark.

The original title of this paper was:

Improving Nutrition and Activity Behaviors Using Digital Technology and Tailored Feedback: Protocol for the LiveLighter Tailored Diet and Activity (ToDAy) Randomized Controlled Trial

The title has been changed to:

Improving Nutrition and Activity Behaviors Using Digital Technology and Tailored Feedback: Protocol

for the Tailored Diet and Activity (ToDAy) Randomized Controlled Trial

In the originally published paper, the caption of Table 1 read:

Table 1. Frequency of assessment of variables in the LiveLighter ToDAy study for the tailored feedback, active control, and online control groups.

The caption of Table 1 has been changed to read:

Table 1. Frequency of assessment of variables in the ToDAy study for the tailored feedback, active control, and online control groups.

Under the first paragraph of the section "Process Evaluation" in the originally published paper, the sentence:

Selected program completers and noncompleters (tailored feedback and active control groups) will be invited to participate in one-on-one interviews concerning their perceptions of the LiveLighter ToDAy intervention.

has been replaced by the sentence:

Selected program completers and noncompleters (tailored feedback and active control groups) will be invited to participate in one-on-one interviews concerning their perceptions of the ToDAy intervention.

In the originally published paper, the Acknowledgments section read:

Funding for the LiveLighter ToDAy study is provided by a Healthway Health Promotion Research Grant and the East Metropolitan Health Service. The mFR app is funded by NIH-NCI (1U01CA130784-01) and NIH-NIDDK (1R01-DK073711-01A1, 2R56DK073711-04). CC is supported by an NHMRC Senior Research Fellowship and a University of Newcastle (Faculty of Health and Medicine)–Gladys M Brawn Senior Research Fellowship. Funding for Fitabase is provided by a Curtin Institute of Computation grant. The sponsors had no role in the design of the study; collection, analyses, or interpretation of data; writing of the manuscript; and decision to publish the results.

This section has been changed to read:

Funding for the ToDAy study is provided by a Healthway Health Promotion Research Grant and the East Metropolitan Health Service. The mFR app is funded by NIH-NCI (1U01CA130784-01) and NIH-NIDDK (1R01-DK073711-01A1, 2R56DK073711-04). CC is supported by an NHMRC Senior Research Fellowship and a University of Newcastle (Faculty of Health and Medicine)–Gladys M Brawn Senior Research Fellowship. Funding for Fitabase is provided by a Curtin Institute of Computation grant. The sponsors had no role in the design of the study; collection, analyses, or interpretation of data; writing of the manuscript; and decision to publish the results. The term "LiveLighter" is a registered trademark. The LiveLighter campaign is funded by the Western Australian Department of Health and at the time of this study, delivered by the National Heart Foundation (WA Division), and currently delivered by Cancer Council Western Australia.

The correction will appear in the online version of the paper on the JMIR Publications website on December 2, 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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Protocol

Virtual Care for Indigenous Populations in Canada, the United States, Australia, and New Zealand: Protocol for a Scoping Review

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Abstract

Background: Indigenous people in Canada, the United States, Australia, and New Zealand experience an increased burden of chronic diseases compared to non-Indigenous people in these countries. Lack of necessary services and culturally relevant care for Indigenous people contributes to this burden. Many Indigenous communities have implemented systems, such as virtual care, to improve chronic disease management. Virtual care has extended beyond videoconferencing to include more advanced technologies, such as remote biometric monitoring devices. However, given the historical and ongoing Western intrusion into Indigenous day to day life, these technologies may seem more invasive and thus require additional research on their acceptability and utility within Indigenous populations.

Objective: The objective of this paper is to present the protocol for a scoping review, which aims to map existing evidence. This study is based on the following guiding research question: What are the characteristics of virtual care use by Indigenous adult populations in Canada, the United States, Australia, and New Zealand? The subquestions are related to the technology used, health conditions and nature of the virtual care, cultural safety, and key concepts for effective use.

Methods: This scoping review protocol is informed by the methodology described by the Joanna Briggs Institute and is supplemented by the frameworks proposed by Arksey and O'Malley and Levac et al. A search for published and gray literature, written in English, and published between 2000 and present will be completed utilizing electronic databases and search engines, including MEDLINE, CINAHL, Embase, Indigenous Peoples of North America, Australian Indigenous HealthInfoNet, Informit, and Native Health Database. Search results will be uploaded to the review software, Covidence, for title and abstract screening before full-text screening begins. This process will be repeated for gray literature. Upon completion, a data abstraction tool will organize the relevant information into categorical formations.

Results: The search strategy has been confirmed, and the screening of titles and abstracts is underway. As of October 2020, we have identified over 300 articles for full-text screening.

Conclusions: Previous reviews have addressed virtual care within Indigenous communities. However, new virtual care technologies have since emerged; subsequently, additional literature has been published. Mapping and synthesizing this literature will inform new directions for research and discussion.

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KEYWORDS

virtual care; Indigenous; Indigenous health; accessibility; cultural competency; feasibility; acceptability; utility

Introduction

Indigenous people in Canada, the United States, Australia, and New Zealand carry an increased disease burden of many chronic illnesses compared to non-Indigenous residents [1]. The reasons for this are multifactorial. The common history of colonialism, residential school systems, and forced removal of Indigenous children from their families resulted in an intergenerational trauma for many people [2,3]. In addition, the ongoing discrimination, lack of appropriate services, and limited culturally relevant care, especially for Indigenous people in remote and rural locations, contribute to worse health outcomes for Indigenous people in these countries [2-4].

To address these and other harms, federal governments in these countries are working with Indigenous nations and groups to develop policies to improve health. The report of the Truth and Reconciliation Commission of Canada [2] announced several calls to action to improve the health of First Nations people in Canada, while simultaneously acknowledging the Indigenous rights in determining how research and health care will be conducted, including "a focus on chronic diseases and the availability of appropriate health services." The *Truth Telling Symposium Report* by Reconciliation Australia and the Healing Foundation [3] acknowledged past and current harms and called for truth telling to improve relationships and shape policy. In New Zealand, the Waitangi Tribunal [4] provides a mechanism where treaty violations, including those related to health and welfare, are addressed. The United States signed into law the Apology to Native Peoples of the United States [5]. Within many of these documents, there is an acknowledgement of the need for culturally safe health care initiatives to address health care inequities related to acute and chronic disease health care.

Many Indigenous communities have already implemented innovative systems, such as virtual care services, to improve chronic disease management for their members. For example, Carrier Sekani Family Services (CSFS) is a nonprofit, First Nations health care provider in Canada with the mandate to provide health, social, and research services on behalf of its member First Nations. CSFS recognized that their member communities were disadvantaged when trying to access timely and culturally sensitive health care for acute and chronic disease management. In 2010, CSFS developed a videoconferencing telehealth system that connects patients and providers so that communities have regular access to a primary care physician most days of the week. An evaluation of the CSFS system [6] found that 52% of survey respondents had used the service at least once, and of those respondents, 83% attended more doctor's appointments, and 78% had fewer out-of-community trips for health care, compared to before the service was introduced. Other jurisdictions have similar programs and have reported similar benefits [7-11].

Virtual care, however, is more than videoconferencing. Additional technologies such as internet-delivered care, remote biometric monitoring, wearables, and smartphone apps are now used in virtual care. These technologies have the potential to support the ongoing management and transitions in care of people with chronic diseases living in remote and rural communities. Additional research into the acceptability and utility of virtual care technologies for Indigenous people is necessary, given the past and current harms of Western intrusion (colonization, creation of reserve lands and surveillance, and residential school systems) into the Indigenous day to day life. Monitoring devices may seem all the more invasive to Indigenous peoples, and there may be concerns about the privacy of data, ease of using the system, reliability of devices, suitability of technology where remoteness impacts connectivity, and concerns about technology replacing genuine relationships between patients and care providers. The potential benefits of increasing technology in virtual care must be weighed against individual or community harms that may result from increased surveillance.

Indigenous communities, researchers, and advocates have explored how virtual care technology, from basic to more advanced, can be used to improve health outcomes of Indigenous peoples as well as to identify the limitations of these systems, issues related to cultural safety, and current gaps in information. Their knowledge has been published in peer-reviewed journals, community reports, best practice guidelines, and government documents and includes insights into barriers, facilitators, and key principles for telehealth for Indigenous peoples. We undertook an environmental scan of the published and gray literature to confirm the feasibility of a scoping review and to test keywords and search strategies. A preliminary search of 3 databases using relevant search terms, plus a gray literature search, revealed at least 50 documents related to virtual care in Indigenous communities. A brief review of the papers identified relevant topics, including the benefits of telehealth (eg, reduces alienation), the challenges (eg, requires reliable internet services and sustainable infrastructure support), and important principles (eg, requires culturally appropriate care and transparency of the data). A structured scoping review of this knowledge would provide a mapping of the current knowledge, identification of key concepts, description of how virtual care (including invasive technologies) is used, and recommendations for future research and care. The purpose of this paper is to describe the protocol for the scoping review of virtual care for Indigenous populations in Canada, the United States, Australia, and New Zealand.

Methods

This scoping review protocol is informed by the methodology devised by the Joanna Briggs Institute [12]. This methodology is supplemented by the frameworks proposed by Arksey and O'Malley [13] and Levac et al [14].

Consultation

Consultation is an important part of the scoping review process. The executive director of the CSFS primary care services (TH) is an investigator on this project and participated in the development of the search strategy. In addition, we will convene

meetings throughout the review process with the entire CSFS virtual care team to gain feedback on the document summaries, interpretation of the results, and creation of the knowledge translation materials.

Identifying the Research Questions

Using the Population-Concept-Context (PCC) framework, the review will focus on Indigenous adults' (Population) utilization of virtual care (Concept) in Canada, the United States, Australia, and New Zealand (Context). These geographical areas are relevant due to many similarities of these locations in terms of their history of European colonization, their worldviews, and the leadership of Indigenous peoples in virtual care. We identified 13 subquestions as detailed in Table 1. We considered virtual care and its equivalents as health care whereby health care providers interact with their patients through technology, including video, audio, messaging, the internet, apps, or wearables.

Table 1. Guiding research question and subquestions.

Category of questions	Questions
Guiding research question	• What are the characteristics of virtual care use by Indigenous adult populations in Canada, the United States, Australia, and New Zealand?
Subquestions	
General	• What is the total number of documents published each year? • What terms or keywords are being used to describe these documents? • What are the characteristics of the authors and institutions, communities, or agencies producing the knowledge? • Where are the authors located, according to their affiliations? • What is the geographical scope of the knowledge?
Technology	• What types of virtual care technology are being used? • What is the chronological evolution of virtual care?
Health condition and virtual care intervention	• For what health conditions is virtual care being used? • What are the key elements of the virtual care provided? • Who provides the intervention? (remote, local, academic, or community) • What is the involvement of Indigenous people in the provision of virtual care—as a provider, organization, developer?
Cultural safety	• What are the key concepts of cultural safety when using virtual care?
Effective use	• What are the key concepts of the effective use of virtual care?

Identifying and Selecting Relevant Studies and Documents

Published Literature: Search Strategy

The following licensed electronic databases (from 2000 to present) will be used to systematically look for published literature: (1) MEDLINE, (2) EMBASE, (3) CINAHL, (4) PubMed, (5) Indigenous Peoples of North America, (6) Indigenous Studies Portal, (7) Informit, and (8) Native Health Database. The sources selected will be limited to papers in English. The search strategy, based on the PCC framework, focuses on Indigenous peoples receiving virtual care in Canada, the United States, Australia, and New Zealand. Table 2 lists the general search strategy; this strategy will be adapted to each database as appropriate.

Table 2. General search strategy.

Elements of the PCC[a] framework and line	Search terms
Population	
1	exp Indians, North American/
2	exp Alaska Natives/
3	exp Inuits/
4	exp Indigenous Peoples/
5	exp Health Services, Indigenous/
6	exp Oceanic Ancestry Group/
7	(Indigenous adj3 Australia*) OR (aborigin* adj3 Australia*) OR (Torres Strait Islander*) OR (Maori).mp
8	(Indigenous OR First Nation* OR Inuit* OR Metis OR Aborigin* OR (Native* adj3 America*) OR American Indian* OR America* adj3 Native* or Amerind* or (Alaska* adj3 Native*)).mp
9	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8
Concept	
10	exp Telemedicine/
11	exp Telemetry/
12	exp Telenursing/
13	exp Telerehabilitation/
14	exp Mobile Applications/
15	exp Smartphone/
16	exp Cell Phone/
17	exp Biometry/
18	exp Biometric Identification/
19	exp Wearable Electronic Device/
20	exp Biosensing Techniques/
21	exp Self-Help Devices/
22	exp Monitoring, Physiologic/
23	(telehealth* OR tele-health* OR telemedicine OR tele-medicine OR tele-psychiatry OR teleophthalmology OR telecare OR tele-care OR telenurs* OR tele-nurs* OR mobile health* OR ehealth OR e-health OR mhealth OR m-health OR telemonitor* OR tele-monitor* OR telerehabilitat* OR tele-rehabilitat* OR remote medicine OR remote health* OR distance medicine OR digital health* OR remote biometr* OR (remote adj2 monitor*) OR (virtual adj2 care) OR wearable* OR smart device* OR health sensor* OR health monitor* OR biosensor* OR biometric* OR mobile technolog* OR mobile monitor* OR smartphone* OR smart phone* OR cellphone* OR cell phone* OR mobile phone* OR app OR apps OR Fitbit* OR fitness tracker*).mp
24	10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23
25	9 AND 24
Context	Canada, the United States, Australia, New Zealand (applied at the full-text review stage)

[a]PCC: Population-Concept-Context.

Gray Literature: Search Strategy

A gray literature search (from 2000 to present), using the search strategy in Table 2, will be conducted in the institutional and governmental electronic databases and search tools, including (1) The New York Academy of Medicine, (2) OpenGrey, (3) Canadian Agency for Drugs and Technologies in Health, (4) Canadian Institute for Health Information, (5) Health Canada, Government of Canada, (6) OAIster, (7) Agency for Healthcare Research and Quality, (8) Circumpolar Health, (9) Department of Health, Australia, and (10) Australian Indigenous HealthInfoNet. An additional search of Google and Google Scholar will be conducted with the first 50 relevancy-ranked results reviewed. The resources selected will be limited to those in English.

Selected documents or studies will have a specific focus on the use of virtual care in Indigenous populations in Canada, the

United States, Australia, and New Zealand and will have been published or made available from 2000 to present. The studies will not be limited by the study design, age group, or type of health condition addressed via virtual care. For gray literature, the document types selected for inclusion in this review will be limited to conference proceedings, government or agency reports, practice guidelines, annual reports, program evaluations, literature reviews, and policy papers.

All citations will be uploaded to the review software Covidence. Each title and abstract will be screened by 2 independent team members who will make a yes or no selection. A third team member will resolve any discrepancies. We will then obtain the full-text articles for all selected citations. Each full-text article will be independently reviewed by 2 team members with discrepancies resolved by a third team member.

For the gray literature, we will upload documents to Covidence and will use the same procedure for title screening as described for the published literature. For those search results that cannot be uploaded to Covidence, a document will be generated that lists each result. These will all be independently reviewed by 2 team members with discrepancies resolved by a third team member. For the Google search, search results may change from one minute to the next. Therefore, a team member will generate the search results and will review the first 50 sources. This same search result list will then be reviewed separately by a second team member, and discrepancies will be resolved by a third team member.

Charting and Synthesizing the Data

A document to abstract the data (Textbox 1) from selected documents will be designed, pilot tested, and used by 2 team members to independently extract data from the selected documents. If there is any disagreement between the 2 team members, it will be resolved through the help of a third team member.

Textbox 1. Data abstraction for the guiding research question and subquestions.

Summary

- Title
- Authors
- Author's affiliation
- Type of literature
- Keywords
- Study Location
- Participants in study
- Study population
- Objective of study

Subquestion 1: technology and intervention

- Technology being used
- Intervention—description, provider, agencies involved
- Involvement of Indigenous peoples

Subquestion 2: health condition

- Type of health condition

Subquestion 3: cultural safety

- Key concepts discussed

Subquestion 4: effective use/outcomes described

- Key concepts discussed

The abstracted information will be summarized by subquestions using tables, bar graphs, and narratives where appropriate.

Results

The search strategy has been confirmed, and we are reviewing the published and gray literature. As of October 2020, we have identified 2928 titles and abstracts from MEDLINE, EMBASE, and CINAHL; 395 of those have moved to the stage of full-text screening. We are completing the gray literature database searches and to date have identified 2645 gray literature documents for screening.

Discussion

Previous work has reviewed virtual care in Indigenous communities. In their 2010 report for the British Columbia Alliance on Telehealth Policy and Research, Lavoie and

colleagues [15] reviewed available published and gray literature pertinent to telehealth development in First Nations communities within British Columbia, Canada. Findings from the review demonstrated the importance of the development and implementation of contextualized telehealth delivery in First Nations communities. Others have reviewed telemedicine in Indigenous populations, but those studies are often focused on one country or only included knowledge from peer-reviewed journals [16,17]. A reflective analysis of this wide breadth of knowledge across several relevant topics will synthesize the knowledge from many knowledge sources from Canada, the United States, Australia, and New Zealand and will reveal new directions for research and discussion.

Acknowledgments

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Conflicts of Interest

PC received research grants from the Canadian Institutes of Health Research and the Canadian Lung Association. PC is a member of the American Thoracic Society Pulmonary Rehabilitation Assembly Executive. TH received grants from the Canadian Institutes of Health Research. All other authors have no conflicts to declare.

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Abbreviations

CSFS: Carrier Sekani Family Services
PCC: Population-Concept-Context

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Protocol

Challenges and Strategies for Promoting Health Equity in Virtual Care: Protocol for a Scoping Review of Reviews

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Abstract

Background: The rapid virtualization of health services during the COVID-19 pandemic has drawn increasing attention to the impact of virtual care technologies on health equity. In some circumstances, virtual care initiatives have been shown to increase health disparities, as individuals from underserved communities are less likely to benefit from such initiatives.

Objective: The purpose of this paper is to describe a protocol for a scoping review of reviews that aims to map review-level evidence that describes challenges and strategies for promoting effective engagement with virtual care technologies among underserved communities.

Methods: Our methodology was adapted from seminal scoping review guidelines provided by Arksey and O'Malley, Levac at al, Colquhoun et al, and the Joanna Briggs Institute. Our search strategy was developed for the following databases: MEDLINE (on Ovid), EMBASE (on Ovid), CINAHL (on EBSCO), Scopus, and Epistemonikos. Supplementary searches will include the use of Google Scholar and reference tracking. Each citation will be independently screened by 2 researchers at the title and abstract level, and full-text screening will be performed in accordance with our eligibility criteria. The eligibility criteria focused on the inclusion of methods-driven reviews (ie, systematic reviews, scoping reviews, meta-analyses, realist reviews, and critical interpretative syntheses) to enhance rigor and quality. Other inclusion criteria included a focus on virtual care services that facilitate bidirectional patient-provider communication (ie, video, telephone, and asynchronous messaging visits) for underserved populations (ie, those who experience social disadvantage due to race, age, income, and other factors related to the social determinants of health).

Results: This scoping review of reviews will provide a broad overview of identified challenges associated with the accessibility of virtual health care services among underserved communities. In addition, strategies for improving the access to, uptake of, and engagement with virtual care technologies among underserved communities will be identified. The knowledge synthesized from this review will aid in developing and implementing virtual services that acknowledge the unique needs of populations who experience barriers to care and disproportionately worse health outcomes. The results will also inform gaps in current research.

Conclusions: The rapid shift toward virtual health services has highlighted the urgent need to critically examine the intersection of virtual care and health equity. Although technology-driven innovations in health care generally aim to improve access, quality, and health outcomes, it is also possible for these innovations to produce intervention-generated inequities. Assessing current

review-level evidence on the key challenges and strategies for improving the application of virtual care in underserved communities is imperative for ensuring that virtual care benefits all populations.

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KEYWORDS

health equity; digital health; virtual care; telemedicine; scoping review; COVID-19; challenge; strategy

Introduction

In response to the COVID-19 pandemic, virtual visits have rapidly transitioned from representing a small fraction of health care delivery to being the primary means of connecting patients and providers [1-4]. Virtual care is a broad term that encompasses diverse forms of health services that occur outside of traditional face-to-face clinical encounters, including telephone calls, video visits, secure messaging, and email consultations [5]. Recognizing the urgent need to maintain care while supporting physical distancing measures, government agencies and other stakeholders have enabled the use of virtual care, and in some cases health care payors have implemented reimbursement policies to facilitate the provider uptake of virtual care services [6]. Some jurisdictions have also permitted the use of nonencrypted technologies, such as FaceTime, Google Hangouts, and Skype, for patient care by waiving penalties for noncompliance with pre-existing privacy and security regulations (ie, the Health Insurance Portability and Accountability Act in the United States) [7]. This has resulted in the rapid implementation of virtual care [8]. The potential benefits of virtual care include reductions in emergency department visits, conserved health care resources, and improved access to care for some patients [4,6].

Many anticipate that several of the physical distancing measures that were implemented due to the COVID-19 pandemic may continue for the long term and that virtual care will continue to be ubiquitous in health service delivery [9]. However, given the immense speed at which health care services are being virtualized, a central concern is that considerations for health equity may be overlooked during the implementation of virtual care services [9,10]. In some circumstances, virtual care initiatives have been shown to increase health disparities, as individuals from underserved communities (ie, those who experience social disadvantage due to factors such as race, gender, income, or other social determinants of health) are less likely to benefit from such initiatives [9]. There are a variety of documented reasons for this, including the lack of language accessibility within certain apps, lack of cultural relevance, lack of skill or comfort in using certain technologies, and lack of access to the technical infrastructure (ie, internet-enabled devices and high-speed internet) required for engagement [11,12]. These issues must be considered so that the ongoing application of virtual care does not exacerbate existing health disparities between people with the highest access to health systems and people who are the most underserved by health systems.

Although several reviews have identified gaps in technology access, use, or literacy [11-14], few have systematically identified barriers specific to virtual health services among diverse underserved populations, and little is known about strategies for overcoming such barriers. In response to this perceived gap of knowledge, this scoping review of reviews will examine the range, nature, and extent of current research that explores virtual care among underserved communities. We refer to underserved communities as populations defined by social, economic, or geographic characteristics that can lead to their exclusion from mainstream social life, which in turn may directly or indirectly impact their ability to obtain high-quality care and achieve desired health outcomes [15]. The term “underserved” is often used interchangeably with the terms “vulnerable” or “marginalized” to describe populations who are at greater risk of poor health status and health care access. However, in contrast to the concepts of vulnerability or marginalization, our use of the term “underserved” is meant to call attention to prevailing systemic issues that result in unmet needs for those served by the health care system [15]. Our scoping review of reviews will synthesize review-level evidence on the challenges associated with the accessibility of virtual care services. In addition, we will identify strategies for improving the access to, uptake of, and engagement with virtual care among underserved communities. The knowledge synthesized from this review will aid in developing and implementing guidelines for virtual care services that are cognizant of diverse needs and sensitive to various differences in individual and group characteristics. The objective of this protocol paper is to describe the rationale, scope, and methods for conducting this scoping review of reviews.

Methods

Protocol Design

To inform our research question, we chose to conduct a scoping review of reviews to comprehensively, systematically, and feasibly map a large and diverse body of literature. Our approach was informed by guidance from the methodological frameworks created by Arksey and O’Malley [16], Levac et al [17], and Colquhoun et al [18], and further refinements were made by referencing guidelines from the Joanna Briggs Institute [19]. The methodological steps are as follows: (1) identifying the research question; (2) identifying relevant studies; (3) study selection; (4) charting the data; and (5) collating, summarizing, and reporting the results [16-18]. In the absence of established guidelines on a scoping review of reviews, we also drew guidance from other peer-reviewed scoping reviews of reviews [20,21] to develop a methodologically rigorous approach.

Standardized reporting guidelines outline elements that should be included in research studies to enhance their transparency [22]. For this protocol, we used the Preferred Reporting Items

for Systematic Reviews and Meta-Analyses literature search extension (PRISMA-S) to report on the search strategy [23]. Moreover, we will apply the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) for reporting results [22]. This scoping review is registered in the National Collaborating Centre for Methods and Tools [24].

Step 1: Identifying the Research Question

To establish our research questions, we first conducted an exploratory review of the literature on health equity in virtual care interventions. Following this review and extensive consultations with the members of our research team who had subject matter expertise, we made iterative improvements to clarify the concept and purpose of this study. After refining the study purpose, we established the following overarching research question: what challenges and strategies related to enabling the access to, uptake of, and engagement with virtual care for people from underserved communities have been documented in the literature?

The following subquestions will be used to further inform our investigation: (1) what is the review-level evidence regarding challenges that inhibit the access to, uptake of, and engagement with virtual care technologies among underserved communities; and (2) what is the review-level evidence regarding strategies for improving the access to, uptake of, and engagement with virtual care technologies among underserved communities?

Step 2: Identifying Relevant Studies

In order to identify relevant studies that would inform our research questions, we first operationalized the following 2 key concepts within our study: virtual care and underserved populations. We then decided on the types of studies that would be the most relevant to include in the search strategy.

Operational Definition of Virtual Care

For the purposes of this scoping review, we defined virtual care as "any interaction between patients and/or members of their circle of care, occurring remotely, using any forms of communication or information technologies, with the aim of facilitating or maximizing the quality and effectiveness of patient care" [5]. Since the COVID-19 pandemic has increased the need for remote clinical interactions (ie, not in-person interactions), this review will focus on technologies that facilitate bidirectional patient-provider communication that fall under category 2.4.1 Consultations between remote client and healthcare provider, in the World Health Organization's Classifications of Digital Health Interventions [25]. These include established technologies, such as telemedicine (eg, phone or video-based consultations), that have arisen over the past few decades, alongside newer communication platforms, such as asynchronous consultations via SMS text messaging, email, patient portals, and third-party apps.

Operational Definition of Underserved Community

We defined an underserved community as a group of people with increased susceptibility to health and health care disparities due to a combination of individual, environmental, and social factors that have been collectively defined as social determinants of health [15]. This operational definition was created using specific search terms within the search strategy. Our inclusion criteria focused specifically on older age, gender, racial or cultural identity, immigration and refugee status, socioeconomic status, homelessness, and rurality within the broader search criteria. This is in contrast to clinically at-risk populations with behavioral or biological factors that render them at risk for poor health outcomes; reviews that focus exclusively on these populations will not be included within this review.

Type of Reviews

Since our objective is to summarize a broad and diverse range of literature on virtual care, we will limit the inclusion of study types to the following methods-driven reviews: systematic reviews, meta-analyses, meta-syntheses, scoping reviews, realist reviews, and critical interpretive syntheses. Including studies with well-developed and established review methodologies will help reduce the risk of capturing poor quality studies. In addition, synthesizing review-level evidence will allow us to capture the vast amount of published literature on virtual care interventions in a logistically feasible manner [17].

Search Strategy Development

We developed comprehensive search strategies in collaboration with an academic librarian (KF) at the University of Toronto. These search strategies were developed for the following databases: Ovid MEDLINE: Epub Ahead of Print, In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, and Ovid MEDLINE 1946-present; EMBASE (on Ovid), CINAHL (on EBSCO); Scopus; and Epistemonikos. The databases were selected based on subject area coverage and functionality. Additionally, guidelines provided by Goosen et al [26] and Bramer et al [27] were applied to inform the database selection. A date limit of 2005 to the present date was placed on the search to capture the most current literature on virtual care. The search strategies used a combination of text words, keywords, and subject headings for each concept that were relevant to our operational definitions of virtual care and underserved community. To retrieve reviews, a third concept was added to the MEDLINE, EMBASE, and CINAHL search strategies, and review filters were applied in Scopus and Epistemonikos. A draft search strategy for MEDLINE is provided in Multimedia Appendix 1. Citations were exported from the databases into EndNote X9 (Clarivate Analytics) for deduplication using a deduplication methodology adapted from Bramer et al [28]. Results were then imported into Covidence, a systematic review software program that supports the screening and management of citations by multiple reviewers [29].

Supplementary Searching

To supplement our search, we will use Google Scholar to identify relevant reviews that were not captured during the database searches. Key terms for each concept will be applied, and the first 3 pages of the search results will be reviewed. Potentially relevant items will be selected and deduplicated against our original set of search results and sent for screening. In addition, we will hand search the reference lists of included studies to identify any potentially relevant citations that may have been missed during the initial database search.

Step 3: Study Selection

The inclusion and exclusion criteria for study selection (Textboxes 1 and 2) were developed iteratively by the research team based on the previously mentioned operational definitions and search strategy.

Textbox 1. Inclusion criteria for study selection.

Types of participants

- Reviews of interventions that target or describe the impact of the intervention on an underserved population (ie, those who experience social disadvantage due to older age, gender identity, racial or cultural identity, immigration or refugee status, low income or low socioeconomic status, and rurality).

Concept

- Reviews on health care–focused technological interventions.
- Reviews focused on virtual care interventions, as defined in Section 2.4.1, Consultations between remote client and healthcare providers, in the World Health Organization's Classification of Digital Health Interventions. These include telephone communication; video communication; asynchronous SMS text messaging; asynchronous email messaging; portals, apps, and other applications for bidirectional patient-provider communication; and remote monitoring tools that incorporate bidirectional communication functionality (ie, the tools listed previously).

Context

- All health system settings in high-income countries.

Types of evidence

- Methods-driven literature reviews, including systematic reviews, meta-analyses, scoping reviews, realist reviews, and critical interpretive syntheses.

Textbox 2. Exclusion criteria for study selection.

Types of participants

- Reviews of interventions that target or describe the impact of the intervention on a general or clinical population instead of underserved populations as described within our inclusion criteria.

Concept

- Reviews of technological interventions that do not explicitly focus on bidirectional provider-patient communication (eg, patient portals that only focus on providing patients with access to their health information, remote monitoring tools without bidirectional patient-provider communication functionality, and provider-provider communication tools).

Context

- Studies focused on middle-income and low-income countries.

Types of evidence

- Reviews and knowledge syntheses that are not methods based.
- Primary research studies that use qualitative and quantitative methods.
- Opinion papers, commentaries, editorial reviews, and letters to the editor.
- Study protocols, dissertations, and conference abstracts/proceedings.

A screening guide, which was developed by 1 reviewer (SB) with feedback from the research team, will be used to determine if the inclusion and exclusion criteria have been met. In total, 5 researchers (JKF, KD, PC, SB, and TTJ) will independently pilot test the screening guide with a test sample of 200 abstracts. Results will be discussed, and revisions to the screening guide will be made as needed. An example of an included article and an excluded article will also be presented to the project team to ensure the appropriateness of included articles.

After establishing the screening guide and completing a pilot test, a 2-stage screening process will be implemented. First, all available titles and abstracts will be independently screened by 2 reviewers to determine the eligibility of articles for inclusion. Reviewers will meet regularly to discuss any challenges related to study selection and refine the inclusion and exclusion criteria as needed. Conflicts will be resolved by a third reviewer or through group discussion. The second stage of study selection will involve the examination of the full-text articles accepted in the first stage of study selection to determine their eligibility for inclusion. Any included full-text articles will be independently reviewed by 2 reviewers based on the inclusion and exclusion criteria. Once again, any conflicts between reviewers will be resolved by a third reviewer or through discussion with the research team. The study selection process

will be summarized in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

Step 5: Collating, Summarizing, and Reporting the Results

Data Extraction

A data extraction form will be developed and pilot tested by 5 reviewers (JKF, KD, PC, SB, and TTJ). A draft version of this form is provided in Multimedia Appendix 2. The data extraction form will be pilot tested on 2 articles to test for the form's consistency and comprehensiveness in capturing relevant data. Changes will be made through team discussion after comparing pilot test results.

Based on the studies used for developing the search strategy, the proposed fields for extraction include the following: (1) review identifiers (ie, authors, year of publication, review type, number of studies in the review, reported timeframe, place of publication); (2) the nature of the virtual care intervention(s) (ie, categorization and purpose of the technology); (3) setting and population (ie, the physical setting or geographical location of the intervention and demographic characteristics of the population); (4) the reported challenges for implementation, adoption, and engagement; (5) the reported strategies for improving implementation, adoption, and engagement; and (6) key study outcomes or conclusions.

Data Synthesis

A qualitative descriptive approach will be used to synthesize the data collected. The common characteristics of review articles will be identified to descriptively analyze the extent, nature, and distribution of included review articles. These characteristics include the review articles' methodology, technologies described, target population(s), country/region of origin, and content. In keeping with established scoping review guidelines [16-18], the level or quality of evidence will not be formally appraised. An inductive and exploratory analysis of the findings will be conducted to identify emergent concepts and recurring patterns that can be extracted from the included studies. Major themes and subthemes arising from the review literature will be summarized with a focus on describing major barriers to virtual care technologies and strategies for improving engagement, in line with the research objectives. Themes will be iteratively developed over a series of meetings, during which the researchers will cluster the results into higher order categories. This will lead to a narrative summary of major findings. Potential gaps in providing virtual care technologies to underserved populations will also be identified based on our summary of the review literature.

Results

This scoping review is currently in the study selection phase. Electronic database searches were completed in August 2020, yielding 9666 unique references. Following title and abstract screening, 9526 records were excluded based on the inclusion and exclusion criteria. As a next step, the resulting 140 references will undergo full-text review. Data synthesis will follow, and the authors anticipate that the results of this study will be submitted for publication in January 2021.

Discussion

Protocol Overview

Digital health interventions that are developed without context and without sensitivity to diverse needs can exacerbate pre-existing health disparities, thereby widening the gap between those with privilege and those without [9,11,30]. To our knowledge, this is the first scoping review to use review-level evidence to assess the unique considerations of implementing virtual care services for underserved communities. Although documented discrepancies in the access to and utilization of digital health interventions are abundant [11,31], a comprehensive study that maps key challenges and strategies for promoting health equity in virtual care has yet to be conducted. By identifying the predominant barriers and facilitators related to virtual care use among diverse populations, our findings will offer providers, health system leaders, and policy makers evidence-informed recommendations to enhance equity when introducing technology-driven innovations in health care. In addition, unlike traditional scoping reviews, this protocol outlines a methodological approach to conducting a scoping review of reviews that systematically maps and synthesizes review-level evidence.

Limitations

A potential limitation of this study is the lack of quality assessment for included articles. Although a quality appraisal is not required in scoping reviews [16,18,19], we hope to improve the quality and rigor of our approach by limiting our search to reviews with well-established methodologies (ie, systematic reviews, meta-analyses, and scoping reviews). We recognize that our focus on review-level evidence may exclude relevant primary research studies. However, since the literature on digital health interventions and underserved populations is vast, our focus on reviews will allow us to feasibly obtain a succinct overview of the field and increase the heterogeneity and breadth of reported virtual care interventions. In addition, operationalizing the term "underserved community" in our search was challenging due to the diverse characteristics that encompass this broad categorization of people. Several in-depth discussions and a careful review of the health equity literature was performed to help inform our operational definition of "underserved community". Although our operationalization of underserved communities could not encompass every population that faces systematic barriers to health care, we hope that our choice of search terms is purposefully broad enough to identify relevant considerations for improving future implementations of virtual care. Future research should be considered to capture any populations that our scoping review of reviews may have excluded due to feasibility constraints.

Conclusions

The rapid virtualization of health services during the COVID-19 pandemic has highlighted the urgent need to critically examine the intersection of virtual care and health equity. Although technology-driven innovations in health care generally aim to

improve access, quality, and health outcomes, it is also possible for these innovations to produce intervention-generated inequities by differentially benefiting those with more social and economic privilege than others [30]. Our protocol outlining a scoping review of reviews is a methodologically rigorous approach to mapping comprehensive health service research on key challenges and strategies for improving the application of virtual care in underserved communities. The results from our scoping review of reviews will provide valuable insight for the promotion of health equity in virtual care and will reveal current knowledge gaps in research.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy for Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily, and Ovid MEDLINE 1946-Present.
[DOCX File , 43 KB - resprot_v9i12e22847_app1.docx]

Multimedia Appendix 2
Draft data extraction form.
[DOCX File , 27 KB - resprot_v9i12e22847_app2.docx]

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Abbreviations

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-S: Preferred Reporting Items for Systematic Reviews and Meta-Analyses literature Search extension
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Impact of Telemedicine Use by Oncology Physicians on the Patient and Informal Caregiver Experience of Receiving Care: Protocol for a Scoping Review in the Context of COVID-19

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Abstract

Background: During the COVID-19 pandemic, the use of telemedicine by oncology physicians in Manitoba, Canada, has increased to limit the risk of exposure to the virus for both patients and health care providers. It is not clear how telemedicine impacts the information needs of patients or the experience of receiving cancer care.

Objective: The objective of this study is to describe how the use of telemedicine impacts the information needs and experience of patients with cancer and their informal caregivers (ie, family and friends) and identify directions for future research.

Methods: This review will include all studies addressing telemedicine in the cancer context including those using quantitative, qualitative, and mixed methods approaches. This scoping review will be conducted using the methodology described by the Joanna Briggs Institute. In collaboration with a librarian scientist specializing in health sciences, a comprehensive search will be undertaken to identify and retrieve relevant reports published in English from 1990 to the present. Databases searched will include MEDLINE, CINAHL, EMBASE, Scopus, Cochrane Library, and PsycINFO. Data will be extracted by two independent reviewers, synthesized, and reported in a summary table and in a narrative format describing what has been reported regarding the impact of telemedicine by physicians in oncology on the experience of patients and their informal caregivers and their receipt of information.

Results: The results from this scoping review are expected to be available by late spring 2021.

Conclusions: The results from this scoping review will be useful for informing practice as well as directing future research, both in the context of COVID-19 and beyond.

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KEYWORDS

cancer; experience; information needs; telemedicine; telehealth; COVID-19; patient satisfaction

Introduction

The COVID-19 pandemic has transformed how cancer care is delivered. In the Canadian province of Manitoba, most cancer care is delivered by a provincial, centralized agency, CancerCare Manitoba (CCMB). During the COVID-19 pandemic, CCMB implemented changes to mitigate the risk of contracting the virus for patients with cancer as well as health care providers. These changes have included routine screening for signs of infection prior to staff, patients, and informal caregivers entering facilities, limiting the number of informal caregivers that can accompany patients to appointments and procedures, and the routine use of personal protective equipment (PPE) by health care staff who provide in-person care to patients [1]. Perhaps the most remarkable change in clinical practice has been the dramatic increase in the use of telemedicine by physicians.

Telemedicine and telehealth are closely related but distinct concepts [2,3]. The American Academy of Family Practitioners (AAFP) provides clear definitions of these terms [3]. The AAFP defines telehealth as the use of telecommunication strategies to deliver health care and health care–related services such as the education of health care professionals. Telemedicine is more narrowly defined and refers specifically to the delivery of medical care using telecommunications, suggesting that it is a distinct entity within the umbrella of telehealth. It should be noted that the distinction between the two terms is not recognized by all, as the terms telemedicine and telehealth have been used interchangeably by some authors [4].

In Manitoba, a provincial telehealth service has been long-standing, which facilitates telemedicine services through physician-to-patient videoconferencing services. In the cancer setting, these services link specialists working in the urban cancer centers (ie, in the cities of Winnipeg and Brandon, Manitoba) with patients attending appointments in rural and remote centers throughout the province. In response to the COVID-19 pandemic, CCMB physicians rapidly adopted telemedicine solutions outside of the formal Telehealth service. Microsoft Teams, Zoom, and other consumer-level videoconferencing services, in addition to the increased use of telephone calls, have been used in lieu of clinic visits to keep patients, informal caregivers, and health care providers safe by limiting traffic in health centers and reducing the need for in-person clinic visits.

In cancer care, physicians are often required to share sensitive and complex information with patients and those supporting them. Information needs are among the most commonly cited unmet supportive care needs [5,6], and it is not clear how receiving information, including that which is considered to be "bad news," through telemedicine impacts the patient experience. With the rapid increase of telemedicine services during the COVID-19 pandemic, including the use of informal telemedicine services in Manitoba, it is necessary to better understand how telemedicine affects the experience of receiving information from physicians.

Telemedicine and telehealth have been explored outside of the cancer setting, with numerous intervention trials and systematic reviews both completed and underway [7]. Additionally, guidelines exist to help guide best practice for the use of telemedicine [7], such as those developed by the American Association of Telemedicine [8]. However, in the unique setting of oncology, there appears to be a lack of empirical evidence to guide best practices. Prior to undertaking this review, the literature was searched to identify literature that would be helpful for guiding best practices. The search included several databases (JBI Evidence, Cochrane Systemic Reviews, and MEDLINE) and did identify numerous studies that have explored the experience of receiving cancer care through telemedicine, with two reviews identified that summarized the qualitative evidence regarding the experience of patients with cancer and informal caregivers accessing telemedicine [9,10]. However, no review could be identified that addressed specific activities or practices oncology physicians could employ to improve the experience of receiving care through telemedicine. Of note, a recent publication on delivering bad news using telemedicine in the oncology setting based on expert opinion guided by the SPIKES framework [11] was identified, but it is noted that this framework was not specifically designed in the context of telemedicine.

Systematic, scoping, and mapping reviews are 3 different types of systematic literature review methods, each with distinct procedures and outputs. Systematic reviews are useful when a decision regarding changes to current practice is required [12]. Scoping reviews, which may be a precursor to systematic reviews, help to identify the types of evidence available on a given topic, clarify concepts, examine how research has been conducted, and identify knowledge gaps [12,13]. Mapping reviews, on the other hand, do not answer specific questions about a topic, but identify what evidence exists regarding a certain topic [14,15]. As the literature relevant to the required objectives does not appear to have been previously summarized, a scoping review was selected as the best review strategy.

Based on how telemedicine has been adopted at CCMB during the COVID-19 pandemic, the relevant objectives for this review are the following: (1) to identify how telemedicine in the oncology setting has been studied in the literature, (2) to identify what specific clinician practices have either been demonstrated or suggested to be helpful in terms of improving the patient/friend/family experience, and (3) to identify future research directions to improve the integration of telemedicine with clinical oncology care.

Methods

This scoping review protocol is based on the methodology developed by the Joanna Briggs Institute (JBI) [12,16]. In keeping with their procedures, the following section will outline the specific review questions, study inclusion criteria, search strategy, and procedures for study selection, data extraction, and data presentation.

Review Questions

The primary question this review will seek to answer is the following:

Question 1.0: What studies have been conducted examining the relationship between clinicians' use of telemedicine and the experience of patients with cancer and their informal caregivers?

The subquestions this review will seek to answer are the following:

Question 1.1: What clinician factors have been identified as impacting the experience of receiving care via telemedicine in the cancer context?

Question 1.2: What patient/informal caregiver factors have been identified as affecting the experience of receiving care via telemedicine in the cancer context?

Question 1.3: What types of communication strategies have been studied for delivering telemedicine in the cancer context?

Question 1.4: What technological factors (eg, apps, remote monitoring, asynchronous versus synchronous communication) have been demonstrated to impact the experience of receiving care via telemedicine for patients and their informal caregivers?

Question 1.5: What factors related to the type of information being shared have been demonstrated to impact the cancer experience of patients and their informal caregivers?

Inclusion Criteria

Participants

This review will include studies involving patients with cancer aged >18 years and their friends, family, and informal caregivers.

Concept

Any telemedicine use in the oncology context.

Context

The studies included in this review will focus on the receipt of oncology physician care through telemedicine. This review will not focus on specific cultural, racial, or geographic characteristics.

Types of Sources

This scoping review will consider quantitative, qualitative, and mixed methods study designs for inclusion. Additionally, systematic reviews and editorials will be considered for inclusion. Articles published in English will be included. Articles published from 1990 to the present will be included to reflect research conducted at the beginning of the contemporary era of telemedicine [17].

Exclusion Criteria

Studies focused primarily on the pediatric oncology context and non–peer reviewed publications will be excluded.

Search Strategy

The search strategy will aim to locate peer-reviewed published primary studies, reviews, and editorials. An initial limited search of MEDLINE and CINAHL was undertaken to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles, and the index terms used to describe the articles, were used to develop a full search strategy for MEDLINE, and translated for CINAHL (see Multimedia Appendix 1 for the MEDLINE search). The search strategy, including all identified keywords and index terms, will be adapted for each included information source. The reference lists of articles selected for full-text review will be screened for additional papers.

Information Sources

Information sources will include electronic databases and study authors. Databases to be searched will include MEDLINE, CINAHL, EMBASE, Cochrane Library, Scopus, and PsycINFO.

Study Selection

Following the search, all identified records will be collated and uploaded into EndNote X9 (Clarivate Analytics) and duplicates will be removed. Titles and abstracts will then be screened by two independent reviewers for assessment against the inclusion criteria for the review. Potentially relevant papers will be retrieved in full and their citation details will be imported into an Excel (Microsoft Corp) spreadsheet. The full text of selected citations will be assessed in detail against the inclusion criteria by two independent reviewers. Reasons for exclusion of full-text papers that do not meet the inclusion criteria will be recorded and reported in the scoping review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion or with a third reviewer. The results of the search will be reported in full in the final scoping review and presented in a PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension for Scoping Reviews) flow diagram [18].

Data Extraction

Data will be extracted from papers included in the scoping review by two independent reviewers using a data extraction tool developed by the reviewers. The data extracted will include specific details about studies exploring the experience of adult patients with cancer and their informal caregivers receiving telemedicine relevant to the main review question as well as the scoping review subquestions. The extraction tool has been developed based on recommendations and the example provided by JBI [19]. A draft extraction tool is provided (Multimedia Appendix 2). The draft data extraction tool will be modified and revised as necessary during the process of extracting data from each included paper. Modifications will be detailed in the full scoping review. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. Authors of papers will be contacted to request missing or additional data, where required.

Data Presentation

The extracted data will be presented in diagrammatic or tabular form in a manner that aligns with the objective of this scoping review. A narrative summary will accompany the tabulated and/or charted results and will describe how the results relate to the review's objectives and questions.

Results

Study activities related to the scoping review will begin in December 2020. Results will be available by late spring 2021.

Discussion

The protocol for this scoping review has been developed as a pragmatic response to the challenges faced by patients, their informal caregivers, and clinicians in accessing/providing clinical care during the global COVID-19 pandemic. The need to socially distance and take additional precautions to prevent transmission of the COVID-19 virus has likely had significant effects on the experience of receiving and delivering [20] cancer care. How these changes have impacted the delivery and receipt of information provided by clinicians to patients and their informal caregivers is not yet fully understood.

A recent report by the lead author of this protocol (MT) identified key characteristics of high-quality information. These emerged from semistructured interviews with 60 patients with cancer and their friends and family [21]. The interview data were analyzed using Classical Grounded Theory [22-24]. The key characteristics of high-quality information included accessibility, credibility, applicability, and framing. Accessibility was defined as the relative convenience and effort associated with receiving information about cancer. Credibility reflected how trustworthy/reliable the information was considered. Applicability referred to the degree with which the information received applied to the individual who received it. Framing was defined as how the information was presented, with particular focus on whether the information identified ways that the cancer situation could be optimized, either by clinicians or by the individuals receiving the information. Using the framework provided by this previous study [21], both from a patient and informal caregiver perspective, receiving care through telemedicine may be more accessible than through traditional in-person encounters. However, some important information conveyed through in-person interactions maybe not be transmitted. For instance, nonverbal information may not be delivered or received, making it challenging to both provide and receive care in sensitive contexts. This scoping review will be useful in identifying the different factors that have been found to affect the delivery of information using telemedicine in the cancer context as well as what areas have yet to be explored. The results will be useful to both clinicians and researchers in the context of the COVID-19 pandemic and beyond.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 15 KB - resprot_v9i12e25501_app1.docx]

Multimedia Appendix 2
Data extraction instrument.
[DOCX File , 14 KB - resprot_v9i12e25501_app2.docx]

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Abbreviations

AAFP: American Academy of Family Practitioners
CCMB: CancerCare Manitoba
JBI: Joanna Briggs Institute
PPE: personal protective equipment
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension for Scoping Reviews

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Protocol

Telemedicine in Intensive Care Units: Protocol for a Scoping Review

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Abstract

Background: Telemedicine has been deployed to address issues in intensive care delivery, as well as to improve outcome and quality of care. Implementation of this technology has been characterized by high variability. Tele-intensive care unit (ICU) interventions involve the combination of multiple technological and organizational components, as well as interconnections of key stakeholders inside the hospital organization. The extensive literature on the benefits of tele-ICUs has been characterized as heterogeneous. On one hand, positive clinical and economical outcomes have been shown in multiple studies. On the other hand, no tangible benefits could be detected in several cases. This could be due to the diverse forms of organizations and the fact that tele-ICU interventions are complex to evaluate. The implementation context of tele-ICUs has been shown to play an important role in the success of the technology. The benefits derived from tele-ICUs depend on the organization where it is deployed and how the telemedicine systems are applied. There is therefore value in analyzing the benefits of tele-ICUs in relation to the characteristics of the organization where it is deployed. To date, research on the topic has not provided a comprehensive overview of literature taking both the technology setup and implementation context into account.

Objective: We present a protocol for a scoping review of the literature on telemedicine in the ICU and its benefits in intensive care. The purpose of this review is to map out evidence about telemedicine in critical care in light of the implementation context. This review could represent a valuable contribution to support the development of tele-ICU technologies and offer perspectives on possible configurations, based on the implementation context and use case.

Methods: We have followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist and the recommendations of the Joanna Briggs Institute methodology for scoping reviews. The scoping review and subsequent systematic review will be completed by spring 2021.

Results: The preliminary search has been conducted. After removing all duplicates, we found 2530 results. The review can now be advanced to the next steps of the methodology, including literature database queries with appropriate keywords, retrieval of the results in a reference management tool, and screening of titles and abstracts.

Conclusions: The results of the search indicate that there is sufficient literature to complete the scoping review. Upon completion, the scoping review will provide a map of existing evidence on tele-ICU systems given the implementation context. Findings of this research could be used by researchers, clinicians, and implementation teams as they determine the appropriate setup of new or existing tele-ICU systems. The need for future research contributions and systematic reviews will be identified.

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KEYWORDS

tele-ICU; intensive care unit; intensive care; telemedicine; critical care; implementation; scoping review

Introduction

Background

Since the first experiments in the late 1970s, telemedicine has increasingly been adopted in intensive care settings [1]. Recent figures indicate that telemedicine technologies are now in use for approximately 15% of intensive care beds in the United States [1-3]. Similar technologies have also been in use in Europe. An illustration of this trend is found at the *Charité—Universitätsmedizin Berlin*, a large university hospital in Germany, where an intensive care unit (ICU) telemedicine program focusing on quality improvement in postoperative care is being implemented [4].

An ICU is defined as a system for the provision of specialized medical and nursing care to patients located in a specific area of a hospital [5]. The term tele-ICU collectively refers to the telemedical systems that are deployed to extend or complement the capabilities of the ICU. Tele-ICU interventions are defined as the remote delivery of clinical intensive care services through conferencing and monitoring technologies [2,3,6]. Depending on the system setup, this may include audio-visual systems allowing two-way real-time communication between intensivists, bedside clinical staff, specialists, subspecialists, and patients [7]. This scoping review will focus on the implementation of these conferencing and monitoring technologies.

A range of rationales for implementing telemedicine technologies in intensive care has been suggested. Tele-ICU interventions have been described as a cost-effective response to a lack of intensive care availability. In the United States in particular, tele-ICUs have been used to address shortfalls in intensive care staffing, enabling intensivists to remotely monitor a large number of patients [6]. Additionally, tele-ICU technology allows access to populations in remote areas, thereby making specialty intensive care consultations more widely available [8]. Other applications have focused on increasing adherence to evidence-based best practices [3,9], using benchmark performance data [6]. Telemedicine in intensive care has been used as a way to improve patient safety by reducing alarm fatigue [9]. Applications in medical education, for instance, during the training of resident intensivists, has also been described [10].

Telemedicine in intensive care has been characterized by high variability in the modality and context of implementation. This is exemplified by the variety of technology setups found in the literature [6]. Tele-ICU systems may be organized according to numerous models regarding their system architecture, care intensity, and staffing pattern [7,11]. First, tele-ICU system architecture can be centralized (ie, “hub and spokes”) or decentralized (ie, distributed across multiple organizations) [3]. In both configurations, systems can connect multiple institutions across organizational boundaries (ie, different institutions) and, in some cases, in wide geographic areas (from local to international). Second, tele-ICU care processes can be characterized by their care intensity [1]. Higher-intensity models feature escalation protocols for staff response combined with a proactive clinical approach. Lower-intensity setups consist of discontinuous patient coverage combined with a reactive approach to patient events [12,13]. These two tele-ICU types of engagement protocols have also been respectively labeled as “direct intervention” and “monitoring and notify” [13]. Third, staffing patterns and care team composition vary across systems. Tele-ICUs accommodate different intensivist presence times at the bedside during the day, night, or weekend, based on the needs and resources of the ICU and tele-ICU units [14]. The wider care team composition also presents some differences between tele-ICUs. It may include nurses, pharmacists, and nonclinical staff.

More generally, tele-ICUs also reflect the various forms of ICU organization found across countries or regions with different standards of intensive care. ICUs in the United States are characterized by the dominance of the “open model,” with approximately 80% of ICUs staffed by nonintensivists. In contrast, in many countries, the “closed model” is predominant [10]. In this model, patients are systematically transferred to a trained intensivist. It follows that tele-ICUs have been integrated and adapted to ICUs with different models to fulfill different clinical and organizational needs.

Literature Gap

Researchers have suggested that the setup characteristics of telemedicine systems play an important role in the success of tele-ICU implementation [15]. The context of implementation has been a determinant of the form of tele-ICU organization [16]. Implementation context is defined as the structures and processes inside which a technology is deployed [17]. The organizational context is a key aspect to consider when developing new tele-ICU systems and evaluating the effectiveness of telemedicine intensive care interventions.

Extensive literature has been produced on tele-ICU interventions, including several systematic reviews [18-23]. The main focus of these reviews has been on the benefits of telemedicine implementation with regard to clinical and economical outcomes. Most studies have employed semiexperimental research designs, which include before/after comparisons with or without a control group [24]. To date, three meta-analyses have been performed for tele-ICU with hospital mortality and length of stay as outcomes [24]. Other reviews in the domain involve additional outcomes including staff satisfaction, adherence to best practices, and rate of mechanical ventilation [9].

Based on the conclusions of these reviews, benefits derived from tele-ICU implementation appear heterogeneous [15,25]. A recent systematic review by Chen et al [23] identified a positive effect of tele-ICU with a reduction in ICU and hospital mortality. However, in other tele-ICU studies, benefits derived from using telemedicine technologies in intensive care settings could not be detected [15], while other studies pointed to mixed results with a reduction in ICU mortality but no relevant impact on in-hospital mortality [18]. The variability in outcomes highlights that the benefits derived from tele-ICU interventions depend on the organization where it is deployed [11] and how the technology is applied [26]. The choice of a relevant implementation model given its context is therefore an important aspect to achieve efficacy [24]. The need for additional research about technology characteristics and implementation context has been highlighted [17]. For instance, Kahn et al noted a lack of research contributions on the factors influencing organizational and clinical effectiveness [15]. Researchers have also noted that there are currently no recommended guidelines for determining the most appropriate tele-ICU setup or composition [6].

In recent years, scoping reviews have been employed to provide an overview of the field of literature and examine emerging evidence for new types of interventions [27]. This research method has become a valuable tool for providing evidence synthesis for complex systems. A scoping review may be used to efficiently access mapping of evidence and peer-reviewed literature for a range of outcomes and thus serve as a reference for teams involved in the implementation of tele-ICUs. Scoping reviews can also help evaluate research gaps and identify the need for future systematic reviews in specific subdomains [28]. We did not find an existing scoping review on the topic after a preliminary search of online databases.

Aim

The purpose of this publication is to provide a comprehensive overview of telemedicine outcomes in relation to the ICU implementation context. We will map out evidence on outcomes of the use of telemedicine technology in intensive care and seek to offer perspectives on possible configurations of tele-ICU technologies, based on the implementation context and use case.

Methods

Research Team and Study Design

This protocol was developed using guidance from the methodological framework on scoping reviews by Arksey and O'Malley [28], and subsequent developments by the Joanna Briggs Institute [29]. This framework consists of a number of consecutive stages as follows: (1) identifying the research question, (2) identifying relevant studies, (3) selecting studies, (4) charting the data, and (5) collating, summarizing, and reporting results. We will use the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist to report our results [30]. At present, the international Prospective Register of Systematic Reviews (PROSPERO) does not accept scoping review protocols for publication, so this protocol was not registered.

The research team consists of a doctoral researcher with a background in health economics (CG); a professor for digital health, who is a consultant anesthesiologist and a computer scientist (FB); a professor of medical informatics (MB); a consultant anesthesiologist with specialty in intensive medicine, who is a team coordinator for the intensive care telemedicine project (BW); a postdoctoral researcher in anesthesiology residency with a background in digital health (ASP); and a professor of information systems, digital transformation, and information technology infrastructure (DF).

Step 1: Identifying the Research Question

The purpose of this scoping review is to map out findings and evidence about tele-ICU in light of its implementation context. The main research question for this review is as follows: what are the benefits of using telemedicine technology in intensive care? More specifically, the following subquestions are formulated: (1) Are there implementation contexts (eg, hospital type) that are more conducive to positive outcomes of telemedicine in intensive care? (2) What tele-ICU configurations (eg, staffing) are more appropriate for certain implementation contexts? (3) What range of outcomes exist for tele-ICU implementation in the literature and to what extent have these been extensively researched?

Step 2: Identifying Relevant Studies

The databases Web of Science Core Collection, MEDLINE (via Web of Science, Clarivate Analytics), Library, Information Science & Technology Abstracts, ERIC, PsycINFO, PSYNDEX, and CINAHL (via EBSCO Host, EBSCO Information Services), as well as IEEE (via IEEE Xplore, Institute of Electrical and Electronics Engineers) have been searched for peer-reviewed literature. The search queries have been reviewed by both the information specialist and intensive care clinicians in the research team. The electronic database search will be supplemented by a manual search for grey literature. We have scanned the checklist of the Canadian Agency for Drugs and Technologies in Health to look for additional literature references.

We have followed the guidelines of the Peer Review of Electronic Search Strategies (PRESS) to formulate the queries. The exact search query used for Web of Sciences and EBSCO Host can be found in Multimedia Appendix 1. An overview of the search terms is shown in Table 1.

Table 1. Overview of the search terms.

Topic	Search keywords
Intensive care	ICU[a]
	Intensive care unit
	Intensive care
	Acute care
	Critical care
Telemedicine	Tele-ICU
	Remote presence
	Virtual ICU
	eHealth
	mHealth[b]
	Digital health
	Telemedicine
	Telecare
	Telehealth
	Digital intervention

[a]ICU: intensive care unit.

[b]mHealth: mobile health.

The search terms have been used in combination with the appropriate Boolean operators to formulate the search query. Search records, which include titles and abstracts, have been collated and managed using the reference management software Citavi version 6 (Swiss Academic Software). Duplicates have been identified and removed from the selection using Citavi duplicate management functionality.

A first selection of references will be performed based on screening of the titles and abstracts. Based on this selection, the full text will be retrieved and a detailed screening will be performed. The rationale for excluding studies on full-text screening will be documented and reported in the review. Full citations and a copy of the eligible studies will be retrieved and imported into Citavi.

Scoping reviews typically do not require to make a quality assessment of primary research. However, where applicable, we will complete a quality assessment of individual publications using adequate tools to appraise the quality of evidence.

Step 3: Selecting Studies

A screening guide has been developed by the reviewers to lay out the inclusion and exclusion criteria. The selection process will be first conducted by a main reviewer (CG) and then validated by at least one reviewer in the research team. Divergence in classification will be resolved through discussion based on consensus of the reviewers. To ensure consistency in the selection of sources and the review methodology, a feasibility test will be conducted among the members of the research team with a sample of 100 publications from the preliminary search.

The study selection will be divided into two steps to include both secondary and primary literature. A secondary literature screen (“level I screen”) will seek to identify all secondary literature about telemedical technology used in ICUs. Publication titles and abstracts in the search results will be analyzed for inclusion. The criteria applied in the level I screen are as follows: (1) publication about telemedicine technology in intensive care, (2) research approach is a review of the primary literature, (3) no study design restriction (systematic reviews, simple reviews, and narrative reviews), (4) no country restriction, (5) language is English, German, Spanish, or French, (6) no date restriction (database will be searched from inception to present), and (7) publication in a peer-reviewed journal.

A primary literature screen (“level II screen”) will then be applied to identify relevant primary literature. Eligibility criteria in the level II screen are based on the PICO framework (“Patient Problem,” “Intervention,” “Comparison,” and “Outcome”) [31] and are structured as follows: (1) participant: patients admitted and medical staff working in the ICU; (2) intervention: implementation of telemedicine technology in the ICU; (3) comparison: intensive care delivered via telemedicine compared with standard of care or ICU without telemedicine technology; (4) outcome: all outcomes are accepted for inclusion, such as clinical outcomes, economic outcomes, staff and patient satisfaction, and guideline compliance. Publications solely based on expert opinion (ie, editorials) will therefore not be included in the review. Additionally, all study designs will be considered, including both qualitative and quantitative research.

Publications about the use of telemedicine for neonatal and pediatric ICUs (NICUs and PICUs, respectively) will not be included in this scoping review. The rationale for this exclusion is that the characteristics of the patient population and organization of NICUs and PICUs are greatly different from generalist ICUs and would be better addressed in a separate review.

Step 4: Charting the Data

The purpose of step 4 is to determine the data points contained in the publications from the previous step. The data points necessary for the analysis will be tabulated in extraction sheets.

The extraction sheets will then serve as a basis of the review work.

A list of data items will be selected based on the medical and technology expertise of the research team in the domains of intensive care and telemedicine. As Munn et al [27] noted, this process of charting relevant forms is by nature iterative and is expected to evolve as literature is reviewed. Data items will be charted for this review and will enable analysis of the implementation of tele-ICUs.

The extraction process will consist of collecting and codifying information contained in the publications that describe tele-ICU systems and their implementation context. As summarized in Table 2, context is defined according to the following five topics: (1) ICU clinical focus, (2) ICU type, (3) hospital type, (4) tele-ICU system configuration, and (5) implementation rationale. Tele-ICU configuration classification is determined on the basis of the following aspects: technical architecture, staff allocation, and mode of communication within the system.

Draft data charting forms will be developed and approved by the research team after independent pilot testing using a sample of publications (ie, 10 articles). Once consistent results are achieved and forms are approved, data from all included full-text articles will be charted by one member of the research team and verified by a second member to ensure all relevant data are charted.

Table 2. Overview of data extraction topics.

Topic	Description
1. ICU[a] clinical focus	Level of specialization of the ICU. Example: Medical ICU or surgical ICU versus specialized ICU type (eg, neurological).
2. ICU type	Main organization model of the ICU. Example: Open ICU versus closed ICU.
3. Hospital type	Clinical setting where the tele-ICU is implemented. Example: Urban and tertiary hospital versus community and rural hospital.
4. Tele-ICU system configuration	Technical architecture, staff allocation, and mode of communication of the tele-ICU system. Example: A centralized system with a hub architecture providing intensive care expertise in real time versus a decentralized system with an open architecture providing scheduled care.
5. Implementation rationale	Main rationale given for implementing a tele-ICU system. Example: Extending ICU coverage versus improvement of care quality.

[a]ICU: intensive care unit.

Step 5: Collating, Summarizing, and Reporting the Results

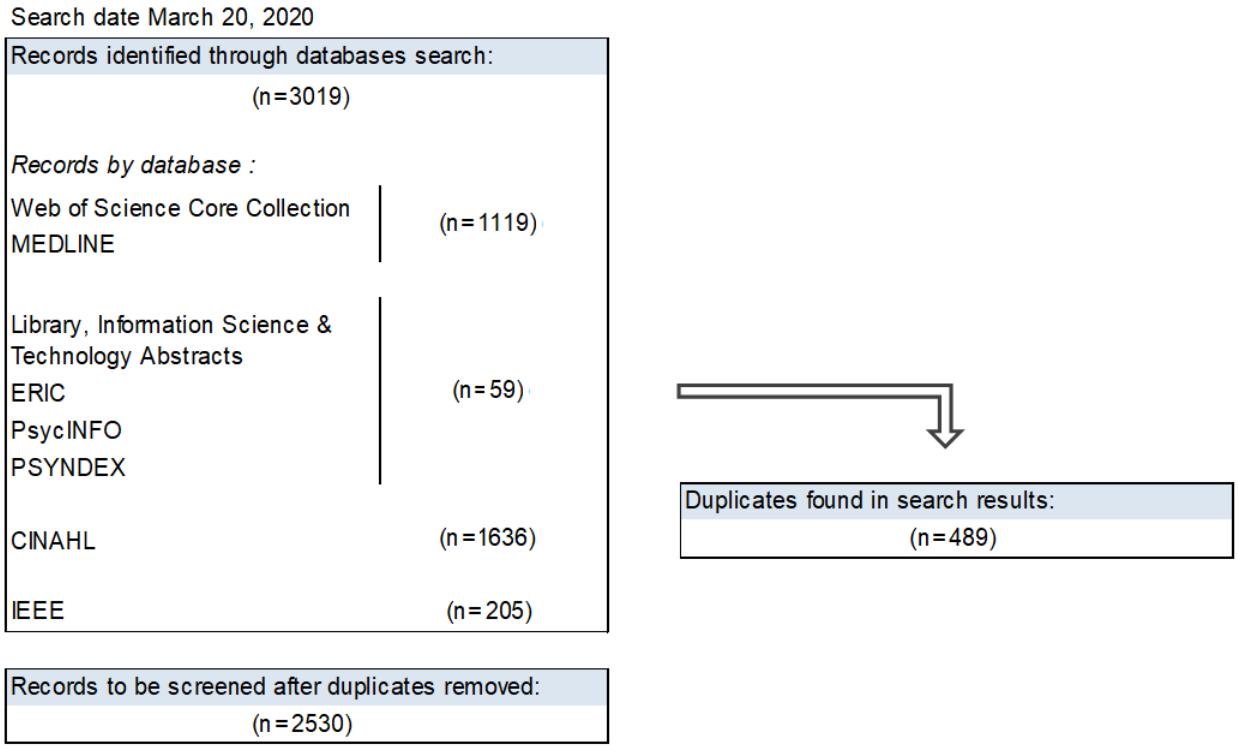
We will group the studies by the context of use and rationale for implementation. To synthesize results, we will form clusters of similar publications by classifying the data items collected. This method will allow us to analyze and compare evidence of tele-ICU implementation within each publication cluster.

We will present the results of the synthesis in the form of a series of tables, graphs, and visual representations.

Results

A preliminary research was completed to assess existing literature and ensure that no other scoping review with the same focus has been published so far. The preliminary electronic database searches were carried out in March 2020. As described in step 2 of this protocol, research results from MEDLINE, IEEE, ERIC, PsycINFO, PSYNDEX, and CINAHL were downloaded. A total of 3019 results were retrieved, of which 489 were identified as duplicates. Figure 1 shows a flow diagram with the records identified through the database preliminary search. The remaining steps (3 to 5) of the scoping review will be completed by spring 2021.

Figure 1. Literature search flow diagram.



Discussion

Preliminary Findings

The literature search yielded 2530 results after removing duplicates. The scoping review will provide a map of existing evidence on tele-ICU given the implementation context. The research findings could be used by researchers, clinicians, and implementation teams as they determine the appropriate setup for new or existing tele-ICU systems.

Limitations

Some limitations can be identified in the research approach proposed in this protocol. First, this review will seek to synthesize evidence from publications that are using heterogeneous methodologies. This will pose a limit on the ability to draw generalization from the findings of this review. Second, the search terms and the study selection described in this protocol have been selected based on the expertise of the research team in the areas of anesthesiology, intensive care medicine, technology, and evidence research, as well as the existing literature, rather than according to pre-existing research frameworks or categories. This may represent a bias that the research team will need to consider when discussing the findings of the scoping review.

Conclusions

We found that sufficient literature is available to complete the remaining steps of the methodology. To our knowledge, this is the first scoping review to examine the use of telemedicine in intensive care with a focus on the implementation context. Our research will contribute to the identification of where more evidence is needed to support the development of tele-ICU technology, with the appropriate configuration for its context and use case. The need for future research contributions and systematic reviews will be identified.

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Conflicts of Interest

BW received personal fees for consultancy and speaking from ORION Pharma Ltd, outside the submitted work. The other authors have no conflicts to declare.

Multimedia Appendix 1
Search query.
[DOCX File , 45 KB - resprot_v9i12e19695_app1.docx]

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Abbreviations

ICU: intensive care unit
NICU: neonatal intensive care unit
PICU: pediatric intensive care unit

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